Harry's Cosmeticology

Eighth Edition

Volumes I-II

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Foreword

Since its first edition *Harry's Cosmeticology* has been a highly respected text for cosmetic scientists and others concerned with skin, hair, and nail health and appearance. This, the eighth edition, continues this tradition, although the current and ever-changing status of the cosmetic industry has created the need for extensive changes. The driving forces for this required updating to include the spectacular advances in biology and dermatology as well as the steady progress in formulation technology. These innovations are reflected in this modernized and comprehensive revision of *Harry's*. The editor has attempted to present the rationale for currently practiced product concepts and to provide a scientifically sound basis for future product innovations. One of the major problems for compounders is the need to deal with the names of thousands of trademarked ingredients available for formulation. In this current edition, this complication was avoided by eliminating trade names and replacing them with the internationally accepted INCI terminology.

The use of the *INCI Dictionary* also allowed elimination of almost all chemical structures in this book. The text is deliberately slanted to alert readers to some of the uncertainties in cosmetic formulation. In addition, an effort was made to provide readers with sufficient background to draw their own conclusions about some of the dogmas that have persisted in the industry for years. The book avoids—as much as possible—the hype and pseudoscience that surround the frequently undocumented biological activity of many topically applied cosmetic ingredients. Citations of the original literature intended to substantiate the validity of specific and widely accepted assertions have been routinely eliminated. References were selected to allow further study by interested readers. The listings of recommended reading are intended to provide access to the classic information that forms the foundation of cosmetic science. Complete titles are included to facilitate the reader's selection of pertinent information.

The preparation of this edition of *Harry's* required the participation of many experts who contributed extensively to almost all chapters. The work of these

contributors is gratefully acknowledged, and their names are listed below. I also wish to acknowledge the help of my wife, Audrey, who contributed unselfishly to the completion of the manuscript. In addition, the guidance provided by the staff of Chemical Publishing Company has been invaluable.

It is my sincere hope that readers and users of this book will find this revision of Harry's a valuable resource in their pursuit of innovative cosmetic products in future years.

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PART ONE

The Substrates

The first five chapters in this edition are designed to introduce readers to the physiology and biochemistry of the human tissues to which cosmetics are applied. The emphasis is clearly on skin and hair, the tissues of primary interest to cosmetic scientists. A short description of ocular tissues is included because eyes play an important role in modern decorative cosmetics. Two additional chapters address the various tissues found in the mouth and, finally, the hard keratin of the nail.

CHAPTER 1
Skin

Structure and Function of Human Skin

INTRODUCTION

The skin is the organ that forms the border between the organism and the environment. Skin prevents dehydration, stops the penetration of noxious foreign materials and microorganisms, cushions against mechanical shock, helps to maintain a constant body temperature, and transduces incoming stimuli. In order to perform these functions, skin must be maintained in good condition, an important objective for cosmetic formulators. For cosmetic scientists, whether they are concerned with the improvement of the skin by pharmacology or with the prevention of damage as a result of artifice, an understanding of skin structure and function is essential. The impact of light on skin and on skin aging has become so important in cosmetics that it requires a complete discussion of this subject.

SKIN MORPHOLOGY

The skin is divided into three layers: the epidermis, the dermis, and the subcutaneous tissue. The epidermis is the outermost layer of the skin and is a stratified squamous epithelium. Its thickness varies, depending on location, from 0.05 mm to 1.5 mm. The epidermis is made up primarily of keratinocytes whose basic function is to produce a filamentous protein, keratin, to serve as a protective barrier in combination with various lipid components. These cells also produce several other proteins, for example, cytokines, which play a role in the cutaneous inflammatory response. Separated from the epidermis by the basement membrane, the dermis is composed primarily of the so-called ground substance, which includes glycosaminoglycans (GAGs) and the structural protein collagen. While its thickness also varies with location from 0.3 mm to 3.0 mm, the dermis is divided into two layers: the papillary

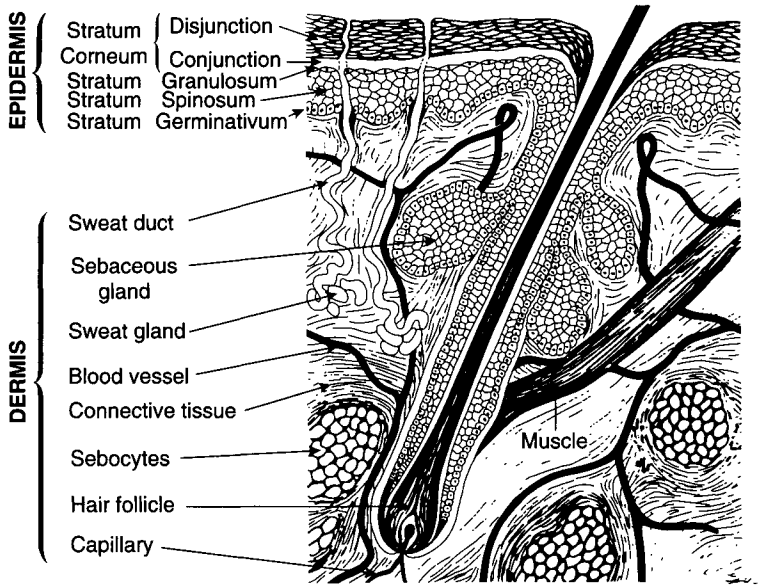

Figure 1.1. Diagram of normal human skin

layer, which interdigitates with the epidermal rete ridges, and the reticular layer, which extends to the subcutaneous tissue. This deepest layer of the skin, also known as the subcutis or hypodermis, is composed primarily of lipocytes (Fig. 1.1).

EPIDERMIS AND THE KERATINIZING SYSTEM

The epidermis consists of a number of layers: the innermost basal layer, the malpighian or prickle layer, the granular layer, and the horny layer or stratum corneum. The stratification is the result of changes in the keratinocytes as they mature and move outward from the basal layer, in which they are continuously formed by the mitosis of self-renewing progenitor cells and are shed on the skin surface. Three other cell types are present: melanocytes, the dendritic pigment-synthesizing cells; Langerhans cells, which are colorless and dendritic in form; and Merkel cells, which are concerned with sensation. The melanocytes and the Merkel cells are confined mainly to the basal layer, while the Langerhans cells are distributed in the basal, spinous, and granular layers.

Dermo-Epidermal Junction

The basement membrane zone forms the junction between the cellular epidermis and the dermis. Under the electron microscope, it is seen to be composed of four components, listed from the outermost layer: the plasma

membrane of the basal keratinocytes, the clear lamina lucida, the electron-dense basal lamina, and the dermal fibrils and bundles of fine filaments [1]. Some details of the components of this junction are provided in a later segment.

Stratum Basale

The stratum basale or stratum germinativum (Fig. 1.1) is a continuous layer that gives rise to all the keratinocytes. It is usually described as one cell thick, but in thick normal or in pathological epidermis it appears that mitosis may not be confined to cells in contact with the basement membrane. A portion of the basal cells is proliferative. These are the cells that differentiate and move up through the epidermis, eventually to become the components of the stratum corneum and later desquamate. The replacement time for the whole epidermis is probably about 42 days and for the stratum corneum about 14 days, and it is generally agreed that the times are considerably less in psoriatic skin. While the process of keratinization remains incompletely understood, in normal skin the desquamation of keratinocytes is in equilibrium with the generation of keratinocytes by mitosis of the proliferating cells. The importance of this equilibrium is best understood by studying examples of those skin diseases with abnormal keratinization. Abnormally rapid transformation of basal cells into horny cells of the stratum corneum occurs in psoriasis. Ichthyosis vulgaris, on the other hand, is a genetic disorder that results from abnormal retention of keratinocytes.

Cells of the stratum basale have a basophilic cytoplasm and dark-staining elongated nuclei; under the electron microscope their cytoplasm reveals many ribosomes, mitochondria, and sometimes smooth membranes. In addition, they contain numerous fine tonofilaments, about 5 nm in diameter, that form the developing cytoskeleton. The basal cells also often contain melanin, transferred from adjacent melanocytes. Intercellular bridges, or desmosomes, connect basal cells with one another and with the overlying squamous cells. Modified desmosomes, or hemidesmosomes, connect the basal cells to the underlying basement membrane zone.

Stratum Spinosum

The stratum spinosum or prickle cell layer is so called because the cells are given a spiny appearance by the numerous desmosomes. These desmosomes, or specialized attachment plates for the cellular tonofilaments, correlate with the intercellular bridges between keratinocytes. The glycocalyx is the intercellular cement between keratinocytes and is composed of glycoproteins. In the upper region of the stratum spinosum, lamellar granules, also known as keratinosomes or Odland bodies, make their appearance. These are ovoid bodies about 100–500 nm long. In the stratum granulosum they ultimately migrate toward the periphery of the cell and are discharged into the intercellular spaces.

Their appearance there correlates with the degradation of keratinocytes. Their lipid contents act to establish a barrier to water loss and may participate in stratum corneum cellular cohesion.

Stratum Granulosum

The thickness of the granular cell layer is usually proportional to the thickness of the stratum corneum. It may be only one cell layer thick in thin skin and up to 10 layers on the palms and soles. The cells contain basophilic granules of a material called keratohyalin, a material thought to be responsible for keratin filament aggregation. The "hard" keratins of hair and nail lack these keratohyalin granules.

Stratum Lucidum

The stratum lucidum, not seen in most formalin-fixed sections, is located at the deepest portion of the stratum corneum. It can be recognized only in palmar and plantar skin.

Stratum Corneum

In the stratum corneum the keratinocytes have lost their nuclei and virtually all of their cytoplasmic organelles and contents, including the keratohyalin granules. This layer of cells is about 10 cells thick (10 μ) and is located on top of the viable epidermis, a 100 μ thick layer of about 10 biologically active keratinocyte cells. This corneal cell layer stains eosinophilic because of the absence of the basophilic nucleus. The cells are flattened and completely filled with keratin, in the form of bundles of filaments embedded in an opaque interfilamentous material. The keratin filaments align into disulfide cross-linked macrofibers under the influence of filaggrin, the protein component of the keratohyalin granule responsible for keratin filament aggregation [2]. The structure of the stratum corneum has been compared to that of a brick wall, with the corneocytes as bricks and the intercellular lipids as mortar [3]. Horny cells are continuously shed from the skin surface.

During epidermal differentiation, changes are also seen in the composition of lipids. Cholesterol, triglycerides, and phospholipids exist in the lower layers of the epidermis. In the stratum spinosum and stratum granulosum, though, lipids are packaged into the lamellar granules. These lipids include phospholipids, glycolipids, and free sterols. These polar lipids are reorganized into neutral lipids in the intercellular spaces once the contents of the lamellar granules are released. The stratum corneum is therefore rich in ceramides, free sterols, and free fatty acids [4]. There are six major classes of free ceramides and two major classes of ceramides bound to cell surfaces in the stratum corneum.

Research conducted about 15 to 20 years ago suggested that the polar lipids found in the lamellar granules and in viable layers of the skin are modified under the influence of enzymes to assume more nonpolar characteristics. Some of these features are summarized in Table 1.1.

The makeup of lipids suggests that hydrophilic lipids are excluded from the stratum corneum to provide a hydrophobic surface.

TERMINAL DIFFERENTIATION

Terminal differentiation describes the change of the cuboidal keratinocytes (on the basement membrane) to the flat cellular remnants that are shed from the skin surface. The progressive changes of keratinocytes are illustrated in Figure 1.2 and are accompanied by biochemical changes, formation of keratins, formation and hydrolytic changes in lipids, loss of water, and cross-linking of cell envelopes.

The formation of keratins proceeds from the intermediate filaments present in keratinocytes.

Intermediate filaments of more than 50 types are synthesized in human tissues. In skin, two types (I and II) are specifically expressed in epithelial cells. In this classification acidic keratins (cytokeratins K9–K20) are identified as type I, while the so-called basic keratins (cytokeratins K1–K8) are classified as type II. In skin the keratins are customarily dimers of one type I and one type II. The fundamental structure of the intermediate filaments includes coil-coil α-helical segments bonded to each other by so-called (nonhelical) linker segments. Both ends of the rod-shaped filament are terminated by peptides. The exact modus of attachment of these filaments to each other to form the

Table 1.1 Level of Epidermal Lipids (%)

Fraction	Basal layer	Stratum granulosum	Stratum corneum	
			Whole	Outer
Polar lipids (phospholipids, cholesteryl sulfate)	45	25	5	2
Neutral lipids (sterols, fatty acids, hydrocarbons, triglycerides)	51	56	80	68
Sphingolipids	8	12	18	27
Glucosyl ceramides	4	5	Trace	Trace

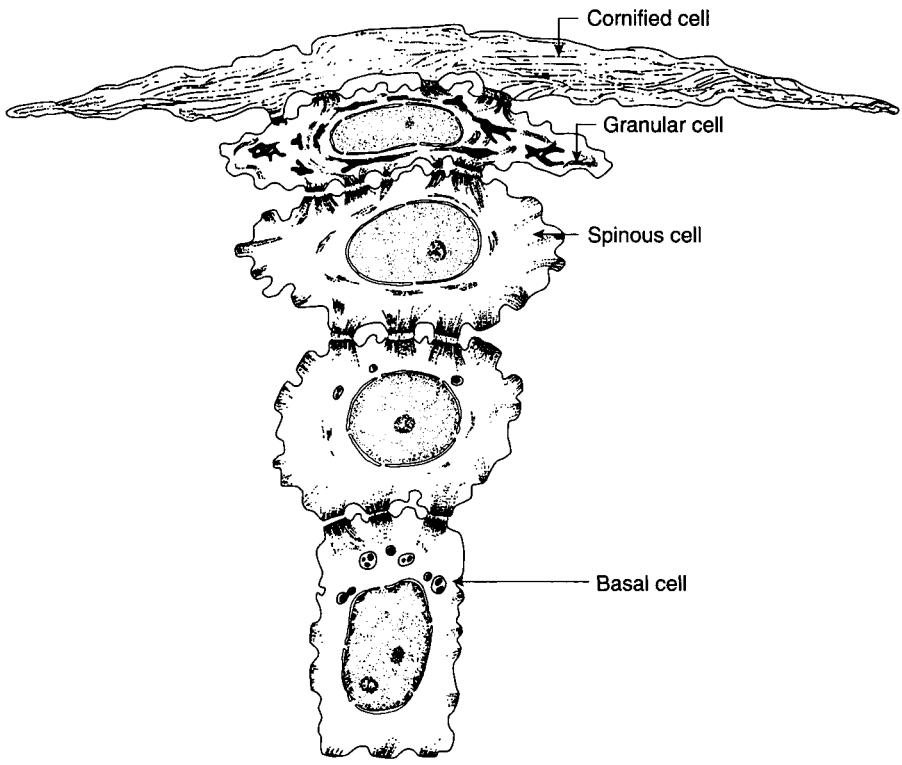

Figure 1.2. Conversion of individual basal keratinocytes into the flat cells of the stratum corneum

keratins within the keratinocytes is still under investigation. As noted, epithelial cytoskeletal filaments generally belong to one of two keratin (acidic or neutral-basic) groups ranging in molecular weight from about 40 to 70 kDa. Fillaggrin has been identified as one of the keratohyalin proteins forms in differentiating keratinocytes. Filaggrin is involved in the aggregation of keratin filaments to form the keratins found in mature keratinocytes or corneal cells. After filaggrin has served its function as a matrix between intermediate filaments, it is hydrolyzed enzymatically to create various free amino acids that form part of the natural moisturizing factor.

The hydrolytic changes of the epidermal lipids are also controlled by keratinocytes, which discharge lipids into the intercellular space after forming the so-called lamellar granules. These lipids are distinctly different from the sebaceous lipids secreted by the sebaceous glands. In the process of terminal differentiation, which requires about three to four weeks, the basal cell (keratinocyte) generates a remarkable set of complex lipids (e.g.,

ceramides). During the cells' passage outward, these lipids are modified (become more hydrophobic) to create the biphasic structure commonly called stratum corneum. The function of this outermost covering of the human body is discussed later in this chapter under "Barrier Function."

During its ascent to the skin surface, the keratinocyte shrinks, primarily through loss of water. The fate of this water is not known, but one may safely assume that it becomes part of the evaporating water generally described as transepidermal water loss. The loss of water during the maturation of keratinocytes is an important phenomenon that must be considered in studies of skin moisture levels (Fig. 1.3). The level of water in the basal layer is about that found in internal tissues, that is, about 80–85%. The water level drops stepwise to about 35% at the border between the stratum granulosum and the stratum corneum. The water level in the topmost layers of the skin is variable and is under the control of the environment and the evaporative flux from lower skin layers.

Finally, the proteins in the cell membranes of the maturing keratinocytes undergo drastic changes due to cross-linking. This provides the terminally differentiated corneal cell with a rigid cell envelope that is chemically resistant and acts as a protective coating. The most important enzymes that play a role in this process are transglutaminases which catalyze ε-(γ-glutamyl) lysine cross-linking. Involucrin is the primary cytoplasmic precursor to the protein making up the cell envelope. Other cross-linked proteins are present and have been identified, for example, loricrin.

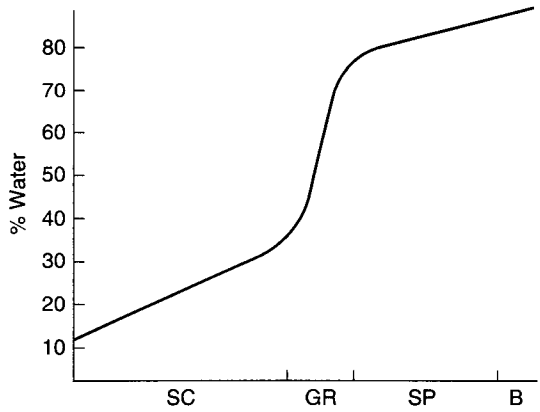

Figure 1.3. Water concentration profile in epidermal layers [SC—stratum corneum; GR—stratum granulosum; SP—stratum spinosum; B—basal layer (stratum germinativum)]

Biologists have further identified some layers within the stratum corneum. The so-called desquamating layer at the surface is frequently called stratum corneum disjunction, while the layer below it is known as stratum corneum conjunction. To complete this highly simplified discussion of the skin, it is important to note that the layer of keratinocytes is frequently identified as viable epidermis. Cells from this layer can be cultured and are commonly used to study the release of cytokines and the like and the impact of drugs and/or cosmetic ingredients. In contrast, the nonviable epidermis includes only the dead cells of the stratum corneum.

Before leaving the life history of the epidermis, the process of differentiation should be considered as proceeding from the inside to the exterior. The outward movement of biological debris, water, and lipids directly opposes human efforts to drive ingredients/drugs into and through the skin unless special efforts are made to create molecules that are shaped and manipulated to permeate.

PIGMENTARY SYSTEM

Melanocytes are dendritic cells that produce and secrete melanosomes, which contain melanin. Melanin is the major determinant of skin color. The number of melanocytes in the epidermis is the same regardless of skin color; it is rather the number and size of melanosomes produced that determine the color of one's skin. Melanosomes in dark skin are nonaggregated, whereas they are smaller and form membrane-bound complexes in light skin. Melanocytes are derived from the neural crest in the embryo and are seen in the basal layer of the epidermis by the eighth week of gestation. They differ from the other cells of the stratum basale by the possession of dendritic processes, by which they transfer pigment to a group of keratinocytes, the whole forming the "epidermal melanin unit" [5]. Typically each melanocyte is associated with about 36–40 keratinocytes in the human epidermis. Melanocytes have no desmosomes and thus, when stained with hematoxylin and eosin, appear to have a halo due to the separation from adjacent keratinocytes. The concentration of melanocytes, though, does vary in different areas of the skin, with the highest concentration on the face and the male genitalia and the lowest concentration on the trunk.

The characteristic feature of melanocytes is a special cytoplasmic organelle known as a melanosome in which the melanin is formed by the action of the enzyme tyrosinase. The melanosomes arise as spherical, membrane-bound vesicles in the zone of the Golgi apparatus and eventually appear as densely pigmented granules [6].

Melanins are quinoid polymers of two kinds. Pheomelanins are yellow or red in color, and eumelanins produce the brown or black color. Both

are formed by the same initial steps, which involve oxidation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and its dehydrogenation to DOPA-quinone. The formation of eumelanins then involves several further steps to produce indole-5,6-quinone, which polymerizes and becomes linked to protein. It is now believed that eumelanin is not a homopolymer composed solely of indole-5,6-quinone units but rather a poikilopolymer that includes several intermediates. Pheomelanins are formed by a different route. The DOPA-quinone interacts with cysteine to form 5-S- and 2-S-cysteinyldopa, and these isomers are further oxidized to a series of intermediates that then polymerize [7].

The formation of melanin depends on the generation of free radical species. The biochemical pathways leading to the formation of melanin pigments in vivo were described by Raper and by Raper and Mason and more recently by Prota. This information can be found in most textbooks of biochemistry and is not repeated here. Once formed, melanin has been identified as a (stable?) free radical that can react with superoxide.

The significance of melanin as a purported photoprotectant and the response of skin to ultraviolet (UV) irradiation are so important to skin appearance and health that these topics are discussed in Section B, "Responses to Sunlight of Human Skin."

LANGERHANS CELLS

Langerhans cells are bone marrow–derived cells of the monocyte-macrophage lineage. They are found scattered among the stratum spinosum and constitute approximately 3–4% of all epidermal cells. These dendritic cells are similar in form and number to melanocytes but contain no pigment. The hallmark of the Langerhans cell is the characteristic cytoplasmic organelles called Birbeck granules. These are formed when a membrane-bound antigen is internalized in the Langerhans cell.

Langerhans cells are responsible for the recognition, uptake, processing, and presentation of antigens in the epidermis to T lymphocytes. It is by this pathway that they play a crucial role in immunosurveillance, contact sensitization, and allograft skin rejection. Langerhans cell function is impaired by UVB radiation, resulting in a decrease in the antigen-presenting capacity and in the production of cytokines.

APPENDAGEAL STRUCTURES

Eccrine Sweat Glands

Humans have several million eccrine sweat glands distributed over most skin sites, but they are more concentrated in the axilla, forehead, palms, and soles.

In some areas they number as many as 600 glands per cm^2. Eccrine sweat glands are the most numerous skin appendages and are responsible for the production of sweat. They have a cylindrical spiral duct lined with epidermal cells extending from their visible opening in the epidermis down into the deep dermis, where the duct becomes coiled and convoluted into a ball [8]. This secretory coil manufactures the odorless sweat, which rises up the duct to be released on the skin surface. It is thought that the duct of the gland has the ability to modify the sweat as it flows upward by removing salts or water. The sweat glands control both body temperature and excretion, and they are under the control of the cholinergic nervous system. The evaporation of sweat has a cooling effect. The glands respond to environmental temperature but also to other stimuli, such as UV light, emotional stress, and rises in body temperature. On the palms and soles, the secretion from the glands serves to increase surface friction.

Sweating appears to involve activation of myoepithelial cells, which line the ducts of the glands. Although sweating is considered to be a continuous process, it seems that sweat is ejected in small bursts, suggesting a peristaltic action by the ducts. The composition of eccrine sweat is similar to that of plasma, although more dilute, and was documented about 40 years ago. It includes, in decreasing relative concentration (mg %): Cl^- (320), Na^+ (200), lactic acid (35), K^+ (20), urea (15), ammonia (5), Ca^{++} (2), $glucose^{++}$ (2), Mg^{++} (1), amino acid (1), and creatinine (0.3). More information on eccrine sweat production is included in Chapter 21.

Apocrine Glands

The apocrine glands are tubular glands attached to the hair follicle and, like the sebaceous glands, develop in association with it [9]. Although rudiments are found covering the entire surface of the fetus, the glands become canalized and functional almost exclusively in the axillae, the anogenital regions, the areola, the external auditory canal, and the eyelids. In humans, apocrine gland secretions are milky and viscous but without odor. Odor production is related to bacterial action at the skin surface.

After puberty, secretion is in response to emotive stimuli. Adrenergic nerves control secretory activity, in contrast to the cholinergic control of eccrine funtion. The function of the glands in the human species has been much debated, but they serve no known function. In other mammals the glands serve a sexual function.

Sebaceous Glands

Sebaceous glands [10] secrete sebum, which forms the majority of the lipid that covers the skin and hair. They are found in all areas of human skin except the palms, soles, and dorsum of the feet. Sebaceous glands are usually

associated with hair follicles, except for those on the nipple, areola, and labia minora. The greatest concentrations (reportedly as high as 400–900/cm^2) are found on the scalp, face, upper chest, and shoulders.

The glands are holocrine and thus form their secretion by decomposition of their cells. New cells are formed continually from the lining of the gland by cell division to replace those lost. No motor innervation has been demonstrated in humans. During the generation of sebum, cells at the periphery of the lobule undergo division. As the daughter cell moves toward the center of the lobule, it synthesizes lipids. As the sebum accumulates, the cell increases in volume as much as 150-fold. When synthesis is complete, cell rupture occurs. This process from cell division to rupture requires approximately 14 days. The relatively long delay must be taken into consideration when designing drugs and therapies aimed at altering sebum.

Sebaceous gland activity is under hormonal control. It is stimulated by androgens of both gonadal and adrenal origin. In human males the glands are minute during the prepubertal period but undergo vast enlargement at puberty, when their output increases more than fivefold. Eunuchs secrete about half as much sebum as normal males but substantially more than boys; it seems that the secretion is dependent on adrenal androgens. Adult women secrete only a little less than men; their sebaceous activity appears to be maintained by androgens from the ovary and the adrenal cortex. Estrogens and anti-androgens, such as cyproterone acetate, inhibit sebaceous secretion in man. On the other hand, relatively small doses of potent androgens can cause enlargement of the glands and an increase in sebum production.

Human sebum is composed of triglycerides (57.5%), wax esters (26.0%), squalene (12.0%), free fatty acids (10%), and to a minor extent cholesterol and cholesterol esters. Epidermally derived lipids differ in lacking wax esters and squalene and having much higher proportions of cholesterol esters and cholesterol. There are marked differences in sebum composition among species. The origins of sebaceous lipids and their composition are different from those of the epidermal lipids [4].

The purpose of sebum is not known. While excessive sebum production has been associated with the development of acne vulgaris, lack of sebum production in prepubertal children is not associated with any skin abnormalities.

HAIR

Perhaps no single structure of the skin plays as important a role as human hair. And despite the vast body of knowledge regarding the anatomy, biology, and function of hair, humans are still unable to induce hair regrowth in the many disorders that result in hair loss or to effect permanent hair removal in states

of excessive hair. The cost of hair care in terms of time and money spent is huge in many cultures, and the psychological impact of hair disorders should not be underestimated.

The hair follicle is quite variable, depending on its location. In adults deep terminal hairs are found on the scalp and male beard area. Hair on the extremities and trunk is located more superficially in the skin. Vellus hairs are present on the female face and on the nonbearded areas of the male face. Lanugo is soft fine hair that covers the fetus and is shed prior to birth.

In general, the cross-sectional shape of terminal Caucasian scalp hair is round and somewhat curly; African American scalp hair is oval, sometimes flattened, and usually kinky; hair in Asians is round in cross-section and straight. These relationships do not apply to pubic hair, beard hair, and eyelashes, which have similar features in all races and are typically oval.

Hair color is due to the distribution of melanosomes within the hair shaft produced by melanocytes in the hair bulb. These are transferred to cells of the hair matrix similar to the transfer from melanocytes to keratinocyte in the epidermis. Three types of melanosomes are present in hair. Eumelanins are seen in dark hair, and pheomelanins predominate in blond hair. The intensity of color is related to the number of fully melanized melanosomes produced. Gray hair and white hair are due to a decreased number of melanocytes that produce fewer melanosomes.

A much more detailed discussion of hair—growth, properties, and chemistry—is found in Chapter 2.

NAILS

The nail plate is composed of keratinized cells that originate in the epidermis of the nail matrix. As discussed previously, there are no keratohyalin granules. The proximal nail fold forms the cuticle. The nailbed does not contribute to the development of the nail plate but serves as a network of parallel longitudinal ridges under the plate. The structure and growth characteristics of the human nail are discussed in greater detail in Chapter 3.

SKIN FUNCTIONS

CYTOKINES

Cytokines are proteins produced primarily by keratinocytes that act on other cells to mediate inflammation. The epidermal keratinocyte is a prodigious source of immunologic molecules and thus participates in cutaneous immunologic and inflammatory reactions [11]. Some of these factors are produced constitutively, while others are produced only after signal

transduction by external or systemic cues. Activated keratinocytes produce a variety of cytokines including interleukins (IL-1, IL-3, IL-6, IL-7, IL-8, IL-10), granulocyte colony-stimulating factor, macrophage colony-stimulating factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-alpha (TNF-α), transforming growth factors (TGF-α, TGF-β), platelet-derived growth factor, fibroblast growth factor, and nerve growth factor. This capability confers upon keratinocytes an active role in regulating the synthesis of extracellular matrix molecules. For example, IL-1, one of the most studied cytokines of the epidermis, appears to be released from the skin in response to UVB. The release of this cytokine after exposure to sunlight may account for some of the features of the sunlight response.

With the advent of recombinant DNA technology, human cytokines have become increasingly available for clinical use, and there are well-documented cutaneous toxicities associated with these agents.

ENZYMES

Enzymes are important constituents of the skin and are located in the epidermis and dermis. Primary lysosomes are membrane-bound and contain a variety of hydrolytic enzymes. They are found in the Golgi region of the keratinocytes primarily within the basal cell layer. Lysosomal enzymes are also found in the lamellar granules, as mentioned earlier. Secondary lysosomes, called phagolysosomes, are present in the basal cell layer of the epidermis. They digest phagocytized melanosomes and cellular constituents following epidermal injury.

Mast cells are rich in enzymes including histamines, heparin, tryptase, chymase, and other enzymes important in allergic reactions. Enzymes also play an essential role in the continuous remodeling of the collagens, elastin, glycosaminoglycans, and glycoproteins of the extracellular matrix. The initial step in the complex process of degradation and replacement involves enzymes called metalloproteinases [12]. Collagenase, one of the metalloproteinases, initiates the proteolytic events that result in the breakdown of collagen. Topical retinoids used in treating the effects of photoaging probably act by decreasing the production of collagenase.

The viable epidermis includes the previously noted proteolytic and lipolytic enzymes. In addition, antioxidant enzymes are available to help in the protection of skin against solar irradiation. A brief discussion of these enzymes is included in Chapter 12. The desquamation of corneal squames is likely to require proteolytic or lipolytic enzymes in nonviable environments. The exact nature of these participants in skin homeostasis is not known, but their need to perform in a benign (moist) environment has been established, as described by Rawlings et al. [13].

BARRIER FUNCTION

Granular cells release small organelles called Odland bodies into the intercellular space. These granules, which contain a trilaminar membrane, establish a barrier to water loss and mediate stratum corneum cell cohesion. The lamellar granules fuse with the granular cell plasma membrane and secrete their contents of polar lipids, hydrolytic enzymes, and free sterols into the intercellular spaces [13]. After they release their contents, the lipids become organized into lamellae, which provide the structural basis for the barrier to epidermal permeability. The hydrolytic enzymes that are released are thought to change polar lipids into more hydrophobic lipid products such as free fatty acids, cholesterol, and ceramides. These coalesce into sheets within the intercellular space of the stratum corneum, thus forming a waterproof barrier. Acid phosphatases, which are also released from the Odland bodies, are thought to promote desquamation by breaking up the intercellular connections of the keratinocytes.

The major barrier to permeation through and penetration into the epidermis is a so-called "intact" stratum corneum barrier. Such a system consists of corneal cells with their proteinaceous envelopes surrounded by the essentially nonpolar lipid remnant sheets of the lamellar granules. Any substance (hydrophilic or hydrophobic) must permeate the lipid sheets formed by a complex network of fatty acids, cholesterol, and ceramides. The sheets of this lipid network are believed to exist as bilayers. Imperfections in the lipid network due to injury, water swelling, or solvent/detergent extraction facilitate the permeation of diverse species through the corneal barrier. Once the permeant reaches the viable epidermis, its progress is much less impeded. Investigators of these phenomena agree that absence of or damage to the corneal barrier leaves the body open to invasion of both desirable and noxious components of topical products. For further details readers are urged to consult Ref. 14.

Skin is not totally impermeable, however, and its permeability shows regional variations and, reportedly, changes from birth to old age. The degree of absorption depends on the properties of the substance and the composition of the vehicle. In general, the faster and more extensively penetrating compounds are relatively nonpolar small molecules. Certain factors are known to influence percutaneous absorption of substances. For example, increased skin temperature and increased water content of the skin result in an increase in absorption through the skin. The increased hydration of the stratum corneum induces swelling of the corneocytes and uptake of water into the intercellular spaces, thus disrupting the physical barrier of the skin and allowing for a more favorable environment for hydrophilic substances.

Vehicles also affect the absorption of incorporated compounds. Important factors include the absorption characteristics of the vehicle, the degree of partition between the vehicle and the stratum corneum, and the concentration of the compound in the vehicle. Most substances traverse the thick palmoplantar stratum corneum in significantly smaller amounts then they do the thin stratum corneum of other regions.

Skin damaged by diseases or chemicals is much more permeable than is intact skin. This change reflects the effect that these agents have on the physicochemical state of the stratum corneum. Diseases such as toxic epidermal necrolysis and pemphigus, which produce complete denaturation of the epidermis, dramatically increase permeability. Chemicals that can damage the skin include solvents, denaturants, and surfactants.

The topical application to the skin of drugs for the treatment of cutaneous and systemic disorders has become an established route of administration. In general, drugs with low molecular weights and some degree of both oil solubility and water solubility can penetrate the skin adequately. Topical drug administration is most certainly useful for intradermal therapy. The currently popular systemic drug administration via topical dosing (patching and the like) requires deliberate damaging of the skin's barrier function to enhance drug permeation. Some drugs that require minimal barrier damage for transdermal therapy include nitroglycerin for coronary artery disease and estradiol for estrogen replacement.

DERMIS

The dermis [15] is a tough and resilient tissue that cushions the body against mechanical injury and provides nutrient to the epidermis and cutaneous appendages. It consists of an association of protein fibers within an amorphous ground substance containing glycosaminoglycans (GAGs), previously known as mucopolysaccharides. There are few cells in this matrix; most of them are fibroblasts, which secrete the dermal constituents. Fibroblasts are derived from the mesenchyme. The mast cell, also of mesenchymal origin, houses granules that contain heparin, histamine, and other active substances. The mast cell is an active participant in skin inflammation and irritation, as well as in several other skin disorders. The dermis also houses blood, contains lymphatic and nervous systems, and surrounds the invaginated epidermal appendages. The GAGs in the dermis can hold copious amounts of water and tend to surround the other constitutents of the matrix. Together with the fibrous portion of the matrix, these substances account for the skin's flexibility and resistance to deformation.

COLLAGEN

The major fibrous constituent of the dermis, accounting for 75% of the dry weight and 18–30% of the volume, is collagen [16]. Under the light microscope collagen fibers appear as eosinophilic branching wavy bands. Collagen fibers are loosely arranged in the papillary dermis and are tightly bundled in the reticular dermis. Pilosebaceous units, eccrine glands, and apocrine and dermal blood vessels are surrounded by a thin meshwork of collagen. Collagen fibers display characteristic cross-striations with a periodicity of 60–70 nm. Collagen is rich in the amino acids hydroxyproline, hydroxylysine, and glycine. The fibroblasts produce a precursor known as procollagen, which includes 300–400 additional amino acids in each of its chains; these extensions are removed after secretion, which results in the conversion to the collagen molecule. Collagen fibrils form by the association of collagen molecules. Vitamin C and copper are two of several cofactors required in the biosynthesis of collagen. Collagen production is a dynamic process that involves continual synthesis by fibroblasts and degradation by collagenases.

ELASTIN AND RETICULIN

Elastic fibers make up only 4% of the dry weight and 1% of the volume of the dermis. They are delicate, straight, freely branching fibers that prove very resilient. These fibers are thicker in the lower portion of the dermis and become thinner as they approach the epidermis. Elastin differs from collagen not only structurally but also chemically. Desmosine is an amino acid unique to elastin.

About 0.4% of the dry weight of the dermis is made up of fine branching fibers which, unlike collagen, stain black with silver nitrate and are known as reticulin. Their axial periodicity is identical to that of collagen. Reticulin fibers in the papillary dermis serve to anchor the basal lamina [16].

GROUND SUBSTANCE

The amorphous ground substance in which the fibers and cells lie contains acidic GAGs. In dermis the major forms are hyaluronic acid, chondroitin sulfate, and dermatan sulfate.

NERVES

The skin is supplied with both sensory and autonomic nerves. It is innervated with about one million afferent nerve fibers; most terminate in the face and extremities, and relatively few supply the back. The sensory nerves, unlike autonomic nerves, possess a myelin sheath up to their terminal ramifications.

The papillary dermis is heavily innervated with unmyelinated nerve fibers that transmit the sensations of temperature, pain, and pruritis. Three types of special nerve end organs also exist in the dermis. Vater-Pacini corpuscles are large end-organs that are located in the deeper portions of the dermis and subcutis and mediate a sense of pressure. They measure up to 1 mm in diameter and have their greatest concentration at the tips of the fingers and toes. A few are present in the nipple and anogenital regions. Meissner corpuscles are located in the dermal papillae and mediate the sense of touch. They occur only on the ventral aspects of the hands and feet and are most concentrated in the fingertips. The mucocutaneous end-organs are found in the papillary dermis of the modified hairless skin of the glans, the prepuce, the clitoris, the labia minora, the perianal region, and the vermilion border.

The autonomic nervous system supplies fibers to the arrector pili muscles, the blood vessels, and the eccrine and apocrine glands. The sebaceous glands are not innervated, and their functioning depends on endocrine stimuli. The autonomic nervous system controls vasoconstriction, contraction of the arrector pili muscles, and glandular secretion.

VASCULATURE

The dermal vasculature consists of intercommunicating plexuses. The subpapillary plexus lies within the papillary dermis and runs parallel to the epidermis to furnish a supply of capillaries, arterioles, and venules to the dermal papillae. The deeper plexuses are composed of larger vessels and surround hair follicles and eccrine glands. The dermal lymphatics are associated with the vascular plexuses.

MUSCLES

Smooth muscle occurs in the skin as the arrector pili muscles of the hair to pull the follicle upward with contraction. There are also smooth muscles fibers in the scrotum and the areolas.

Striated muscle occurs in the skin within the neck as the platysmas and in the muscles of expression of the face.

Special aggregates of smooth muscles are found between the arterioles and the venules in the skin. These serve to shunt blood from the arterial to the venous system directly and thus bypass the capillary system.

SKIN DAMAGE

There are numerous dermatoses caused by damage from external forces; only a few of the more common ones are described in this section.

Thermal burns are caused by excessive heat on the skin. The changes in the skin due to dry heat or scalding are classified in four degrees. A sunburn is the most common example of a first-degree burn and results from active congestion of the skin. This erythema may be followed by peeling of the epidermis. In a second-degree burn there is leakage of serum from capillaries leading to edema and vesicles, but patients recover without scar formation. Third- and fourth-degree burns involve partial and full thickness dermal involvement and by definition heal with scar formation.

Sunburn is defined as the reaction of the skin to sunlight exposure in excess of the dose that causes only erythema. Details of the response of skin to UV light or sun exposure are described in a later section of this chapter. Erythemogenic UV exposure causes edema of the epidermis, depletion of Langerhans cells, and microvascular injury. UV light can also cause damage to cellular DNA by inducing the production of thymine dimers and DNA strand breaks via the activation of oxygen radicals. Chronic sun exposure causes photoaging and is associated with precancerous actinic keratosis as well as malignant basal cell and squamous cell carcinomas. These phenomena, too, are described in some detail in a later segment of this chapter.

Frostbite occurs when soft parts are frozen and deprived of their blood supply. Common areas of involvement include the ears, nose, cheeks, fingers, and toes. The frozen area becomes pale and waxy, usually without associated pain. Various degrees of destruction occur to the skin, similar to those seen in burns.

The effects of ionizing radiation on the skin depend on the amount of radiation and the intensity of exposure. Large doses cause cell death, while smaller doses lead to temporary arrest of mitosis and chromosomal breaks. An acute radiodermatitis occurs after a latent period of a few hours to several days. The symptoms include erythema, edema, vesiculation, and ulceration and may take weeks to months to clear. Chronic exposure to ionizing radiation damages the skin to varying degrees. After a latent period, changes include telangiectasias, atrophy, xerosis, striated and brittle nails, sparse hair, and possible ulcerations and carcinomas.

Callus is a pressure-induced circumscribed hyperkeratosis. It occurs over areas of intermittent pressure, especially over the bony prominences. Treatment considerations include padding to relieve pressure, paring of the lesion, and the use of keratolytics.

CHRONOLOGIC AGING OF THE SKIN

The aging of the skin is attributable to two processes: true aging related to the intrinsic passage of time and photoaging resulting from chronic UV

light exposure. The mechanism by which aging occurs is not known, but the physiologic decline of the skin as one ages is well documented [17]. Major age-related changes in the skin's appearance include dryness, wrinkling, laxity, and development of benign neoplasms (Table 1.2). Functions of the skin that decline with age are numerous but include decreased sebum production, lowered chemical clearance in the dermis, and delayed cell replacement (Table 1.3).

Histologically one sees a flattening of the dermo-epidermal junction, with a 50% reduction in the number of interdigitations between the dermal papillae and the epidermal rete pegs between the third and ninth decades. The reduced smaller contact area between these two tissues allows for less communication and less nutrient transfer as the skin ages. While there is little epidermal atrophy, the aged dermis is atrophic and relatively acellular and avascular. There is a loss of dermal thickness of 20% in elderly persons, thought to be related to the loss of elastin and collagen fibers and contractions of connective tissue septae within the subcutaneous fat [18].

To the casual observer, the major symptoms of aging skin are wrinkles. The abrogation of wrinkles or means for their repair via cosmetic manipulation has become a primary concern. Chronologic aging of skin and sunlight-induced aging are characterized by flattening of the dermo-epidermal junction and various biochemical changes in the dermis. The latter include reduction of

Table 1.2 Histologic Features of Aging Skin

Epidermis	Dermis	Appendages
Flattened dermal-epidermal junction	Atrophy (loss of dermal volume)	Depigmented hair
Variable thickness	Fewer fibroblasts	Loss of hair
Variable cell size and shape	Fewer mast cells	Conversion of terminal to vellus hair
Occasional nuclear atypia	Fewer blood vessels	Abnormal nail plates
Fewer melanocytes	Shortened capillary loops	Fewer glands
Fewer Langerhans cells	Abnormal nerve endings	

Table 1.3 Functions of Skin That Decline with Age

Cell replacement	Vascular responsiveness
Injury response	Thermoregulation
Barrier function	Sweat production
Chemical clearance	Sebum production
Sensory perception	Vitamin D production
Immune responsiveness	

collagen VII and of several GAGs and loss of adipose tissue. At the same time, elastic tissue hypertrophy tends to increase the size of wrinkles. The oxytalon fibers that extend from the dermo-epidermal junction downward into the papillary dermis are lost or at least decreased during both types of aging.

The debate concerning age-associated changes in the percutaneous absorption of substances through the epidermis continues. It has been established, though, that there is an age-associated decrease in the dermal clearance of transepidermally absorbed materials. Clinically this may be observed in the persistence of contact dermatitis in the elderly.

Decreased vascular responsiveness has been documented in older skin, as has mild dermal microvascular wall thickening, probably contributing to vascular fragility of older skin.

Studies have shown an age-associated decrease of 30–50% in epidermal turnover rate between the third and eighth decades, which explains the delayed wound healing seen in the elderly. Experiments have shown easier separation of the epidermis from the dermis with age, which explains the ease with which elderly skin tears and forms abrasions. In vivo studies have shown a significant decline in skin elasticity and extensibility during each decade of life.

While the size and number of sebaceous glands do not decrease with age, there is a 60% reduction in sebum production over the adult life span, secondary to a decrease in androgen production. There is also a reduction in the output of apocrine and eccrine glands. Unlike intrinsic aging, photoaging is related to cumulative damage to the cellular constituents of the skin, at least in part at the DNA level by UV and infrared radiation [19]. Photoaging accounts for more than 90% of the skin's age-associated cosmetic problems and has become synonymous with "true chronologic aging" in the public's mind. Clinically it is characterized by coarseness, wrinkling, mottled pigmentation, solar lentigines ("age spots" or "liver spots"), laxity, telangiectasias, and atrophy. Increased numbers of benign and malignant neoplasms develop with age. A more detailed discussion concerning photoaging—its cause and possible reversal—is included in the following sections of this chapter.

Responses to Sunlight of Human Skin

INTRODUCTION

Exposure to sunlight can have both beneficial and harmful effects on the human body, depending on the length and frequency of exposure, the intensity of the sunlight, and the sensitivity of the individual concerned. For light to interact with any material, it needs to be absorbed. Once the light is absorbed, it raises

the absorbing molecule to an excited state. The excited molecule may then produce photoproducts that may initiate biochemical reactions.

The skin reaction to sunlight that we are most familiar with is sunburn. A sunburn reaction, observed 8–24 hours after exposure, may include erythema (redness), edema (swelling), blistering, pain, and delayed pigmentation, with the intensity of the reaction being proportional to the length of exposure. A whole body sunburn experience will result in burning, stinging, pain, and possibly sunstroke (including headache, stomach upset, and in severe cases vomiting). Lighter pigmented individuals are more likely to experience a sunburn reaction the first time they are exposed to sun after the winter months. While sunburn is associated with light-skinned individuals, it is also experienced by dark-skinned individuals upon exposure to adequate doses of sunlight. The only difference is that the erythema (redness) that follows may be difficult to perceive under native pigment. The sensations of sunburn are similar for dark-skinned and light-skinned individuals.

The most recognized sign of overexposure to the sun is an erythema, which develops in six to eight hours after exposure. The intensity of the sunburn reaction is related to the length of exposure. The erythema is followed by a tanning reaction that appears three to five days after exposure. In the last 50 years a tan has been considered a symbol of well-being. In the nineteenth century and the early part of the twentieth century people remained out of the sun, and a tan was a sign of working out of doors (farmer, sailor, etc.). A tan is also considered as the body's natural mechanism of protection to subsequent exposures, along with epidermal thickening. While erythema is the most familiar result of a sunburn, the cellular component of the skin responds to sunlight by releasing proteins (cytokines), inducing an immunosuppression and a whole cascade of cellular and molecular events.

SKIN OPTICS

LIGHT

Light is the visible part of the electromagnetic spectrum, with a wavelength range of 400–700 nm. Ultraviolet radiation is electromagnetic radiation of wavelengths shorter than visible light, 100–400 nm. Infrared radiation occupies the wavelengths longer than visible light, 700–40,000 nm. The UV is divided into three ranges, UVA, UVB, and UVC (UVA: 320–400 nm; UVB: 280–320 nm; UVC: 200–280 nm). Of these ranges only UVA and UVB exist in terrestrial sunlight; all three exist in interplanetary sunlight.

The molecules that absorb UV (UVA and UVB) radiation (chromophores) in the skin include DNA, proteins, 7-dehydrocholesterol (provitamin D3), NADH (nicotinamide adenine dinucleotide), melanin, hemoglobin, and urocanic acid.

Visible light is absorbed by the chromophores melanin, hemoglobin, bilirubin, β-carotene, porphyrins, and water. The energy content of each photon is given by Planck's law, $E = h \cdot \nu$, where E is the energy of each photon, h is Planck's constant (6.6×10^{-27} erg/sec), and ν the frequency (for UV photons the frequency is in the range of 10^{15} Hz). The energy of each photon in the UV and visible ranges of the electromagnetic spectrum is enough to either raise a chromophore to an excited state or break bonds. The act of breaking chemical bonds results in the formation of free radicals, that is, short-lived reactive species.

PENETRATION OF LIGHT INTO SKIN

Light that falls on the skin interacts with each of the skin components and is attenuated by absorption and scattering. Absorption occurs when a photon interacts with a chromophore, and the chromophore is thus excited to a higher energy state; scattering occurs when a photon suffers a change in its direction of travel by some organelle, due to a change in index of refraction. Light interacts first with the stratum corneum, then with the viable epidermis, and finally with the dermis after it traverses the epidermis. The penetration of light into the skin is limited in the short wavelengths of the UV. It has been shown that wavelengths shorter than 290 nm are very effective in producing DNA damage, with effects limited to the upper two thirds of the epidermis. At wavelengths longer than 300 nm DNA damage is found throughout the epidermis as well as in the dermal fibroblasts and the keratinocytes of the outer root sheath of the hair follicles. DNA damage includes cross-links that interfere with DNA replication, such as the production of cyclobutane pyrimidine dimers and 6-4 photoproducts. Absorption by proteins is the principal source of attenuation of UV radiation in the skin. Incident radiation at about 300 nm is attenuated to 1% at a depth of 28 μm in the skin, but radiation at 400 nm is reduced to the same level at a depth of 240 μm.

ACTION SPECTRUM

An action spectrum is a map of how the threshold of a biological reaction changes in relation to the wavelength of electromagnetic radiation that causes it. If the desired "action" is the dose to produce a threshold erythema response, the "action spectrum" represents the dependence of the skin's sensitivity to UV radiation on wavelength (Fig. 1.4). The action spectrum usually requires a monochromatic source (a source capable of producing single wavelengths at a time) such as a tunable laser. The ordinate of the graph is the reciprocal of the threshold dose to produce the action (erythema) and therefore corresponds

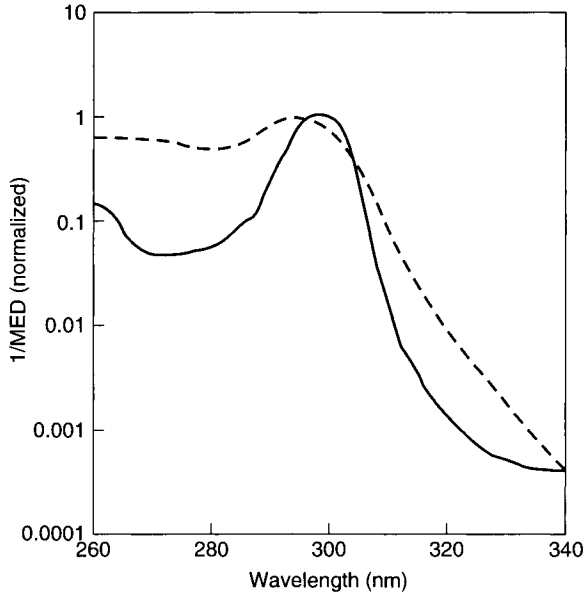

Figure 1.4. Two erythema action spectra are plotted versus wavelength. The solid curve was obtained with a tunable pulsed laser and the dashed curve was obtained with a filtered mercury-xenon arc lamp, the output of which went through a monochromator. The subjects were fair-complexioned Caucasians; the skin sites were on the back for the dashed curve and on the ventral forearm for the solid curve. (MED—minimal erythema dose)

to sensitivity. The more sensitive the skin is to a particular wavelength, the lower the threshold dose and the higher the value of its reciprocal.

Biological responses (end points) need not have the same mechanism of action at all wavelengths. This becomes particularly clear in the case of pigmentation. The end point for UV radiation–induced neomelanogenesis (new pigment formation) is the minimum dose of UV radiation to produce a threshold response seven days after exposure. In the UVB, pigment formation always follows an erythema response (there is no pigment without erythema). In the case of UVA1 irradiation (Table 1.4), pigment appears immediately after exposure without erythema. The histology and biology of these radiation-dependent events are quite different.

SOLAR RADIATION AND ITS BIOLOGICAL EFFECTIVENESS

The spectrum of solar radiation is modified by the atmosphere of the earth; what reaches the surface of the earth is a continuum composed of UVB, UVA, visible, and infrared radiation. The major modifiers of the solar spectrum in

Table 1.4 Distribution of Solar UV Radiation, Measured at 28° North Latitude, at 11:00 A.M., October 2, 1988. These Values May Be Considered Typical, Especially the Ratio Between Components

Wavelength range (nm)	Integrated intensity (mW/cm^2)	Biologically effective intensity (mW/cm^2)
280–320 (UVB)	0.19	1.09×10^{-2}
320–340 (UVA2)	0.67	0.154×10^{-2}
340–400 (UVA1)	2.85	0.047×10^{-2}
320–400 (UVA)	3.52	0.202×10^{-2}
280–400 (UV)	3.71	1.30×10^{-2}

the atmosphere are ozone and water. Water in the atmosphere is responsible for attenuating the infrared component of the solar spectrum. Stratospheric ozone, on the other hand, attenuates the short wavelengths of the UV.

The UV component of the solar radiation that reaches the surface of the earth is only 2–3% of the total incident sunlight spectrum. The distribution of UV radiation on the earth surface is given in Table 1.4.

It can be noted that the UVB band contributes approximately only 5% of the total UV radiation; however, it constitutes more than 80% of the biologically effective radiation. The biologically effective radiation is calculated by integrating over the appropriate wavelength range the product of the intensity at each wavelength by the action spectrum for erythema at the same wavelength. While UVB is defined to include 280–320 nm, actually there is no solar radiation with a wavelength shorter than 292 nm. The biological effectiveness of solar radiation depends on the biological end point used; the end point that has been most precisely determined so far is the minimal erythemal dose (MED). This does not mean that other end points, for example, immunosuppression, are not important; erythema is the most familiar response and is easy to assess. An action spectrum has been measured for minimum pigment response in humans and for photocarcinogenesis (for the hairless mouse).

There has been a considerable effort to assess the changes induced in the skin by UVA radiation, since UVA penetrates deeper into the skin targeting the structural matrix. It has been shown that in photoaging the major changes are induced in the dermis. In view of these results investigators should consider both the solar UVB and the UVA by using a term identified as biological effectiveness (BE). For this purpose, the solar UVB is integrated over the range 280–320 nm and the solar UVA is integrated over the range 320–400 nm. The solar irradiance at each wavelength is then multiplied by the erythema effectiveness at that wavelength and integrated over the appropriate range.

During daytime, BE in the UVB ranges is maximal at about noon. Except at dusk, the contribution of UVA to BE is only about 20–25%. In other words, solar UVB is five times more effective than solar UVA for producing a minimal sunburn reaction. When the UVB reactivity is less than four times that of UVA, it would be practically impossible to get a sunburn. There are two components of solar radiation, one direct and the other diffuse. The direct radiation is responsible for shadows and may be attenuated by the use of an umbrella. Diffuse radiation comes from all directions because the incoming radiation is scattered by particles and molecules in the atmosphere. Scattering is strongest in the UV. Therefore it is possible to get a sunburn staying under an umbrella for a long time or staying outside on a cloudy day. The problem with clouds is that some are very effective in attenuating solar UV, while others are not. Black clouds are always effective absorbers, while a light cloud cover almost always passes enough solar UV to produce sunburn. The intensity of diffuse sunlight remains essentially constant throughout the year, while the intensity of direct sunlight is maximum in the summer months when the average monthly intensity at solar noon is three times greater than in the winter. Therefore, the diffuse component of sunlight plays a more important role in the winter months when it is indistinguishable in intensity from the direct sunlight. A good estimate of need for protection from solar UV radiation is to look at one's own shadow; if the shadow is longer than one's height, there is no need for protection. If the shadow is shorter than one's height, protection is necessary. Sunlight may also be reflected by ground cover, like white quartz sand and snow contributing significantly to the ambient UV load. On the other hand, water is neither a good reflector nor a good attenuator (absorber) of solar UV radiation. People in boats are at risk only from direct and diffuse sunlight, not because of the reflection by the surface of water. It is possible to have a sunburn after swimming because the water does not attenuate sunlight. There are no trees or buildings to cast shadows in the middle of the ocean; therefore solar exposure is at a maximum.

BIOLOGICAL EFFECTS OF INCIDENT SUNLIGHT

BENEFICIAL EFFECTS OF SUNLIGHT

Moderate exposure to sunshine results, psychologically and physiologically, in a general sense of fitness, peace of mind, and well-being. It has been documented that the protein β-endorphin is expressed following exposure to solar-simulated radiation and that this is responsible for the feeling of well-being. Sunlight, in particular UVB radiation, plays a vital part in the prevention and treatment of rickets by producing vitamin D (through the activation of epidermal 7-dehydrocholesterol, provitamin D3).

ADVERSE EFFECTS OF SUNLIGHT

The adverse effects of sunlight have been studied by dividing them into those that are induced by a single exposure and those due to multiple exposures. *Acute effects* (following a single exposure) include sunburn, immunosuppression, photoallergic reactions, photosensitivity reactions of individuals with photodermatoses, and photosensitization following drug intake or topical application. *Chronic effects* include photodamage (photoaging), cataracts, solar keratoses, skin cancer (basal cell carcinoma and squamous cell carcinoma), and some forms of malignant melanoma (i.e., lentigo maligna).

ACUTE ERYTHEMA

A sunburn may be classified by the intensity of the erythema (redness) response that is induced in the skin. The threshold response is expressed at 8–10 hours after exposure, and the reaction reduces in intensity and becomes stable after 24–48 hours. The erythema reaction then subsides, while from three to five days after exposure, pigment starts to appear. In UVB-induced reactions in the laboratory a small area of skin is exposed to a series of doses (fluences) of UVB radiation, and the reaction is graded 24 hours after exposure as

+or− Minimum perceptible erythema (just perceptible redness with patchy appearance over the exposed site)
+1 Minimum erythema with clear borders
+2 Intense erythema without edema
+3 Intense erythema with edema
+4 A violaceous erythema with edema and blistering

These reactions apply to small exposure sites and produce mild sensations on the exposed sites. For exposures producing responses that include edema, as the erythema subsides, pigment starts to form and the site will start to peel within 8–10 days after exposure. In the process of peeling, the stratum corneum is lost, accompanied by a substantial loss of pigment because the stratum corneum at the exposed site contains melanin. When an exposure is made over the whole body, the reactions are quite different in intensity, especially the inflammatory response. An exposure at a dose of +2, whole body, results in a severe erythema with pain, burning sensation, and an overall "not well" feeling complaint. Stronger exposure doses may require hospitalization.

Because of the similarity between the erythema action spectrum and the absorption spectrum of DNA, it is generally accepted that the interaction of UVB radiation with DNA plays an important role in the erythema response [19]. It is believed that the epidermal keratinocytes are the primary locus of damage induced especially by UVB and short wavelength UVA

radiation. Many cytokines and inflammatory mediators are synthesized in the skin and released after exposure to UV radiation, including eicosanoids, histamine, kinins, interleukins (1,6,8,10,12), TNF-α, substance P, calcitonin gene-related peptide, and nitric oxide. These factors play important roles in the recruitment and activation of mononuclear cells and neutrophils in the skin, resulting in vasodilation and inflammation. Intracellular adhesion molecules also have been shown to be upregulated in UV radiation–exposed skin, for example, intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), or endothelial adhesion molecules (e-selectins) [20].

ACUTE TANNING RESPONSE

Melanin pigment is produced by melanocytes that reside on the basement membrane between the epidermis and the dermis. As stated earlier, melanin is synthesized in vesicles in the Golgi apparatus starting with DOPA, which is enzymatically processed to the melanin heteropolymer. Once polymerization starts, the vesicles are converted to melanosomes (egg-shaped membrane–enclosed objects) and are transferred through the dendritic processes of melanocytes to neighboring keratinocytes. Thus the visually perceived pigment is due to melanin distributed into keratinocytes that reside on the basement membrane. Cellular migration toward the stratum corneum distributes melanin throughout the epidermis.

The tanning ability of individuals is genetically determined and is expressed as the capacity of the melanocytes to produce melanin, the amount of melanin formed within each melanosome, and the distribution of melanosomes. Light-skinned individuals have melanosomes (0.6–0.7 μ long) that are only partially melanized and appear in clusters and therefore are less effective in producing visible pigment. In dark-skinned individuals the melanosomes (1 μ long) are more completely melanized and appear singly dispersed, making them more effective absorbers.

The tanning responses of human skin depend on the wavelength of the radiation. When the skin is exposed to UVB (280–320 nm), the first response is erythema. It is followed by pigment as the erythema subsides. It is impossible to produce pigment with UVB radiation unless there is a preceding erythema response. UVA radiation has been divided into two bands for practical reasons, UVA1 (340–400 nm) and UVA2 (320–340 nm). UVA2 induces skin reactions like UVB. In light-skinned individuals there is an erythema response before the appearance of pigment. For melanocompetent individuals and those with a tolerance for UV radiation (UVB), UVA2 induces a pigment reaction immediately after exposure, without erythema. When the skin of both light-skinned and melanocompetent individuals is exposed to UVA1 radiation, it induces a pigment reaction immediately after exposure. The color of

this pigment is gray, and it disappears within 10–20 minutes after the end of the exposure. The threshold for immediate pigment response is 1–2 J/cm^2. If human skin is exposed to larger doses of UVA1 radiation (>10 J/cm^2), the immediate pigment is more intensely gray and decreases in intensity over the next two hours, leaving behind a pigment that persists for weeks. The pigment that persists after two hours of the end of exposure is called persistent pigment and is brown. In lighter-skinned individuals some immediate erythema may be evident, which will disappear with time, leaving behind a lasting pigment.

The (immediate) pigment formed immediately after a UVA1 exposure is believed to result from a photochemical reaction involving preexisting melanin pigment as well as melanin precursors and metabolites. It is also believed that some reorganization of microtubules and microfilaments occurs in immediate pigment. Immediate pigment is reversible for doses smaller than the threshold for persistent pigment. Persistent pigment is a photochemically initiated enzymatically controlled production of melanin polymer from preexisting monomers and melanin precursors. Within three to five days we observe melanogenesis, that is, the biological process of producing native pigmentation as a result of stimulating the melanocytes to produce more pigment. Melanogenesis has been documented both for UVA and for UVB five days after exposure by assessing the distribution and amount of melanin in the epidermis with $AgNO_3$ staining and DOPA staining (activity of the enzyme tyrosinase). The message here is that UVA1 produces a pigment that may persist depending on the dose of UVA1 radiation, and the skin response may include an erythema in the early phases of the reaction. In contrast, UVB first induces an erythema reaction that is then followed by a pigment that may last for weeks or months. Both reactions to UVA or B result in de novo melanogenesis five days after exposure.

UVB radiation also induces proliferation of epidermal keratinocytes, resulting in a thickening of the epidermis [21]. This proliferative response may be thought of as a repair following the DNA damage in epidermal keratinocytes. The new keratinocytes are loaded with melanin from adjacent melanocytes and progress up the epidermis toward the stratum corneum over the next five days. In this way we may think of UVB pigmentation as due to melanin that is distributed fairly uniformly throughout the epidermis. In contrast, UVA radiation does not induce a proliferative response. Thus the pigment that is stimulated by UVA radiation is produced in the melanocytes and is then transferred to the basal keratinocytes. UVA-induced epidermal melanin pigmentation thus resides in the vicinity of the basement membrane, while UVB-induced epidermal pigment is distributed throughout the epidermis.

Epidermal pigment formation also may be stimulated by visible light. Visible light does not produce an erythema (no effect on the blood vessels). The

pigment that is produced resembles UVA2 pigment in that it appears immediately after exposure, and if the dose of light is sufficient it may last for weeks or months.

Over the years Gilchrest and coworkers have tried to elucidate the mechanism of melanin production and its dependency on DNA damage, nerve growth factor, and related signaling mechanism [22]. These investigators have also shown that DNA fragments like those produced by UV radiation (thymine dimers and 4-6 photoproducts) can stimulate melanogenesis in an animal model. Their interpretation is that DNA cross-links formed by UV exposure undergo excision repair by endonuclease, and the fragments removed from the DNA chain then signal melanogenesis. It has been shown that POMC (pro-opiomelanocortin) and the downstream hormones—MSH, ACTH, β-endorphin, and lipotropin—play important roles in melanogenesis.

In summary, sunlight is made up of UVB, UVA, and visible radiation; therefore it is the balance among these components that determines the skin responses. The UVA pigment responses include an immediate pigment (a transient response that lasts minutes to hours) and a persistent pigment that lasts for weeks to months. Visible light induces a response similar to that of UVA except that the appearance of the pigment is slightly different. The UVB response starts with an erythema and develops into a melanin pigment, which may be lost when peeling occurs.

SKIN TYPES—THE GENETIC BASIS OF RESPONSES TO ULTRAVIOLET RADIATION

The responses of the skin to UV radiation are to a great extent genetically determined. The first-hour exposure to midday sun following the winter months of no exposure has been used to characterize skin types for white-skinned persons.

Skin Type I : always burns, never tans
Skin Type II : usually burns, rarely tans
Skin Type III : rarely burns, usually tans
Skin Type IV : never burns, always tans.

"Skin typing" of individuals in practical situations usually means a visual classification of individuals based on their pigment level; persons planning studies should keep in mind that skin color and skin UV reactivity, although probably related, are not the same. While this classification scheme is useful to identify individuals at risk from UV radiation–induced skin cancer, it remains controversial when its use is extended to predicting the threshold dose of UVB or UVA to produce an erythema or pigment. These skin types have also been

called "sun-reactive" skin types because this scheme classifies the response to UV rather than the skin color. There have been modifications of the scheme for nonwhite individuals.

Epidermal melanin pigmentation has been classified as constitutive and facultative pigmentation. Constitutive pigmentation refers to the pigment found in skin areas that have never been exposed to UV radiation or any chronic insult. Facultative pigmentation is pigment produced in response to UV radiation exposure or other pigment-inducing insult. Persons with the genetic ability to pigment following a UV exposure are called melanocompetent and those individuals who produce essentially no pigment are called melanocompromised.

IMMUNE RESPONSES TO ULTRAVIOLET RADIATION

It is accepted that UVB causes immunosuppression and that this effect has important implications for photocarcinogenesis and exacerbation of infectious diseases. Assays for immunosuppression have included local and systemic suppression of contact hypersensitivity to DNFB (dinitrofluorobenzene) and systemic suppression of delayed-type hypersensitivity to *Candida albicans* or alloantigen. Studies have been conducted in both animal models and human subjects. While UVB-induced immunosuppression has been well documented, the effects of UVA on the immune system are still under study. Initial results indicate that it also plays a role. UV-induced immunosuppression in humans was recently reviewed in depth [23].

Exposure of skin to UV light impairs sensitization to haptens applied directly to the irradiated area of the skin. Hapten-specific tolerance may develop due to the generation of specific T suppressor cells, and it has been proposed that apoptosis plays an important role in immune reactions. In particular, data indicate that T suppressor cells may induce the death of antigen-presenting cells in the presence of the specific hapten and that the Fas/FasL system is involved in the process. (Fas, also called CD95 or APO-1, is a surface molecule that induces apoptotic cell death.) Studies to assess the effectiveness of sun protection products (sunscreens) have shown that UVC (wavelengths shorter than 290 nm) is also very effective in inducing immunosuppression. A controversy has developed relating to the protective ability of sunscreen products against immunosuppression, which may be associated with improper definition of the output of the light source used in the studies.

ULTRAVIOLET RADIATION–INDUCED SKIN CANCER

Photocarcinogenesis is not a cosmetic concern except for the generally held opinion that the UV light–absorbing agents used in cosmetic (over-the-counter) sunscreens help to lower the incidence of dermal malignancies.

Skin cancer has been classified as nonmelanoma skin cancer and as cutaneous malignant melanoma. Nonmelanoma skin cancer (NMSC) includes basal cell carcinoma and squamous cell carcinoma. These malignant lesions are formed in the epidermis and may invade the dermis. NMSC has the highest incidence of any cancer, approximately one million new cases a year in the United States. Mortality from NMSC is low, but morbidity is considerable with respect to disfigurement. Sun exposure is linked to the skin cancer epidemic as the incidence of NMSC increases in proportion to the cumulative sunlight exposure and is highest in people in skin types I and II. In the case of melanoma, the effects of UV are not clear except in lentigo maligna melanoma (a subclass of cutaneous melanoma), where sun exposure has been shown to increase the incidence.

UV radiation causes cancer in the skin by damaging the ability of the skin cells to control proliferation. The cells have three ways to combat UV damage and minimize cancer risk, including DNA repair, apoptosis, and immunosurveillance. UV radiation can damage skin cells by forming dimers in DNA between adjacent pyrimidine residues, potentially leading to UV "signature" mutations that can accumulate over time. The cell can respond to the damage by repairing the DNA to avoid the effects of the mutations or if the damage is too great by inducing cell death through apoptosis to remove potential cancer cells from the population.

UV radiation is a complete carcinogen; it can act alone as an initiator and a promoter in formation of cancer. UV can also act as a promoter with initiating events inside the cell, such as DNA mutations arising from DNA polymerase incorporation errors, depurination, deamination of 5-methylcytosine, or oxidative damage from free radicals. UVA, while a complete carcinogen, is much less effective than UVB. However, it may act as a cocarcinogen in combination with UVB, as in solar radiation.

There is an additional premalignant, benign lesion—actinic keratosis—in which the epidermis proliferates, producing a hyperkeratotic lesion [19]. These lesions are characteristic of photodamaged skin of individuals with skin type I or II, and they may spontaneously disappear. However, actinic keratoses have p53 mutations as NMSC.

CHRONIC EFFECTS OF ULTRAVIOLET RADIATION

The chronic effects of UV radiation or sunlight (photoaging,wrinkles, freckles, leathery appearance, red neck) have been recognized for a long time. Clinically the syndrome is characterized by coarseness, wrinkling, mottled pigmentation, solar lentigos ("age spots" or "liver spots"), laxity, telangiectasias, and atrophy. Increased numbers of benign and malignant neoplasms develop with age. The importance of these changes impacts the cosmetic industry.

Unlike intrinsic or chronologic aging, photoaging is related to cumulative damage to the cellular constituents of the skin, at least in part at the DNA level by UV and infrared radiation [19]. Photoaging accounts for more than 90% of the skin's age-associated cosmetic problems and is almost synonymous with "true chronologic aging" in the public's mind. It has been pointed out lately that photoaging changes start in skin at a very young age. The increase of freckles (solar lentigenes) is noticeable by the age of three to five years. The perception that sun exposure and tanning are signs of well-being, together with the proliferation of tanning salons, has increased the occurrence of skin photoaging in the general population. Chronologic aging of the skin without sunlight exposure leads to remarkably few visible changes. In contrast, photoaging leads to marked changes in the skin such as wrinkles, roughness, sallowness, mottled hyperpigmentation, telangiectasias, laxity, and a variety of benign and malignant neoplasms. Evidence of photoaging is found primarily in the dermal connective tissue, although sun-damaged skin typically has a thicker stratum corneum. The extracellular matrix of the dermis consists mainly of type I collagen, some type III collagen, elastin, proteoglycans, and fibronectin. Chronically sun-exposed sites show a loss of mature type I collagen and a relative increase in type III collagen. The most familiar feature of photoaging is a massive accumulation of elastotic material in the upper and middle dermis. This phenomenon, known as solar elastosis, involves a marked increase in the elastin content of the dermis, an increase in the size of the elastin fibers, and the displacement of structural material from the dermis. The "elastotic material" that fills the dermis is so called because it stains well with elastin-specific histologic stains.

While the acute responses of skin to UV radiation have been studied extensively, photoaging studies have been less prominent. Evidence is now forthcoming that photoaging changes may be produced in the laboratory with a relatively small number of exposures.

REVERSAL OF PHOTOAGING

There have been a number of pharmacologic developments to reverse the visual signs of photoaging. These include retinoic acid and its derivatives, alpha-hydroxy acids, antioxidants, and many natural products. These materials have been tested and have performed with variable effectiveness. Solar photoaging is a profound change in the skin architecture that evolves over a long time to the final state with elastotic material in the dermis. However, it has been shown that solar elastosis can be found histologically in young people—therefore prevention is a better approach than repair [23–25].

PHOTOSENSITIZATION

A number of materials including pharmaceutical and cosmetic ingredients are potential photosensitizing agents. A photosensitizer absorbs light and induces a photochemical action that may result in the production of free radicals in the skin. Organic free radicals and reactive oxygen substances (which include superoxide anion, singlet oxygen, hydroxyl radical, and hydrogen peroxide) are very reactive—short-lived—chemical species that can cause inflammatory reactions by producing damage to subcellular organelles, which may lead to tissue damage. They may also damage cell membranes or induce cell death by apoptosis. The release of photoproducts may lead to photoallergy. Another expression of photosensitization is hyperpigmentation induced by the combination of a drug and UV light, as in Berloque dermatitis (bergamot oil). Photosensitizing compounds can be used therapeutically. The psoralens, for example, are potent photosensitizing agents that produce cross-links in the DNA and thus act as antiproliferative agents. This is useful for conditions such as psoriasis. Psoralens are also used to treat vitiligo (a disease of hypopigmentation) because of their high pigment-producing potential.

There is another group of skin diseases that are induced by UV light, the photodermatoses, like actinic prurigo, porphyrias, polymorphous light eruption, actinic reticuloid, and others. It is not clear whether an endogenous photosensitizer plays a role in all cases such as in porphyrias. Photosensitization is a common phenomenon, especially in countries with severe winters when people receive little sun exposure. It is reported that as many as 10% of the population has some form of photosensitization disorder. It is therefore important to maintain a high degree of vigilance in conducting tests for the photosensitizing potential of cosmetic materials.

PROTECTIVE MECHANISM OF THE SKIN

The skin develops tolerance to UV radiation following multiple exposures. Two factors, skin thickening and tanning, have been identified as playing significant roles in protecting the skin from the adverse effects of solar UV radiation. Skin thickening results from exposure to UVB only. The other mechanism of adaptive photoprotection is pigmentation. Tanning occurs following exposure to both UVB and UVA. Because of the simultaneous induction of proliferation along with new pigment formation, the UVB pigment is distributed throughout the epidermis. The stratum corneum of UVB-exposed skin is well stained with melanin granules following a UVB exposure. Therefore the UVB tan is protective, although the protection factor is low. The controversy of whether melanin is an effective photoprotectant has raged for years. The absorbance of melanin in the critical UVB range is modest.

The unanswered question is: Is the end product of melanogenesis, melanin, a photoprotectant against subsequent irradiation, or does the very process of melanogenesis—free radical quenching by DOPA—per se act as a photoprotectant at the time of irradiation?

The presence of urocanic acid has been shown to provide some protection on the surface of the stratum corneum. Urocanic acid is produced in the epidermis as an enzymatic breakdown of filaggrin, a protein in the keratinocytes. It is a weak UVB filter providing a protection factor of approximately 2. Urocanic acid also undergoes a *cis-trans* isomerization reaction when exposed to UV radiation, which has been shown to play a role in the induction of immunosuppression.

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CHAPTER 2
The Hair

INTRODUCTION

The profound psychological and social significance of hair in humans is in contrast to its complete lack of vital function. In mammals fur provides an insulating coat for the conservation of body heat, but in humans the hair on the body became sparser and shorter. The eyebrows and eyelashes remained, as did the hair on the scalp. The beard remained as a badge of maleness. The genital and axillary hair, which was probably associated with glandular scent-producing units, became conspicuous in both sexes.

THE HAIR FOLLICLE

DEVELOPMENT AND STRUCTURE

A diagram showing the structural arrangement of a maturing hair within the dermis and the epidermis has been provided in Figure 1.1, Chapter 1. Figure 2.1 provides greater detail about the development of terminal hair and its morphological constituents. The mature hair follicle is surrounded by an epidermal layer that extends inward, tapering and ending in a single cell layer surrounding the follicle bulb [1]. This epidermal layer forms the outer root sheath (ORS), which is the outermost of a number of concentric cell layers forming the complex structure of the human hair follicle. The next layer is the inner root sheath (IRS), which actually consists of three layers, that is, the Henle, the Huxley, and the IRS cuticle layers, the latter being in direct contact with the cuticle cells of the growing hair fiber. In its terminal form the hair fiber consists of three cell types, that is, the multiple layers of the flat and overlapping cuticle cells, the elongated, spindle-shaped cortex cells that form the bulk of the fiber, and finally in some of the coarser fibers the more or less empty cells of an intermittent or continuous medulla.

The follicle bulb is the source of germinative cells, which proliferate at an extremely high rate in a zone that is limited by the "critical level" at the upper

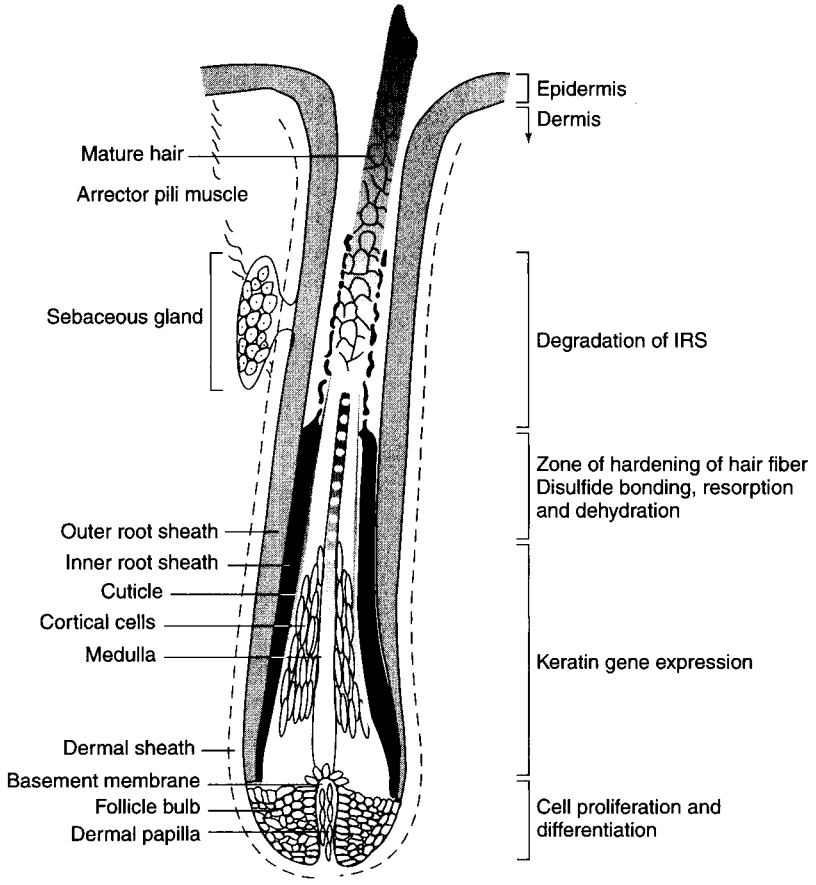


Figure 2.1. Schematic representation of the hair follicle outlining various features and the regions where the main events of cell proliferation and keratinization take place [1]

end of the dermal papilla. This is also the zone of cell differentiation, where the ultimate function of each cell is determined. The high level of cell division in this zone causes pressure (that might be equated to the extrusion pressure of polymer molecules in the spinning of thermoplastic fibers), which leads to some deformation of the cells in the narrowing zone above the follicle bulb.

The energy required for this high rate of cell division and for the protein synthesis occurring in the keratin gene expression region (Fig. 2.1) is generated from glucose. The growth rate of human hair depends on an adequate supply of the necessary amino acids in this region of protein synthesis, and nutritional considerations are of obvious importance. This is also the region where protein deficiency in the diet causes serious disruption of hair growth and leads to characteristic conditions such as kwashiorkor and marasmus.

It is assumed that the so-called intermediate filaments (IFs) are expressed first in the cortical cell cytoplasm and form fibrillar aggregates, the macrofibrils, oriented in the direction of fiber growth. Initially spaces exist between the IFs in the macrofibril, which are later filled with a matrix of sulfur-rich keratin associated proteins (KAPs).

The next zone shown in Figure 2.1 is a zone of keratin hardening in which IFs and KAPs undergo cross-linking reactions involving the rapid and almost complete oxidation of the sulfhydryl groups of the numerous cysteinyl residues to form disulfide bonds. Over a very short length of only a few cells, the concentration of sulfhydryl groups decreases from about 1100 to 12–30 μ equiv/g of hair. The mechanism of this remarkably fast oxidation reaction is not clear, but the involvement of copper ions or copper-containing enzymes as catalysts has been suggested. Other events in this terminal stage of fiber formation are the major removal of the cell cytoplasm, the destruction of cell organelles and their resorption, and finally the dehydration of the cells. The mechanisms of these degradative events are still largely not known.

The total number of follicles on an adult male is about 5 million, of which about 1 million are on the head and perhaps 100,000 in the scalp. A significant loss occurs with age; young adults have an average of 615 per cm^2 on the scalp, but by the age of 80 the density has fallen to 435 per cm^2. Some follicles are lost in baldness; a comparison of ages gave averages of 306 per cm^2 for bald scalps against 459 per cm^2 for hairy scalps.

The first hairs to grow from hair follicles, which are fine and usually unpigmented, are known as lanugo and are normally shed in utero in the seventh or eighth month of gestation. Postnatal hair may be divided, at the extreme, into two kinds; short, fine unmedullated vellus on the body, and longer, darker, terminal hair on the scalp. The infantile pattern is not definitive, for at puberty vellus is replaced by terminal hair in the pubic and axillary regions and, in the male only, on the face. This sexual hair continues to increase in area and rate of growth until the late twenties.

CYCLIC ACTIVITY

Virtually all hair follicles undergo cyclic growth activity. An active phase, anagen, in which a hair is produced alternates with a resting period, telogen, in which the fully formed club hair remains anchored in the follicle by its expanded base and the dermal papilla lies free of the epidermal matrix, which is reduced to a small, quiescent secondary germ (Fig. 2.2). Between anagen and telogen is a relatively short transition phase, known as catagen, in which the newly formed club hair moves toward the skin surface. The follicle becomes active again at the end of telogen by a downgrowth of the secondary germ to reinvest the dermal

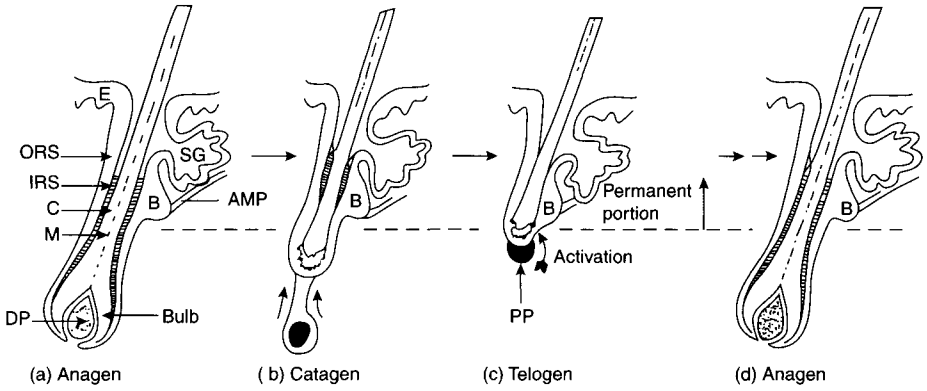


Figure 2.2. Schematic representation of the asynchronous hair growth cycle [1] (ORS = outer root sheath; IRS = inner root sheath; C = cuticle; M = medulla; DP = dermal papilla; SG = sebaceous gland; B = bulb; AMP = arrector pili muscle); PP = permanent papilla

papilla, so that the matrix becomes reconstituted and a new hair starts to form (Fig. 2.2). In effect the follicle re-enacts its embryonic development.

Ultimately the old club hair is shed. All hairs thus reach a terminal length which is determined mainly by the duration of anagen and partly by the rate of growth.

GROWTH RATE OF HAIR

The growth rate of human hair has been determined by direct measurement of marked hairs in situ, by shaving or clipping at selected intervals, and by pulse labeling ^{35}S cystine and autoradiography. The average growth per 24 hours has been stated to range from about 0.21 mm on the female thigh to 0.38 mm on the male chin. Terminal hair on the male vertex grows about 0.4 mm; beard hair grows slower, about 0.3 mm per day. The average for the vertex in women is about 0.45 mm per 24 hours. Though scalp hair appears to grow faster in women than in men, before puberty the rate is greater in boys than in girls. In both sexes the growth rate is highest between the ages of 50 and 69 years. Some workers believe that the growth rate remains constant in any follicle, while others think that it usually decreases or increases.

Daily variations in temperature have no effect on hair growth, and it is generally agreed that shaving does not alter the rate of hair growth.

HORMONAL INFLUENCES

There is ample experimental and clinical evidence that hormones influence hair growth, although in a poorly understood and complicated way. The

follicular cycle is disturbed by the high level of estrogen during late pregnancy, apparently leading to postpartum alopecia. The successive growth of pubic and axillary hair in both sexes at puberty and the growth of the male beard are brought about by rising levels of androgens. Paradoxically, androgens are also prerequisites for the development of male pattern alopecia.

NUTRITIONAL INFLUENCES

Certain vitamins, particularly some of the B complex, are necessary for normal hair growth and keratinization of the epidermis. On the other hand, it has been shown that vitamin A inhibits the differentiation of the stratified squamous epithelium. Thus hyperkeratotic papular dermatosis is a symptom of vitamin A deficiency, and an excess of this vitamin appears to cause hair loss.

Protein deficiency causes *kwashiorkor* and has serious consequences for hair growth. The hair becomes sparse, thin, and brittle, and loses its pigment. The changes in the hair reflect considerable alterations in the follicular cycle, resulting in a considerably reduced proportion of the follicles in anagen (26% for children with kwashiorkor vs. 66% for healthy children). Furthermore, even the anagen follicles are severely atrophied with loss of inner root sheaths and outer root sheaths. Even more severe changes were found in children with *marasmus*, where only 1% of the follicles were in anagen.

Experimental protein malnutrition leads to rapid, although fully reversible, effects, with significant reduction of the mean root diameter followed by reduced pigmentation and progressive atrophy of the follicle bulb and loss of root sheath.

HAIR DISORDERS

Only a brief mention of the major conditions that affect the hair shaft and the hair follicle will be given here, since most of the cosmetically treatable defects will be covered in other chapters. For more comprehensive coverage, the books by Orfanos and by Ebling and Rook may be consulted.

Hairdressers may need to be able to recognize several abnormalities of the hair shaft with genetic origins (monilethrix, pili torti, trichorrhexis nodosa), each of which may be associated with sparse, brittle, and often short hair. These disorders must be differentiated from various types of hair loss in which the hair shaft remains structurally normal.

Hair loss may be either rapid or gradual. Sudden shedding of hair is often, though not invariably, transient, whereas gradual loss, observed only by its long-term effect, is usually hopelessly chronic. There appears to be some hope, however, that some of these gradual hair loss disorders can be at least partially reversed by certain well-known drug treatments. Rapid loss can be

further subdivided into two types, according to whether the fallen hair is a club or is a growing hair shed from an active follicle.

Loss of club hairs is known as telogen effluvium and seems to have several possible causes. One, namely childbirth, is well established, and the ensuing condition is known as postpartum alopecia. Loss of growing hair is known as anagen effluvium. It occurs after administration of cytotoxic drugs, and it seems likely that the shedding of hairs in patchy baldness, or alopecia areata, is a similar process.

Slowly developing hair loss, causing baldness in a symmetrical pattern, is well known in males, where it is named *male-pattern alopecia* or *alopecia androgenetica.*

MORPHOLOGICAL COMPONENTS OF HAIR FIBERS

As stated earlier, the terminal hair contains three morphological components that develop in cellular form in the hair follicle. These cellular structures are held together by layers of intercellular material, which as a whole are referred to as the cell membrane complex (CMC). A schematic diagram shown in Figure 2.3 illustrates the arrangement of the various structural components in the hair fiber with the exception of the pigment granules, which

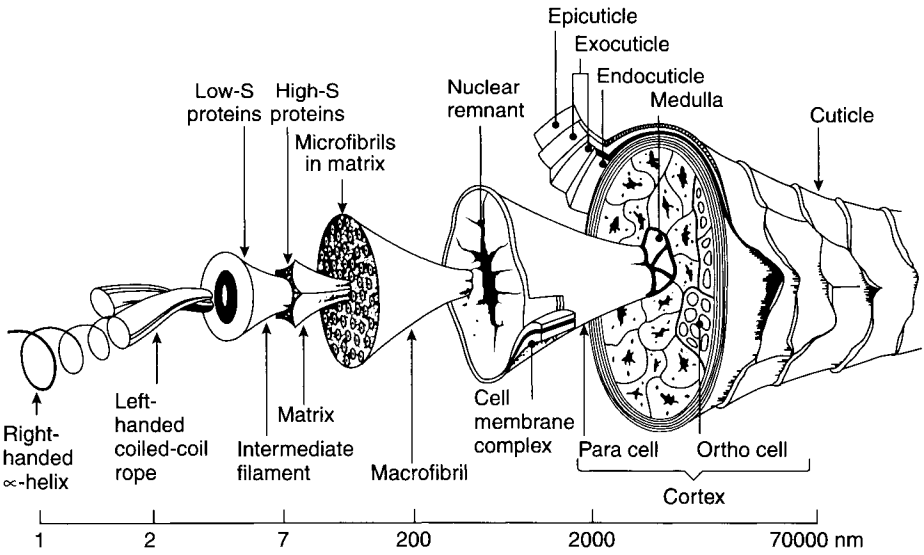


Figure 2.3. Schematic diagram of human hair fiber showing the major structural features except pigment granules [2]

are usually found in the cortical cells [2]. The following paragraphs offer a brief description of these four major constituents of the terminal hair.

CUTICLE

From a cosmetic point of view the cuticle is probably the most important component of the hair fiber, since it forms an envelope around the bulk of the fiber and provides the outer surface on which all topical treatments are deposited. The cuticle consists of 5 to 10 flat, overlapping cells that are stacked like shingles on a roof and are oriented toward the distal (tip) end of the fiber. This orientation and the slight angle (3–4°) of the cells relative to the fiber axis are responsible for the directional frictional effect (DFE), which is discussed later and which can cause irreversible hair entanglements (e.g., rat's nest). The cuticle cells are 0.5–1.0 μm thick and about 45 μm long with unbroken rounded edges near the scalp. The scalp edges become increasingly ragged toward the fiber's distal ends, thus reflecting the susceptibility of this outer envelope to grooming damage.

The cuticle cell consists of three layers of protein, which are distinguishable in the transmission electron microscope by their intensity of staining, for example with osmium tetroxide, which is an indication of the protein's cross-link density. These layers are shown schematically in Figure 2.4. The most highly cross-linked layer with a half-cystine content of ~35% is the outermost A-layer of the exocuticle, with another layer (also called B-layer) with a half-cystine content of ~15% being directly beneath it. The exocuticle also contains a relatively high concentration (~70 μ mol/g) of very stable (ε-amino (γ-glutamyl) lysine). Underneath the exocuticle lies the endocuticle, a mechanically weak, easily deformable, and highly swellable layer with a half-cystine content of ~1% and a much lower cross-link content. Because of its extensive swelling, it is generally assumed that diffusion, at least of larger molecules, occurs through the endocuticle or possibly through the CMC rather than in a transcuticular fashion through the highly cross-linked exocuticle. Underneath

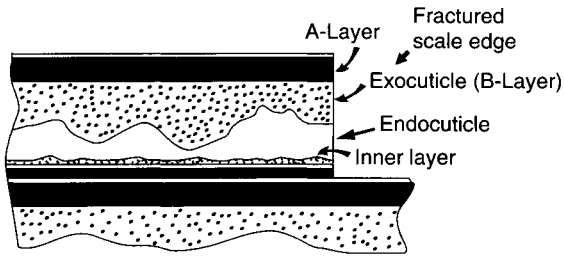


Figure 2.4. Composition of cuticle cell [3]

the endocuticle lies another cystine-containing, relatively thin layer, which Swift calls the "inner layer" [3]. This layer borders on the surrounding cell membrane and may actually be covalently linked to it.

The cell membrane that surrounds the whole cuticle cell is a poorly defined histological membrane, called the epicuticle, which is chemically quite inert and consists of ~25% fatty acids and ~75% protein. This membrane is about 2–5 nm thick. The hydrophobicity of the fiber, which persists even after solvent extraction, is attributed to a hydrophobic surface layer of covalently bound lipids (as thioesters) with a thickness of about 0.9 nm.

CELL MEMBRANE COMPLEX

In its final stage of formation, the terminal hair fiber develops a continuous layer of intercellular material between cuticle cells, between cortex cells, and between cuticle and cortex. This layer is referred to as CMC and consists of free fatty acids and sterols, cholesterols, and desmosterols. Glycoproteins have also been reported. The exact composition of the CMC is still uncertain, but it appears to have a layered structure with alternating lipid and protein layers that enclose an intercellular region of globular proteins and a "contact zone" containing reductant-soluble hydrophilic proteins. The integrity of the CMC is affected by various chemical and mechanical treatments, which in turn have consequences for the intercellular adhesion in the cuticle and in the cortex and thus may affect the mechanical properties of the fiber.

CORTEX

The cortical cell is spindle-shaped, about 100 μm long, and at its widest point about 5–10 μm wide, although there are considerable variations in these dimensions. The cortical cells are packed in an overlapping manner, and some interdigitation with the ends of other cells has been reported. The latter would provide additional adhesive contacts between the cells and thus may have some influence on the mechanical properties of the cortex and, with it, of the fiber itself.

The hierarchical arrangement of the various constituents of the cortical cell was illustrated in Figure 2.3. One approach to understanding the complex morphology of these cells would appear to be a discussion of the chemical composition of the various proteins that form their building blocks. About 21 different α-amino acids are found in hydrolysates of human hair.

Of these, the sulfur-containing amino acid cysteine with its sulfhydryl group and its oxidation product cystine, which is formed from cysteine during the keratinization process in the follicle, are among the most reactive and important constituents of the fiber proteins. Cystine provides inter- and intramolecular

Table 2.1 Covalent Cross-Links in Human Hair

Naturally Occurring:

Cystine disulfide bond, very reactive (oxidation, reduction, hydrolysis)
$K-CH_2-S-S-CH_2-K$
Isopeptide ε-amino-(γ-glutamyl) lysine, chemically very stable
$K-CH_2-CH_2-CO-NH-(CH_2)_4-K$

Derived from alkaline degradation of cystine:

Lanthionine, very stable thioether
$K-CH_2-S-CH_2-K$
ε-Lysinoalanine
$K-CH_2-NH-(CH_2)_4-K$
where K is the protein chain to which the groups are bonded.

cross-links within and between proteins, and many of the morphological components are characterized by their cystine content. Table 2.1 lists the covalent cross-links that either exist naturally in the keratin proteins or are formed from cystine through alkaline degradation.

While the nature of the amino acids in hair is known with some certainty, there are considerable problems in establishing the relative amounts. The most frequently used method of analysis is total hydrolysis of the fiber with hydrochloric acid, which leads to partial destruction of some of the amino acids. Amino acid composition of the whole hair yields relatively inaccurate data about the average concentration of a particular amino acid in the total proteinaceous material consisting of all the protein-containing morphological components. Over the last decade various research groups have made considerable efforts to fractionate, identify, and determine the amino acid composition and sequence of these proteins [4]. It is estimated that about 50–100 different proteins exist in human hair fibers.

Keratin-associated proteins form the matrix between keratin IFs in the cortex and exist in the cuticle. Originally an arbitrary classification was used for matrix proteins, that is, high sulfur <30% cysteine, ultra-high sulfur >30% cysteine, and glycine/tyrosine-rich proteins. It is known that there are at least eight families of sulfur-rich proteins with cysteine contents ranging from 12% to 41%, while there are at least three families of gly/tyr-rich proteins with gly/tyr contents from 35% to 60%. Readers interested in the α-helical nature of intermediate filaments and how they aggregate to dimers and tetramers are urged to examine some recent reviews [1,4–6].

The formation of protofilaments is visualized as an end-to-end arrangement of tetramers with disulfide cross-links between C- and N-terminal domains.

Eight protofilaments aggregate to form the intermediate filament, formerly known as microfibril. As pointed out earlier, in the follicle the intermediate filaments are expressed first in the cortical cell cytoplasm and then aggregate into larger units, the macrofibrils, which are oriented in the direction of fiber growth. Spaces between the intermediate filaments are later filled in by a matrix consisting of KAPs. The macrofibrils, which are 40–200 nm in diameter, extend the full length of the cell and fill it almost completely, although intermacrofibrillar spaces filled with residual cytoplasmic material and nuclear remnants near the center of the cortical cell can be seen in stained transmission electron micrographs.

Two different kinds of cortical cells have been reported, differing in their amino acid composition and showing differences in their dye uptake, which resulted in their discovery. These cells are termed ortho- and paracortical cells, which either have a radial or a bilateral distribution, in the latter case determining the natural wave or crimp of wool fibers; they are also believed to exist in highly crimped human hair. The orthocortical cells are found on the outside of the wave and the paracortical cells on the inside. The difference between these two cell types is believed to be mainly due to a higher IF to KAP ratio in the orthocortex.

MEDULLA

In the center of some human hair fibers, one can find a continuous or discontinuous array of more or less empty cells, which can assume a diameter of up to one-third that of the fiber. There is little deposition of protein material in these cells during their gene expression phase in the follicle. The protein that is formed differs strikingly from that of the cortex by the virtual absence of half-cystine, the high concentration of glutamic acid (41%), and the presence of the amino acid citrulline.

NONPROTEINACEOUS MATERIALS

The most abundant nonproteinaceous compound found in hair is water, which plays a very important role in its physical and cosmetic properties. The fiber's sorption/desorption behavior of water will be discussed in a subsequent paragraph in the context of hair mechanical properties.

Hair lipids are another important group of compounds, some of which have been mentioned earlier in connection with their structural functions. One can indeed distinguish human hair lipids as extractable lipids and as structural lipids. The composition of extractable or "free" lipids, which is quite similar to that continuously produced by the sebaceous glands of the scalp, is controlled hormonally by androgens and also varies seasonally or

even daily. Part of the free lipids of the cell membrane complex can also be extracted. Extraction of hair clippings with solvents produces from 1% to 9% of lipids depending on the nature of the solvent, that is, the ability to swell the fiber, such as ethanol, or nonswelling solvents, such as hexane, which remove mainly surface-held lipids derived from sebum, as reported by Robbins ("Recommended Reading").

The inorganic constituents of hair (less than 1% of the hair mass), in particular the trace metal content, have received some attention over the years, especially as methods of analysis have become more accurate and sensitive. It has been reported that the concentrations of cadmium, arsenic, mercury, zinc, and lead and probably others in hair correlate with concentrations in internal organs, which points to the potential of hair as a diagnostic tool in medicine, and to some extent in forensic science. For example, arsenic poisoning leads to an accumulation of arsenic in hair, nails, and skin. Higher than normal concentrations of cadmium in hair have been found in dyslexic children, pointing to the possibility that cadmium may be involved in this learning disorder. Elevated levels of zinc have been found in the hair of children with the protein deficiency disease kwashiorkor. These are just a few examples, which reflect the importance of trace metal analysis in hair in the diagnosis of several human diseases. However, heavy metals do not have to enter the hair through the blood stream via the follicle as they are readily absorbed directly from externally applied solutions or sweat deposits. The water supply usually provides considerable amounts of calcium, magnesium, iron, and manganese to the hair, and copper from swimming pools has been reported to turn blond hair green.

In other words, trace metals can be introduced into the hair from external or internal sources, and it is difficult to establish to what extent they fulfill a necessary function in the formation of the hair fiber. For example, the functional trace metal copper has a direct influence on the oxidation of the sulfhydryl groups of cysteine to the disulfide cross-links of cystine during the keratinization and hardening phase of hair formation in the follicle.

PHYSICAL PROPERTIES OF HUMAN HAIR

While the consumer-perceived changes due to cosmetic treatments are probably best reflected in hair assembly properties, it is the change in the properties of the single hair fiber that affects the assembly and therefore must be considered the basic parameter for assessing responses to cosmetic treatments. Single fiber properties can be measured much more accurately than assembly properties and can be interpreted in chemical or structural terms based on models that have been developed over the years. Since single fibers determine the

behavior of the hair assembly, it is possible to define assembly properties from a few fundamental single fiber properties. This concept has been proposed as a general hypothesis by Robbins ("Recommended Reading"). Bulk fiber properties such as stress-strain responses, bending and torsion, and fiber curvature or surface properties such as friction, static charge, luster, wettability, and adhesion are among the single fiber properties that are accessible to quantitative, objective evaluation. Empirical relationships can be developed between them and consumer assessments based on subjective ratings.

TENSILE PROPERTIES

The tensile or mechanical properties of keratin fibers are thought to reflect the behavior of the cortex and specifically that of the intermediate filament/matrix structural unit. In other words, there are no contributions to the extensional stresses from the cuticle, which means that the cuticle cells have to slide over each other to accommodate the fiber strain. Sliding would be expected to occur along the cell boundaries involving the intercellular cement with possibly some shearing deformation in the endocuticle. It is unlikely that the cuticle cell itself extends to any large degree, since the outermost layer, the A-layer, is very highly cross-linked and therefore mechanically quite strong. In

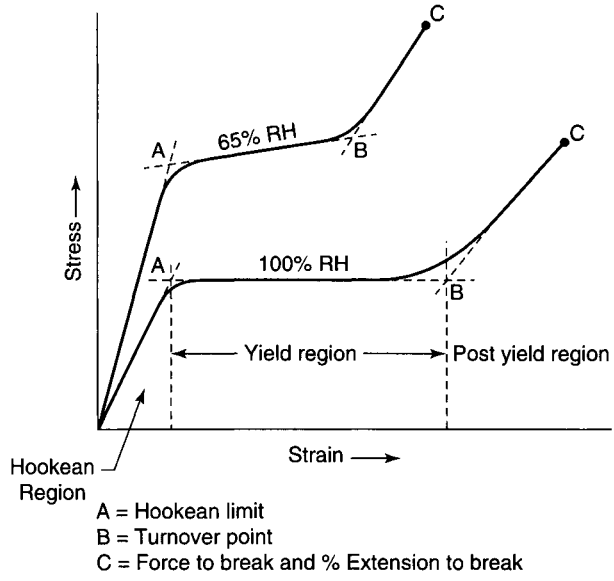


Figure 2.5. Schematic stress-strain curve of keratin fiber (From Robbins, "Recommended Reading")

contrast to the cuticle cells, the cortical cells do not slide along each others' cell boundaries, suggesting that the intercellular packing in the cortex is such that the intercellular cement in this region is strong enough to maintain the relative positions of the cortical cells, possibly with some help from the "interdigitating" connection of some cortical cell ends.

Keratin fibers have a unique response to extensional strains, as illustrated in Figure 2.5, which shows a schematic stress-strain curve obtained under constant rate of extension conditions. This unique response is based on the reversible deformation of the intermediate filaments involving an unfolding of the α-helices to extended pleated-sheet β-structures (Fig. 2.6). After an initial "Hookean" deformation region, which is thought to involve limited bond angle stretching in the helical domains until a critical stress level is reached, unfolding begins at the "yield" point. Further extension requires little energy, and usually the "yield slope" or modulus is quite low. At an extension level of about 25–30%, a "turnover" point is reached, where resistance to extension increases again and the "post-yield region" begins, continuing more or less linearly to fiber failure.

Complete reversibility of deformation under ambient conditions is possible up to an extension level of about 25–30%, provided the fiber is released immediately and is then permitted to recover in water for a few hours. This reversibility has been used in the study of wool by Speakman to establish a damage index for a particular treatment. The work to extend 20% is determined on a fiber, the fiber is permitted to recover, and it is then exposed to the treatment in question. The decrease in work required to extend the same treated fiber provides the "20%-index," which is an internally normalized damage parameter for the treatment. The long-range reversibility of this $\alpha \rightarrow \beta$ transformation depends on a number of conditions, which reflect the contributions of the surrounding elastomeric matrix or at least the interactions between matrix and IFs. During the stretching and unfolding of the IFs the disulfide cross-linked domains of the matrix have to extend, and eventually stresses have to fall on these disulfide cross-links. As long as the disulfide bonds remain intact and stable, the deformation is totally reversible in terms of length recovery and the mechanical properties and the fiber structure totally recover upon immersion of the fiber in water. The limits of this reversibility are reached when disulfide instability permits irreversible flow, which is reached at extensions beyond the "turnover" point, at very slow extension, by holding the fiber in the extended state, or at elevated temperature. The observation that sulfhydryl blocking reagents extend the range of disulfide stability to a considerable extent suggests that a sulfhydryl-disulfide interchange is the mechanism of removing disulfide bonds from stress-supporting positions thus causing irreversibilty.

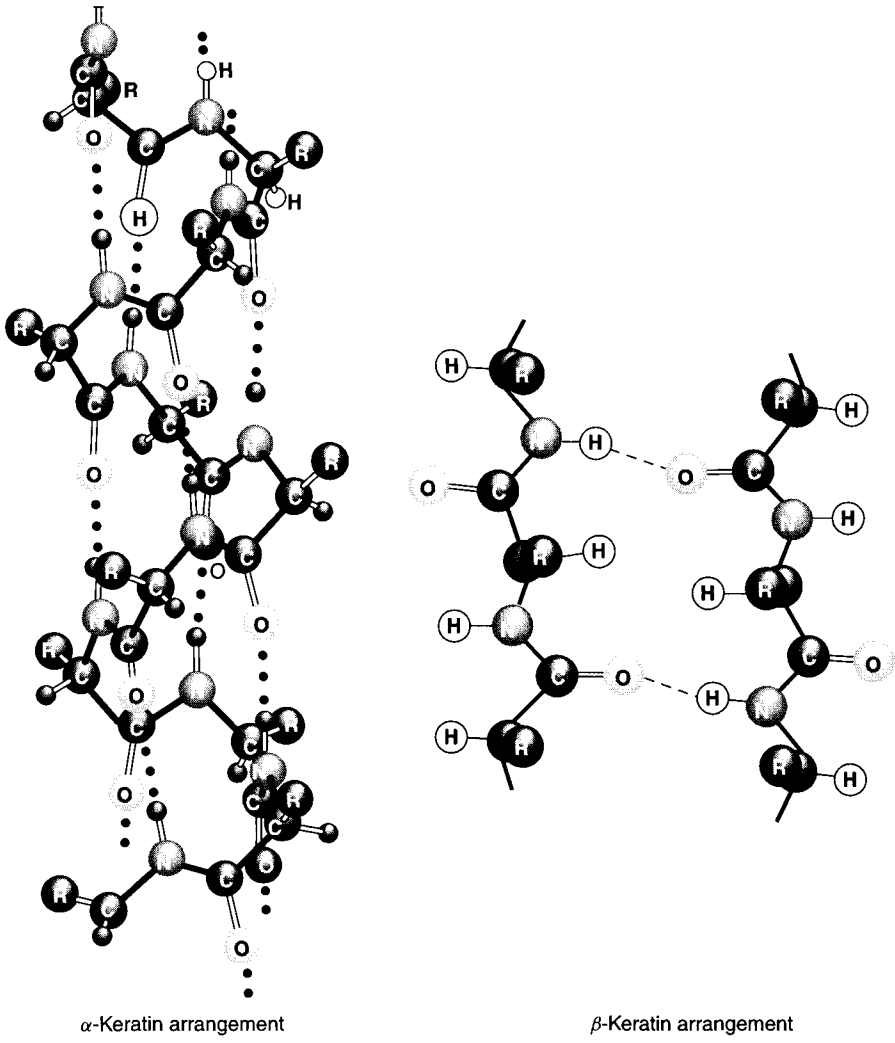


Figure 2.6. (a) α-helical structure of IF domains (b) extended β-structure of IF domains after fiber extension

A number of models have been proposed to provide a structural interpretation of the stress-strain curve, and there has been controversy for several decades over their relative validity. All the models currently under consideration are based on the simplifying concept of parallel filaments separated by a matrix with more or less direct bonding between the two of them. Feughelman has provided a vast amount of detailed data, and he summarized this information in a recent book [7].

The turnover point reflects the onset of the post-yield region, where the removal of disulfide bonds from stress-supporting positions becomes a major mechanism of stress release. An interchange between catalytic amounts of free sulfhydryl groups and these disulfide bonds provides the means for this process [8]. A transition temperature of about 80 °C in buffer solutions of pH 7 reflects the rate of this interchange reaction, which depends on the concentrations of the catalyst in the form of ionized S^- groups within the fiber. At elevated SH-contents as in reduced fibers, this transition temperature moves into the room temperature range, indicating that reduced fibers undergo irreversible deformation, that is, they can be permanently set at low temperatures, as is done in cold waving.

Stretching hair fibers to failure results in fracture patterns that depend on the conditions of stretching and can range from smooth radial fractures (mostly encountered under wet conditions) to various forms of step fractures, splitting, and fibrillation. Fibers fracture when cracks in them reach critical size. Most of these cracks originate in the cortex or at the interface between cortex and cuticle. Under ambient conditions (65% RH) healthy, unmodified hair fibers pull out of the follicle at stress levels considerably lower than the breaking stress, although an analysis of combed out fibers indicated that only about 50% of the fibers contain bulbs while the others apparently had broken. During stretching at ~45% RH, irreversible cuticle separation resulting in scale edge lifting occurs at extension levels of 10–20% depending on the position along the fiber. Even though the mechanical properties of the fiber are totally recovered upon release of the fiber in water, the cuticle cohesion is irreversibly damaged, with all the resulting consequences for the viability of the cuticular sheath and its protective function for the fiber.

The mechanical properties of keratin fibers are strongly dependent on the environmental conditions under which they are determined. Especially the relative humidity and the resulting moisture content of the fiber have a strong influence on its stress-strain curve. Most data in this field were obtained on wool fibers, but the assumption seems justified that the stress-strain/RH relationship is similar in hair fibers. The yield stress (stress at points A, Fig. 2.5), which is a reflection of the strength of the hydrogen bonds stabilizing the α-helices in the IFs, predictably decreases dramatically with increasing RH, and the elastic or Young's modulus (given by the slope in the Hookean region, Fig. 2.5) and fiber extensibility show considerable response to RH. It is interesting to note that the post-yield modulus (given by the slope B-C, Fig. 2.5) is insensitive to humidity, which supports the concept that hydrogen bonding does not contribute to deformation processes in this region and that disulfide bonds become stress-supporting.

SORPTION AND SWELLING

Even though the surface of the keratin fiber is hydrophobic and the fiber shows negative wettability in water, it absorbs considerable amounts of water depending on the relative humidity of the environment. In Figure 2.7 an equilibrium sorption/desorption isotherm is shown, in which the fiber's water uptake is plotted against the relative humidity. This is followed by a desorption cycle. The typical sigmoidal shape of sorption/desorption curves with their pronounced hysteresis is believed to reflect the nature of bonding of the water molecules within the fiber structures. The initial relatively high increase up to ~5% is associated with chemical bonding at specific sites, while uptakes up to ~25% are associated with the breaking of hydrogen bonds, with accompanying changes in mechanical properties. The final sorption to ~33% may be due to the formation of "free" water with little consequences for elasticity and heat generation. Theories of sorption and desorption have been discussed extensively and have been summarized in a somewhat dated version in the book by Alexander et al. ("Recommended Reading").

The keratin fiber shows some pronounced anisotropy in dimensional changes upon swelling in water with 1.5–2% in axial and about 16% in diametral swelling. This anisotropy is determined by the structure of the fiber. Swelling in the axial direction is controlled by the intermediate filaments, which are oriented parallel to the fiber axis and act like rigid rods, as long as their helical structure is intact. Any irreversible loss of their structure, such as that experienced during permanent waving or high temperature treatments, results

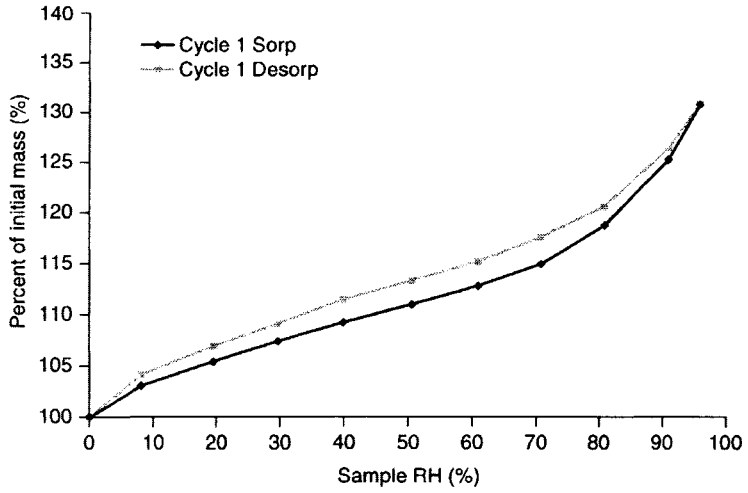


Figure 2.7. Water sorption/desorption isotherm of wool at room temperature

in an increase in axial swelling corresponding to the extension during the treatment.

Diametral swelling constitutes the bulk of the swelling and has long been assumed to take place in the matrix proteins. However, recently questions were raised about this concept, and it has been suggested that extensive swelling of nonkeratinous proteins in the cell membrane complex, the endocuticle, and conceivably in the intermacrofibrillar spaces may contribute to swelling. Swelling in the matrix is restricted by the high level of disulfide cross-links, which provide a counterforce to the osmotic pressure. However, when these bonds are broken, as for example in a reductive mode under alkaline conditions, additional hydrophilic groups are generated, causing an increase in osmotic pressure at the same time when the elastic restraint by the cross-links is decreased. This leads to an enormous, virtually destructive increase in swelling ranging up to 150–200%, which the fiber cannot survive. Upon deswelling and drying the fiber is brittle, and the cuticle has a corrugated appearance.

Volume swelling is strongly pH-dependent with an extended minimum in the vicinity of the iso-ionic region, where an equal number of ionized groups of opposite charge exists. The large increase in swelling at pH values above 10 is mainly associated with the ionization of the diacidic amino acid residues (aspartic and glutamic acid), while the increase in swelling from neutral to about pH 3 is due to the protonation of the dibasic amino acid residues (lysine, arginine, and histidine). At both extremes pH-dependent keratin hydrolysis begins to play a role during long-term equilibration.

STRESS RELAXATION

Stress relaxation occurs when a fiber is extended and kept at that extension. The decrease in stress is measured as a function of time. The method is useful for exploring the kinetics of structural rearrangements that go on while bonds are gradually removed from stress-supporting positions. Under various conditions of pH, different temperatures, and the presence of specific reagents that diffuse into the fiber during the experiment one can establish the nature of the bonds active at a particular extension level, the mechanism of their removal, and the recovery from extension after various levels of stress relaxation. For example, it has been established that an SH-group catalyzed disulfide interchange occurs at most extensions, increasing in rate with increasing temperature and catalyst concentration and having a direct bearing on the extent and reversibility of the structural rearrangement. Suppression of the interchange mechanism by blocking the catalyst, that is, the SH-group, either with a specific blocking agent or by reducing the pH to reduce the concentration of the active S^--group

prevents the structural rearrangement and makes the deformation reversible. It is also possible to establish the kinetics of disulfide reduction by following stress relaxation in the presence of reducing agents and thereby determining the relative effectiveness of the reducing agent.

BENDING PROPERTIES

The bending behavior of hair fibers is important for a number of hair assembly properties that are affected by cosmetic treatments. Several methods have been developed to measure the bending properties of fibers and to explore the validity of theoretical relationships for the complex morphology of human hair. For isotropic fibers theory predicts a fourth power relationship of stiffness with diameter, which surprisingly appears to apply to keratin fibers, provided small angles of deformation are involved. Cantilever bending, the balanced fiber method of Scott and Robbins [9], and the vibrating reed method have all been applied to hair, despite experimental difficulties. Bending involves the extension of the outer layers of the fiber, while the inner layer is compressed and a neutral plane near the center of the fiber remains unchanged. The resistance to this mode of deformation is expressed as stiffness. The bending modulus is approximately equal to the tensile or elastic modulus determined by stress-strain measurements, although the fact that most hair fibers have more or less ellipticity has to be considered. Fibers bend over their minor axis following the path of least resistance. As would be expected, the effect of the fiber's moisture content on its bending behavior is quite significant, with stiffness decreasing with increasing moisture.

TORSIONAL PROPERTIES

Another mode of fiber deformation that is involved in various kinds of hair assembly behavior such as combing, brushing, and setting is a twisting of the fiber, which is quantified as torsional resistance or rigidity. Most methods of measurement involve the torsion pendulum, in which the damping of free oscillations and their period are measured [10]. Similar to the bending modulus, the torsional modulus shows a fourth power relationship to fiber diameter and is strongly dependent on moisture content. The torsional modulus is, however, significantly lower (factor of $\sim$4) than both the bending and the extensional moduli, and it shows a much higher dependence on moisture content (factor of $\sim$2). While the tensile properties reflect deformation behavior of the cortex, torsion involves the cuticle, which is especially noticeable in the damping behavior (logarithmic increment) when comparing dry versus wet torsional properties. It appears that the highly swollen endocuticle and intercellular cement in the cell membrane complex absorb

a significant amount of the torsional energy. Any damage to these domains is not detectable by measuring tensile properties, and Robbins ("Recommended Reading") suggests that torsional methods may be more reflective of whole-fiber damage and should be used as a quantitative tool for this purpose.

SURFACE PROPERTIES

Most cosmetic hair treatments are topical, and the surface properties of the fiber are therefore of great importance to the cosmetic chemist. Over the years a considerable number of methods has been developed to characterize the fiber surface and its modifications by chemical, mechanical, and topical treatments. Since the fiber surface properties are also critical for many hair assembly properties, fiber friction, adhesion, and electrostatic charge buildup will be mentioned only briefly. (A more comprehensive treatment is provided in the book by C.R. Robbins and its extensive literature references). It has not been possible for the cosmetic industry to agree on standard test methods that would permit industry-wide comparisons of treatment claims. However, this development is probably just a question of time as more and more international regulations require proof of treatment claims.

WETTABILITY

As pointed out earlier, the fiber surface as it emerges from the follicle is covered by a hydrophobic lipid layer, which is part of the epicuticle. Even as cuticle cells are lost through abrasive or ablative wear during grooming, each newly exposed cuticle surface has these hydrophobic properties. The presence of this low energy surface layer prevents the uniform wetting of the hair by high surface tension liquids such as water. Individual fibers actually float on water despite the fact that the density of the fiber is considerably higher than that of water. The hydrophobicity of the fiber surface strongly influences the nature and substantivity of any surface deposits, but it can be modified through a variety of topical or chemical treatments. It is obviously very important to be able to characterize fiber surface properties and their modification by various cosmetic treatments to optimize hair care products and substantiate claims made in conjunction with such treatments.

The wettability of hair fibers can be determined by a method based on the Wilhelmy balance principle, in which the force exerted by the wetting liquid on an individual fiber is scanned along its length [11]. Two situations are illustrated in Figure 2.8, both for the advancing mode of wetting. In one case the contact angle between fiber surface and wetting liquid (water) is larger than 90°, reflecting the hydrophobic surface of untreated hair; the other case

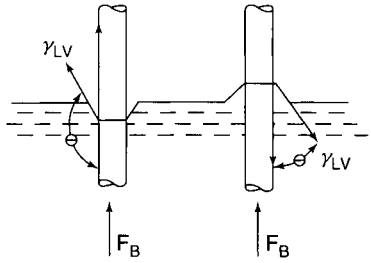


Figure 2.8. Schematic representation of wetting forces generated during contact between hair fiber with wetting and nonwetting liquids [11]

in Figure 2.8 illustrates a hydrophilic surface with (smaller than 90°, as might be experienced with oxidized or bleached hair. The force that is recorded (F_w) is the difference between the wetting force (w) and the buoyancy force (F_B). The wettability (W) is then given by normalizing the wetting force by the wetted perimeter (P) and according to the Young-Dupre equation is equal to

$$W = w/P = \gamma_{LV} \cos\theta,$$

where γ_{LV} is the surface tension of the wetting liquid.

The surface energy of a fiber, as reflected in its wettability, depends on the intactness of the hydrophobic surface layer of the cuticle cells. This layer is damaged during grooming, frequently resulting in a change from hydrophobicity to hydrophilicity as one moves from the root to the tip of a fiber. As might be expected, chemical treatments such as oxidation or reduction also result in making the surface more hydrophilic because of the creation of cysteic acid or sulfhydryl groups near or at the surface. The deposition of hydrophilic compounds such as polymeric cationic conditioners can be characterized and the surface coverage and the substantivity of these deposits can be determined, the latter by multiple immersions in the wetting liquid.

LUSTER—SHINE

Hair luster is a very significant property for the cosmetic industry, mainly because high luster (shine) is desired by consumers. Luster as a fiber property is measured by determining the way in which light is reflected off the fiber surface by a technique known as goniophotometry. An incident beam is reflected partly in a specular (S) fashion, in which the beam is reflected at the same angle as the incident beam or diffusely (D) reflected at angles different from that of the incident beam.

Fiber alignment is probably the most important aspect for improvement of luster, since the consumer-perceived property is that of a hair assembly rather than that of a single fiber. A number of hair treatments designed to improve luster involve fixatives that keep fibers aligned within the hair assembly. Nevertheless, the surface of the single fiber is an important component, and its luster depends on the intactness or smoothness of the scale structure, the presence of debris or dirt on the scale faces, and so forth, and can be strongly affected by mechanical or chemical damage and shine treatments.

FRICTION

Another important surface property of the hair fiber is frictional interaction either with other fibers or with grooming implements. Obviously the frictional properties of the fiber are directly dependent on the nature of the cuticle cell faces and on the cuticle cells' orientation. Due to this orientation the frictional properties are directional, that is, the frictional forces in the against-scale direction are much higher than those in the with-scale direction. This directional frictional effect (DFE) is a well-known factor in wool fibers, where it is either used commercially in the production of felts or has to be reduced to prevent felting of garments. Especially in damaged hair, it can lead to unattractive and sometimes irreversible entanglements and felting. The effect has been used in the process of back-combing to enhance the fluffiness of hair styles. The DFE is quite sensitive to moisture content and with it to the swelling of the various layers of the cuticle cell and is most pronounced in the wet state.

Friction is usually measured by attaching the appropriate end of the fiber to a load-measuring device such as the Instron® tensile tester, wrapping the weighted fiber around a capstan of appropriate dimensions and material (e.g., a cylindrical rod of rubber or nylon) mounted on the Instron crosshead, and moving the crosshead downward. The coefficient of friction (μ) can be calculated from the equation,

$$\mu = 1/\phi \times \ln T_2 / \ln T_1,$$

where ϕ is the angle of wrap in radians, T_2 is the recorded force, and T_1 is the weight on the fiber, usually ~1g. In another similar method the capstan is rotating while the crosshead remains stationary. These test methods with their high contact loads between fiber and capstan are intended to evaluate the effects of various treatments on the interactions between hair and comb and are used under dry (60% RH) or wet conditions with the fiber immersed in water or in the solutions to be evaluated. Combing is the most frequently used grooming process and is probably also the most damaging to

the fiber. Under dry combing conditions the surface cuticle cell is abraded, especially at the edge of the surface scale, while under wet conditions the swollen endocuticle as the weak point makes the cuticle prone to break off, resulting in a gradual ablative process and finally leading to the complete loss of the cuticle sheath. Once the cuticle is lost, the intercellular cohesion in the cortex is weakened, and the well-known "split end" phenomenon can occur.

Interfiber friction under low contact load conditions contributes to fiber-fiber interactions associated with body and style retention, where cohesive forces between product deposits determine relative fiber movement within the hair assembly.

ELECTROSTATIC CHARGE GENERATION

Hair fibers have a tendency to develop electrostatic charges that lead to difficulties in manageability. Charge buildup and the well-known phenomenon of "fly-away" can result in entanglements and thus in severe fiber damage during subsequent attempts at grooming. Triboelectric charging occurs upon intimate contact between materials with different electrochemical surface potential, which results in transfer of electrons and the generation of charges of equal magnitude but opposite sign upon separation of the contacting surfaces. It has been suggested that the forces acting between fibers and comb are directly related to the area of contact and thus determine the magnitude of charging [12]. This means that the level of friction is directly involved in electrostatic charging and that antistatic agents such as long-chain quaternary ammonium salts act by reducing interfiber or fiber-comb friction. Any treatment of the fiber surface that affects its deformability, such as bleaching and its effect on the disulfide cross-link density in the cuticular A-layer (Fig. 2.4), also modifies its frictional properties and electrostatic charge [13].

However, it is not only the magnitude of the charge that contributes to the severity of fly-away but also its mobility on the fiber surface, its rate of dissipation, and its distribution along the length of the fiber. Reduction of fly-away can be achieved by modifying any one of these contributing factors. The effect of moisture content on electrostatic charging is particularly striking and is directly related to charge mobility or surface conductivity. The resistance of wool fibers, which is very similar to that of human hair, varies by a factor of $\sim 10^5$ between 10% and 90% RH and by a much larger factor between 0% and 100% RH.

The sign of the charge that is generated on the hair surface depends on the direction of rubbing. Interfiber friction in the with-scale or against-scale direction causes differences not only in the magnitude of friction and of the

charge generated but also in the sign of the charge. If a fiber is pulled out of a bundle of equally oriented fibers by its root end, a positive charge is generated, but if the fiber is pulled out by its tip end, a negative charge is generated. This surprising effect has been attributed to the nature of the contact between the scales and the differences in triboelectric position between scale face and scale edge, which are vastly different as the scale face is hydrophobic, hydrocarbon-like in nature while the broken-off scale edges expose a more hydrophilic, proteinaceous material. A related effect is observed after treatment with an anionic shampoo, which produces a "fly-away" effect during combing, while deposition of a cationic creme rinse without subsequent rinsing causes fly-away due to charges of the opposite sign. Since there is considerable interest in this topic from a cosmetic point of view, a lot of research has been undertaken to understand the physical and chemical background of these phenomena and a number of methods that permit the quantitative measurement of the relevant parameters have been developed.

CHEMICAL PROPERTIES OF HAIR

As described earlier, the bulk of the fiber consists of proteins of the cortex (~70–75% of total mass), which belong either to the families that make up the intermediate filaments, that is, low cystine content, or to the families of the KAPs, that is, high cystine content, or the gly/tyr-rich proteins. The considerable variety of the proteins of the cuticle cell (~10–12%) and the cell membrane complex (~1%) is very important from a cosmetic point of view. The proteins include a wide range of cystine contents from the ultrahigh of the A-layer of the exocuticle to the lower cystine content of the endocuticle. As a result of their proximity to the fiber surface they are involved in the diffusion processes. The importance of the nonkeratinous proteins of the residual cytoplasmic and nuclear remnant material (~12%) and of the lipids (~2%), either extracellular or part of the lipid envelope of the cells, has been emphasized only relatively recently. The relative amounts of these various morphological components vary considerably depending on the nature or the origin of the keratin fiber under consideration, and the values provided here represent only approximate averages.

The bonds and interactions between the constituents of the various morphological components have been mentioned earlier (Table 2.1). Covalent bonds, such as the peptide bonds between the amino acids forming the proteins; the disulfide bonds, which form intra- and intermolecular cross-links within and between structural proteins; the isopeptide bonds, especially of the exocuticle; and the thioester bonds between the lipid envelope and the protein below it are the major bonds that are formed during the synthesis

of the proteins or in the subsequent keratinization process. The structure, especially that of the helical portions of the IFs, is stabilized by intramolecular hydrogen bonds between amide groups and by hydrophobic interactions between hydrocarbon side chains. Electrostatic and hydrophobic interactions between side chains of the two types of monomeric units participate in the formation of the fundamental dimer of the IF, as mentioned earlier. In general, the complex structure of proteins is stabilized by interactions between polar, charged, and nonpolar moieties, all of which respond to intrusions and reactions with reagents to which either nature or the cosmetic chemist decides to expose the hair. Water is without any doubt the most pervasive and intrusive presence in the life of a hair fiber and the vehicle for almost all cosmetic treatments. The response of the fiber to water in terms of fiber swelling and mechanical properties has been discussed previously.

Disulfide bonds are by far the most reactive group that is modified by a number of cosmetic treatments, such as permanent waving, bleaching, oxidative dyeing, straightening, and so forth, all of which are discussed in pertinent chapters of this book. However, some of the most important reactions of these bonds are reviewed in the following few paragraphs.

WATER AND STEAM

Hair is best described as a tough fiber, and any process for changing its shape requires softening the keratin, reshaping it in the desired configuration while it is still soft, and finally hardening it in its new shape.

The simplest softening process is the application of water, which enters the hydrogen bonds of the hair and imparts flexibility. Reshaping is possible by the deformation of the wet hair, and after drying the new shape will be held. However, the hair will not deform appreciably and remains elastic; more importantly, water in a shampoo or even moisture in the atmosphere resoftens the hair so that it returns to its original shape. Setting lotions may give it a little mechanical help, but their effects do not last beyond the next shampoo.

If the water is applied as steam, the softening process goes further, and the resultant set is not easily disturbed by water at ordinary temperatures. If the water is made alkaline, softening occurs below 100 °C, and adequate conditions have been proposed to obtain the setting of hair thereby. These treatments are effective because they affect not only salt, electrostatic, or hydrogen bonds of the hair but also a number of stress-bearing covalent disulfide cross-links. It is apparent that significant and permanent deformation of keratin fibers require some manipulation of disulfide bonds.

REACTIONS OF THE DISULFIDE BOND

The reductive scission of the disulfide bond in human hair is one of the most important chemical cosmetic reactions and as such probably the most thoroughly studied. This is particularly true for the reversible reduction reactions, which permit the temporary scission of disulfide bonds to effect their removal from stress-supporting positions, followed by a structural rearrangement and then reformation of disulfide bonds in stress-free positions by reoxidizing the free sulfhydryl groups formed in the initial reduction. This is essentially the mechanism of permanent waving, although one has to keep in mind that a significant number of the disulfide bonds that change position do so via a sulfhydryl-catalyzed disulfide interchange, while the initial reduction reaction essentially provides increases in the concentration of the catalyst and thus increases the rate of the interchange reaction. This disulfide interchange reaction is widely believed to be involved in the onset of the above-mentioned structural rearrangements, which form the basis of the irreversible deformation processes that were discussed in earlier paragraphs.

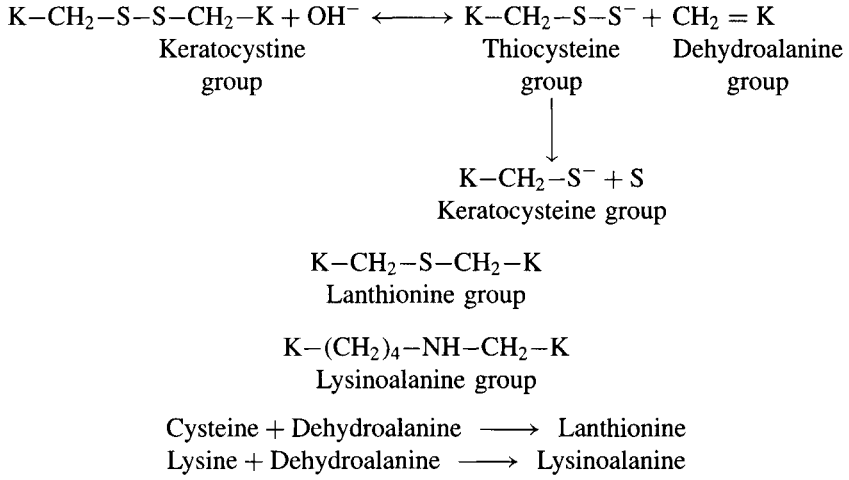
Disulfide scission is achieved through alkaline hydrolysis and some metathetical reactions but mainly through a large variety of reducing agents, including thiol and dithiols (disulfide interchange), sulfides (reduction), alkali (hydrolysis followed by lanthionine, lysinoalanine formation), cyanide (lanthionine formation), sulfites and bisulfites ("Bunte salt" formation), phosphines such as trihydroxymethyl phosphine (reduction), borohydride (MBH_4; reduction), and dithionite ($M_2S_2O_4$; reduction similar to sulfites).

Alkaline Agents

Disruption and transformation of keratin disulfide linkages have been shown to occur through the action of hydroxyl ions. The mechanism of this action and the nature of the newly created bonds and their contribution to the mechanochemical properties of keratin have been much discussed and investigated for over 30 years. The formation of a thioether derivative of cysteine was suggested as early as 1933 and confirmed in the 1940s, when lanthionine was isolated in hydrolysates of wool treated by sodium carbonate at the boiling point.

Among the reaction sequences proposed to explain lanthionine formation, two appear to prevail. One entails a direct attack on a cross-linking disulfide bond of keratocystine, implying a bimolecular nucleophilic substitution mechanism. The second, more widely accepted mechanism relies on β-elimination induced by attack on a hydrogen located on the carbon atom in β-position to the disulfide bond and leading to the intermediate formation of a dehydroalanyl group. This highly reactive group undergoes further addition with thio and amine functions. Thus the cysteine group (formed from thiocysteine through

loss of sulfur) reacts with the dehydroalanine group to form lanthionine or with any amino group existing in keratin side chains to form lysinoalanine residues, as shown in Scheme 1.



Scheme 1

This mechanism seems to be the most likely when hair is treated with alkali, as shown by the fact that lanthionine formation in alkaline medium is greatly enhanced by increasing the ionic strength. Important evidence for the transformation of disulfide bonds into a thioether bond stable against reducing agents without hydrolysis of peptidic bonds may be found in the low solubility or insolubility of "lanthionized" fibers in urea-sulfite or phenol-thioglycolic acid media.

SULFITES

The reaction of sulfites with cystine in keratin is commonly referred to as a reduction of the disulfide bond, and this terminology is retained here. The reaction of sulfites with disulfide bonds is not simple because of the reversibility of the basic processes involved and its high sensitivity to pH. The maximum reducing action of sulfite occurs between pH 3 and 6, but there may in fact be two maxima, one at about pH 3.25 and another at about pH 5.0. The sulfite reaction involves the nucleophilic attack of the bisulfite or sulfite ion on the disulfide bond. The result is the single step asymmetric scission of the disulfide bond with the formation of one equivalent each of Bunte salt (a thiosulfate) and cysteine (Scheme 2).

This scission reaction is at least partially reversible by simply rinsing the hair with water at slightly elevated pH and thereby re-forming some cystine

$$\underset{\text{Keratocystine group}}{K{-}CH_2{-}S{-}S{-}CH_2{-}K} + SO_3H^- \leftrightarrow \underset{\text{Bunte Salt}}{K{-}CH_2{-}S{-}SO_3H} + \underset{\text{Keratocysteine group}}{{}^-S{-}CH_2{-}K}$$

$$K{-}CH_2{-}S{-}S{-}CH_2{-}K + SO_3^{2-} \leftrightarrow K{-}CH_2{-}S{-}SO_3^- + {}^-SCH_2K)$$

Scheme 2

cross-links in new stress-free positions. When this reaction is used for permanent waving or straightening, reoxidation of the sulfhydryl groups formed is necessary to ensure stability of the wave. For this purpose, weak oxidizing agents should be used to preclude oxidation at the disulfide stage.

THIOLS

The most effective way of breaking disulfide bonds in hair is through use of a thiol. The volatility and disagreeable odor of most thiols severely limit the choice of thiols, and thioglycolic acid or one of its salts has assumed a dominant role in permanent waving practice.

The reduction of disulfide bonds with 2 mols of a thiol is a two-step reaction with the formation of a mixed disulfide as the initial step, as shown in Scheme 3.

$$\underset{\substack{\text{Keratocystine}\\\text{group}}}{K{-}CH_2{-}S{-}S{-}CH_2{-}K} + \underset{\text{Thiol}}{R{-}CH_2{-}SH} \leftrightarrow \underset{\substack{\text{Mixed Disulfide}\\\text{group}}}{K{-}CH_2{-}S{-}S{-}CH_2{-}R} + \underset{\substack{\text{Kerato-}\\\text{cysteine}\\\text{group}}}{K{-}SH}$$

$$\underset{\substack{\text{Mixed Disulfide}\\\text{group}}}{K{-}CH_2{-}S{-}S{-}CH_2{-}R} + \underset{\text{Thiol}}{R{-}CH_2{-}SH} \leftrightarrow \underset{\text{Dithiol}}{R{-}CH_2{-}S{-}S{-}CH_2{-}R} + \underset{\substack{\text{Kerato-}\\\text{cysteine}\\\text{group}}}{K{-}SH}$$

Scheme 3

The equilibrium constants at pH 7 and below are all approximately 1, so that it takes a considerable excess in thiol concentration to shift the reduction equilibrium to the right, that is, to extensive scission of the disulfide bond, although the effective scission of the cystine cross-link is already achieved in the first reaction step. The effective agent in the reduction is the ionized form of the thiol, the mercaptide ion:

$$R - SH \longleftrightarrow R - S^- + H^+.$$

The reduction reaction is therefore strongly pH-dependent. The pK value (the pH value at which ionized and un-ionized forms are present at equal concentrations) of thiols ranges from about 4 to 10, depending on the presence of electron-withdrawing or electron-donating groups; the thiols used in cosmetic practice have pK values in the upper ranges (9–10). With thioglycolate, for example, most reducing reactions are therefore carried out at pH values of about 9–9.5. At higher pH values, secondary reactions occur involving the previously discussed β-elimination of a proton from the CH-group in the β-position and formation of combined dehydroalanine or lanthionine.

The equilibrium constant of the reduction reaction, especially that of the second step (Scheme 3) can be shifted to much higher values (10^4) by using appropriate dithiols, such as dithiothreitol or dithioerythreitol, where the final "oxidation" product is a sterically favored dithiane. The reduction in hair can become almost quantitative with reagent concentrations only slightly above the stoichiometric amounts.

The sulfhydryl group formed in the fiber is the most reactive functional group in protein chemistry and can be used to introduce other covalently bonded groups into the fiber. As noted earlier, the presence of mercaptan groups in keratin fibers plays an important role in the sulfide-disulfide interchange reaction. Thus a cysteine group in a fiber may react with a cystine group in its vicinity, creating another cysteine grouping. This type of reaction can continue indefinitely as long as the temperature, pH, and moisture conditions are favorable. It is important, therefore, to eliminate any residual mercaptide group by mild oxidation in hair following a permanent wave to avoid "relaxation" of the wave via this interchange.

The product of disulfide scission, the sulfhydryl groups in the fiber, is the most reactive functional group in protein chemistry and has been used to introduce a large number of other covalently bound groups into the fiber. Among these are bifunctional compounds with a large range of spacings between their reactive sites to control the span of the cross-link replacing the disulfide bond, and all sorts of monofunctional reagents in which the sulfhydryl group acts as a powerful nucleophilic displacement agent. For example, alkyl halides have been used to introduce a large range of nonpolar, hydrophobic groups with different chain lengths into the fiber structure. The reaction with blocking agents or with alkyl mercury halides has been used for the quantitative analysis of sulfhydryl and disulfide groups. There are many more instances in which sulfhydryl groups have been used as the reactive site in the fiber structure.

OXIDATION

An unavoidable side-reaction during the oxidative destruction of the melanin pigments in bleaching of hair is the attack of the oxidizing agent on the protein

and specifically on the disulfide bond. Oxidation of other amino acid residues, such as tyrosine, methionine, lysine, histidine, and possibly tryptophan, occurs to a smaller extent, and the discussion in this paragraph will therefore be restricted to the oxidation of the disulfide bond. The irreversible oxidative scission of cystine disulfide groups during bleaching is not a minor effect; 15% to 25% of cystine is oxidized during normal bleaching operations and up to 45% during severe bleaching of black or brown-black hair to light blond or during frosting.

As mentioned earlier, mild oxidizing agents are used for the reoxidation of reduced hair after perming, while the destruction of melanin requires more severe oxidative conditions. Oxidative scission of the disulfide bond is caused by hydrogen peroxide (alkaline), halogens, permanganate, and peracids. The oxidants useful for reoxidation of reduced keratin include bromates and iodates, perborates, hydrogen peroxide (acidic), and air oxidation (metal catalysis).

The overall reaction of disulfide oxidation during the bleaching process is rather complex, with a number of potential oxidation intermediates being formed, some of which have been identified. Since the reaction is usually carried out under alkaline conditions, disulfide hydrolysis and the hydrolysis and disproportionation of some of the intermediate oxidation products take place.

It is generally agreed that $K-SO-S-K$ is the first oxidation product; continuing oxidation leads to $K-SO_2-SO_2-K$. Next, the S-S bond splits, creating the final oxidation product in hair, cysteic acid, which is a sulfonic acid bound by peptide links to the keratinous proteins.

Two mechanisms for the oxidative scission of the cystine cross-link have been discussed, sulfur-sulfur scission and carbon-sulfur scission. An analysis of the endproducts of the oxidation process has conclusively established that S-S scission is the mechanism occurring during commercial bleaching (Scheme 4), while C-S scission occurs under ultraviolet-irradiation conditions, as shown in Scheme 5:

$$K-CH_2-S-S-CH_2-K \rightarrow K-CH_2-SO-S-CH_2-K \rightarrow\rightarrow 2K-CH_2-SO_3H.$$

Scheme 4. Chemical Oxidative Rupture of S–S Links (S–S Scission)

$$K-CH_2-S-S-CH_2-K \rightarrow K-CH_2-S-S-OH + K-CH_2-OH \rightarrow K-CH_2-SO_3H.$$

Scheme 5. UV-controlled Oxidative Rupture of S–S Links (C-S Scission)

The alcohol formed during C-S scission is a serine residue ($K-CH_2-OH$). No increased serine content can be found in chemically bleached hair, although

the cysteic acid content increases in accord with the S-S scission mechanism (Scheme 4).

RESPONSE TO SUNLIGHT IRRADIATION

Unpigmented hair and protein fractions absorb light between 250 and 350 nm. The absorption is mainly due to the presence of the sulfur-containing amino acids (cystine, methionine), the amino acids with an aromatic ring in the side chain (phenylalanine, tyrosine, tryptophan), or other heterocyclic ring-containing amino acids (proline, histidine). It appears that these UV light–absorbing amino acids are the sites of sunlight-caused degradation in the hair fiber, primarily in Scheme 5. Surprisingly, the amino acid leucine has also been mentioned as being degraded by sunlight. The UV-degradation of tryptophan can be followed by fluorescence spectroscopy, and it has been suggested that this amino acid, which is particularly vulnerable to UV light, acts as an indicator for incipient UV degradation and may even be involved in sensitizing other amino acids to UV light.

From the point of view of the physical properties of the hair fiber, the most important UV damage occurs at or near the fiber surface, where the amino acid cystine is present in particularly high concentrations. Cysteic acid, the ultimate oxidation product of cystine, has been found by electron spectroscopy for chemical analysis (ESCA) in higher concentrations near the tip of the fiber, suggesting that in the presence of air and water the major reaction involves the oxidative cleavage of the disulfide bond. As pointed out earlier, the mechanism of disulfide scission under these conditions is a C-S scission with the initial formation of an S-sulfonic acid and the amino acid serine.

Extensive irradiation in the UV range of the sunlight spectrum results in the decrease of wet mechanical properties. During long-term exposure involving alternating cycles of low humidity followed by high humidity in the dark, degradation of the outermost cuticle cell leads to its thinning—probably through diffusion of soluble fragments with high cysteic acid content into the interior of the fiber—and an embrittlement of the fiber with "cathedral spire" fracture ends. This fiber embrittlement is probably due to the fact that superimposed on the decrease in cross-link density via disulfide scission is a radical-induced cross-linking process within the cortex proteins, which destroys the ability of the native structure to absorb extensional stresses.

The observation that sunlight irradiation leads to color loss, especially in light brown hair, suggests the degradation of the highly absorptive melanin granules. This photobleaching effect has been attributed mainly to the visible range of the spectrum, although UVA and UVB also contribute to color loss in light brown hair. The more pronounced UV damage to the proteins in

light brown hair as opposed to dark brown hair suggests a protective function for the melanin pigment. The most widely accepted mechanism for this UV protective function is light absorption by melanin; this mechanism assigns no role to melanin, which as a free radical may scavenge other UV-formed free radicals.

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CHAPTER 3
The Nails

BIOLOGY OF THE NAILS

STRUCTURE

The nails are located at the dorsal distal ends of both fingers and toes and protect them from trauma [1]. Nails create the shape of the distal digit and enhance the capacity for fine digital movements and tactile sensation. This allows humans to use them as precise tools for picking up objects. The discussion of nail structure starts with the "nail unit," which is composed of four distinct keratinizing epithelial structures: the proximal nail fold, the nailbed, the hyponychium, and the matrix (Fig. 3.1). The proximal nail fold is an extension of the overlying epidermis and produces a thin layer of stratum corneum that adheres to the nail plate and is known as the cuticle. The cuticle acts as a barrier to protect the nail unit from environmental irritants. Loss of the cuticle leads to paronychia. The nailbed begins at the distal end of the matrix and continues until the hyponychium. The nailbed adheres to the nail plate in a unique interconnecting manner such that it grows distally and at the same rate as the nail plate. Many conditions affect the nailbed, leading to nail disease. The hyponychium is the most distal component of the nail unit. It begins at the distal end of the nailbed and ends at the distal groove. The matrix is the most significant component of the nail unit; it is responsible for the production of the nail plate. The nail plate is composed of hard keratin and is the end product of differentiation of the matrix. Conditions affecting the matrix will lead to abnormal nail plate formation. The lunula is the whitish half-moon pattern, which is the visible portion of the matrix seen through the translucent nail plate, and represents the distal matrix. The shape of the lunula determines the shape of the nail plate. The greater surface area of the lunula and nail plate of the dominant thumb can be used to ascertain cerebral hemispheric dominance (handedness). The nail unit is more than a cosmetic unit; it can also serve as a tool for diagnosing underlying systemic and cutaneous disease.

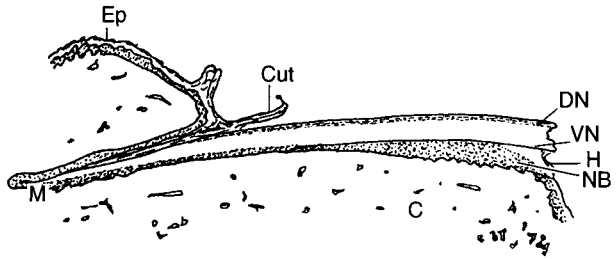

Figure 3.1. Schematic representation of human nail: DN—dorsal nail plate; NB—nailbed; C—connective tissue; Ep—epidermis; Cut—cuticle; M—matrix of dorsal nail plate; H—hyponychium; VN–ventral nail plate

DEVELOPMENT AND FORMATION

The earliest signs of fingernail development appear in the ninth week in utero. Skin folds and grooves begin to form at the distal end of the digits that will eventually define the structure of the nail unit. The first structure to appear is the matrix at week 11. By week 20 matrix cells exhibit adult keratinization. At the week 32 a hard nail plate is formed. At birth, a long thin nail plate which overhangs and curls over the distal digit that is present. This will quickly be wiped clear back to the hyponychium as the newborn infant gets cleaned. Fingernails and toenails develop by the same process; however, toenail development is slightly slower and about four weeks behind that of fingernails.

In the discussion of nail formation, one must look at each component of the nail unit and what it contributes.

The proximal nail fold is the wedge-shaped structure on the proximal edge of the nail unit. Its dorsal side differentiates to normal epidermis, while its ventral side differentiates to form the cuticle, which adheres to the dorsal surface of the nail plate.

The hyponychium is similar in that the distal portion contributes to the normal epidermis of the volar skin, while the proximal portion helps in adhering to the nail plate.

The matrix or lunula (visible matrix) differentiates to form the nail plate as we know it. It occurs by specialized tissue kinetics, as described by Zaias [2], who showed this in monkeys and rats by introducing a radiolabeled marker; this was later confirmed by Norton [3] in humans. These studies materially advanced our understanding of matrix kinetics. The matrix lies flat in the proximal nail unit. It produces a sheet of onychocytes (corneocytes), which grow diagonally along its entire length and move distally in a contiguous fashion. This development of multiple sheets of onychocytes eventually forms

the nail and produces the dorsal surface of the nail plate; the midportion of the matrix produces the midnail plate; and the distal portion produces the ventral surface of the nail plate. Based on this anatomical arrangement, it can be concluded that the thickness of the nail plate is directly related to the length of the matrix.

The nailbed epithelium differentiates both in an upward and a lateral motion. The upward growth produces specialized epithelium, which adheres in a special interconnecting manner to the developing nail plate, thus aiding in the adherence of the nail plate to the nailbed. The lateral growth is toward the distal edge and moves at the same rate as the nail plate formation. Other authors have suggested different theories of nail plate formation, included here primarily for historical reasons [4,5]. A disruption of any of the processes discussed earlier will produce specific diseases of the nail at specific sites, which will be discussed later.

HISTOLOGY, ULTRASTRUCTURE, AND COMPOSITION

The epidermis of the proximal nail fold is similar to the normal epidermis dorsally except that it is devoid of adnexa, while ventrally it produces the cuticle. The epidermis of the nailbed is similar to that of the skin, but has no stratum lucidum or stratum granulosum and no hair follicles or sweat glands. There is a unique arrangement of the dermal papilla and rete ridges, which form a parallel pattern in the nailbed and interconnect in a tight fingerprint-like pattern to the nail plate. The nailbed moves forward with the growth of the nail plate [2,3]. The epidermis of the matrix is thick and passes into the substance of the plate, which is formed by changes similar to keratinization in the epidermis; however, the end product is nail plate instead of stratum corneum. The appearance of the lunula probably reflects incomplete keratinization in the matrix just before incorporation into the nail plate [6]. The nail plate is made up of impacted and adhering layers of flattened cornified cells (dead onychocytes) that have lost their nuclei. The cells contain hard keratin, similar to that of hair (Chapter 2), with a high sulfur content mainly in the form of cystine, which comprises about 9–12% of the weight of the nail. The keratin fibrils are mainly oriented parallel to the nail surface from side to side. Nail contains about 7–12% of moisture and 0.15–0.76% of fat, a little more (1.38%) in infants. The composition of the nail plate varies slightly from the early in utero plate to that in adults. Baden [7] showed that water content of the nail plate is related to environmental relative humidity. Calcium constitutes about 0.02–0.04% of the weight and does not contribute to the hardness. Other trace elements have been detected and measured in nail clippings. The nailbed and matrix have a rich supply of blood from two arteries that run

laterally along the digits and form oxygen rich capillary beds, which lie below the nail plate [1,6].

RATE OF NAIL GROWTH

Nails, unlike hairs, grow continuously throughout life. The rate of growth of the nail plate is determined by the turnover rate of the matrix cells. Early measurement of the growth rate in undergraduates and schoolchildren were made by notching the nail about 2 mm from the margin of the lunula and recording its progressive displacement in each succeeding month. No differences were found within the age range of 19 to 23 years, no sexual difference, and only a very slight difference between hands, with growth on the right being faster. However, there were differences between fingers, growth being fastest on the third digit and least on the little finger. Bean [8] studied his own thumb for over 30 years and found growth to be faster during the second to third decades, followed by a slowing-down trend and then a leveling-out over time. The rate of fingernail growth varies between 0.5 and 1.2 mm per week. Fingernails grow faster than toenails. Family tendencies favoring similar growth rates have been noted, as well as increased growth during the summer and diminished growth in cold climates. After death nail growth ceases. Certain conditions affect the rate at which the nail plate grows. On average, it is higher in psoriasis, pregnancy, and nail-biting trauma. Regrowth is temporarily depressed in infective diseases, particularly in viral conditions such as measles or mumps, yellow nail syndrome, and starvation [1]. To replace a fingernail completely takes about 5–6 months; toenails require 12–18 months.

NAIL PATHOLOGIES

Abnormalities of structure and appearance of the nails are more than cosmetic. Many work hours are lost each year due to absenteeism of patients who suffer from nail disease. There are many causes of nail disease: genetic, infective, inflammatory, environmental, traumatic, secondary to systemic disease, and idiopathic. Only the most common conditions are discussed here, but readers may consult complete texts such as Scher and Daniel [6] for a comprehensive account of the various conditions that affect the nail unit.

Absence of Nails (Anonychia)

Complete absence of nails from birth, anonychia, is rare and appears to be associated in several ways with other hereditary defects. Absence of nails may be individual, multiple, or total in some congenital conditions. Loss of nail plate may occur with some inflammatory conditions such as lichen planus and irritant dermatitis to artificial nails, or secondary to trauma.

Nail Shedding (Onychomadesis)

Nails can be lost either by loosening at the proximal end or by separation from the nailbed. Shedding can follow trauma or severe illness or can be caused by drugs. More serious loss with scarring sometimes follows trauma, defective circulation, lichen planus, epidermolysis bullosa, or drug eruptions.

Nail Separation from the Nailbed (Onycholysis)

The separation of the nail from its bed is fairly common. There are many causes, but quite often none can be found. It may result from external damage both traumatic and self-induced, that is, overaggressive cleaning, fungal and yeast infections, acute and chronic dermatitis, or drug eruptions. Various conditions such as psoriasis, tumors, and many genetic disorders can also cause onycholysis [1,6]. Of particular interest are reports of onycholysis caused by cosmetic products [9,10] and the use of acrylic [11] or artificial nails that cause a contact or irritant dermatitis leading to nail separation [12]. Nail hardeners containing formaldehyde [9], nail varnish containing phenol, ultraviolet nail dryers [13], and similar agents have all been implicated. Once onycholysis is present it is not unusual for colonization by either a *Candida* sp. or *Pseudomonas* sp., giving the nail a yellowish or green color, respectively.

Brittleness

Brittle nails are among the most common cosmetic complaints. They tend to occur in advancing age. While sometimes they may be associated with some underlying conditions, no good data are available, and the cause is mostly not known. Environmental factors are certainly important. Nails are kept pliable by their moisture content, and long thin nails are especially susceptible to very dry climates. Frequent immersion of the hands in surfactant solution is conducive; some time ago it was believed that soaps and detergents removed the protective lipids from the keratin. The continuous use of nail varnishes and varnish removers has also been blamed [6]. Almost 60 years ago the reactions of 25 businesswomen to the same brand of nail lacquer were studied. It was found that although nearly half of them showed brittleness and splitting of the nails, the rest were unaffected. Thus there is no support for attributing nail brittleness to the use of conventional nail lacquers. Some investigators have reported improvement with gelatin, but no consistently effective therapy is known. Other researchers recommend avoidance of frequent immersion and nightly use of a hand cream.

Striations (Onychorrhexis)

Longitudinal striations are common in healthy nails and become more prominent with aging, and in lichen planus, psoriasis, and some other clinical or occupational conditions. More prominent longitudinal ridging is seen in

median nail dystrophy, which is attributed to habit tics (self-induced behavior). Regular transverse striations can occur as a developmental anomaly. Severe depressions, known as Beau's lines, indicate a period of severe systemic disease, such as measles, mumps, pneumonia, or coronary thrombosis; drugs may also induce inhibition of normal matrix production of nail plate.

Spoon-Shaped nails (Koilonychia)

In koilonychia or spoon nails, the nails are thin, soft, and concave in the center. The condition results from iron-deficiency, usually, but not invariably, associated with anemia. It can also be seen in onychomycosis and has been noted in motor mechanics, where perhaps it is due to softening with oils or soaps.

Splitting (Onychoschizia)

The splitting of nails horizontally, parallel to the nail plate, so that pieces of the surface break away, is very common in women and in advanced age. The main causes are probably repeated immersion in water and the use of nail polish and polish removers. The suggested treatment is to rub some moisturizer into the nail plate after bathing and avoid frequent use of nail polish and removers.

Pitting

Pitting of the nails is found most commonly in psoriasis. Pits represent punctuated or depressed sites in the nail plate secondary to irregular matrix production. They can vary in size, shape, depth, and number. They are the most common manifestation of nail psoriasis but can also be seen in chronic dermatitis, fungal infections, alopecia areata, Reiter's syndrome, and lichen planus.

Leukonychia

Leukonychia is complete or partial whitening of the nail plate and can be divided into acquired and congenital. Complete leukonychia occurs very rarely as an inherited abnormality; often epidermal cysts on the glabrous skin are associated with it. Partial leukonychia is very common and may take the form of white spots or white transverse streaks. It may be associated with many types of illnesses, exposure to chemicals, and traumatic events to the matrix. A white appearance of the nails is not necessarily due to leukonychia; it may result from changes in the nailbed, not in the nail plate.

Onychomycosis

Fungal infections of the nail unit are the most common conditions affecting nails. There are four distinct types of clinical presentation: distal subungual, superficial white, proximal subungual, and candidal onychomycosis: distal subungual is the most common type and has been shown to be an autosomal dominant inherited condition in the chronic dermatophyte syndrome. Proximal

subungual is a marker for HIV infection, and superficial white produces a white powdery appearance. Onychomycosis in which *Candida* sp. is responsible is seen in patients with mucocutaneous candidiasis syndrome.

Paronychia

Paronychia is defined as inflammation of the proximal or lateral nail folds or a combination of the two. Paronychia occurs after loss of the cuticle either by trauma or by aggressive cuticle trimming or cuticle pulling. It can be acute or chronic. Acute paronychia is caused by introduction of an infectious agent into the nail folds, usually through trauma, cuticle pulling, or exposure to an irritant agent. Chronic paronychia occurs over time due to continuous exposure to an irritative behavior, constant exposure to water from hand washing, or a specific contactant such as food items or chemical irritants.

Discoloration

Nails may be discolored for a wide variety of reasons. External causes include hair and other chemical dyes, smoking, and chemical compounds such as mercury salts, dithranol, and picric acid. Tints may leak out of nail varnish and after repeated use may penetrate the nail [14–16]. The use of artificial nails and either acrylic or preformed plates can cause discoloration. Abnormal formation or very slow growth of the nail can also produce color changes. Psoriasis and onychomycosis, among other abnormalities, cause opaqueness and a yellowish discoloration. In the 'yellow nail syndrome' the nails almost cease to grow and several months later become yellow or greenish. They may also be thickened and curved from side to side. Yellowish, green, or gray nails can also occur as growth of nails slows down in old age. Infection by *Pseudomonas aeruginosa* under the nail may cause a greenish, black, or blue discoloration. Systemic drugs can alter the color in many ways. Prolonged administration of tetracycline may occasionally turn nails yellow. Mepacrine or Zidovudine (AZT) makes them bluish black, and chloroquine may produce blue-black pigmentation of the nailbeds.

The pigmented discoloration or pigmented bands are the most important to distinguish. Although most pigmented bands seen in nails represent benign lesions, such as nevi or traumatic or splinter hemorrhages, one must always be suspicious of pigmented bands that are malignant, such as malignant melanomas. Any new onset or rapidly changing pigmented band in the nail should be evaluated by a dermatologist for possible biopsy. Early diagnosis can save serious sequelae of malignant melanoma.

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CHAPTER 4

Anatomy and Physiology of Ocular Tissue

INTRODUCTION

Cosmetics are designed not to contact the complex tissues required for vision. On the other hand, decoration of the orbital area and some exterior components of the eye with eye makeup is widely practiced. Safety of preparations used near the eye is the responsibility of formulators and is in part mandated by regulations. Nevertheless inadvertent introduction of makeup and other cosmetics into the eye is common, and compounders should be familiar with the structural components of eyes and how they might be affected by cosmetics. The major frontal (external) eye tissues are identified in Figure 4.1. Adverse eye responses might be the result of any type of cosmetic that may be used on the scalp or the face. Most readers are familiar with the stinging caused by accidental entry of traces of shampoo into the eye. Readers have also learned about the troublesome history of eye damage due to quaternary surfactants. The following brief review of eye physiology is intended to aid cosmetic formulators in the creation of safe products for use in and near the eye.

MAJOR ANATOMICAL FEATURES

THE EYELIDS

The lids of the eye are representative of skin elsewhere in the body. The major function of the lids is protection of the cornea and its avascular tissue. For this reason the inner surfaces of the lids are lined with conjunctival tissue, which is membranous in nature and in contact with both the precorneal tear layer

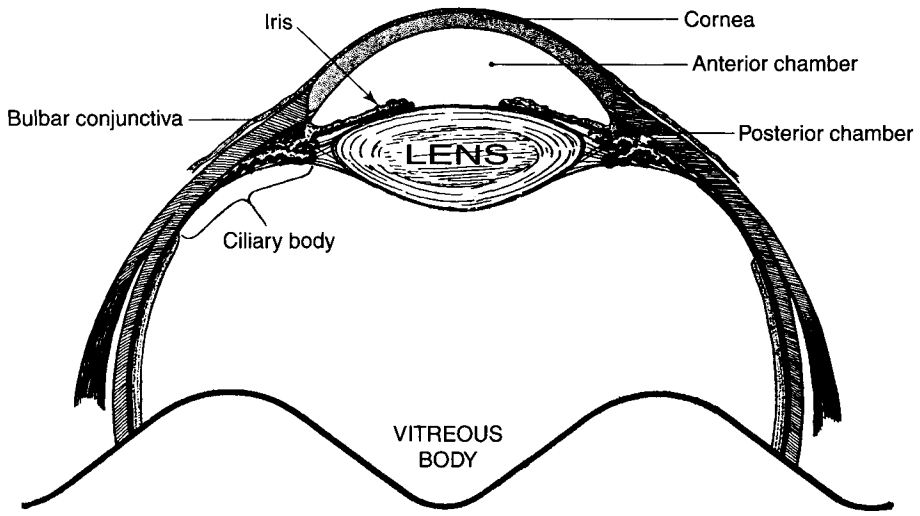

Figure 4.1. Schematic representation of the exterior portion of the human eye

and the epithelial cells of the cornea. The eye has both a superior and a inferior lid, with the functionality of both well defined to facilitate tear movement and drainage during the blink. The lids contain an inner tarsal plate, muscle fibers, and surface epithelium from posterior to anterior. The cilia exit from the middle portion of the lid margin inferiorly. Apocrine sweat glands, sebaceous glands of Zeis, and hair follicles of the surface hairs are represented in both lids.

The musculature and innervation is such that the superior lid moves reflexively inferiorly as the tear film begins to evaporate. In so doing, the margin of the lid dips into the tear lake, which is located at the inferior lid margin, and spreads a uniform tear film over the cornea as it sweeps superiorly. This tear film will remain in place between blinks despite the forces of the gravity working against it. Inferiorly the lid moves primarily in a lateral fashion, directing the tear pool to the nasolacrimal ducts located medially in both the inferior and superior lid margins. In this way the tear components produced by the meibomian glands, goblet cells, and lacrimal glands are spread across the cornea and drained by the action of the lids. Because of its similarity to skin elsewhere, the lids suffer from the same dermatologic problems. Differences arise in terms of the effect of cosmetics that are placed on a daily basis at the lid margins. Cosmetic preparations may lead to problems of the glands associated with the lid margin and result in corneal trauma, toxicity, and hypersensitivity. Such adverse events may be clinically observed as either a lid problem or a corneal problem, depending on the

etiology. Other effects on the corneal surface manifest themselves as a result of drainage problems that may occur in the lids, aging of the lids with flaccidity and incomplete blinking, blepharitis, and staphylococcal endotoxin affecting the cornea.

CONJUNCTIVA

The conjunctiva covers the outer surface of the eye (the scleral tissue) and is reflected to cover the inner eyelids. It is a flexible mucous membrane and is in constant motion with the action of the lids and movement of the globe. Functionally the conjunctiva provides protection and lubrication for the various ocular structures. It also contains lymphoid tissue for immunologic protection. Similar to all mucous membranes, the conjunctiva has an epithelial cell layer and a submucosal lamina propria.

Morphologically, the cellular structure of the epithelium differs by region. Stratified squamous epithelium is present on the lid margin and surrounds the limbus, the transition zone between the cornea and the sclera. The remainder of the tarsal conjunctiva and the conjunctiva in the fornices contain cuboidal basal cells, cylindrical superficial cells, and polyhedral cells between them.

Secretory goblet cells are found in abundance throughout the conjunctiva. They are most numerous over the tarsic and least numerous in the interpalpebral bulbar section of the tissue. Goblet cells are oval with flattened nuclei near the base and large intercellular collections of mucin.

The surfaces of the conjunctival epithelial cells are covered with microvilli and a thin coating of glycocalyx and mucin. This increases the surface area of the cells and aids in the adherence of the tear film to the tissue. In fact, the tear film should be considered to be anatomically a part of the tissue, as any disruption in this relationship leads to significant tissue pathology.

The epithelial cells are attached to a typical basement membrane by hemidesmosomes, which in turn maintain attachment to the conjunctival stroma. The conjunctival stroma consist of a lymphoid layer and a fibrous layer. The lymphoid layer contains a population of lymphocytes. Deeper than this layer is a fibrous layer through which the vessels and nerves supplying the tissues run.

The conjunctival tissue includes nerves, ciliary arteries, lymphatics, and two types of accessory lacrimal glands. Sensory innervation comes from the ophthalmic division of the fifth cranial nerve, similar to that of the lids. The only sensory modality is pain.

The conjunctiva derives its blood supply from the various branches of the ophthalmic artery. They supply the entire conjunctiva other than an area lying just beyond the limbus. The conjunctival capillaries are fenestrated. Under

conditions of inflammation this leads to leakage at a rate that exceeds the ability of the fluid to permeate the conjunctiva to the ocular surface. This leads to an accumulation of fluid and the clinical sign of conjunctival chemosis.

CORNEA

The cornea, also known as the window of the eye, is the transparent anterior portion of the globe. As the major refracting medium of the eye, the cornea must remain clear throughout life to allow the passage of light. Anatomically the cornea consists of five layers: the epithelium, Bowman's layer, the stroma, Descemet's membrane, and the endothelium. The cornea is avascular and devoid of lymphatics.

Epithelium

The epithelium is an approximately five-layer deep, stratified, nonkeratinizing layer, which is phenotypically distinct from the conjunctival epithelium. The superficial cells exhibit numerous microvilli and have an extensive fibrillar glycocalyx on their surface membrane. This network enhances the adherence of the tear layer to the cells. Tight junctions between cells serve as an anatomic barrier to substances penetrating the intercellular space. The deeply situated basal cells are mitotically active and rest on the basement membrane. The daughter cells move anteriorly toward the surface of the cornea.

Epithelial cells migrate centripetally toward the inferocentral cornea and toward the surface where desquamation occurs.

Beneath the basal layer lies the basement membrane, which along with its hemidesmosomes anchors the epithelium to the corneal stroma.

Bowman's Layer

Bowman's layer is an acellular zone of collagen fibrils which are densely arranged. Anteriorly Bowman's layer attaches to the basal epithelium and posteriorly transforms gradually into the remainder of the stroma. Bowman's layer acts as a barrier to corneal invasion and has poor regenerative capacity.

Corneal Stroma

The corneal stroma constitutes 90% of the cornea. It consists of collagen fibers, stromal cells, and ground substance. The collagen fibrils are regularly arranged in such a way that destructive interference of light prevents reflection, thus maintaining transparency. Type I collagen predominates, with types V and VI present in small percentages. Ground substances surrounding the collagen fibrils are proteoglycans. Glycosaminoglycan (GAG) side chains are primarily made up of keratan sulfate and chondroitin sulfate.

The keratocyte is the predominant cell in the stroma. These keratocytes maintain the collagen and extracellular matrix of the stroma. In response to injury keratocytes migrate to the site and transform into fibroblasts, creating scar tissue within the normally transparent stroma.

Descemet's Membrane

Descemet's membrane is the basal lamina produced by the endothelium. It is relatively easily detached from the stroma and regenerates rapidly after injury. In some pathologic disease states metallic substances are deposited in Descemet's membrane; adverse events affecting the endothelium may result in metaplasia of the membrane—resulting in thickening and irregular formations.

Endothelium

The endothelium lies posterior to Descemet's membrane and consists of a single layer of hexagonal cells. There is a gradual decrease in the number of cells throughout life. The endothelial cells do not regenerate, and, as cells are lost over time, adjacent cells increase in size to fill in the space. This leads to an increase in cell area with a decrease in density over time. Usually there are approximately 4,000 cells/mm^2 at birth and 2–3,000/mm^2 in the adult cornea. Generally, cell loss beyond 600/mm will result in significant functional impairment.

The Tear Layer

The tear layer may be considered as an integral necessity for the survival of the corneal tissue. Without it the corneal surface and subsequently all of the corneal layers become compromised. The precorneal tear film provides lubrication to the surface and is necessary for the health of the tissue. It consists of three layers: the outermost lipid layer, the middle aqueous layer, and the innermost mucin layer. The lipid layer is derived from the secretions of the meibomian glands at the lid margins; its major function is to inhibit evaporation. Chemically, meibomian lipid resembles the sebum of skin.

The middle layer is derived from the main and accessory lacrimal glands. It is the thickest part of the tear film and contains electrolytes, proteins, glucose, urea, enzymes, immunoglobulins, and complement. Also present in the epithelium, the limbal vasculature and conjunctival lymphoid tissue are lymphocytes, polymorphonuclear neutrophils (PMNs), and desquamated epithelial cells.

The innermost layer is mucin, which coats the epithelial surface and is derived from the goblet cells in the conjunctiva. The mucin reduces the friction between the epithelial surface and the tear film, thus facilitating the uniform spreading of the tears. It also reduces friction between the cells and the lid during the blink.

CORNEAL TRANSPARENCY

The major function of the cornea is to maintain transparency and facilitate the refraction of light. Ultimately the light must reach the retina and be delivered via the optic nerve to the occipital lobe of the brain. To make this happen, all of the layers of the cornea act in concert to maintain transparency. Major nutrients required by the epithelium are glucose, oxygen, vitamins, and amino acids. Most of the glucose is derived from the aqueous humor, which is in contact with the endothelial layer.

Oxygen for the most part is derived from the atmosphere, diffuses through the tear layer, and is used mainly by the epithelial and endothelial layers. Thus at night with the lids closed, the oxygen partial pressure drops, and physiologic edema ensues. This is exacerbated with those types of contact lenses that are worn overnight and which do not have enough oxygen permeability to maintain the partial pressure encountered at night with no lens in place. Typically corneas swell overnight from 2.5% to 4% with rapid return to baseline soon after awakening. With a typical soft contact lens in place, even those currently approved for "extended wear," the swelling on awakening is 9–12%. Adverse effects of corneal hypoxia cannot be clearly differentiated from problems due to access of eye makeup to this site. Recent findings have indicated that bacterial adhesion to epithelial cells exposed to contact lens–related hypoxia is significantly increased.

Control of stromal hydration is critical in maintaining clarity of the cornea. The stroma has physiologic tendency to imbibe water, which accounts for 78% of the weight of the cornea. The endothelium is responsible for active dehydration through an active transport mechanism. The epithelium passively prevents water from entering the stroma through a barrier function. There appears to be evidence for active ion transport in the epithelium. The epithelium secretes chloride into the tears resulting in active transport of Na^+ and Cl^- into the cells. Along with the active systems evaporation of water from the tear film results in hypertonicity, thus drawing water from the stroma to the corneal surface. On average the cornea is 5% thinner during the day because of this effect.

TOXIC AND ALLERGIC REACTIONS

Due to its sensitivity, the cornea is an excellent marker for biological activity, which can be seen clinically in a relatively short period of time. Toxic and allergic reactions in the eye will affect the lids, the conjunctiva, and the cornea, depending on the challenge. All, however, are readily seen using common ophthalmic equipment. Toxic and allergic conditions as a result of topical

application of drugs, cosmetics, or preservatives are extremely common in ophthalmic practice. Toxicity is the result of direct application and subsequent irritation of ocular tissue by chemical entities. Allergy, on the other hand, requires sensitivity of the host and subsequent immune reaction manifested by clinical signs of inflammation.

Toxicity generally occurs as a result of repeated use of a substance in contact with the epithelial cells of the cornea and conjunctiva. Use of sodium fluorescein or rose bengal make this response clinically detectable at an early stage as a result of the dye staining of chemically insulted epithelium. Keratoconjunctivitis sicca (dry eye) and prolonged use of offending chemical substances predispose to such toxic reactions.

Allergic contact dermatoconjunctivitis is commonly seen in clinical practice. Allergic contact reactions occur after sensitization of T cells and represent delayed hypersensitivity. Topical chemicals act as haptens and need to interact with tissue proteins to form complete antigens and sensitize lymphocytes. This delayed reaction can take as little as a week or as long as years to develop. If the offending agent is a cosmetic being applied to the tissue, the eczema occurs first wherever the hapten happens to be applied. Secondary infection is common, usually by staphylococcal or streptococcal species, with candida being less likely but a possibility. Preexisting skin lesions will make contact allergy more likely to occur even with substances known to be poor sensitizers. Other reactions that may ensue and are peculiar to the eye are phototoxic and photoallergic reactions. These are generally the result of interactions between light and chemicals being used in or on the eye. The use of systemic drugs for infections or other conditions may also make certain patients more susceptible to dermatokeratoconjunctivitis and should be considered in reactive cases.

COSMETICS AND THE EYE

Cosmetics around the tissues of the eye are probably among the most commonly used substances in society today. The testing of cosmetics depends in principle on standard toxicological in vitro and in vivo techniques. Unfortunately these do not predict with any certainty the response of the human eye to chronic application of these chemicals. As described previously, the eye is a complex structure with both vascular and avascular tissues, a complex tear layer that is essential for ocular function, and external skin to protect these structures. The use of cosmetics and any other chemical in or around the eye can produce any number of pathological changes that may result in either acute or chronic events on any of the various structures.

These effects may be exacerbated if there is underlying disease and must be considered when evaluating the cause of any problems that may or may not be related to the cosmetic being used. The use of cosmetics and how they are applied and the chemicals and preservatives being used in them may elicit any of a wide variety of responses. These include trauma, toxicity, and hypersensitivity. These reactions may be found in any of the specialized ocular structures including the cornea, the conjunctiva, and the lids. Fortunately the clinical instrumentation and laboratory tests that are available in clinical practice should make differential diagnosis with respect to etiology reasonably certain. Thus the relative contribution with respect to the cosmetic being used can be determined and appropriate treatment undertaken. In most cases this will simply mean the removal of the offending chemical and a switch to one less troublesome to the patient. There is a significant population wearing contact lenses, and these people should be apprised of the relative risk of using both contact lenses and cosmetics. Contaminated cosmetics trapped underneath a contact lens with less than desirable oxygen transmissibility, reduced tear exchange, or the presence of an epithelial abrasion could place the patient at high risk for infectious keratitis. Incorrect application of the cosmetic could damage the surface of the contact lens, making it more likely to cause tarsal conjunctival problems.

All of these are important issues that the physician should be aware of in light of the widespread and for the most part problem-free use of cosmetics. The tissues of the eye, however, are an effective barometer for the biological compatibility of cosmetics. This is primarily due to the complex interrelationships that exist and the sophisticated methodology available for clinical evaluation.

RECOMMENDED READING

Newell, F.W., *Ophthalmology: Principles and Concepts*, 8th edition, Mosby Yearbook, 1996.

Davson, H., *Physiology of the Eye*, 5th edition, McGraw-Hill, New York, 1990.

Kanski, Jack J., *Clinical Ophthalmology*, 3rd edition, Butterworth Heinemann, New York, 1994.

CHAPTER 5
The Mouth and Oral Care

INTRODUCTION

While much of cosmetic chemistry and formulation is directed at maintaining or enhancing the appearance of the external surface of the body, the formulator of products for use in the human mouth must consider a more complex set of issues. Many oral care products address multiple consumer concerns at once, and it is common for an individual product to deliver both drug and cosmetic benefits. Understanding critical elements of oral biochemistry and microbiology will greatly help the formulator design products to deliver these benefits.

In addition to presenting some fundamentals of oral anatomy, physiology, and microbiology, this chapter will focus on the biology behind a variety of oral care consumer needs, the health and cosmetic problems behind these needs, and some approaches to solving these problems that can be introduced into oral care cosmetic or over-the-counter (OTC) drug products. Some of these concerns are summarized in Table 5.1.

THE TEETH AND THEIR SURROUNDINGS

The oral cavity contains the teeth, tongue, cheeks, palates, and gums (gingival tissues), and is bathed in saliva. The teeth and gums are major sources of consumer concerns, many of them related to dental plaque and other tooth deposits. However, oral care needs arise in other parts of the mouth as well. The following provides an overview of the biology of the oral cavity.

THE TEETH

The normal human dentition consists of 20 primary ("baby") teeth, which erupt from six months to four years of age, starting with the incisors, and are

Table 5.1

Consumer needs	Underlying problems	Functional solutions
	"Cosmetic" Indications	
• Attractive teeth/"bright smile"	• Dental stain/discoloration • Potentially unsightly dental deposits	• Tooth stain removal/prevention • Tooth whitening • Plaque/calculus reduction
• Fresh breath	• Intrinsic/extrinsic oral malodor	• Antimicrobial malodor prevention • Malodor masking/neutralization
• Fresh/clean mouth feeling	• Food/microbial residues (?)	• Flavorants, astringents, remove dental deposits(?)
• Clean mouth • Uncomfortable dental visits	• Dental plaque, calculus, stain • Uncomfortable dental cleaning to remove calculus or stain	• Plaque/calculus reduction • Stain reduction/prevention
• Dry mouth	• Insufficient saliva flow or altered saliva composition	• Lubricating/moisturizing rinses or gels • Artificial salivas
	"Drug" Indications	

• Healthy teeth/strong teeth	• Dental decay	• Decay prevention
		  • Fluorides
		• Aid salivary function
		  • Remineralization
		  • Saliva stimulation
		  • Plaque acid reduction

• Healthy gums	• Gingivitis • Periodontitis (*not* an OTC indication)	• Plaque/gingivitis reduction and prevention
• Sensitive teeth	• Exposed, hypersensitive dentin	• Tooth desensitization
• Oral comfort	• Ulcers of the oral mucosa (e.g., canker sores)	• Topical anesthetics • Antimicrobial agents

replaced by 32 secondary (adult) teeth, starting with incisors at about six years of age and culminating with the third molars ("wisdom teeth"), which erupt (in people who have them) around 20–21 years of age. Tooth makeup and form are influenced by genetics, the preeruptive environment (notably nutrition), and the posteruptive environment. Dental anatomy and alignment as well as

individual oral care habits and salivary chemistry can have a profound effect upon the quantity, quality, and pathogenicity of the dental deposits that form on the teeth. Different parts of the tooth exhibit markedly different structure and characteristics, which make them prone to different types of problems.

Tooth Anatomy and Structure

Teeth are divided into two types: the crown (the enamel-covered part of the tooth that extends into the mouth) and the root, which is normally held firmly in place by the bone of the upper and lower jaws (Fig. 5.1). Tooth crowns are covered by dense, hard dental enamel, the hardest tissue in the body. Enamel is thickest at the tip of the tooth and tapers to its thinnest point at the cemento-enamel junction (CEJ), where the crown gives way to the tooth root, which is covered by a thin mineralized layer called cementum. Underlying the enamel and cementum is a less dense mineralized tissue (dentin) that surrounds the dental pulp, which is rich in nerves and blood vessels. In most individuals, the teeth are closely spaced and often touch side-to-side; the spaces

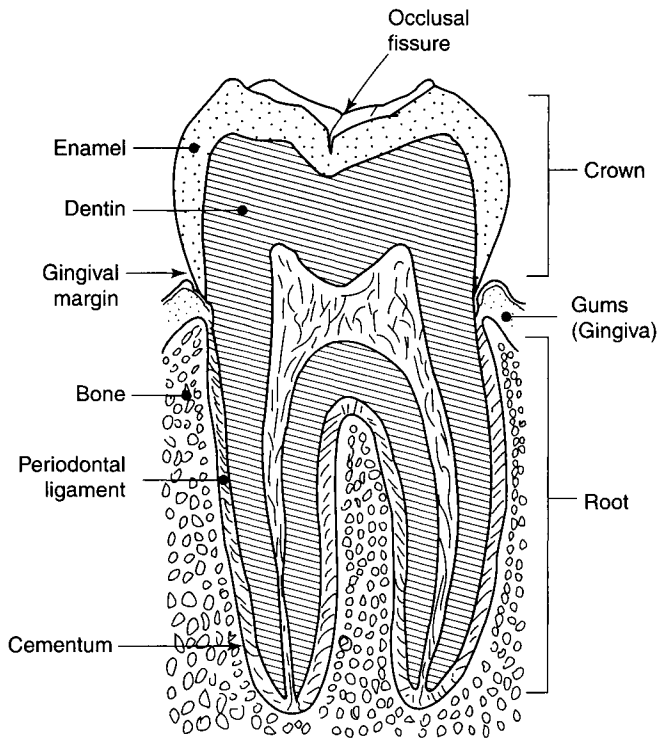

Figure 5.1. Simplified sketch of tooth anatomy

between the teeth are referred to as interproximal spaces. The tooth roots are held firmly in place in the jaws through periodontal ligaments. In normal healthy teeth, the gums surround the teeth and come to an apex just above the CEJ, so that the roots are not exposed to the oral cavity. The physical shape of teeth varies with tooth type, from the chisel-shaped incisors to the blocky molars, which often have pits and fissures on their biting surfaces. As discussed later, tooth shape can have a profound effect on processes that can lead to various dental problems.

Dental Enamel

Dental enamel is composed mainly of a partially carbonated form of the calcium phosphate mineral hydroxyapatite [$3Ca_3(PO_4)2.Ca(OH)_2$], which accounts for about 98% of its composition. Minor amounts of collagen-like protein, remnants of the organic matrix mineralized during tooth development, also remain in the enamel structure. Hydroxyapatite is capable of ion exchange, and anions such as F^- and CO_3^{2-} may replace the OH^- group, while cations such as Zn^{2+}, Sr^{2+}, and Mg^{2+} may replace Ca^{2+}. Caries susceptibility may be influenced by this ion exchange; for example, the extent to which OH^- has been replaced by F^- has a protective effect on the vulnerability of the enamel to acid demineralization. The hydroxyapatite, of which enamel is largely composed, is present in the form of crystallites which make up rods oriented at right angles to the surface. Water and selected ions can penetrate a small distance into the dental enamel surface along the plane of the crystallites, which can facilitate ion exchange.

As with all calcium phosphate minerals, dental enamel is soluble in acid. A substantial body of data indicates that tooth mineral is highly stable above a pH level of approximately 5.5, referred to as the "critical pH," and that tooth demineralization occurs when the pH falls below this critical level. The extent of enamel solubility is determined largely by the amount of acid present (measured as pH), the duration of exposure to acid, the amount of soluble calcium and phosphate ions in the fluid bathing the enamel, and the presence of other ions that influence the balance between mineral dissolution and crystallization. Thus the concept of "critical pH," while useful, should not be considered to be an absolute value.

Dentin

The layer of material beneath tooth enamel and cementum is the dentin. It contains approximately 70% hydroxyapatite, with the balance of its composition being collagen. Unlike the structure of enamel, which is characterized by densely packed crystals, the dentinal matrix is perforated by a number of tiny, fluid-filled canals (dentinal tubules) that radiate from the pulp cavity to the surface. Dentin can be exposed to the oral cavity through damage to the

enamel or gingival recession and wearing of the cementum (the mineral layer covering the dentin of the tooth root). The presence of open dentinal tubules can lead to hypersensitivity, in which the exposed dentin may be painfully sensitive to various stimuli, including heat, cold, pressure, sugar, acid, and so forth. This is discussed in more detail later in this chapter.

Dentin, like enamel, is also acid-soluble. Because it has less mineral content, and possibly because its structure more readily permits penetration of bacteria and acid, exposed dentin is generally believed to be more susceptible to decay than enamel. This explains the rapid advancement of dental decay after it penetrates the enamel layer and the vulnerability of exposed tooth roots to decay.

THE GUMS

The gums (gingival tissue) surround the teeth and overlie the bony structure in which the teeth are anchored. In health, the gum tissues directly adjacent to the teeth (the gingival margin) are firm and pink, extend just above the CEJ, and form a crevice that is not more than 3 mm deep. If dental plaque is permitted to accumulate adjacent to the gingival margin and within the gingival crevice, the gum tissue can become irritated, inflamed, and liable to bleeding. In some cases this inflammatory state stabilizes as chronic gingivitis, while in other cases the inflammation can advance to the destructive disease periodontitis.

ORAL FLUIDS

Saliva

Saliva is a major factor in the maintenance of a healthy mouth. Saliva is continuously being produced, bathing teeth and oral tissues in a dynamic environment that serves to lubricate the mouth, remove harmful materials from the oral environment, and maintain the mineral balance of the teeth.

Saliva is produced by three pairs of major glands and the smaller glands of the oral mucosa (labial, lingual, buccal, and palatal). The secretions differ from one another in composition and may also differ according to the rate of flow, time of day, and so forth. For instance, it is well known that salivary flow is reduced at night; this makes it extremely important to cleanse the teeth between that previous midnight snack and going to bed, as the protective effects of saliva are substantially reduced during sleep.

Saliva contains mucopolysaccharides, proteins, enzymes, and inorganic materials such as calcium, sodium, potassium, chloride, bicarbonate and phosphate ions, and bacteria shed from the oral surfaces and a variety of their constituents. The organic constituents of saliva are thought to be responsible for the development of the acquired dental pellicle (as described later). The presence of calcium and phosphate ions and the bicarbonate buffer system are

believed to be significant both in the control of dental caries and in calculus formation. The pH of resting saliva ranges from about 6.5–7.2, while that of stimulated saliva can range up to about 8.0; the pH increase reflects a higher bicarbonate content in simulated supply.

The importance of saliva in preventing tooth decay following eating was demonstrated in the 1940s by R.M. Stephan. He devised a miniature pH electrode from antimony and used it to determine the pH of dental plaque at various sites on the teeth. His experiments showed that the pH of dental plaque decreased rapidly from about pH 6.82 to about pH 5 within a few minutes after consuming a sugar challenge and slowly returned toward neutrality over the next 20 to 60 minutes. If saliva flow to the teeth was restricted, the pH would remain depressed below the critical pH for enamel demineralization for much longer periods. The importance of saliva in maintaining oral pH may partially explain why an inadequate flow of saliva resulting from head and neck irradiation, drug-induced hyposalivation, or pathology can result in increased caries susceptibility and other oral problems.

Gingival Crevicular Fluid (GCF)

GCF exudes from the epithelium within the gingival sulcus or pocket. It is more similar to blood plasma than to saliva and can serve as a source of nutrients to the bacteria growing within the sulcus and along the gingival margin; it can also carry a variety of specific and nonspecific host defense factors.

THE ORAL SOFT TISSUES

The oral soft tissues consist of the tongue, gums, cheeks, hard and soft palate, and sublingual region. The oral soft tissues are covered by a variety of nonkeratinized and keratinized epithelia. The surface of the soft tissues, most notably the tongue, can harbor large populations of oral bacteria that can serve as a reservoir to recolonize the teeth after cleaning. The microbial flora of the tongue can also play a prominent role in the generation of oral malodor (bad breath). Additionally, certain oral soft tissues are prone in some individuals to develop painful sores or ulcers, for example, aphthous ulcers (canker sores), which are addressed at greater depth later in this chapter.

DENTAL DEPOSITS

As soon as a tooth erupts into the mouth, and subsequently after every cleaning, it is prone to coverage with a variety of dental deposits that can cause diverse conditions that concern consumers. The enamel of a freshly cleaned tooth is rapidly covered by a pellicle of proteins adsorbed from saliva, followed by

salivary bacteria that form dental plaque. Dental plaque bacteria can, under certain conditions, release by-products that can be harmful to the teeth or gums. Dental pellicle and plaque are also liable to accumulation of stain and neutralized deposits (dental calculus or tartar).

Dental Pellicle

Immediately after cleaning, the enamel surface is covered very rapidly by a 1–3 μm thick film of proline-rich phosphoproteins, peptides, and glycoproteins absorbed from the saliva; thus the presence of a truly "clean" enamel surface in the oral environment is a fleeting phenomenon. The adsorption of salivary peptides and proteins appears to be relatively specific, starting within minutes of a tooth cleaning and continuing for several hours. While the acquired enamel pellicle is free from bacteria, it has been shown to contain a variety of bacterial constituents including enzymes such as glucosyltransferase, soluble polysaccharides, and various bacterial cell wall constituents.

Dental Plaque

Dental plaque has been recognized for centuries as a sticky film that forms on the teeth and has been the subject of concern as far back as the ancient Greeks. Over the years, the composition of dental plaque was thought to consist of food debris, mucus, denatured saliva, or "evil humors." It was Anthony van Leeuwenhoek, the inventor of the microscope, who first observed "tiny animalcules" (bacteria) in dental plaque in 1677. Around 1895, W.D. Miller established quite convincingly that dental plaque contained bacteria that could form acids from foods and that the acids could dissolve tooth enamel. This chemoparasitic theory of dental disease evolved to the belief that the way to control dental disease was to eliminate dental plaque, if not all bacteria, from the mouth. However, it was not until the 1960s through the 1980s that oral microbiologists started to understand the complexity and sequence of dental plaque and how it contributes to oral health and disease. Understanding the ecology of dental plaque and its effect on the character and pathogenicity of the plaque flora can provide strong insight into how a healthy balance with our natural oral flora can be established.

A central concept in our understanding of dental plaque and its pathogenicity is that plaque is actually a complex and heterogeneous microbial biofilm that varies substantially from site to site within the mouth, changes in nature over time, and is sensitive to a number of ecological parameters that can affect both its quantity and its quality. Dental plaque grows in an ordered manner, starting with the attachment of certain classes of bacteria (Gram-positive cocci) to the salivary pellicle through a set of relatively specific binding reactions similar to the interaction of antigens and antibodies. In general, these early colonizers are not associated with dental disease. Further plaque

accumulation is a process combining growth of the early colonizers, elaboration of a sticky extracellular matrix that helps the bacteria adhere to the teeth and each other, and attachment and proliferation of additional bacterial species. Just as a plowed field can over time undergo succession from bare soil to grasses and weeds to shrubs to various species of trees, culminating in a mature forest, dental plaque changes and becomes more complex over time. While the initial colonizing bacteria on smooth tooth surfaces are generally tolerant of oxygen and relatively nonpathogenic, later colonizers (especially in the region along the gumline and between the teeth where plaque tends to be thickest) become much richer in oxygen-intolerant anaerobic bacteria that can be associated with gum disease. In contrast, the microbial flora of tooth sites with reduced access to saliva (e.g., in the pits and fissures of the molars or in the interproximal spaces where teeth are tightly pressed together) can become dominated by bacteria that are relatively resistant to acid and can continue to produce acid at levels that can lead to tooth decay. The importance of particular populations of oral bacteria to oral problems such as dental decay, gum disease, and oral malodor will be discussed in more detail later.

For further reading on dental plaque formation and ecology, its relation to disease, and strategies for controlling its pathogenicity, see the reviews by Burne and by Marsh et al. [1,2].

Dental Calculus

The term *tartar* was commonly used to describe the mineralized deposits formed on neglected teeth. The origin of the term was derived from the similarity of mineralized dental deposits to the crystalline deposits formed in wine. The most common term in use is *calculus*. It may occur both above (supragingival) and below (subgingival) the gumline. Although these two forms of calculus may differ somewhat in composition, they both appear to originate from the mineralization of dental plaque bacteria and extracellular matrix.

Dental calculus varies in composition but always consists of about 80% of inorganic material containing calcium, magnesium, phosphorus, and other elements. The calcium and phosphorus are present in early plaque as Brushite ($CaHPO_4 \cdot 2H_2O$) and octacalcium phosphate [$Ca_8(HPO_4)2(PO_4)4$]. Whitlockite [$Ca_3(PO_4)_2$] may also be found, but the ultimate stage is probably apatite [$3Ca_3(PO_4)_2 \cdot Ca(OH)_2$]. This transition, which is also characterized by increasing mineral hardness and tenacity, is helped by the presence of fluorine, which is present in calculus to the extent of about 400 ppm. The remaining 20% of calculus is an organic matrix containing carbohydrate, protein, lipid, and bacteria and their constituents.

Calculus is first observed when the plaque on the enamel surface begins to mineralize. Today the most generally accepted explanation is that calculus is formed by a seeding mechanism, followed by calcium phosphate crystal growth and maturation. Rates and amounts of calculus formation can vary widely among people and within the mouth. This is probably due to a variety of factors, including salivary chemistry, local pH, plaque accumulation, and oral hygiene.

MAJOR ORAL PROBLEMS AND THEIR REMEDIES

OVERVIEW

The major oral care problems that concern consumers can be broadly categorized as medical or cosmetic, although some conditions may fall within both categories. Medical concerns for oral health include dental decay and gum disease (both associated with distinct pathogenic dental plaque floras), dental hypersensitivity, and dry mouth. Cosmetic concerns include dental staining and tooth whitening, oral malodor, and dental calculus. Some of these problems are widely distributed in the population worldwide, while others are less common.

DENTAL PLAQUE

Dental plaque is not actually a problem, as it is ubiquitous in individuals exhibiting both dental health and dental disease. However, as discussed earlier, certain populations of microorganisms in dental plaque exhibit characteristics that play a major role in the causation of dental decay and gum disease. It is important to remember that the pathogenicity of dental plaque is related not only to its mass but also to relatively specific classes of microorganisms. For instance, individuals with active dental decay tend to harbor higher populations of plaque bacteria that can produce and tolerate higher levels of acids, which are responsible for the destruction of tooth enamel. In contrast, dental plaque associated with gum disease tends to be highly populated with anaerobic Gram-negative bacteria that produce toxic substances such as volatile sulfur compounds, short-chain fatty acids, or bacterial toxins. These substances may directly damage or irritate gum tissues or might cause an inflammatory response that can lead to pathological changes in the gum tissue. In many cases the microbiological character and pathogenicity of dental plaque can be markedly modified by behaviors, such as oral hygiene or dietary habits, which can have a profound influence on plaque ecology and the rise or control of pathogenic microbial communities in the plaque.

DENTAL CALCULUS

It has been recognized for some time that there is an association between the presence of calculus and the incidence of periodontal disease, although enthusiasm for this concept waned considerably in the middle part of the twentieth century. The commonly accepted theory is that calculus irritates the gingival tissues and encourages the formation of a pocket between tooth and gingivae, in which food debris and bacteria may lodge. However, dental calculus is considered a cosmetic issue. Even in the absence of concern regarding pathogenicity, consumers have reason to care about controlling calculus. Its accumulation can be unsightly, and it is a frequent cause for uncomfortable visits to the dentist that are required for its removal from the teeth.

While mechanical treatment by a dental professional is the only means of removing calculus, it is possible to prevent or slow its formation by a number of physical and chemical means. Mechanical plaque control (i.e., brushing and flossing) can be very effective in reducing calculus formation by removing the plaque matrix required to initiate calculus calcification. For those individuals who require additional assistance in calculus control, there are a variety of oral care products, primarily toothpastes, that contain agents that inhibit calcium phosphate crystal growth and thereby calculus formation. The most common agents in tartar control toothpastes are pyrophosphate and zinc salts such as zinc citrate, although there are a variety of other calculus-inhibiting compounds in products and in the patent literature. At present there is one tartar control mouthrinse on the market, which uses zinc chloride as the antitartar agent. The current mechanism of action of anticalculus agents is thought to lie in their ability to interfere with the initiation or maturation of calcium phosphate crystals, resulting in less mineral mass and a less mature mineral structure that is softer and more easily removed by mechanical scaling. For further reading on dental calculus formation and control, see the reviews by Ciancio [3], Mandel [4], and White [5].

DENTAL CARIES (TOOTH DECAY)

Dental caries, commonly known as tooth decay, is a disease that is widely distributed worldwide and is associated with more frequent consumption of foods containing sugars or refined starches. Tooth decay used to be considered a disease of children, especially in affluent societies with plentiful access to sugary foods, since most tooth surfaces became decayed by early adulthood. In recent years, preventive measures such as water fluoridation, the use of fluoride toothpastes, and the placement of occlusal sealants has resulted in very significant reductions of childhood caries. While these reductions in tooth decay

may carry over into adulthood, an intact tooth surface is at risk throughout the life of an individual, and adults must also pay attention to caries prevention.

Dental decay occurs as the results of tooth demineralization by acids produced during carbohydrate fermentation by dental plaque bacteria. It is interesting to note that consumption of carbohydrates always results in the production of plaque acids but does not always result in tooth decay. This is because saliva can often neutralize and wash away plaque acids and deliver calcium and phosphate salts to remineralize enamel before irreversible damage is done to the tooth structure. Tooth decay occurs only if the magnitude and frequency of carbohydrate consumption cause decreases in plaque pH of magnitude and duration sufficient to overcome the natural reparative power of saliva.

Enamel decay usually starts in small circumscribed areas and spreads beneath the intact tooth surface. Early carious lesions, frequently referred to as "white spot" lesions, are characterized by a thin layer of intact dental enamel overlying partially demineralized dental enamel. A critical feature of these incipient lesions is that under the right conditions they may be reversed or arrested by the process of remineralization. This process is significantly enhanced by the presence of fluoride and extra calcium and phosphate ions in saliva and plaque fluid.

If the acid challenge is great enough in both magnitude and duration, the demineralization penetrates deeper into the enamel and spreads within it, roughly assuming the shape of a cone with its apex orientated toward the dentino-enamel border and the base still below the enamel surface. The lesions may still be reversed by conscientious use of fluoride or other remineralizing strategies. At this stage of the process there still may be no visible break or cavitation evident on the enamel surface. It is generally accepted that the dentin begins to demineralize or soften before an actual cavity becomes visible. Gradually the tissue softens sufficiently so that it breaks. At this point, the carious lesion becomes a cavity and can no longer be repaired by natural means, requiring restoration by a dentist.

Control of Caries

Reduction of Fermentable Carbohydrate Intake and Removal of Fermentable Debris from the Mouth. A very large body of clinical and experimental evidence implicates the consumption of fermentable carbohydrates, especially sucrose, as a major causative factor in tooth decay. Reducing the consumption of fermentable carbohydrates, most especially reducing the frequency of intake, can markedly lower caries risk. A major cause of this reduction is almost certainly a decrease in the magnitude and duration of acid formation by dental plaque, permitting more effective remineralization by saliva. Any

action that accelerates removal of fermentable food residue from the mouth, such as rinsing and brushing of the teeth, can also shorten the duration of acid attack. Furthermore, a substantial number of studies indicate that stimulation of salivary flow by chewing a nonacidogenic substance such as sugarless gum can also accelerate the removal of fermentable residue and increase the rate of salivary buffering in the mouth. For further reading on the impact of diet and eating patterns on dental caries, see the review by Geddes [6].

Reduction in Bacterial Activity and Plaque Pathogenicity. Bacteria present in the mouths of most individuals will ferment carbohydrates, especially sugars, causing a pH drop to levels ranging from about 5.5 to under 4.5, below the critical pH for enamel demineralization. This fall in pH is represented by the classic Stephan curve, which can be reproduced in vitro and in vivo. Certain microorganisms, including *Lactobacillus acidophilus* and *Streptococcus mutans*, have been identified as specific caries causative pathogens. These microbes are particularly effective at producing acid and are particularly resistant to acid environments, which can lead to their domination in precarious and carious dental lesions. Thus practices that reduce the amount and duration of plaque acid production, such as less frequent snacking, may also produce reductions in these particularly cariogenic plaque bacteria. There is also evidence suggesting that some substances such as fluoride, chlorhexidine, or the sugar substitute xylitol may inhibit the metabolism of cariogenic plaque bacteria.

Tooth decay tends to occur more frequently on regions of the tooth that have relatively restricted access to saliva (e.g., in the pits and fissures on the tops of the teeth, or between the teeth) or on areas of exposed dentin, such as exposed tooth roots, which are more acid-soluble than tooth enamel. Thus measures that decrease bacterial access or accumulation to these restricted areas, such as placing occlusal sealants or flossing between the teeth, can substantially reduce their susceptibility to dental decay. There is also some evidence that placing occlusal sealants not only reduces caries but also may help reduce overall risk of dental caries by eliminating sites that are the primary ecological niches for *S. mutans* and other acid-tolerant, potentially cariogenic bacteria.

Decrease of Susceptibility of Tooth to Acid Attack

It is clear that fluoride ions decrease the acid solubility of hydroxyapatite; the two strongest hypotheses for this protective effect are that fluoride may ion-exchange with the hydroxyl group in hydroxyapatite to produce more resistant fluorapatite, and fluoride ions present during acid challenge may decrease solubility at the enamel surface. This effect on enamel solubility may be a principal mechanism by which water fluoridation and fluoride-containing toothpastes

and mouthwashes exert their effect. In 1952, it was established in the United States that there was an inverse relationship between the incidence of caries in children and the fluoride content of the local water supply, and subsequent clinical and public health studies have firmly established the value of water fluoridation as a safe and effective way of reducing dental decay. In the 1950s, fluoride toothpastes were introduced in the United States and are now available worldwide. A substantial body of experimental and clinical data clearly supports the highly significant clinical value of fluoride dentifrices and mouthrinses in the prevention of dental decay. The most common sources of fluorides used in oral care products are sodium fluoride, stannous fluoride, monofluorophosphate, and amine fluoride (amine fluoride is not approved for use in the United States). Anticaries fluoride products are regulated as drugs; in the United States, requirements for active ingredients, specifications, and testing of anticaries drug products for OTC human use are detailed in a final monograph (21 CFR Parts 310, 355, and 369, and Docket No. 80N-0042).

Remineralization

An additional approach to reducing dental decay is promoting the remineralization of dental enamel. As stated earlier, dental plaque acids act to dissolve dental enamel, and this is counterbalanced by the remineralizing action of saliva. Increasing the oral concentration of ions that enhance this reparative process may substantially reduce dental decay. Fluoride is well known to increase the rate of remineralization and the resistance of dental enamel to subsequent acid attack. A growing body of work suggests that increasing levels of available calcium may also increase the rate of remineralization. Approaches to increasing orally available calcium include methods as diverse as using two-phase systems to promote the deposition of calcium fluoride on the tooth surface and the use of calcium- and phosphate-rich milk proteins to speed remineralization. Currently additional remineralizing strategies to reduce dental caries are still under development. One issue that is still unclear is the potential effect of aggressive remineralizing strategies on the rate of dental calculus formation, which would be an undesired side effect.

For additional reading on dental caries prevention, see the reviews by Bowen [7], Edgar et al. [8], and Mandel [9].

PERIODONTAL DISEASES (GINGIVITIS AND PERIODONTITIS)

Teeth are attached to the basal bones of the jaw through the periodontal tissues and are surrounded by gingival tissues. In health, the gingival tissues are firm and the gingival crevices are relatively shallow. However, the gingival and periodontal tissues are susceptible to a variety of inflammatory diseases,

generally classified as periodontal diseases. The most common of these are gingivitis and periodontitis.

Gingivitis is a reversible inflammation of the gums that is not accompanied by irreversible destruction of the periodontal support tissues. Gingivitis is associated with increased dental plaque accumulation and/or high populations of Gram-negative anaerobic bacteria in the plaque and is characterized by inflamed and easily bleeding gums. Gingivitis appears to be caused by substances produced in plaque that irritate the gum tissues and induce inflammation. There is a considerable body of evidence suggesting that, while gingivitis is not associated with a single pathogenic species, different groups of organisms are clearly associated with higher or lower capacity to promote gingivitis. Dental plaques dominated by species associated with early plaque colonization (e.g., Gram-positive streptococci) are more highly associated with gingival health, while more mature dental plaques dominated by Gram-negative anaerobic species such as *Fusobacterium nucleatum* and *Prevotella intermedia* are more highly associated with gingivitis. These Gram-negative species produce a variety of toxic or irritating substances including volatile organic acids (e.g., butyric or propionic acid), volatile sulfur compounds (e.g., H_2S or methyl mercaptan), various antigens, and endotoxins. These irritating substances are hypothesized to penetrate the gingival epithelium and provoke the body's inflammatory defense systems, which ultimately leads to the swollen and bleeding gums characteristic of gingivitis.

Gingivitis prevention has focused on mechanical and chemotherapeutic measures that reduce plaque mass and inhibit the emergence of more pathogenic microbial species. Many clinical studies have demonstrated that gingivitis can be reduced or eliminated by improved mechanical oral hygiene (i.e., better brushing and flossing), which reduces the amount of dental plaque and also selects for a less pathogenic, Gram-positive dominated plaque flora. As adjuncts to mechanical oral hygiene, a number of oral hygiene products containing antimicrobial agents has been formulated to help prevent gingivitis by chemical means. These compositions apparently exert their therapeutic activity by killing and inhibiting the growth and metabolism of plaque bacteria (thereby reducing plaque mass), slowing the progression of the plaque microflora toward enrichment for more pathogenic Gram-negative anaerobes, and reducing the production of microbial irritants. Agents that have been clinically demonstrated to reduce gingivitis include chlorhexidine, a fixed ratio of essential oils (thymol, menthol, methyl salicylate, and eucalyptol), triclosan, stannous fluoride, and cetylpyridinium chloride. In 1998, the United States Food and Drug Administration concluded panel hearings on antiplaque, antigingivitis drug compositions. The panel voted to accept all these agents (with the exception of chlorhexidine, which remains a prescription drug) as

antiplaque, antigingivitis agents. The report of this panel, expected in 1999, will be the first step toward completing a monograph for OTC antiplaque, antigingivitis drug products.

A number of other chemical interventions for plaque and gingivitis control have been proposed, although these technologies are not yet available. These approaches include measures to prevent colonization or aggregation of one or more species of plaque bacteria, measures to disaggregate plaque to make it easier to remove, and measures to reduce the host inflammatory response.

Periodontitis is a more serious form of periodontal disease characterized by severe inflammation, increased pocket depth, and irreversible loss of alveolar bone supporting the teeth. Current thinking about the etiology of periodontitis suggests that it results from an interaction between certain classes of particularly pathogenic microorganisms and the patient's specific and nonspecific inflammatory defense mechanisms. The pathogenic bacterial species associated with gingivitis and periodontitis overlap to some extent, although periodontitis-associated dental plaques contain some particularly pathogenic species such a *Porphyromonas gingivalis* and *Bacteroides forsythus*, which are not generally associated with gingivitis. Periodontitis is frequently preceded by and accompanied by gingivitis, but not all dental sites with gingivitis will progress to periodontitis. Periodontitis appears to progress in an episodic fashion characterized by short periods of rapid bone loss (possibly caused by a severe acute inflammatory episode) followed by extended periods of chronic inflammation and relative clinical stability. Periodontitis can only be diagnosed and treated by dental professionals, and there are no OTC oral care products specifically directed to reduction or prevention of periodontitis. However, prescription and OTC products clinically proven to reduce plaque and gingivitis are often included in supportive oral hygiene regimens after periodontal treatment.

For further reading on the pathogenesis and treatment of gingivitis and periodontitis, see the reviews by Ciancio [3] and Page [10].

DENTINAL HYPERSENSITIVITY

In healthy teeth the dentin of the crown and tooth root is generally covered completely by enamel or gum tissue. However, when dentin is exposed by enamel decay or fracture or gingival recession that exposes the tooth root, it becomes susceptible to a variety of problems. Gingival recession can occur for a variety of reasons, including periodontal disease, gingival injury from improper brushing of the teeth, and so forth. Once exposed, the cementum covering the root can be quickly worn away to expose the dentin. In a substantial number of individuals, exposure of dentin can lead to sensitive teeth (dentinal hypersensitivity), in which a variety of stimuli (e.g., heat or

cold, pressure, or high-sugar foods) can trigger discomfort ranging from a mild twinge to severe pain. It is estimated that one in seven people is affected by some degree of dentinal hypersensitivity. In its more severe forms this condition can be debilitating, affecting the dietary and oral hygiene habits of the patient.

While several theories have been advanced to explain the mechanism of dentinal hypersensitivity, the most accepted model is the hydrodynamic theory. This theory proposes that exposed, unblocked dentinal tubules provide a channel from the outer surface of the tooth to the nerves in the pulp. Physical and chemical stimuli are postulated to affect the pressure on the fluid within the dental tubules, and these changes in hydrodynamic pressure are transmitted to the pulp nerves and interpreted as pain signals. The elements of the hydrodynamic theory, (i.e., open dentinal tubules and responsive pulpal nerves) suggest two possible approaches to the reduction of dentinal hypersensitivity: blocking the tubules or reducing the stimulation of pulpal nerves.

There are a variety of currently available professional and self-applied treatments for dentinal hypersensitivity. The OTC products are dentifrices which provide agents that either promote blockage of open dentinal tubules (e.g., strontium chloride or stannous fluoride) or reduce the sensitivity of pulpal nerves by depolarizing the nerve membranes (e.g., potassium nitrate, potassium chloride, or potassium citrate).

For further reading on the origin and treatment of dentinal hypersensitivity, see the reviews by Orchardson et al. [11] and Ciancio [3].

DENTAL STAINING

While it does not contribute to dental disease, dental staining is of considerable concern to a large number of consumers who believe that stained teeth detract from their overall appearance. This concern is possibly most acute in the United States, although there is evidence that the desire for "cleaner, brighter" teeth is increasing in other parts of the world. Dental stain or discoloration can be roughly categorized as either intrinsic or extrinsic. Intrinsic discoloration exists within the tooth structure itself and may result from discoloration laid down during tooth formation, thinning of tooth enamel (permitting the color of the underlying dentin to show through), or loss of tooth vitality. Extrinsic discoloration results from deposition of exogenous colored material (chromogens) on the tooth surface. There are a variety of theories concerning the chemistry of extrinsic tooth staining, which probably results from a number of causes. These may include binding of ingested chromogens (e.g., pigments from tea, coffee, or tobacco) to the tooth surface either directly or through mediation of "bridging" molecules, binding of metal ions such as tin or iron

(which can form a variety of pigmented complexes) to the tooth surface, or the binding to the tooth surface of colorless substances which later undergo a chemical reaction that transforms them to colored compounds. For further reading on the chemistry and mechanisms of dental staining, see the review by Nathoo [12].

There are a variety of measures to reduce or prevent dental staining, which can be grouped into measures that remove extrinsic stain by mechanical or chemical means, measures that prevent extrinsic stain buildup, and measures that chemically bleach extrinsic or intrinsic dental stain. Consumer products that mechanically remove dental stains are probably the most abundant and are dominated by dentifrices containing a variety of abrasive systems. Some of these products, most notably some targeted to smokers, are more abrasive than "normal" toothpastes; care must be taken while formulating or selecting these products that a safe range of abrasivity is not exceeded. There are also a number of OTC dentifrices or mouthrinses that claim to bind to complex staining compounds and prevent their accumulation.

There is a growing number of professional and self-applied products that contain bleaching agents that can reduce the color of extrinsic or intrinsic dental stain. Bleaching products contain a variety of peroxides (e.g., hydrogen peroxide, carbamide peroxide) and chlorine compounds (e.g., chlorine dioxide), and exhibit a range of clinical effectiveness. Because it is possible that some of these bleaching agents could be harmful to the teeth or oral soft tissues, especially if misused, this class of products has come under increasing scrutiny from regulatory and professional agencies. For instance, oral care products containing peroxide are not permitted in Canada. While it is possible to make a variety of safe and effective bleaching products to reduce dental staining, the formulator is well advised to become familiar with applicable standards and regulations to ensure product safety and regulatory compliance.

Oral Malodor

Another concern of consumers of cosmetic oral care products is oral malodor (also known as bad breath or halitosis). Bad breath has been of documented concern since ancient Greek and Roman times and continues to be of concern. Oral malodor can be classified into two basic categories, intrinsic and extrinsic. Intrinsic oral malodor has its origin within the individual and is most commonly caused by substances produced by bacteria in the oral cavity. Malodorous substances of bacterial origin are primarily produced by anaerobic species (some, but not all, of which may be associated with gingivitis or periodontitis) and include volatile sulfur compounds, volatile organic acids, and a variety of other volatile malodorous compounds. A smaller, but still significant, source

of intrinsic oral malodor is a variety of systemic diseases or disorders that result in the exhalation of malodorous substances in lung air.

Extrinsic oral malodor originates from the ingestion of substances (such as garlic, cheese, tobacco, etc.) that contain malodorous compounds. The duration of extrinsic oral malodor is proportional to the amount and frequency of ingestion of the offending substance and the amount of time required to "wash out" the malodorous substances.

While there is relatively little that can be done to alleviate intrinsic oral malodor arising from systemic disease or disorder short of correcting the underlying condition, there are many of approaches and products directed at reducing extrinsic and intrinsic malodor of oral origin. These approaches can be categorized into those that remove or wash away the malodorous substances, those that mask or cover up malodorous substances with more pleasant smelling flavors or fragrances, those that chemically bind and neutralize the malodorous substances, and those that prevent or reduce the elaboration of intrinsic oral malodors.

Mechanical means of removing oral malodor include rinsing the mouth and brushing or scraping the teeth and tongue. In addition to washing away malodorous substances, improved oral hygiene can affect the ecology of the microbial communities in dental plaque and on the tongue, reducing the populations of anaerobic bacteria that are responsible for a large portion of intrinsic oral malodor and for gingivitis and other oral diseases.

Numerous products are employed to cover up bad breath; these include a variety of cosmetic mouthrinses, toothpastes, mints, chewing gums, and breath sprays whose principal function is to introduce flavors (such as mint) that can overpower or mask unpleasant mouth odors. Note that many of these approaches also increase the wash-out of odorous substances either directly (e.g., mouthrinses) or indirectly through salivary stimulation (e.g., chewing gums or breath mints). For these products, a formulator's concern is primarily directed at improving the delivery and residence time of the "reodorant" flavor systems.

Another very popular approach to reducing oral malodor is to interfere with the ability of oral bacteria to produce malodorous substances. The most common means of achieving this is through the use of products containing antimicrobial systems which either kill or metabolically inhibit substantial populations of bacteria that produce the offending substances. Since bacteria that are dead or injured are incapable or less capable of metabolizing and producing malodorous substances, this approach can be highly effective in reducing malodor originating from bacteria growing in dental plaques or on the tongue. Many of the antibacterial products used to reduce plaque and

gingivitis (e.g., a mixture of four essential oils, chlorhexidine, triclosan, or stannous fluoride) may also be useful in controlling intrinsic oral malodor.

A fourth approach to control oral malodor is to ingest materials capable of binding with volatile odorous compounds and either neutralizing them or rendering them nonvolatile. Examples of products embodying this approach include those that contain metal ions such as copper, zinc, or tin (i.e., stannous ion), all well known to bind with volatile sulfur compounds. Other products in this class contain baking soda, which is also claimed to neutralize a variety of volatile malodorous compounds. These anti-odor substances have been formulated into mouthrinses, toothpastes, chewing gums, mints, and other oral dosage forms. Another class of compounds that has been proposed to systemically inactivate malodor consists of herbs or herb extracts (such as parsley oil) that are consumed as powders, tablets, or capsules. These products, which claim to inactivate malodorous substances in the stomach and thereby lower oral malodor, have not been demonstrated to have any value in reducing oral malodor. For further reading on the causes and management of oral malodor, see the review by Scully et al. [13].

DRY MOUTH (XEROSTOMIA)

Reduced saliva flow leading to dry mouth syndrome (xerostomia) can originate from a number of sources, including systemic disease, destruction of salivary gland tissue by radiation or chemotherapeutic cancer treatment, and medicinal drug use. While systemic diseases (such as Sjögren's syndrome) that destroy salivary function are relatively rare, induced dry mouth syndrome, especially that caused by drug use, occurs to some extent in a substantial percentage of the population. Total or near total destruction of salivary function such as that exhibited by patients with Sjögren's syndrome or head and neck irradiation for cancer treatment can have a devastating effect on the oral cavity. Rampant caries, severe fungal infections such as candidiasis (thrush), loss of ability to taste, discomfort due to a pronounced sense of dryness, and irritation of the oral soft tissues are common in patients affected by severe xerostomia. Dry mouth of lesser severity, for instance that caused by some drugs, can also result in some of these problems, although usually to a less severe degree. There are now over 200 prescription and nonprescription drugs known to reduce saliva flow, including antidepressants, antihypertensives, and antihistamines; therefore this is more than a minor problem, especially in older individuals taking multiple medications.

Management of patients with dry mouth generally involves first reducing their susceptibility to oral disease. This commonly includes daily use of fluoride mouthrinses or gels and the use of antifungal drugs when necessary.

A number of other products generally classified as "artificial salivas" are also available to increase the patients' comfort by reducing the sensation of oral dryness. These products typically contain a variety of humectants and lubricants to increase the sensation of oral moistness, as well as buffers and sometimes fluoride.

For further reading on xerostomia evaluation and management, see the review by Bivona [14].

APHTHOUS ULCERS (CANKER SORES)

While oral ulcers, most notably canker sores (aphthous ulcers), are not as widely distributed a problem as gingivitis, they still affect millions of patients yearly and can be very troublesome and painful to those unfortunate enough to suffer them. Canker sores most commonly arise on the tongue and buccal mucosa. Their cause is still a matter of some debate and has been variously attributed to bacterial, viral, and autoimmune factors, although the evidence for an autoimmune origin is currently the strongest. A variety of factors has been suggested to predispose susceptible individuals to a canker sore attack, including minor injuries or irritation to the tongue or oral mucosa, selected foods, sodium lauryl sulfate (in toothpaste), and the like. Canker sores are characterized by shallow crater-like lesions approximately 2–10 mm in diameter (although sometimes larger) with sunken, grayish centers and slightly raised borders. They can occur singly or in multiple clusters. Once manifested, they last approximately 5–10 days and can be quite painful.

There is no known prevention for canker sores except to avoid things that the patient's experience suggest are predisposing factors. Treatment of existing canker sores is generally targeted at reducing discomfort or speeding healing. Several products aimed at reducing discomfort contain topical anesthetics such as benzocaine or lidocaine, while others include agents such as diphenhydramine or corticosteroids to reduce the inflammatory response. Antimicrobial mouthrinses, most notably mouthrinses containing essential oils or chlorhexidine, have been shown to speed healing or reduce the incidence of canker sores. Agents such as silver nitrate or sulfuric acid have also been suggested to cauterize canker sores; this approach is generally regarded as unsafe and not recommended. As additional information regarding aphthous ulcers becomes available, additional approaches to treatment and prevention can be expected.

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PART TWO

Formulation Approaches and Requirements

The second segment of this edition introduces the reader to the basic approaches of product development and the need for meeting various legal requirements.

CHAPTER 6

Fundamentals of Cosmetic Product Development: Getting Started

INTRODUCTION

Arguably the most important, and most satisfying, job of cosmetic chemists is to translate new product ideas into reality. To accomplish this task chemists must wear many hats and use a variety of skills. They must formulate functional products, evaluate packaging materials, and test the product/package combination to ensure its stability. They must also confirm that the product can support the required claims and that it complies with all relevant regulations. Furthermore, they must make sure the product can be conveniently manufactured at an acceptable cost. Juggling these responsibilities is a mammoth task, but the result is well worth the effort. This chapter discusses the philosophy and objectives of new product development. The requirements of a successful formula are described and the factors that should be considered in its development are outlined. Also reviewed are key steps in the development process, including tips on how to define product descriptions, determine appropriate product forms, and select compound and optimize formulations.

PHILOSOPHY AND OBJECTIVES OF COSMETIC PRODUCT DEVELOPMENT

All new products start as someone's idea. Ideas can come from many sources, depending on corporate culture. Marketing may have access to consumer

product usage information that can indicate potential consumer wants and needs; R&D may learn about new functional raw materials; or the Packaging Group may present new packaging elements that could allow a new product to be prepared. In addition, other departments or individuals may participate in new idea generation. Furthermore, these ideas can come in many forms. Some are very focused on specific objectives; while others may involve pure research. A "Grocery List/Restaurant Menu" analogy is used to describe two different ways that chemists might approach researching new product ideas. The "grocery list" approach applies to situations in which one seeks specific technology to solve particular product development problems. This approach is comparable to making a grocery list of desired items and then going to appropriate stores to shop for these items. For example, if a thickener is needed to increase the viscosity of a low pH emulsion, one would "shop" with suppliers who have expertise in thickener chemistry. The principle can be broadly applied to product development, as outlined below.

Step 1 involves preparation of a "shopping list," looking at a wish list of desirable technological items (based on desired functionality). These items could be quantitative or qualitative in nature. Quantitative items are materials or processes that allow the chemist to do something better or cheaper than before; qualitative items are those that allow one to do something that could not be done before.

Step 2 identifies the "stores" to be visited. The selection of the sources of technology that may be the useful depends upon the nature of the information being sought. Potential sources include industry suppliers such as surfactant vendors, specialty chemical manufacturers, and fragrance houses. Consideration should also be given to sources that currently do not possess the desired technology but that are willing to enter into co-development programs. University research departments are an example of the latter.

Step 3 allows one to "shop" for the necessary items in the appropriate stores. For this purpose, the information available through the sources identified above are reviewed to determine which store provides the best solutions to the previously identified problems for further pursuit of various technologies.

The "Restaurant Menu" approach represents the second part of this analogy. It applies to situations where one is conducting "blue sky" technology research that has a potential (but yet to be defined) application to personal care product development. With this approach, specific applications are not established at the onset of the project. Instead various pure research options will be pursued in the hope that one will trigger an idea for a personal care product application. (The idea could be for a new product, for a way to improve an existing product or process, or for an entirely new product category.) This process is analogous to browsing the menus in different restaurants for interesting foods.

When an item on the menu looks tempting, it can be tried to see whether it is satisfactory. Similarly, we can look at novel technology from a variety of fields to determine if any satisfies our "technical appetites." The process can be summarized as follows:

Step 1 identifies interesting "restaurants." The key to successful implementation of this approach is to find sources of new technology that have interesting technological menus. Good targets include universities, technical journals, outside inventors, and emerging technology conferences/seminars. Formulators should explore their personal favorite areas of technology in their search for new ideas. Allied industries (e.g., paints and coatings or pharmaceuticals) are another potentially lucrative source of new product ideas and techniques.

Step 2 is a survey of "menus" from these "restaurants." One should look for interesting technological "meals" (i.e., review information from these sources in hope of finding something of potential use). The technology uncovered in this stage may immediately spark an idea, or it may merely provoke curiosity, in which case further brainstorming will be required for application development.

Step 3 is a request for "meals" that look interesting. In this, the final step, the focus is on items that appear capable of satisfying one's technological appetite. This phase will require classifying and prioritizing those technologies that are potentially transferrable to the cosmetic industry.

Regardless of the source of the idea or the nature of the technology, the primary objective of the chemist is to translate new ideas into reality. Rudolph Boznak, in his book *Competitive Product Development*, cites three basic tenets that can help ensure that this translation is successful [1]. First, it is important to know the competition to understand the events that occur in the market place. Second, it is critical to realize the company's product development capabilities in order to assess what the company can accomplish financially and operationally. It is not profitable to develop a new product that cannot be manufactured or marketed. Third, Boznak says to act precisely and decisively. In other words, plan the work and work the plan. He illustrates this point with a quote from Abraham Lincoln, who once said: "If I had eight hours to fell a tree I'd spend the first four sharpening my ax" [1]. The importance of this proper planning should not be underestimated because, according to Boznak, marketers of winning products spend more than twice as much resources in planning than do marketers of failed products [2]. Boznak defines several other key product development management principles [3]. He stresses the importance of defining the product to ensure that the initial vision is thoroughly understood and faithfully executed; he stresses managing change aggressively since change is a normal part of any product development process. The trick is to keep the product development process flexible. Once it has been decided to

make a change, mechanisms must be in place to ensure product development takes place as planned.

REQUIREMENTS OF A SUCCESSFUL FORMULA

There are a variety of factors that the formulator must consider at the onset of any product design project. B. Radd proposes the critical steps in product development [4]. He states that product vision, product form, essential ingredients, critical ingredients, project schedule, product performance, and regulatory requirements should be considered. This list is expanded below.

A. Marketing Objectives
Chemists must be aware of marketing concerns when developing new products. Typically, Marketing determines the direction for new product development, but it is essential that all development personnel involved in the project have a sense of what the product is intended to do, where it will be sold, who its major competitors are, and so forth. All team members should know the current trends in the marketplace that could affect the failure or success of the product. This notion applies to functional technical issues as well as asthetic concerns such as fragrance and color.

B. Product Functionality
The functionality of the product refers to its performance characteristics. For example, does a skin lotion moisturize as it is intended to or does a hair color impart the appropriate shade. There are numerous methods chemists can use to evaluate these attributes; for example, the foam properties of a body wash or shampoo can be assessed with foam height testing, or the moisturizing ability of a hand and body lotion or facial cream can be measured by instrumental methods (i.e., skin impedance studies) or in vivo (regression studies).

C. Formula Stability
In addition to establishing efficacy of the formula, one must determine that it will not change significantly over time. Products can undergo age-related changes for any of several reasons, including microbial growth, oxidation, UV radiation–induced color fading, or a variety of chemical and physical reactions between formula components. A methodical evaluation of the product's ability to resist changes over time is a critical part of formula development. Stability testing is a necessary evil; most chemists do not enjoy this kind of work, but it can yield much useful information.

D. Safety
Cosmetic chemists have a responsibility to ensure that any product they develop is safe for its intended purpose. In the majority of cases, formulas use common ingredients that have been tested and proven safe. In such cases, little if any additional safety testing is required. However, if novel raw materials, or unique combinations of raw materials, are used in the formula, some additional testing may be prudent. Also,

when formulating products to be used on or near sensitive areas of the body (the oral cavity, genitalia, the eyes) special testing may be required. In addition, the delivery form may necessitate safety testing. Products that are safe in a solid or liquid form may present additional health risks when delivered via an aerosol because of the enhanced penetration into the lungs. Corporate guidelines combined with good judgment and experience will dictate the appropriate level of testing.

E. Regulatory Considerations

The development chemists must be aware of the regulatory environment in which their product will be sold. An example of current concern to the industry is the regulatory limits imposed on volatile organic compounds (VOCs) found in hair sprays and other products. Assessing regulatory issues is an area that requires specific expertise, but every development chemist should have some familiarity with regulations that govern cosmetic products.

F. Cost

Cost is an important consideration in any product development project. Marketing, R&D, Operations, and Packaging departments should agree on cost guidelines for the product at the onset of the project. This cannot be stressed enough. A formulator can create the best shampoo in the world but if it costs $1.00 per pound and Marketing can only afford to spend $0.22, then the project is doomed to failure. Therefore formulators should have a clear price target in mind when they begin to select ingredients. Timetables do not always allow formulators to create the most cost-effective formulation in time for launch of a product. In such situations it may be possible to continue to optimize the formulation after the product has reached the market. The cost-reduced formula can then be introduced at a later date.

G. Operational/Manufacturing Considerations

Operational considerations are important, and it is advisable to think of these issues early in the development process. Operational considerations include the availability and purchasing requirements of raw materials. These issues go beyond simple cost considerations and include details such as determining that ingredients are available, that they can be supplied to established specifications, and that they can be shipped globally if necessary.

The experienced formulator should also be mindful of manufacturing capabilities. It is important to understand how ingredients are stored, mixed, heated, and cooled during compounding. While liquids are easily pourable or pumpable, certain ingredient forms are inherently more difficult to process. For example, powders can be problematic because they are harder to disperse and they may create dusting, which could necessitate special breathing or ventilation equipment. Solid materials (such as waxes) may have to be cut into small pieces or premelted before they can be added to a batch. This kind of extra effort can put an unnecessary strain on the compounding staff.

Chemists can further facilitate the compounding process by employing preblended ingredients. Although ingredient blends can be problematic in some respects, (e.g., it is harder to control their quality), they can have many advantages. Andrew Banham gave an example of how blends can simplify the compounding of a hypoallergenic nonirritating, soap-free cleanser [5]. He shows that blends can result in less time spent on quality assurance (because only one product is being tested instead of eight), minimize drum handling and disposal time (because there are fewer containers to deal with), and reduce processing energy (since the ingredients in the blend are premixed). In his example, preblended ingredients lead to shorter compounding times, which is always desirable.

PRODUCT FORMS

From a technical standpoint, there are two aspects of formula development that are most important when developing a new product. The chemist must choose the proper product form and the appropriate raw materials to meet the desired functions. There are many different product forms, and the one that is ultimately chosen will depend on all the different parameters outlined prior to formula development.

SOLUTIONS

One of the simplest forms of personal care products are solutions. These are liquid systems in which all the components are soluble. They are products characterized by clarity. They can be made thin or thick, depending on whether a thickening system is incorporated. Most often, solution products are aqueous and the active ingredients are water-soluble. However, they can be based on an oil such as mineral oil or lipophilic materials. In reality, few cosmetic products are true solutions, as they may contain both oil- and water-soluble or water-swellable or water-dispersible materials. However, some clear-appearing cosmetic compositions are generally classified as solutions.

From a compounding standpoint, solutions are generally simple to manufacture. They typically involve filling a tank with the main diluent and simply mixing in the rest of the ingredients. Since all of the ingredients are soluble, heating and cooling are generally not required. Their ease makes them ideal candidates for continuous processing in which the raw materials are mixed in pipes and pumped straight to the filling lines. While solution-based products are easy from a manufacturing standpoint, they have the drawback of offering only limited functionality. Many functional cosmetic ingredients have limited or no solubility in water and require other product forms.

CREAMS

Perhaps the most common product form used for incompatible materials are creams. From a technical standpoint, creams are emulsions. For practical purposes, an emulsion is defined as a heterogeneous system composed of an immiscible liquid dispersed as tiny droplets in another liquid. The simplest creams are mixtures of water and water-insoluble materials made compatible by the addition of a surfactant or emulsifier. Emulsifiers are molecules that have both a water-soluble portion and an oil-soluble portion. When added to a system containing oils and water, they can emulsify the oils into tiny droplets and disperse them throughout. This type of cream is an example of an oil in water emulsion. Water in oil emulsions are also possible. Other types of emulsions include multiple emulsions in which there is a discontinuous inner phase (e.g. water dispersed in oil that is dispersed in water) and microemulsions that have particles so small they are almost invisible. For the interested reader, a more rigorous discussion can be found in Becher's *Encyclopedia of Emulsion Technology* [6].

Since creams are made up of mutually incompatible materials, they are opaque or hazy in appearance. Their increased viscosity may be the result of the nature of the emulsified particles or the result of an adjunct thickening system. Creams can be made to feel oily or greasy depending on the amount and the nature of ingredients used. Various cosmetic products are ideal for the cream form. For example, skin creams are typically oil in water emulsions with approximately 10–25% oil phase. Other cream systems include antiperspirants, moisturizing creams, and shaving creams.

From a compounding standpoint, creams can be more complex than simple solution products. While single-tank manufacture is possible, compounding conditions often require that separate tanks are used for blending oil and water phases. These are then mixed to form the final emulsion. For even more complicated systems such as multiple emulsions, three tanks may be required. Heating is also required since many of the lipophilic materials are solids at room temperature and only by heating them above their melting point can they be blended properly.

Creams are luxurious products and have great aesthetic appeal. However, they have drawbacks that can produce significant barriers to successful product development. For example, since creams are emulsions, they are inherently unstable. The laws of nature preclude formulation of a permanently stable emulsion; therefore, stability testing is required each time a change is made to a formula because the slightest ingredient imbalance can lead to stability problems. Generally, a wider array of functional ingredients can be formulated into this product type.

LOTIONS

For some applications creams are too heavy, and lotions are preferred. Lotions are loosely defined as thin creams. They are also emulsions but contain lower levels of waxes and oils than those associated with creams. This makes them feel lighter and less greasy. The lotion form is used for products such as skin and facial lotions, hair conditioners, and moisturizing cleansers. Lotions can have an elegant feel. Since they are emulsions, lotions suffer from many of the same compounding problems as creams. Generally they are easier to produce than creams because they are thinner, and heating and cooling times are lessened. Since they are thinner, stability problems are even greater than in creams because the viscosity of a cream will generally slow the natural destabilizing forces.

OINTMENTS AND PASTES

Whenever a product is supposed to be extra thick, ointment or paste forms can be used. For practical purposes ointments and pastes represent the same product form. These products are thicker than creams and can either be anhydrous or contain a relatively low amount of water. Some are oil-based, opaque mixtures containing ingredients such as petrolatum, lanolin, or mineral oil. Consequently, they are heavy and greasy. They are used for products such as hairdressings or medicated skin products where a viscous coating is desired. They are also used for ethnic hair products such as relaxers that are applied to the hair with a brush. Since ointments are essentially oil-based mixtures, they present few stability issues and do not suffer from microbial contamination problems. Their thickness can create problems in manufacturing such as compounding and filling.

SUSPENSIONS

Another product form that is related to emulsions are suspensions. These are water-based products that contain larger, often visible particles suspended throughout. Like the particles in emulsions, suspended particles are generally not soluble in water. Suspensions can be made with a wide range of viscosities. Since the particles can be seen, suspensions offer a unique visual effect not found in other product forms. Suspensions provide a means for delivering noncompatible ingredients. A common suspension product includes shampoos in which gelatin beads are suspended. Sunscreen lotions represent another type of suspension in which the inorganic mineral zinc oxide or titanium dioxide is suspended throughout. Suspensions typically contain a structurizing polymer such as an acrylate or an inorganic thickener such as bentonite clays. When

put into an appropriate system, these materials form a molecular network that locks particles in place. This network inhibits the forces that would normally cause instability such as van der Waals or hydrophobe/lipophobe interactions. If not formulated properly, suspensions create the same stability problems as emulsions. What can happen is that the suspended particles may float or sink, depending on the relative specific gravity. Production of suspensions is generally easier than that of emulsions as separate tanks are rarely required. Suspensions represent a moderately priced product form.

GELS

Another product form that has a unique look and feel is a gel. While a wide variety of products are sold as gels, gels should be defined as clear, shear thinning products. This means that when a force is applied to the product it tends to spread easily. In the simplest sense, these products are composed of water or alcohol solutions thickened with gelling agents. Various gelling agents are used, including acrylic polymers, natural gums, or cellulose-derived polymers. Special microemulsions can produce a product form known as a "ringing gel." Depending on the manufacturing procedure, gels may have air bubbles suspended throughout the product. This gives them a unique look and makes them useful for a host of cosmetic products. In hair care they are used to deliver styling resins. For body care they are used for shower gels. Shaving gels are also common. Finally, some toothpastes are formulated in gel form.

Large scale production of gels is complicated by their thickness. Generally two tanks are used; one contains the functional ingredients and the other the gelling ingredients. When they are mixed the batch becomes extremely thick and difficult to mix. For this reason, the gelling agents are added late in the process.

STICKS

For those cases in which a solid is desired for delivery of active ingredients the stick form was developed. Sticks are best used for products that consumers do not want to handle directly such as antiperspirants, deodorants, or lipsticks. This product form can be used to deliver insoluble materials such as pigments, fragrances, and emollients. Sticks can be made from a variety of materials. For example, lipsticks consist of waxes and oils. Deodorants are hydroalcoholic solutions solidified by sodium stearate. Antiperspirants are thickened with fatty alcohols and volatile silicones. Typically stick products are opaque. Depending on the type of stick, manufacturing can be moderate to very complex. Two methods of production are common. In both methods, the ingredients are mixed in a suitable container. For lipsticks, this mixture is then poured into

molds, shaped, and then put into its packaging. For deodorants, the molten liquid is poured into the packaging and allowed to solidify as it cools. Stick products generally have good stability profiles as their solid structure inhibits most destabilizing processes.

TABLETS AND CAPSULES

Other solid product forms are tablets and capsules. Unlike all the product forms discussed thus far, these products are mostly physically blended solids. A binding agent is typically included to make them more stable. They can be mixed in a horizontal mill with a screw agitator. To produce a tablet, the solids blend is filled into a tableting machine that uses pressure to force the powdered product to hold together. While capsules are similar to tablets, they are different in that the outer shell of the product is not necessarily of the same composition as the rest of the formula. For example, gelatin capsules are produced which can be filled with a variety of powder or liquid formulations. These types of product forms are relatively expensive to produce because they contain little water and must be made small. They are commonly used for makeup or other specialty cosmetic products.

POWDERS

Powder is perhaps the simplest form of a solid product. Powders consist of solid raw materials blended together in a fine mixture. This form is useful for such products as foot powder, baby powder, makeup, and feminine hygiene products. Common ingredients that are used for powdered products include materials such as talc, rice starch, silicates, or titanium dioxide. When compounding these products, special gear is required because of dusting of the powders. The powdered form is a relatively stable product form. One challenge in working with this product form is to prevent contamination with water. For this reason packaging plays a key role in the stability of the product.

AEROSOLS

While most of the product forms discussed so far have relied on the physical or chemical properties of the ingredients to give them form, aerosols depend more on the packaging. In general aerosols are composed of a concentrate solution that is pressure-filled with a propellant into a metal can. When an actuator button is activated, the product is dispensed in a fine mist or foam. This product form is used for such products as shaving creams, deodorants, hairsprays, and other hair styling products. Nonaerosols are aerosol-type concentrates that are put into manually operated pumps for dispensing. These formulations are

technically solutions as they are water- and alcohol-based. Aerosols can be formulated as solutions, emulsions, powders, and even gels. Environmental concerns have led to a decrease in the use of the aerosol product form for new products.

While the active ingredients in aerosol products are in the same range as other product forms, there is a significant additional cost for aerosol products when the propellant and packaging costs are considered. Compounding of an aerosol product is slightly more complicated than that of other products because the finished product depends so much on the packaging. The active ingredients are mixed with the solvent; then this concentrate is filled into cans, a propellant is added, and the can is sealed. Stability concerns consist mainly of can corrosion. To prevent corrosion, corrosion inhibitors are added to formulations that contain high levels of water.

While it is convenient to classify products by their various forms, in reality most cosmetic products are combinations of product forms. For example, shampoos are primarily solutions. However, they typically contain a solubilized water-insoluble fragrance. The resulting product is really more technically an emulsion, even though it is still referred to as a solution.

It is possible to combine product forms. For example, aerosols can be combined with gels to produce a foaming gel. In this product form, the gel is combined with a low vapor pressure hydrocarbon, which is then put into a bag within an aerosol can. The primary propellant is then filled around the outside of the bag in the can. When the actuator is depressed, the product dispenses as a gel that foams as the propellant escapes.

THE PRODUCT DEVELOPMENT PROCESS

The product development process may be outlined as follows: The chemist must first define the product as noted above. Formulators must then collect and evaluate information regarding raw material functionality and safety to help determine an appropriate starting point for formulation efforts. At this stage they can begin to prepare prototypes and evaluate them for stability and functionality. Next they can refine prototypes based on these evaluations until a satisfactory formulation is achieved. They can then consumer-test their leading prototype(s) and modify the product as necessary. Lastly the formulation is finalized and stability and production feasibility are confirmed.

DEFINING THE PRODUCT

As noted early by Boznak, preparing and understanding the parameters of the product to be developed are crucial steps that must occur before formulation

efforts can proceed. These steps prevent the danger of expending effort against the wrong target. The point is that product description parameters must be defined before formulation begins, not after the product has been developed. This provides chemists with a way to measure the success of their product development efforts.

A typical description of a new hair product is provided in the Appendix. It requires all concerned with product definition to be aware of the need for identifying various—and sometimes minute—details.

Mort Westman expands upon this point [7]: "Prior to initiating formulation, it is essential the formulating chemist possess both in-depth knowledge of conditioning ingredients and strategic understanding of the chemical and non-chemical aspects of the project. This must include a clear description of the targeted product and the method or parameters by which the performance of candidate prototypes is to be determined (i.e., establishment of criteria for project completion). From this point the chemist can, in an organized manner, conduct research towards the development of viable prototypes. The successful formulator must also have a thorough understanding of the testing by which prototypes are to be optimized and eventually judged."

Westman proposes that all key team members agree on a written product profile that defines the product as fully as possible. Such a profile should encompass a variety of considerations including aesthetic factors (such as color, appearance, viscosity, texture), product form, performance targets, packaging attributes, financial considerations, and marketing claims. All these factors may impact the formulation process. A sample product profile that encompasses these factors and more is reproduced below.

For a further discussion of how to define the product development process, the reader is referred to an excellent article by Roger Miller, who describes ways to make the front end of the product development process less "fuzzy" [8].

SELECTION AND SOURCES OF INGREDIENTS

After the product has been defined, the appropriate raw materials and starting formulations must be obtained in order to produce prototypes. Information about the raw materials to be used and starting formulations can be collected from a variety of sources. The following are a listing of a few of the many sources for raw materials and formula information.

1. ***Suppliers' literature.*** All of the major raw material suppliers have developed formularies that they make available to chemists working in the industry. These formulas can be a good starting point that can provide direction about the more

useful types of materials; often these vendors have application laboratories and can offer technical support.

2. ***Reference books***. Books such as the one you are reading now can give basic information about raw materials and formula composition. One of the best known set of volumes containing starting formulations is the Bennett formulary series [9]. This collection describes thousands of different formulas for everything from cosmetics to car soap. The advantage of these texts is that they are thorough and typically provide some scientific background about many of the suggested formulas. Unfortunately, they are published infrequently and often do not contain the most up-to-date information [9].
3. ***Patents***. Another area that can be useful is a review of the patent literature. A patent search can reveal a wealth of information related to different formulation approaches or specific raw materials. It will also describe how others in the industry have made similar products and helps to avoid infringement of a competitor's patent.
4. ***Trade journals***. Various monthly technical trade journals contain the most up-to-date information and may provide in-depth reviews of a specific area of interest. They also provide information about trends in the marketplace and newly released products.
5. ***Internet***. In addition to the printed word, the Internet has become a vast depository of all information about cosmetic ingredients. Most suppliers have an Internet site that provides formulations and ingredient information. Also, new technology can be found. Patent searches and a variety of other information can be made through a short run on the Internet. This promises to become a greater resource in the future.
6. ***Peers***. One of the most obvious resources available are your peers. There are relatively few completely unique cosmetic compositions and most are derived from previously created formulas. A co-worker may have experience in a certain area and may be able to suggest raw materials to consider.

The initial research phase is helpful in two ways. First, basic research can provide background information about the chemical interactions that are essential to understand before developing products that are based on innovative technologies. Second, this research can provide a master list of ingredients to study or starting formulations to try. This list can then be tailored for the specific project.

BASIC RULES OF COMPOUNDING

The Empirical Approach

There is no single right or wrong way to create a formula. However, working within certain consistent guidelines can make the process much smoother. There is no need for a formulator to start cold because prior art has established that certain types of materials (within specific concentration ranges)

are effective for any given product category. Formulators can find an abundance of suggested use levels for ingredients in trade and supplier literature. These starting formulations help determine safe and efficacious use of concentrations. This is important for obvious reasons: using suboptimal levels of ingredients can affect formula performance and may increase the risk of instability. Insufficient amounts of a detergent result in poor cleaning and create a cheap-feeling shampoo. Too much may unnecessarily increase cost and might make the product, harsher and more stripping to skin and hair than it needs to be. Likewise too little pigment in a lipstick or makeup cake can result in an aesthetically inferior product, while too much can affect product integrity.

An element of uncertainty is introduced into the process whenever the chemist prepares truly new types of products or uses new classes of ingredients. In such cases a new learning curve must be established until the technology becomes commonplace. An example of this can be seen in the early days of two-in-one shampoo formulations. Until the industry found levels that provided appropriate levels of conditioning, nobody had a sense of the required target in a formulation. This can be a moving target as exemplified by the reformulation by a major shampoo marketer to make formulations cleaner rinsing in order to keep pace with current consumer expectations. The lesson to be learned here is that formula optimization does not stop once a product is successful in the marketplace but should be an ongoing process that never truly ends.

Once a comfortable starting point for prototype development has been identified, laboratory batches can be prepared. It is rare that these first attempts are successful; in most cases the first formulation efforts will not pass the required standards (with regard to either stability or performance), and formulation refinements will be necessary.

FORMULA OPTIMIZATION

Formulating a cosmetic product can often be a "hit or miss" enterprise. However, some cosmetic chemists have had a degree of success using experimental design to develop optimized formulations quickly. Experimental design is a process by which a variety of variables are tested simultaneously to determine each factor's significance in affecting the final result. This process works extremely well with formulations because each ingredient can be examined using as few prototypes as possible, as briefly described in the Appendix and by Wiechers [10]. One way to optimize a formulation is by determining the effect that each ingredient has on the various characteristics of the formula. This would include effects on the formula's physical properties and its functionality. A simple experiment is a "knock-out" experiment, which involves making a series of prototypes by leaving out one ingredient.

These knock-out prototypes are compared to the control formula. Relatively simple modes of testing provide information about how much effect every ingredient has on each feature of the formula. It can provide data on how ingredients affect a product's rheology or physical appearance. It can also help determine which ingredients could be minimized to reduce formula cost without significantly impacting product functionality. When more information about a formula is desired, this approach could be expanded by modifying the levels of ingredients instead of removing them altogether. This helps to optimize the formula but becomes more difficult because, as the difference between ingredient levels get smaller, the differences in formula effect are harder to identify.

This type of optimization technique will, however, not give information about how various ingredients interact with each other. For example, certain ingredients may have a synergistic effect with other ingredients. A knock-out experiment will not give data about these interactions. Also, some of the formulations predicted by the experimental setup cannot exist. For instance, it would not be possible to create a cream prototype without the emulsifier.

Computers are playing an increasing role in the development of new formulations. Formulation software is available from several companies and physical properties of a formulation can be calculated and adjusted. Currently, computer software program is limited to tracking and storing information about prototype formulations. Eventually, however, these software programs will combine online databases of raw materials with simulators that can predict formula functionality, stability, and physical characteristics. This ultimately may lead to a system in which the chemist enters a list of desired parameters and the computer then suggests formulation approaches [11].

Test Batches

In the early stages of formula development, informal testing of prototypes for stability, functionality, and safety should be done. Eventually full stability testing will be required on manufactured products. Raw material suppliers can provide basic toxicology data about their materials, but medical safety testing of the finished product may be required. In addition to stability and safety testing, performance testing is another important aspect of formula development. If the job was done correctly, a product will have been formulated that achieves all of the technical benchmarks set out at the onset of the project. It will be stable, functional, safe, cost-effective, easily manufacturable, and compliant with relevant regulations.

Future of Product Development

Using techniques developed by computational chemists, new product development should also become more streamlined. Currently, these techniques are

being used in the pharmaceutical industry. Scientists are able to enter specific parameters about molecules they desire and then have the molecules synthesized. This allows them to screen thousands of potential new drugs by having a computer calculate the structure and create the molecule. In the future, this technique should find application in cosmetic product development. For example, new conditioning agents for hair or skin could be developed by modeling molecules designed to bind to specific sites on biological surfaces. Using the geometry of the binding site, a diversity of potential new compounds can be calculated and then synthesized. Ultimately these will have to be tested under actual use conditions to determine their effectiveness [12,13].

Appendix: Typical New Product Description for Hair Products

Project Identification: _____
General Product Category: _____
Form Prepared by: _____ Date: _____

AESTHETICS

APPEARANCE

1. Comparative Standard(s): _____
2. Color/Hue: _____
3. Intensity: Pale Light Moderate Dark
4. Clarity: Clear Translucent Opaque
5. Visual Effects: Pearlized Other
6. Other

CONSISTENCY

1. Comparative Standard(s)
2. Description of Flow Characteristics (choose one)
   a. Water-like
   b. Very flowable but not water-thin
   c. Flowable, slow-pouring
   d. Barely flowable, thick
   e. Flowable only after squeezing or shaking package
   f. Nonflowable Gel
   g. Nonflowable Cream
   h. Nonflowable Paste
   i. Nonflowable Wax
   j. Other (describe)

PERFORMANCE/FUNCTIONALITY

FOAM PROPERTIES

(1) Comparative Standard:
(2) Volume: None _____ Slight _____ Moderate _____ Copious _____
(3) Feel: Thick/Rich with Lubricious Film ___ Thick/Rich ___ Moderate ___
(4) Thin _____ or Describe:

Other (describe):

CLEANSING PROPERTIES

(1) Comparative Standard:
(2) Degree of Cleansing: Deep ___ Moderate ___ Everyday ___ Mild ___
(3) Feel of Hair After Rinsing: Scale: Squeaky clean = 0 to Conditioned film = 10

Enter number based on above

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CHAPTER 7

Regulatory Requirements for Cosmetic Products

INTRODUCTION

The regulation of cosmetics was justified originally on the basis of consumer protection and safety. Somehow the safety of cosmetics intended for human (personal) beautification became a controversial nationalistic issue in which a product or ingredient was safe for distribution in one location but not in another. Only recently with the creation of the European Union (E.U.) has it become apparent that "harmonization" was required to achieve the Holy Grail of uniform global cosmetic regulations. This desirable goal cannot be attained without resolving some troubling controversies. For example, the debate on how racial characteristics affect safety may have to be adjudicated. Can agreement be reached on what constitutes a safe cosmetic ingredient and what type of testing is required to establish (worldwide) safety? The concept of globalization has suddenly become a forum for animal rights activists. The fossilized identification of dyes and their purity in diverse countries have assumed political or chauvinistic roles. The resolution of many issues is years away. In the meantime, fragments of the emerging worldwide regulations impact formulators and those who ship and distribute cosmetic products. Another stumbling block to harmonization is the cosmetic versus drug issue, which is likely to become exceedingly controversial. Commercial interests in the United States can be expected to maintain that thioglycolate-containing hair products are cosmetics (they are intended to modify dead hair outside of the body), while other political entities view thioglycolate-containing products as pseudo- or quasi-drugs. Three major trade organizations, the Cosmetic Toiletry & Fragrance Association (CTFA) in the United States, the European Cosmetic, Toiletry, and Perfumery Association

(COLIPA) in Europe, and the Japanese Cosmetic Industry Association (JCIA) in Japan, believe that global agreements can be reached, but the political establishment is not likely to condone or agree to changes that may affect voters. (COLIPA is an acronym of Comité de liaison des associations Europeennes de l'industrie de la parfumerie, des produits cosmetiques et de toilette and is referred to in English as The European Cosmetic Toiletry and Perfumery Association).

The important goal of global harmonization of cosmetics is likely to require some radical changes in political or emotional arguments; instead, the desirable agreements must be based on rational scientific reasoning. To date, there is no agreement on the following points:

- A succinct worldwide definition of a cosmetic and a drug
- Uniform worldwide agreement on labeling of cosmetic ingredients without linguistic chauvinism
- Establishment of an agency with worldwide responsibility for the safety of ingredients and of their blends, that is, finished products
- Worldwide establishment of protocols for establishing the safety of cosmetic ingredients
- Agreement between countries or legislative units enforcing such rules globally and their modification whenever newly developed information should require this.

The simplistic belief that a combination of so-called safe ingredients should yield a safe cosmetic is probably not valid. Even in the absence of overt chemical reactions, the blend of cosmetic ingredients remaining on the skin surface is subject to photooxidation. The nature of the sometimes sensitizing photoproducts used is largely unknown and needs to be considered during the legislative process [1].

The outcome of these attempts to globalize rules for cosmetics is unpredictable. For the time being formulators and marketers will be guided primarily by the regulations of the country in which they operate. Export and import rules, trade and advertising restrictions, and safety issues require knowledge of all applicable laws. A comprehensive presentation along these lines is impossible; instead, some of the features that govern cosmetics in selected legislative areas are reviewed briefly in this chapter.

REGULATORY REQUIREMENTS FOR COSMETICS IN THE UNITED STATES

LEGAL ASSESSMENT

The Cosmetic Definition and "Intended Use"

Whether a product falls under the Food and Drug Administration's (FDA) jurisdiction as a cosmetic depends largely on its intended use. The Food Drug and

Cosmetic Act (FDCA) defines cosmetics as "(1) Articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body, or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap." To determine a product's intended use, the FDA relies on the representations made for the product in its labeling, that is, from "any display of written, printed, or graphic matter" either on the immediate container (the label), or any outside container, or on a wrapper (except package liners), or on any materials that accompany the product. The interpretation of product labeling by the FDA and the courts includes circulars, leaflets, and other descriptive material inserted in the shipping container, plus point-of-sale displays, promotions, and advertising materials.

On the other hand, drugs are defined as follows: The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in human beings or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of human beings or other animals; and (D) articles intended for use as a component of any articles specified in clauses (A), (B), or (C); but does not include devices or their components, parts, or accessories.

FDA regulations identify specific categories of products normally considered cosmetics [2], including baby shampoos, lotions, powders, and creams; bath oils, capsules, and salts; eyeliner, shadow, lotion, makeup remover, and mascara; fragrance preparations including sachets, dusting powders, perfume, cologne, and toilet water; hair conditioners, sprays, rinses, shampoos, tonics, straighteners, and permanent waves; hair dyes, tints, coloring rinses and shampoos, bleaches, and lighteners; makeup powders, foundation, paints, lipstick, rouges, and blushers; nail enamels, cuticle softeners, enamel removers, nail creams, and lotions; nontoothpaste, dental rinses, mouthwashes, sprays, and breath fresheners; bath soaps and detergents, douches, and feminine hygiene deodorants; aftershave and preshave lotions, creams, shaving soaps, and beard softeners; cleansing creams, lotions, liquids, and pads; depilatories; body, hand, and face lotions, creams, and liquids; foot powders and sprays; face masks; skin fresheners, moisturizing, and night skin care preparations; self-tanning preparations and suntan preparations not intended to protect against sunburn. This list is not exhaustive; but as long as a product is intended for the purposes described in the Act's cosmetic definition, it may be regulated as a cosmetic. Soap is not included in the cosmetic definition, having been explicitly omitted from the definition in the statute (Chapter 19).

Regulation as a cosmetic is not a burdensome classification. Products that are represented for other purposes, such as drugs, bear a much heavier regulatory obligation. Cosmetics are the least regulated of products subject to the FDA jurisdiction. Cosmetics may be placed on the U.S. market without premarket clearance as long as they comply with individual state regulations, including environmental legislation affecting cosmetic products. A product will be considered a drug if it is intended for a use that is either therapeutic or that is intended to affect the body's structure or function. The two definitions are not mutually exclusive, and a product intended for cosmetic and drug uses must comply with the regulations governing both product categories. A discussion of the cosmetic versus drug issue will be found later in the text.

Nevertheless, the classification of products based on intended use, rather than on chemical composition, has created a regulatory dilemma. When cosmetic identity is based on the representations made for the product, a product may be a cosmetic even though it affects the structure or function of the body in a way that exceeds the FDCA cosmetic definition. For example, many skin care products contain α-hydroxy acids (AHA), which may increase the production of new skin cells. The FDA has been reluctant to reclassify all products containing an effective level of an AHA as drugs, since it has become evident that many, if not most, cosmetic ingredients can or do have some effect on the body's structure or function. As a result, AHA-containing products are regulated as cosmetics as long as the labeling does not include a direct claim related to a structure or function effect. The manufacturer is given control over a product's regulatory status merely by describing the product in terms that stay within the intended uses outlined in the cosmetic definition.

Adulteration

Neither the FDCA nor the Fair Packaging and Labeling Act (FPLA) require premarket approval or notice before a cosmetic product is placed into commerce. Any enforcement actions against an adulterated or misbranded cosmetic product can by necessity be taken only after the product is already on the market. Enforcement considered as adulteration may result from the presence of a poisonous or other harmful substance (that may injure users under customary or labeled conditions); presence of any "filthy, putrid, or decomposed substance", or if it has been produced, packed or held in insanitary conditions, or if it contains an unapproved color additive (21 U.S.C. §361 and 362). [The abbreviation U.S.C. refers to U.S. Code of Federal Regulations.]

The term "misbranded" refers to statements, designs, or pictures in product labeling that are misleading if they fail to bear all the information required

under the FDCA. Misbranding may result from insufficient information for the consumer, from an improperly formed or filled container, or if packaging or labeling does not comply with applicable requirements of the Poison Prevention Packaging Act of 1970.

FDA'S RESPONSIBILITY

Establishment Inspections

In the absence of any authority for cosmetic premarket clearance, enforcement of the Act generally occurs after the product is already on the market. The FDA's primary discovery tool is the establishment inspection, which is authorized by the FDCA for investigation of regulated products and facilities (21 U.S. Code, §374). The FDA inspectors may, at reasonable times and after presentation of appropriate credentials, enter and inspect any establishment in which cosmetics are manufactured, processed, packed, or held. In addition to its routine inspection activities, the FDA also investigates products and establishments on the basis of consumer complaints or in response to a trade competitor complaint that alleges a possible violation of the law.

The FDA Modernization Act (of 1997) amended the FDCA to extend the FDA's inspection authority to nonprescription drugs, including over-the-counter (OTC) drugs that are also cosmetics. The inspection includes a review of good manufacturing practices, of product ingredients to determine if any are prohibited or restricted, and of labeling, including ingredient declarations and required warnings.

Any decision to take regulatory action following an inspection is made by the FDA district office with the concurrence of the FDA headquarters. The FDA is authorized to bring both civil and criminal actions against persons and firms responsible for violations. However, adulterated or misbranded products may be seized, and their further manufacture or distribution may be enjoined only on orders obtained by the FDA in federal court. If the offense is egregious, deliberate, or repeated, the FDA may bring a criminal suit against the company and its responsible officials.

Although formal cases have been brought against cosmetic violators or products, the FDA tends to work with domestic companies toward voluntary recall or correction of illegal goods and practices, and has recently initiated an inspection feedback program to encourage speedy correction of observed violations. On the other hand, the FDA can also move quickly to seize or force the recall of a potentially harmful product, such as contaminated eye area products. Despite the absence of legal requirements, the FDA has access to this material via the Internet or print, and a comparison with equivalent guidelines published by the Council of Europe is available in a column by D.C. Steinberg [3].

Cosmetics, nevertheless, remain the most lightly regulated products within the FDA's jurisdiction because more stringent restrictions were obviated by voluntary compliance programs initiated by industry, such as the CTFA's Cosmetic Ingredient Review (CIR) and the Voluntary Reporting Programs. As a result, cosmetic products may be marketed in the United States without prior notice or approval and without federal registration of either the manufacturer, distributor, or importer.

Cosmetic Safety

Cosmetic manufacturers are responsible for using only safe and suitable ingredients in their products and for substantiating the safety of the finished product. In fact, the FDA regulations require products whose safety has not been substantiated to bear a warning statement, "Warning—the safety of this product has not been substantiated (21 C.F.R. §740)." The FDA has never enforced this regulation. The existing misbranding provisions of the FDCA have been sufficient to ensure the general safety of cosmetics.

Prohibited and Hazardous Substances

The FDA has published a short list of restricted or prohibited substances, namely bithionol (photosensitizer), hexachlorophene (neurotoxin), mercury compounds (allergen, neurotoxin, irritant), vinyl chloride (carcinogen), halogenated salicylates (photosensitizer), zirconium salt in aerosols (lung toxin), chloroform (carcinogen), methylene chloride (carcinogen), and chlorofluorocarbon propellants (ozone depletor).

In addition to these codified substances, the FDA inspectors are instructed to determine if other substances that the FDA considers to be hazardous are in use. These substances include acetyl ethyl tetramethyl tetralin (AETT), 6-methylcoumarin, musk ambrette, and dioxane, a contaminant that may appear in ethoxylated surface-active agents and has been found to produce cancer in animals.

Nitrosamine contaminantion may occur in cosmetics that contain amines and amino derivatives, such as di- and triethanolamine, together with a nitrosating agent such as the preservative 2-bromo-2-nitroprane-1,3-diol or contaminants such as sodium nitrite. N-nitrosodiethanolamine (NDELA) contamination of cosmetic products, including some OTC suntan products, has concerned the FDA for at least 20 years. The FDA has devised a validated method for detecting nitrosamines in products, and inspectors are instructed to report and sample products that contain ingredients likely to contribute to nitrosamine formation.

Additional Concerns

Depilatories and Hair Straighteners may cause serious skin irritation if improperly formulated or if adequate directions and warnings for use do not appear

in the product labeling. The FDA inspectors are instructed to review labeling, quality control procedures, and information about consumer complaints, and to report all findings in the Establishment Inspection Report (EIR).

Permanent Wave Neutralizers for home use that contain sodium bromate in amounts over 600 mg and potassium bromate in amounts over 50 mg must be packaged in childproof containers due to the serious effects of accidental ingestion.

Nail Products containing methyl methacrylate must be packaged in childproof containers. In addition, nail builders, hardeners, and enamels that contain (5% or more) formaldehyde should bear warnings and directions for proper use.

Estrogenic Hormones, Placental Extract, or Vitamin containing products may be considered drugs or misbranded cosmetics if the labeling includes representations about treatment of disease or menopausal symptoms. Products containing a natural estrogen ingredient or carrying a "hormone" label are considered unapproved new drugs. Rulings for the case of pregnenolone acetate or progesterone specifiy maximum usage levels. Cosmetic products containing placental extract may also be deemed to be unapproved drugs or misbranded cosmetics if hormones and other biologically active substances have not been removed from the extract.

The FDA maintains the traditional view that cosmetic products that contain vitamins may be considered misbranded if the labeling implies that the vitamins offer any kind of nutrient or health benefit or if the vitamin is not listed in the ingredient declaration by its chemical name.

Cosmetic Color Additives

Color additives must be approved by the FDA through regulation before they may be used in cosmetic products. Cosmetics that contain color additives not covered by a regulation are adulterated. The regulations list the color additives that may be used in cosmetic products and set forth color specifications, permitted diluents, areas of permitted application, concentration limits in the final product, and required label warning statements (21 C.F.R. §§73 and 74). The list of permitted color additives is divided into those that must be batch certified prior to sale (all "FD&C" and "D&C" colors) and those that are the so-called "natural" colors for which no certification is required. Most certified colors have not been authorized for use in products intended for the eye area. The exceptions currently are FD&C Yellow 5, FD&C Green 5, FD&C Blue 1, and FD&C Red 40.

The FDCA defines a color additive as "a material which—

(a) is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and

(b) when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with another substance) of imparting color thereto; except that such term does not include any material which the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring.
(c) The term "color" includes black, white, and intermediate grays."

The FDA regulations identify a food ingredient that imparts its own natural color when mixed with other foods as a color additive if it is deliberately used to color a product, for example, beet juice in a lotion. The FDA also considers ingested drugs intended to impart color to the body as color additives, for example, canthaxanthin tablets. Finally, the FDA considers suntan accelerators, such as bergapten, tyrosine, or synthetic melanin, as unapproved new drugs when they are represented as tanning accelerators.

The FDA regulations provide a limited exception to the color additive definition for substances that are intended or used solely for a purpose(s) other than coloring. The substance must be used in a way that any color that is imparted is "clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned." The exemption will not apply if the primary, but not the sole, purpose of the material is other than to impart color. This leaves a narrow loophole that the FDA has not further defined, although some producers have toyed with metallic and plastic materials that arguably also impart color to cosmetics.

Hair Dyes

Finally, as discussed above, coal tar hair dye colors are not included in the statutory definition of a color additive and therefore can be used without prior FDA approval. The Act's prohibition of the use of "poisonous or deleterious substances" in cosmetic products does not apply to coal tar hair dyes as long as the statutory warning statement appears on the product containers: "Caution—This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to the accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness."

Preservation

One of the FDA's chief concerns has been the potential for microbial contamination of cosmetics. The FDA considers cosmetic products that contain alcohol (10% or more) and cosmetics in self-pressurized containers (aerosols) to be self-preserved. All other cosmetics are susceptible to contamination by various microorganisms, some of which may be pathogens. An adequate preservation system is therefore needed to maintain the purity of the product, both at the

point of production and also during the lifetime of its use. While the FDA has not published official microbial standards, industry and the FDA use the following criteria as benchmarks:

- Cosmetic products may not contain any gram-positive or gram-negative pathogens.
- Cosmetic products, except for eye area and baby products, may not contain more than 1,000 microorganisms per colony g or ml.
- Eye area and baby products may not contain more than 500 microorganisms per g or ml.

Individual companies use internal standards, many of which are more stringent. For additional details Chapter 14 should be consulted.

Registration of Non-U.S. Drug Manufacturers

The FDA Modernization Act requires that all foreign (that is, non-U.S.) drug manufacturing establishments register with the FDA. The registration requirement applies to manufacturers of both prescription and nonprescription (OTC) drugs. This is not expected to have a great impact, however, since for some time the FDA has required that foreign drug manufacturers submit a portion of the drug establishment registration form to the agency as part of the drug listing procedure. The drug listing requirements have always applied to both domestic and non-U.S. drug manufacturers.

Many products considered to be cosmetics in other countries are regulated in the United States as OTC drugs. These products include antiperspirants, antidandruff shampoos, sunscreen products, skin protectants, skin lighteners, acne products, anticaries and antiplaque dental products, hair loss prevention/hair growth promotion products, and antibacterial hand and body cleaners. The FDA does not inspect the production facilities of foreign OTC drug makers for compliance with current Good Manufacturing Practices (GMPs). The FDA does not expect to review OTC drug ingredients (within the parameters of the OTC drug review program) unless the ingredients were marketed for use in the same drugs in the United States before the cut-off date of inclusion in the OTC review, that is, before December 4, 1975.

Industry Response

The safety of cosmetic components and the safe use of finished products is not just a legal requirement as interpreted by the FDA but is a major concern to the cosmetic industry. The industry also has a stake in the continued safety of cosmetics, if for no other reasons than to avoid bad publicity, product liability, and the possibility of mandatory controls. Industry has to a large part filled that void, both through private company studies of new ingredients (to substantiate ingredient and product safety as required by the FDA cosmetic regulations) and through funding of cosmetic ingredient safety reviews conducted by the

International Fragrance Research Institute (IFRI) and its national members, and the CIR. The CIR was established in 1976 by the CTFA to facilitate safety review and assessment of ingredients used in cosmetics in an open, unbiased, and expert manner. The review is conducted by an independent panel of individuals recognized as experts in the fields of dermatology, toxicology, chemistry, and related disciplines. Although funded by the CTFA, the CIR has emerged as a credible source of safety evaluations and to date has reviewed more than 735 ingredients, the final reports of which are published in the *International Journal of Toxicology*. In addition to the expert panel, the CIR meetings are also attended by nonvoting representatives from the industry, the FDA, and the consumer community.

The CIR addresses all types of information on the safe usage of cosmetic ingredients. CIR's recent request for information from botanical suppliers concerning the identity and safety of plant-based cosmetic materials is typical. Another case concerns the use of α-hydroxy acids. The FDA has concentrated on the ingredient's safety by conducting safety evaluation simultaneously with that of the CIR. The CIR's conclusion that α-hydroxy acids are safe for use in cosmetics at up to 10% is not disputed by the FDA. On the other hand, the FDA has not issued a final ruling on the potential drug status of α-hydroxy acids.

Developed scientific evidence shows that most topically applied substances affect the structure or function of the skin. The FDA appears to be willing to rely on the safety judgment of external safety assessors and to permit the marketing of "active" cosmetic ingredients, as long as the intended result is couched in cosmetic terms. The CIR is therefore likely to increase its activities as long as industry believes it provides an alternative to mandatory safety reviews. The CIR is clearly the industry forum of choice for the assessment of cosmetic ingredient safety; for the FDA, the CIR safety decisions are attractive because the latter provides a credible safety assessment without infringing on the ingredient's regulatory classification. The other safety assessment of ingredients available to the FDA is the National Institutes of Health (NIH) and the National Toxicology Program (NTP). A case in point is the safety evaluation of cosmetic ingredients, such as di- and triethanolamine (DEA and TEA). More recently, the NTP has been asked by the National Cancer Institute to test dihydroxyacetone (DHA) for skin penetration because of increased consumer exposure to "sunless" tanning products and suspicion of genotoxicity. Both the NTP and the FDA are likely to test DHA for percutaneous penetration using a human skin model.

LABELING

Cosmetic Labeling

The FDA has issued detailed rules for the labeling of cosmetic products under the authority of the FDCA and of the FPLA (21 C.F.R. §701). Because the

FPLA requirements apply only to the outermost containers of retail packages, the regulations for the cosmetic ingredient declarations, product identity statements, and placement and type size of net content declarations apply only to the outermost retail container.

Product Identity. The product identity may be the common name of the cosmetic, a descriptive name, or a fanciful name (if the nature of the cosmetic is otherwise obvious). Product identity statements nevertheless often appear on exempt products and inner containers in order to avoid consumer confusion if the use is not evident and to deter potential misuse that could result in injury and product liability suits.

Net Content (in English and Metric Units). The net content should appear in English and metric units in the lower third of the Principal Display Panel (PDP) in lines parallel to the bottom of the package.

Name and Address of the Manufacturer. The name and address of the manufacturer must identify the actual corporate name; trade names and company divisions are insufficient. If the name that appears on the container is not that of the manufacturer, it must be prefaced by an explanatory phrase such as "Distributed by," "Manufactured for," "Packaged by," or a similar description. The name and address must be placed conspicuously on the product, although specific type size and placement are not stipulated.

Ingredient Declaration. The ingredient declaration must appear on the outermost retail container of all cosmetics. The primary purpose of ingredient labeling is the need to alert users to idiosyncratic responses to a cosmetic ingredient. The FDA regulations permit three different formats for the ingredient declaration:

(1) In order of predominance in the product by weight or volume.
(2) In order of predominance, except that color additives may be grouped at the list's end without regard to predominance.
(3) In order of predominance, except that ingredients in the product at 1% or less may be grouped at the list's end without regard to predominance.

Contrary to a common misperception, all of the ingredients in the cosmetic product must appear in the declaration. The only exceptions to this rule are incidental ingredients and ingredients that the FDA has confirmed in writing as being trade secrets.

Label Warnings Required by Regulation. Warning statements are required by regulation for aerosol products, foaming bath products, feminine deodorant sprays, and hair dyes and, as discussed earlier, for products without adequate

safety substantiation (21 C.F.R. §740). Warning statements must be conspicuous and prominently displayed on both the inner and the outer containers. Most recently, as a by-product of the FDA's final monograph for sunscreen OTC drug products, the FDA added the following new warnings for suntanning preparations: "Warning—This product does not contain a sunscreen and does not protect against sunburn. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn."

Expiration Dating. Expiration dating and lot or batch codes are not required by specific regulation for cosmetics. Most companies include an expiration date if the product is not likely to be sold and used within its period of stability. In addition, lot and batch codes are commonly added to the cosmetic product labeling to facilitate recall and identification of products in the marketplace, in accordance with good manufacturing practices.

Country of Origin. The country of origin must be identified. U.S. Customs Service regulations require that all imported cosmetic products be marked with the country of origin, or if direct marking is not possible, that the product containers identify the origin of the contents.

Hypoallergenicity. Hypoallergenicity is a term intended to describe cosmetics with a reduced tendency to elicit sensitization. Although the proposal was subsequently withdrawn as a result of a judicial challenge by industry members, some of the concepts related to substantiating a claim to hypoallergenicity have subsequently been accepted by industry. Thus, companies that claim product hypoallergenicity are generally prepared to show that each step in the formulation and production of the product was designed to minimize the creation or addition of allergens.

Tamper-evident Packaging. Tamper-evident packaging is required by the FDA for cosmetic liquid oral hygiene products, such as mouthwashes, and feminine hygiene products. These products must be packaged in an immediate container or outer packaging system that includes an indicator or barrier to show when tampering has occurred. The indicator or barrier must be identified with a proprietary symbol that cannot be easily duplicated, and the location and nature of the tamper-evident feature must be described on the packaging or container. A description of acceptable packaging appears in the FDA's Compliance Policy Guide.

OTC DRUGS

Relationship of Cosmetic Products to Drugs

The distinction between cosmetic and drug products is based on the definitions of these articles in the FDCA. The definitions are not mutually exclusive, and a

product can be both a drug and a cosmetic, in which case the product must meet the applicable requirements for both categories. As drugs may be marketed only if the FDA determines that they are generally recognized as safe and effective for their intended uses, classification as a drug raises the regulatory burden. The statutory definitions of cosmetics and drugs were provided earlier in the text.

Over the years, the FDA has regularly challenged representations for cosmetic products it considers either false and misleading or those that fall within the FDCA's drug definition.

As most companies faced with misbranding or new drug charges choose to modify product labeling rather than to develop the data required to support drug approval, only a few judicial decisions address the cosmetic-drug distinction in any detail. The chief cases stem from the 1960s, at which time the FDA initiated civil seizures of three skin care products widely promoted to smoothen, reduce, or prevent wrinkles. The decisions in these litigations confirmed the FDA's position that wrinkle removal claims make such products drugs under the FDCA.

Since these cases were decided, the FDA has taken administrative action against products represented for uses the Agency believes are intended to affect the structure or function of the user's body. In a letter to cosmetic skin care companies in 1987, the FDA stated that

> *We consider a claim that a product will affect the body in some physiological way to be a drug claim, even if the claim is that the effect is only temporary. Therefore, we consider most of the antiaging and skin physiology claims to be drug claims. For example, claims that a product "counteracts," "retards," or "controls" aging or the aging process, as well as claims that a product "rejuvenates," "repairs," or "renews" the skin, are drug claims."*
>
> *The FDA further stated "we would not object to claims that products will temporarily improve the appearance of outward signs of aging. . . . We would consider a product that claims to improve or to maintain temporarily the appearance or the feel of the skin to be a cosmetic. For example, a product that claims to moisturize or soften the skin is a cosmetic. (Letter from John M. Taylor, Associate Commissioner for Regulatory Affairs, to Stuart Friedel, Davis & Gilbert, re: Cosmetic Regulatory Letters, November 19, 1987.)*

In the same letter, the FDA stated that a cosmetic product represented for nonprescription, over-the-counter (OTC) drug purposes will be held to the applicable OTC drug standards. Other representations that the FDA has considered to be either misleading cosmetic claims or unapproved new drug claims include anticellulite and skin renewal effects that are described as affecting the structure or function of the body.

The "cosmetic" and "drug" definitions have not changed since the FDCA was enacted in 1938. In the meantime, cosmetic producers have become

more sophisticated, and the line between cosmetic and drug products has often blurred. Although the FDA has recognized in OTC drug review documents that limits for materials used in drug products do not apply when used in cosmetic products, the presence of certain ingredients in a cosmetic product is nevertheless likely to cause its regulation by the FDA as a drug. These tend to be the ingredients for which no cosmetic use is known (for example, penicillin) or which have been heavily promoted by the manufacturer for drug purposes (for example, the UV absorber avobenzone). The FDA's response to date to technology advances such as fluoride toothpaste, antiperspirants, and sunscreens has been to designate and regulate the products as drugs.

OTC Drugs and Their Status

One of the consequences of drug status is that the product moves from regulation by the FDA Office of Colors and Cosmetics to regulation by the Division of OTC Drugs in the Office of Drug Evaluation.

The OTC Drug Review Process was initiated in 1972 as a way to assess the safety and effectiveness of OTC drugs on the U.S. market prior to the cut-off date of December 4, 1975, or drugs so similar in composition, dosage form, and intended use as those on the market as to present no additional safety or effectiveness questions. The review involves a three-step process: initially, advisory committees of medical and other experts review the active ingredients in each OTC drug category, such as sunscreens, and publish a report for public comment. The FDA then publishes a proposed rule based on the advisory committee report and the comments received, and after review of the comments on the proposal, the FDA publishes a final rule. The final rule–or monograph–sets forth the permitted active ingredients, concentrations, ingredient combinations, occasionally the dosage form and test methods, and the required labeling for each OTC drug product category. As long as a drug product complies with the monograph conditions, it is exempted from new drug status and may be marketed without prior FDA approval.

Some drugs classified by the FDA as OTC drugs have been categorized as cosmetics in the past in the United States and are considered as cosmetics in other countries. The OTC classification is unique to the United States, and the OTC drugs that are widely viewed as cosmetics are discussed in various chapters in this book, especially Chapter 19.

Acne products (Chapter 22)
Antidandruff products (Chapter 19)
Antimicrobial products (Chapter 19)
Antiperspirant products (Chapter 21)
Astringent products (Chapter 19)

Oral care products (Chapter 33)
Skin protectant products (Chapters 18 and 19)
Sunscreen products (Chapter 20)
External analgesic products (Chapter 19)

OTC Drug Labeling

Labeling of OTC drugs is similar to that required of cosmetics, such as the statement of identity, the net quantity of contents, the name and place of business of the manufacturer, packer, or distributor, the declaration of active ingredients, adequate directions for use, any warning statements required to prevent a health hazard, and expiration dating (if the product is stable for less than three years) [21 C.F.R. §201]. OTC drugs that are imported into the United States for sale in this country must also bear labeling that states the country of origin.

Current FDA regulations require nonprescription drugs, including cosmetic drugs, to carry labeling information in a uniform format and to separate the information from any other information such as cosmetic labeling. The principal display panel of OTC drugs must still bear the net content statement and established drug name. Additional required information includes (1) "Drug Facts"; (2) the active ingredients, including the amount in each dosage unit; (3) the purpose of the product, for example, skin protectant; (4) the indications for use as permitted in the appropriate FDA OTC monograph; and (5) any applicable warnings. If side effects may occur, purchasers are alerted to seek professional help.

In addition, OTC labeling must declare all the inactive ingredients. In the case of a product represented solely as an OTC drug, the inactive ingredients should be listed in alphabetical order. In the case of OTC drugs represented for cosmetic as well as drug uses, the inactive ingredients should be listed in order of predominance in accordance with the applicable cosmetic regulations.

Some final monographs covering the (cosmetic) OTC drugs have not been published by the FDA despite passage of the Modernization Act by Congress in 1977. Until the issuance of the final monographs, industry operates in compliance with the existing "tentative final monographs."

Inspection of OTC Drug Facilities

The FDA Modernization Act expands the permissible scope of the FDA inspection of OTC drug facilities, including cosmetic-drug manufacturing plants, many of which also make purely cosmetic products. Inspectors will now have access to the same records and items previously only requested during inspections of prescription drug establishments. The FDA has always been authorized to inspect the factory, warehouse, establishment, or vehicle in which regulated products are made, processed, packed, or held the packaging,

labeling, ingredients, and finished goods in them. The FDA may now also inspect the records, files, papers, processes, controls, and laboratory results in factories, warehouses, establishments, and consulting laboratories in which OTC drugs, including the so-called cosmetic-drugs, are manufactured, processed, packed, or held. The inspector may not have access to any financial data, sales or personnel data, other than shipping records and personnel qualifications of technical and professional staff, or to research data, unless it pertains to new drugs, biologicals, or devices. The FDA has indicated that the inspection of cosmetics-only facilities will be limited to "for cause" visits, such as follow-up to product recalls, complaints, and safety-related problems. Since the FDA shares its inspection duties with state food and drug inspection teams, some routine inspection of cosmetic facilities may still take place. This is already apparent in the discussions of cosmetic-drug safety and efficacy within the framework of the OTC Review.

CURRENT CONCERNS

Antimicrobials

Safety will continue to be a major issue for the cosmetic industry, as new–and frequently adverse–information about cosmetic ingredients emerges. For example, it has recently been reported that the use of triclosan can lead to bacterial resistance and that the use of triclosan in hand soaps and hand washes may be accelerating the process. Triclosan is also used in consumer products such as toothpaste, deodorants, body washes, hand sanitizers, and soaps and washes for household items. The FDA and other agencies are currently reviewing triclosan's use as an antimicrobial drug agent in body and hand wash products, both in regard to its effectiveness and in regard to its role in antimicrobial products in the development of bacterial resistance.

The question is one of public health policy, that is, whether there are any benefits to be derived from the use of antimicrobials in hand and body soaps, and if these benefits are worth the risk of increase in bacterial resistance due to the ubiquitous use of these substances. Industry has argued that antibacterials in personal soaps reduce bacteria that may cause diseases, while the FDA has suggested that antimicrobial soaps are no more effective than are ordinary soaps at reducing bacteria on the skin surface. Based on this assumption, the FDA deleted the OTC personal antimicrobial hand wash category from its proposed regulation of topical OTC antiseptic drugs. The FDA does not regulate the use of triclosan in cosmetic products, including cosmetic soaps that are not represented for antimicrobial purposes. However, if triclosan or any other antimicrobial were to be determined to be unsafe or a danger to public health, the FDA could limit or prohibit triclosan's use in cosmetics through its customary notice and comment procedures.

At the time of writing this book the future cosmetic/OTC/drug status of triclosan and other topical germicides was uncertain. For example, the FDA has requested studies to determine the dermal penetration and bioavailability of benzethonium chloride in different OTC drug vehicles and formulations. Broadening of the OTC drug review to include formulations and dosage forms presumably not on the market is evidently included in the FDA's regulatory responsibility. The recently published "final monograph" for sunscreen drug products for OTC human use [Fed. Register **64**, 27666–27693, May 21, 1999] is evidence that the FDA can be expected to issue other final monographs. This monograph includes 16 sunscreening agents and combinations but fails to identify acceptable excipients. The monograph describes procedures for determination of the sun protective factor (SPF) and of the product's water resistance; these procedures differ from those acceptable in other countries.

International Concerns

Three matters in the early stages of development are likely to open the doors further to using the OTC Drug Review procedures for new ingredient and OTC drug product approvals: (1) the FDA's advance notice of proposed rulemaking to expand the OTC Drug Review to make products sold for a material time and extent outside the United States eligible for inclusion in the Review; (2) the petition filed by the European-American Phytomedicines Coalition (EAPC) requesting that the OTC Drug Review include herbal medicines marketed for a material time and to a material extent in Western Europe; and (3) the petition filed by the CTFA requesting that the FDA harmonize its cosmetic regulations with those of the E.U. by accepting the safety of ingredients on the E.U. cosmetic positive lists such as sunscreens.

Likewise, the CTFA submitted comments endorsing harmonization of the United States and the E.U. cosmetic requirements to the Transatlantic Business Dialogue, a multiindustry group interested in developing a closer transatlantic economic partnership. The CTFA is interested in the universal adoption of the International Nomenclature Cosmetic Ingredients for cosmetic ingredient labeling and, as mentioned, the FDA recognition of the E.U. safety decisions on positive list ingredients that are regulated in the United States as OTC drug substances.

None of these matters will be quickly resolved and may require judicial review. At the moment, the FDA is an active participant in efforts to eliminate direct conflicts in regulatory requirements for pharmaceutical products through various organizations, including the Office of Economic Development (OECD) and, more recently, the International Conference on Harmonization (ICH). For all these reasons, the FDA's treatment of "cosmetic-drugs" will likely be more

internationally focused despite legal and budgetary restraints and industrial pressures.

Regulation of Cosmetics by Other Agencies

The Federal Trade Commission (FTC) and the FDA have overlapping and concurrent jurisdiction over the advertising and labeling of foods, drugs, medical devices, and cosmetics. The FTC regulates "deceptive" or "unfair" advertising, including promotional claims that appear on packages or in the media, and is chiefly concerned that the consumers have reliable, substantiated information upon which to base purchasing decisions.

The FDA regulates "false or misleading" statements made in product "labeling" and, although its jurisdiction extends to economic deceptions, the FDA is primarily concerned that the public health and safety are not endangered through consumer reliance on unsubstantiated claims to safety and effectiveness. As part of the agreement between the two agencies, the FTC and the FDA exchange information about enforcement proceedings as needed. The FTC regulates advertising claims through industry wide rulemakings, through administratively adjudicated cease-and-desist orders entered against specific companies, through issuance of FTC Policy Guidelines, and through prosecution of specific cases in the federal courts. An FTC investigation of advertising claims may be prompted by requests made by consumers, competitors, state officials, or the Commission itself. Advertising claims may be considered deceptive because they contain a "material" representation, omission, or practice that is likely to mislead consumers "acting reasonably under the circumstances."

An FTC request for substantiation is nonpublic and is "directed to individual companies via an informal access letter or, if necessary, a formal civil investigative demand." Requests may be directed to one company or to several companies within the same industry. Unless the claim made in advertising is substantiated, the advertiser may be held to have violated the prohibition Section 5 of the Federal Trade Commission Act (FTCA), which prohibits "unfair or deceptive acts or practices in or affecting commerce."

Cosmetics and the Consumer Product Safety Commission. Cosmetics are explicitly excluded from regulation under the Consumer Product Safety Commission (CPSC). However, in the absence of the FDA jurisdiction, CPSC has regulated such items as soap. The CPSC also has authority to issue regulations establishing special packaging requirements under provisions of the Poison Prevention Packaging Act.

Regulation of Cosmetics by the States. Each state has the authority to regulate products and to impose additional requirements that do not conflict with federal

regulation of cosmetics. Most states have adopted "mini FDC Acts" that in general are identical to the federal statute. Some states, however, go beyond the FDCA to require registration of cosmetic establishments and products.

Furthermore, state environmental legislation has tended to include cosmetic products and ingredients. For example, at the time of this writing, at least eight states have either proposed or issued regulations restricting the levels of volatile organic chemicals in cosmetic products such as deodorants, fragrances, and/or hair products; similar regulation by a federal agency, the Environmental Protection Agency (EPA), is expected. California's Proposition 65 requires a warning statement on products that contain ingredients known to the state to be carcinogenic or reproductive toxins. Other states are beginning to actively regulate the composition and disposal of plastic and other cosmetic containers.

REGULATORY REQUIREMENTS FOR COSMETICS IN THE EUROPEAN UNION

LEGAL ASSESSMENT

The E.U., at the time of this writing, comprises the following Member States: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, and the United Kingdom. Before the recent admissions of the latest Member States, the term European Community was used and the legislation is still referred to by the abbreviation E.C.. There are a number of Central and Eastern Europe countries that are negotiating with the E.U. The major requirements for joining the E.U. are economic, but a consequence of joining the E.U. is alignment of legislation on cosmetic and medicinal or drug products with those of the E.U. In addition, there are some nonmember countries with close economic ties to the E.U. that have aligned their cosmetic regulations to match closely those of the E.U.. Thus the number of countries that are adopting the E.U. model of cosmetic product regulation is increasing.

The population of the E.U., especially after the entry of additional countries, far exceeds that of the United States and dwarfs that of Japan. Thus the efforts to harmonize definitions, nomenclature, and safety concerns are likely to impact the sale and distribution of cosmetic products significantly. Those requiring up-to-date information are forced to consult regulations in this changing environment. Even the well-established rules in the United States may not escape revisions in the future.

Legislation Governing the Sale of Cosmetics in the European Union

The regulation governing the sale of cosmetic products in the E.U. is the 1976 EC Cosmetics Directive [4]. This directive was originally drafted as an economic instrument for harmonization to ensure that goods could freely move

throughout the European Community constituted at that time. The legislation was required to harmonize the regulations in the different Member States and to allow a free market to develop. However, this 1976 directive, while achieving a great deal, nevertheless fell short of its main objective, and subsequent negotiations created a substantial revision, known today as the 6th Amendment [5]. In order for an EC Directive of this type to take effect in the Member States, the legislation must first be incorporated into the law of each separate State, so directives require some time before they have practical effect.

In recent years, the cosmetics directive, originally a harmonization directive with an economic purpose, has evolved into an instrument for the regulation of quality, safety, and efficacy of cosmetic products manufactured and sold in the E.U.

A detailed discussion of the most relevant provisions of the Cosmetics Directive as far as product formulators are concerned will follow in this chapter.

Differences within the Member States in the structure of their national legislative and regulatory frameworks affect the interpretation of E.U. regulations in the individual States. Most of these differences arise from historical decisions and interpretations of national law and reflect how the different regulatory authorities dealt with the borderline between the different product types. The legislative borderline of most concern to the cosmetic product manufacturer is that between cosmetic and medicinal products. This is largely a problem of product claims, and it cannot be assumed, for example, that a given claim for a cosmetic product that is acceptable to the regulatory authorities in the U.K. will be viewed in the same way in France.

Few court decisions that explore the borderline between cosmetics and other products exist at both the national and the European level. To ensure that a product falls into the definition of a cosmetic, close attention has to be paid to the claims for the product, the ingredients in the formulation, and the presentation of the product.

E.U. Legislation Governing the Sale of Medicinal Products

In the E.U. a medicinal product is defined as follows:

> *Any substance or combination of substances presented for treating or preventing disease in human beings or animals. Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis, or to restoring, correcting, or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.*

Whereas the Cosmetics Directive defines a cosmetic product as:

> *Any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips, and external genital organs) or with*

the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, 'and' or 'or' correcting body odors, and/or protecting them or keeping them in good condition.

Unlike in the United States, it is not possible for a product to be both a cosmetic and a drug; it can only be one or the other. In order to decide whether a product is cosmetic or medicinal a number of factors must be considered, including the claims that are made, the presentation (that is, the packaging, color, and similarity to medicinal product packaging), how the product is marketed and sold (for example, through pharmacies or supermarkets), and the contents of the formulation. The ingredients that are used in the formulation may appear to be important, but of the factors mentioned the claims are usually the most significant in deciding the classification of a product. Often marketers are keen to push the claims of cosmetic products to the limits, and this is where they frequently come into conflict with their regulatory colleagues and with the authorities.

There is a current vogue for so-called cosmeceuticals; however, this term is not recognized in the E.U. legislation; products are either medicinal or cosmetic.

Certain products are categorized differently in the United States, in the E.U., and in Japan. Examples include sunscreens, antiperspirants, antidandruff shampoos, and toothpastes containing fluoride. It is true to say that products classified as cosmetics in the E.U. may be classified in the United States and in Japan as medicinal products, whereas the reverse is not usually the case. European formulators of cosmetic products need to be aware that in developing products such as sunscreens for marketing in the United States, the regulations will have a restrictive impact on the claims, labeling, and manufacturing of such products.

FEATURES OF COSMETIC PRODUCT REGULATION IN THE EUROPEAN UNION

The Cosmetics Directive consists of two parts: the text (Articles) and the Annexes. The text of the Directive itself is rarely modified, the last revision being the 6th Amendment in 1993. Attached to the Directive is a series of Annexes, which contain the lists of substances that are subject to restriction. The Annexes are revised on a yearly basis, and it is essential that formulators keep up to date with the revisions because the entries in the lists of various substances determine what may be used in product formulations and at what levels, in some cases. Amendments to the Annexes are published in the *Official Journal* (of the European Communities), and revisions are widely reported in the cosmetic industry press.

The Cosmetics Directive addresses the three key aspects of product–quality, safety, and efficacy. Those familiar with drug legislation will recognize that these three aspects of a product are given equal weight with respect to premarketing approval and registration of medicinal products. Cosmetics legislation in the E.U., in common with that of other countries, places the emphasis with regard to control of cosmetic products on the safety aspects of such products, with emphasis also on quality (but in regard to safety). However, the 6th Amendment took the first steps toward placing a greater emphasis on the quality and efficacy aspects of product than had hitherto been the case, as it introduced a requirement for cosmetic product manufacturers to be able to demonstrate the efficacy of their products where strong and nongeneric claims are made for formulations and their performance, and mandated the need for a Product Information Package (also referred to as the Technical Dossier).

To help in understanding the various aspects of the regulation of cosmetics in the E.U. it is useful to discuss the following seven points:

1. Ingredients
2. Safety assessment
3. Labeling
4. The Product Information Package
5. Good Manufacturing Practice
6. Efficacy testing
7. Animal testing.

COLIPA, the organization in the E.U. that represents the national cosmetic industry associations, has issued a series of technical guidelines to help manufacturers comply with the requirements of the Cosmetics Directive.

Ingredients

The E.U. model for regulating cosmetic ingredients is situated between the regulations in the United States and in Japan. In general, any ingredient may be used in a cosmetic product formulation, provided it is not listed as a banned or restricted substance, and provided that the manufacturer has sufficient data to show that the ingredient is safe. In this respect the E.U. legislation resembles that of the United States; however, unlike the United States and similar to the positive listing model of Japan, certain ingredients merit special attention. These ingredients may only be used for the purposes and in the quantities specified in the Annexes to the Directive. Furthermore, the inclusion of certain ingredients will trigger a labeling requirement, also defined in the Annexes.

The Annexes to the Directive are organized by function as follows:

Annex II—List of substances that must not form part of the composition of cosmetic products (banned substances)

Annex III—List of substances that cosmetic products must not contain except subject to the restrictions and conditions laid down (restricted substances)

Annex IV—Colors

Annex V—Excluded substances

Annex VI—Preservatives allowed

Annex VII—UV filters allowed.

These ingredient listings are subject to change, and formulators must continuously monitor the latest regulations covering cosmetic raw materials. There is not sufficient space here to list all the entries in all the Annexes or to discuss each entry in detail; what follows is a summary of the contents of each Annex and examples of some of the materials that are controlled via these listings.

Annex II (Banned Substances). This currently contains hundreds of entries and includes among others drug substances, toxic plant materials, heavy metals, and coloring materials. The last entries banned are crude and refined coal tars, 1,1,3,3,5,-pentamethyl-4,6-dinitroindane (moskene), and 5-*tert*-butyl-1,2,3-trimethyl-4,6-dinitrobenzene (musk tibetene). At the time of this writing, the Scientific Committe for Cosmetic and Non-Food Products (SCCNFP) faces the complicated issue of banning diethanolamine (DEA)-containing products because of nitrosamine formation. The presence of traces of the substances listed in Annex II is allowed, provided that such presence is technically unavoidable in good manufacturing practice and that the formulation conforms to the general safety requirement.

Annex III (Restricted Substances). This Annex currently includes a diverse range of substances; for example, the active ingredients used in fluoride toothpastes are listed. These materials are restricted to a maximum concentration of 0.15% calculated as F and, when mixed with other fluorine compounds permitted under Annex III, the total F concentration must not exceed 0.15%. Toothpaste products must be labeled on the primary and secondary containers with the active material, for example, "*Contains Sodium Fluoride.*"

Another example is triethanolamine, the use of which is restricted under an entry for trialkanolamines in non–rinse-off products, with the additional restrictions: "Do not use with nitrosating systems. Minimum purity 99%. Maximum secondary alkanolamine content 0.5% (concerns raw materials). Maximum N-nitrosodialkanolamine content 50 μg/kg. Keep in nitrite-free containers." SCCNFP is considering the inclusion of diethanolamine salts in Annex II and related restrictions.

Annex IV (Colors). Like the United States and most other countries that have well-developed cosmetic product regulations, the use of colors is tightly

controlled. Only those colors that are positively listed may be used, and these are further subdivided into area of use:

1. Coloring agents allowed in all cosmetic products
2. Coloring agents allowed in all cosmetic products except those intended to be applied in the vicinity of the eyes, in particular eye makeup and eye makeup remover
3. Coloring agents allowed exclusively in cosmetic products intended not to come into contact with the mucous membranes
4. Coloring agents allowed exclusively in cosmetic products intended to come into contact only briefly with the skin.

Formulators need to be cautious in using colors in product formulations that are intended for the international market because there are differences between the coloring materials allowed in the above categories in the United States, in the E.U., and in Japan. The best reference guide to the permitted colors worldwide is the CTFA *International Color Handbook* [6], which contains comparative information by country.

Annex V (Excluded Substances). This Annex currently has no entries and requires no comment.

Annex VI (Preservatives). Only those preservatives listed in Annex VI may be used in cosmetic products at the maximum concentrations allowed (if specified) and subject in some cases to product type (area of application). In addition, the use of certain preservatives will trigger a labeling requirement (e.g., chlorobutanol is allowed at a maximum concentration of 0.5% but prohibited in aerosol dispensers (sprays) and must be labeled with *"Contains Chlorobutanol"*). It is recognized that certain preservatives may also be used in cosmetic products as "active" antibacterials. Entries in Annex VI with a + symbol may be used at concentrations exceeding those specified if the purpose of their use is other than as a preservative. For example, triclosan is a widely used antibacterial substance, and its entry in Annex IV includes a +. It is permitted at a maximum concentration of 0.3% w/w when used as a preservative, but it may be used without restriction as an antibacterial 'active' and finds such use in deodorants.

The preface to this Annex also recognizes that certain other materials, such as essential oils, have preservative or preservative-enhancing properties. It is not allowed under E.U. legislation to claim that a formulation contains a "natural preservative" because a material cannot officially have a function as a preservative unless it appears in Annex IV, and this list includes no "natural" preservatives at the time of this writing.

Annex VII (UV Filters). About 20 UV filters are listed, together with allowable maximum concentrations. At the time of this writing there is only one entry for which there is a labeling requirement–Oxybenzone. Its presence as a UV sunscreen, up to a maximum of 10%, triggers the need for the phrase *"Contains Oxybenzone"* on the product label. However, it is permitted in formulations at a level not exceeding 0.5% to protect the color of the formulation; when used for this purpose no such labeling is required. UV-absorbing substances used for the purposes of protecting the skin from the effects of UV radiation are listed in Annex VII. Materials that have a UV-absorbing ability that may be used for product protection as opposed to skin protection are not listed. (Oxybenzone, which has this common dual purpose, is an exception). However, it is not allowable to make sunscreening and Sun Protection Factor (SPF) claims for materials that are not listed in Annex VII.

Addition of New Materials to the Annexes

The Annexes to the Directive are maintained by the SCCNFP. This Committee was established in 1978 to assist the European Commission in the application of the Cosmetics Directive and in 1982 issued "Guidelines for the Testing of Cosmetic Ingredients for Their Safety" (the "SCCNFP guidelines"). These guidelines were revised for the second time in 1997 [7] and established testing parameters that should be followed for the approval of (unlisted) raw materials. This latest edition is a very useful and comprehensive guide to safe testing of ingredients and finished products. The guidance notes are not intended to be a checklist. Instead, the SCCNCP stated that they can be adapted case by case, depending, for instance, on the ingredients used, the formulation of the finished product, and the degree and route of consumer application; in fact, the information outlined in the guidelines may not always be needed.

The guidelines recommend test procedures for the toxicity studies needed to evaluate different toxicological endpoints and to represent the basic toxicity testing procedures internationally accepted as being the result of long-term scientific agreement. These procedures include 27 studies based on in vivo animal models and 10 studies based on in vitro models (genotoxicity). However, the SCCNFP has accepted all types of testing procedures based on a scientifically justified model and procedure (for instance, in vitro studies on percutaneous penetration), or in accordance with Organization for Economic Cooperation and Development (OECD) Guidelines for the testing of chemicals.

Materials that are included in the list of banned substances (Annex II) usually appear after a safety concern is brought to the Commission's attention by a Member State. New preservatives and UV filters usually appear following an application for listing of a new material by a supplier.

In order to meet the need for information required by the E.C. Commission for ingredients requiring prior authorization (coloring agents, preservatives,

and UV filters), the SCCNFP Committee identified several tests as having relevance to the evaluation of the safety of a material.

1. Acute toxicity (oral or by inhalation for volatile substances)
2. Skin absorption
3. Skin irritation
4. Mucous membrane irritation
5. Skin sensitization
6. Subchronic toxicity
7. Mutagenicity
8. Phototoxicity and photomutagenicity (in the case of UV light–absorbing substances)
9. Human data (if available)

When considerable oral intake can be expected or when the data obtained on dermal absorption indicate a considerable level of penetration of the ingredients through the skin, the following further data may be required, after taking the toxicological profile and chemical structure of the substance into account:

10. Toxicokinetics
11. Teratogenicity, reproductive toxicity, carcinogenicity, and additional genotoxicity

The submitted dossier should include data on the identity and physicochemical properties of the chemical, and substances used in the toxicological studies should have specifications similar to those in the commercial material.

Test procedures and methodologies to be followed for toxicity studies are those given in guidelines included in Directive 87/302/EEC and in Annex to Directive 92/69/EEC (annexes to the Directive on the classification, packaging, and labeling of dangerous substances). It is acknowledged that at present there is no alternative but to use in vivo animal studies in most areas of toxicity testing. Persons conducting toxicity studies must take into account the requirements of Directive 86/609/EEC on the use of animals in toxicity testing of chemicals. Article 7.2 of this Directive requires that "*an experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonably and practically available*,"

The requirements given are specifically intended for those categories of ingredients requiring prior authorization, but they would also be considered applicable to any other new cosmetic ingredient. A cosmetic ingredient that is classified as a "new" chemical substance under the E.C. legislation on chemicals is not exempt from the requirement for premarketing notification under the chemicals legislation. Hence, a new chemical intended for use as a preservative in cosmetic products requires notification under the chemicals

legislation as well as prior authorization for use under the Cosmetics Directive. A new chemical intended for use as an emulsifier in cosmetics would only require premarketing notification under the chemicals legislation. In both cases, notification as a "new" chemical would require the generation of the Base Set of data if the substance was to be marketed in quantities of one ton or more per year. The toxicity data requirements of the Base Set cover items 1, 3, 4 (eye irritation), 5, 6 (subacute toxicity), and 7 (mutagenicity) of the requirements of the SCCNFP guideline outlined previously.

Special Requirements for Sunscreen Materials

The SCCNFP guideline recognizes that substances used as sunscreen agents require a distinct type of safety evaluation. Annex 2 to this Guideline gives specific requirements for testing for phototoxic effects–photoirritancy, photosensitization, and photo-mutagenicity Testing for photoirritancy and photosensitization will be required on all new sunscreen agents, and photo-mutagenicity testing will be required unless evidence of complete stability of the substance after 10 hours' exposure to solar simulated radiation is provided.

The SCCNFP guideline contains no specific requirement for data from human studies, although clearly any data obtained from testing in humans will be relevant to the overall safety assessment of a cosmetic ingredient.

SAFETY ASSESSMENT OF FINISHED PRODUCTS

The Directive requires that:

> *A cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use, taking into account, in particular, the product's presentation, its labelling, any instructions for its use, and disposal as well as any other indication or information provided by the manufacturer or his authorised agent, or by any other person responsible for placing the product on the Community market.*

How a manufacturer complies with this requirement is addressed by guidelines issued by COLIPA [7] and by the SCCNFP [8]. The safety assessment must be carried out by a qualified person and must be kept available for inspection by the regulatory authorities of the Member States as part of the Product Information Package (PIP), which is discussed later in this segment. In making an assessment of the safety of the finished product for human health, the Directive advises:

> *The manufacturer shall take into consideration the general toxicological profile of the ingredient, its chemical structure, and its level of exposure.*

In practice this means that a manufacturer has to have available a toxicological profile of the finished product, including all its constituent ingredients, and a signed safety statement by a qualified person who has to be qualified

in the disciplines of pharmacy, toxicology, dermatology, medicine, or similar areas of study, for inspection on demand. The assessment of the safety for human health has to be accessible to the competent authorities of the Member States; it must be transparent and accurately documented; any testing must be carried out in accordance with the principle of Good Laboratory Practice. The SCCNFP "Notes of Guidance for Testing of Cosmetic Ingredients for Their Safety Evaluation" state that the safety evaluation of finished products can in general be based on knowledge of the ingredients' toxicity, provided supplementary information is available in certain cases: when the vehicle used in the formulation is different from the solvents used in the toxicity tests and when there is a likelihood of an increase in skin penetration or skin irritation; and when a new, potentially toxic substance is liable to be created through the combination of ingredients present in the finished product.

Details of the scientific reasoning adopted by the safety assessor must be set out in the safety assessment. This should cover all intended and likely routes of human exposure during use. The SCCNFP guideline recommends that the following factors must at least be considered in calculating the exposure:

1. Class of cosmetic product(s) in which the ingredient may be used
2. Method of application; rubbed-on, sprayed, applied, washed off, and so forth
3. Concentration of ingredients in product
4. Quantity of product used at each application
5. Frequency of application
6. Total area of skin contact
7. Site of contact (e.g., mucous membrane and sunburned skin)
8. Duration of contact (e.g., rinse-off products)
9. Foreseeable misuse which may increase exposure
10. Nature of consumers (e.g., children and people with sensitive skin)
11. Quantity likely to enter the body
12. Projected number of consumers
13. Application on skin areas exposed to sunlight

All toxicological data available on the formulation and its ingredients, both favorable and unfavorable, should be taken into account, including an assessment of the potential for chemical or biological interaction of/in the formulated product. The safety assessor must clearly set out the specific reasons for his conclusions, taking into account the acceptability of the inclusion in the formulation of particular ingredients that may have a low safety threshold.

LABELING

The following information must appear on both the inner and the outer container, and must be indelible, easily legible, and visible. Unlike in the United States and in some other countries, there is no concept of a "Principal Display Panel" in E.U.

legislation. Items requiring labeling may therefore appear anywhere on the pack, provided that they meet the three criteria of indelibility, legibility, and visibility. However, common sense dictates that items such as the contents declaration cannot appear on the base of the container as this will then not be visible to the consumer at the point of sale.

Name and Address of the Manufacturer or Importer. This must be an address located in one of the 15 Member States. It may be abbreviated if the abbreviation makes it possible to identify the undertaking.

Contents. The nominal content at the time of packaging, given by weight or volume, using the metric system of measurement. The following are exceptions when this declaration does not need to appear: packages containing less than five grams or five milliliters, free samples, and single application packs. For prepackages normally sold as a number of items, for which details of weight or volume are not significant, the content need not be given provided the number of items appears on the packaging. This information need not be given if the number of items is easy to see from the outside or if the product is normally sold individually. At the time of writing, dual weight declarations are permitted (metric and U.S. foot-pound systems).

Expiration Date. The date of minimum durability is mandatory, except for cosmetic products that have a minimum stability of more than 30 months. The date of minimum durability of a cosmetic product is defined as *"the date until which a product, stored under appropriate conditions, continues to fulfill its initial function and, in particular, remains in conformity with Article 2 of the Directive"* (product safety). The date of minimum durability should be indicated by the words *"Best used before the end of ...."*

Instructions and Warnings. The label must include precautions that should be observed in use, especially the mandatory warnings listed in the column *"Conditions of use and warnings which must be printed on the label,"* which appears in Annexes III, IV, VI, and VII. As mentioned previously, these Annexes contain warnings related to the use of specific ingredients in cosmetic formulations as well as any special precautionary information on cosmetic products for professional use, in particular in hairdressing. Where it is impossible for practical reasons to include the instructions for use and warnings on the inner and outer containers, an enclosed leaflet, label, tape, or card must contain the information to which the consumer is referred either by abbreviated information or the symbol given in Annex VIII to the Directive (the "Hand and Book" symbol), which must appear on the inner container and outer container.

Batch Number. Where it is impossible for practical reasons because the cosmetic products are too small, this information need appear on the packaging only.

The Function of the Product. This does not have to appear if the function of the product is clear to the consumer from its presentation.

List of Ingredients. The following information is required to appear on the outer container only, and in normal circumstances this is the only item of labeling that does not have to appear on both the inner and the outer containers.

This list is to be in descending order of weight of ingredients at the time they are added, preceded by the word *ingredients*. Where this is impossible for practical reasons, an enclosed leaflet, label, tape, or card must contain the ingredients to which the consumer is referred either by abbreviated information (e.g., *"See leaflet for ingredients"*) or the symbol given in Annex VIII (the "Hand and Book" symbol), which must appear on the packaging.

All coloring agents used in the range may be listed for decorative cosmetic products marketed in several color shades preceded by the term *may contain*. The European Cosmetic Industry has adopted the symbol +/− preceding the colors, all enclosed in square parentheses [+/− *list of colors*] to denote *may contain*; this is the best way to deal with this topic as it is not language-specific.

Where it is impractical, for reasons of size or shape, for the instructions and warnings and the ingredients list to appear in an enclosed leaflet, they must appear on a label, tape, or card, that is enclosed or attached to the cosmetic product.

In the case of soap, bath balls, and other small products where it is impracticable for the ingredients listing to appear on a label, tag, tape, or card, or in an enclosed leaflet, they must appear on a notice in immediate proximity to the container in which the cosmetic product is presented for sale.

The system used for labeling of ingredients is the International Nomenclature of Cosmetic Ingredients. However, while close to the system used in the United States, there are important differences that arise because English is the official language of only two of the Member States. Certain of the nonEnglish speaking countries would not accept the use of terms for "common" ingredients in English (for example, water, liquid paraffin, and common names for plants). Hence the adoption of Latin terminology and, for plant names, the Linnaean botanical nomenclature. In this system, water becomes *aqua*, liquid paraffin is *paraffinum liquidum*, and plants have the Linnaean species names, for example, *Musa sapientum*. The use of the botanical name of a plant to refer to all extracts regardless of the part of the plant or the extraction process used means that the description is less specific than that used in the CTFA *International Cosmetic Ingredient Dictionary* [9].

The EC published a list in 1996 [10] of cosmetic ingredients currently in use on the basis of information submitted to it by the cosmetic industry, in which the official nomenclature is listed (more than 6,000 entries). It is important to

note that this is an indicative list. It is not a "permitted" list; ingredients that do not appear may be allowed in cosmetic products, provided that they meet the criteria for safety as outlined previously. The inventory will be updated regularly, and manufacturers are expected to obtain official names for new ingredients by application to the CTFA International Nomenclature Committee. For reasons of trade secrecy, manufacturers may wish not to include one or more ingredients on the aforementioned list and may apply for an exemption.

Perfume and aromatic compositions, and their raw materials are referred to by the words *parfum* and *aroma.*

Ingredients present in concentrations below 1% may be listed in any order after those in concentrations of more than 1%. Coloring agents may be listed in any order after the other ingredients, using the Color Index (CI) number.

Animal Testing. A reference to testing on animals on the product label or associated printed material must be clarified by statements that make it clear whether the tests carried out involved the finished product and/or its ingredients. Thus, statements such as *"This product has not been tested on animals"* are not acceptable without qualification to inform the consumer that, while the finished product has not been tested on animals, the ingredients have been tested on animals at some time in the past (if this is the case). This labeling requirement has been the subject of extensive lobbying and debate; the practical enforcement of this requirement is yet to be seen.

Country of Origin. At the time of this writing, there is no E.U. legislation governing the aspect of country of origin in product labeling; this is left to the Member States. If there is any likelihood that a consumer could think that a product has an uncertain origin, then it is wise to identify the country of origin on the label. In any case, many non-E.U. countries have this labeling requirement, so this will become a requirement for packages that are also intended for use outside the E.U..

Language. All Member States require that certain of the label information is in a language that can be understood by the consumers, and the national implementing legislation specifies the language to be used. In practice, the items that require translation are function(s) of the product (unless obvious), instructions for use, and warnings, as the remainder are universally understood. This does not preclude the use of diagrams if this is feasible.

OTHER REQUIREMENTS

The Product Information Package (PIP)

The manufacturer or importer must keep accessible at the address shown on the label a PIP. Manufacturers must be able to produce a PIP containing all

the required information in a format that is suitable for use by the enforcement authorities. The time allowed for the collation of this document is not specified. Manufacturers located outside the E.U. need to be sure that all the required information can be collated and transmitted to an E.U. address within this time frame, should they choose to hold the information in a non-E.U. location. The PIP information must be available in the national language or languages of the Member State where it is held, or in a language readily understood by the competent authorities. Manufacturers should be prepared to translate certain information if this is necessary; this may include the key documents, including the safety assessment report/statement by the qualified person.

Inspection of the PIP is likely to be required in case of a product recall because of a safety issue and if the enforcement authorities have reason to investigate. In the absence of centralized E.U. enforcement and inspection authorities, means for implementation have not been clarified.

The contents of the PIP are as follows:

Formulation. This refers to the qualitative and quantitative composition of the product. In the case of perfume compositions and perfumes, it implies the name and code number of the composition and the identity of the supplier. This should be listed in the format of the International Nomenclature Cosmetic Ingredients (INCI) names, although it is helpful to the authorities if it is cross-referenced to the trade names of the raw materials used to allow these to be tied together.

Raw Material Specifications. The physicochemical and microbiological specifications of the raw materials.

Finished Product Specification. The purity and microbiological control criteria of the cosmetic product.

Method of Manufacture. The method of manufacture must comply with the guidelines for Good Manufacturing Practice (GMP) laid down by E.U. legislation or, failing that, laid down by the law of the Member State concerned. Both COLIPA [11] and the Council of Europe [12] have issued guidelines for GMP. According to the Directive, persons involved in the manufacture or first importation into the E.U. of a cosmetic product *"must possess an appropriate level of professional qualification or experience in accordance with the legislation and practice of the Member State which is the place of manufacture or first importation."* This requirement is not defined but is clearly intended to ensure that appropriate persons (with the generally accepted qualifications and experience) confirm that cosmetic products are manufactured to standards of quality and safety.

Assessment of the Safety for Human Health of the Finished Product. As described earlier, the qualified person must take into consideration the general toxicological profiles of the ingredients, their chemical structure, and the level of exposure. Where considered necessary, other testing must be carried out at the discretion of the manufacturer, and this will include patch testing of groups of human volunteers to assess the irritation and sensitization potential of the formulation.

Proof of the Effect Claimed for the Cosmetic Product. This is required where justified by the nature of the effect or product. Products whose function is obvious and which make only generic claims will not be required to provide efficacy data. For example, hair cleansing claims for shampoos that contain detergents will not normally require substantiation. However, if strong and/or unique claims are made for a cosmetic product, then the manufacturer will be expected to be able to provide data to support such claims if requested. COLIPA has issued a guideline outlining the test data that may be required in particular circumstances [13].

Registration of Manufacturers

Before a cosmetic product may be marketed in the E.U., registration of the place of manufacture or initial importation of a cosmetic product into the E.U. is required. This is the responsibility of the individual Member States and is not centralized.

Poison Center Notification

Unfortunately, again there is no centralized or mandatory requirement to supply formulations of products to poison centers. All the Member States operate emergency poison centers from which medical professionals may obtain information about, for example, accidental ingestion of products. In some Member States it is compulsory to send the formulation of a product to the poison center or centers prior to marketing a product (e.g., in France and Germany). In others it is not yet mandatory, but if a problem arises, then this information must be supplied at short notice. COLIPA has been working with the poison centers in the Member States to try to introduce a common frame formulation system.

Animal Testing

The 6th Amendment contained the controversial requirement that cosmetic products may not contain "*ingredients or combinations of ingredients tested on animals after 1 January 1998 in order to meet the requirements of this Directive.*" In the absence of satisfactory methods for replacing animal testing, the Commission has postponed the date of implementation of this provision

until after June 30, 2000. This approach recognizes that replacement of animal tests to assess safety of materials requires reliable test procedures.

The present Article of the E.U. Cosmetics Directive concerning animal testing specifies that the Member States must ban the marketing of cosmetic products containing ingredients tested on animals after June 30, 2000, whether such products are manufactured in the E.U. or imported from third countries. However, the rules of the World Trade Organization forbid any discriminatory measures between similar products. In order to counter this problem, the proposed wording of the 7th Amendment bans the performance of tests on animals in the territory of the Member States for the purpose of complying with the Cosmetics Directive but not the marketing of products tested on animals. The current status of these rules and the ultimate results are uncertain [3].

Packaging Waste

The Packaging Waste Directive holds industry segments to be accountable for the recovery and recycling of the packaging used. This Directive allows the individual Member States to develop their own national schemes to collect and recycle waste. Any impact on cosmetic packaging cannot be assessed at this time.

REGULATORY REQUIREMENTS FOR COSMETICS IN JAPAN

LEGAL ASSESSMENT

This segment describes the current system of cosmetic product regulation in Japan. Revisions of this Japanese regulatory model for cosmetic products are contemplated, and it seems likely that in the long term the Japanese system of regulation for these products will change to resemble more closely those of the United States and of the European Union. At the time of writing, cosmetic products may not be sold in Japan unless they are registered with the Ministry of Health and Welfare (MHW) prior to marketing; in order to do this the formulation must comply with the requirements of the cosmetic licensing system.

The current approach for regulating cosmetic products in Japan is quite different from that in the United States and the European Union. In these latter two territories the control on the use of raw materials in formulations is by exception, and restrictions on the use of particular materials is confined to certain classes such as those materials that are banned or restricted (e.g., preservatives, colors, and UV absorbers). The Japanese system of regulation takes a completely different approach; all raw materials used in cosmetic product formulations are positively controlled. Hence in order for a material to be used it must be listed as approved for a particular type of cosmetic product;

this can lead to problems for formulators. It is necessary to determine whether a raw material is listed for use in a particular cosmetic product category in Japan at a very early stage of the development process, whenever a formulation is being designed for global use.

Legislation Governing the Sale of Cosmetics in Japan

The Pharmaceutical Affairs Law No.145 of 1960 regulates drugs, quasi-drugs, cosmetics, and medical devices to ensure their quality, safety, and efficacy. In 1986 the introduction of the comprehensive licensing system by category of cosmetics simplified the licensing procedures; and in 1997 it was again revised and further simplified. The MHW is responsible for regulation and licensing of cosmetics. A comprehensive review of the regulations governing cosmetics and quasidrugs in Japan is available in English [14]. This publication includes a very detailed description of the data requirements, layout of application forms, and some of the approved lists of raw materials.

The definition of a cosmetic is as follows:

"The term 'cosmetic' means any article intended to be used by means of rubbing, sprinkling, or by similar application to the human body for cleaning, beautifying, promoting attractiveness and altering the appearance of the human body, and for keeping the skin and hair healthy, provided that the action of the article on the human body is mild."

The term *mild* refers to the exclusion of certain categories of product that are regulated as quasidrugs and which will be discussed in detail later in the text.

Drugs are defined as:

1. Articles recognized in the official Japanese pharmacopoeia;
2. Articles (other than quasidrugs) which are intended for use in the diagnosis, cure, or prevention of disease in human beings or animals, and which are not equipment or instruments (including dental materials, medical supplies, and sanitary materials);
3. Articles (other than quasidrugs and cosmetics) which are intended to affect the structure or any function of the body of human beings or animals, and which are not equipment or instruments.

Quasidrugs are articles that have the purposes described later in the text and which exert mild actions on the human body, or similar articles designated by the MHW. This category of products excludes equipment and instruments, and any article intended for use as a drug as defined in (2) and (3) earlier.

1. Prevention of nausea or other discomfort, or prevention of foul breath or body odor
2. Prevention of prickly heat, sores and the like
3. Prevention of hair loss, promotion of hair growth, or removal of hair

4. Eradication or repellence of rats, flies, mosquitoes, fleas, and so forth for maintaining the health of humans or other animals

Quasidrugs

The identification of some personal care products as quasidrugs appears to be unique to Japan. The MHW has designated the following types of products as quasidrugs:

1. Cotton products intended for a sanitary purpose
2. Products with the following functions:
   A. Hair dyes
   B. Agents for permanent hair waving
   C. Products that combine a cosmetic purpose of use with prevention of acne, chapping, itchy skin, chilblains, and so forth or disinfection of the skin and mouth
   D. Bath preparations

The products described in C are referred to as "medicated cosmetics."

Quasidrug types, purpose of use, principal product form, indications, and effects are described in various Notifications issued by the MHW and are described later. The list covers all the categories of quasidrug designated by the MHW, but it is not an exhaustive list of the scope of indications and effects. However, the indications and effects mentioned are those that, if intended for a product for sale in Japan, may lead to a different classification from that in its country of origin, that is, a product could be classified as a cosmetic in its country of manufacture but be viewed as a quasidrug in Japan.

(i) Mouth refreshers (oral preparations for prevention of nausea or other indisposition, including the prevention of foul breath)
(ii) Body deodorants (external agents to prevent body odor including perspiration odor)
(iii) Talcum powders (agents to prevent prickly heat, sores, and so forth, including razor burn)
(iv) Hair growers (external agents to prevent loss of hair and to grow hair)
(v) Depilatories (external agents for hair removal)
(vi) Hair dyes and dye removers (external agents for dyeing hair and removing hair or dye colors)
(vii) Bath preparations (external agents to be dissolved, as a rule, in the bath (excluding bath soaps) indicated for use against prickly heat, eczema, athlete's foot, acne, and so forth)
(viii) Medicated cosmetics (including medicated soaps), further classified by type (as given later)
(ix) Medicated dentifrices (prevention of gingivitis and caries—includes fluoride toothpastes)

(x) Insecticides (agents for killing and repelling insects such as flies, mosquitoes, fleas, and so forth)
(xi) Rodenticides (agents for killing and eliminating rats and mice)
(xii) Permanent waving agents (creation and retention of waves in the hair)
(xiii) Sanitary cotton products (cotton, including paper cotton used for sanitation—includes sanitary napkins and baby-cleaning wipes)

Medicated cosmetics are further broken down by product type as follows, including a partial list of indications):

1. Shampoos (prevention of dandruff and itching; prevention of perspiration odors in the hair and on the scalp)
2. Rinses (prevention of dandruff and itching, prevention of perspiration odors in the hair and on the scalp, supplementing and maintaining moisture and oil of the hair; prevention of split, broken, or branched hairs)
3. Skin lotions (for prevention of chapping and roughness of the skin; for prevention of prickly heat, frostbite, razorburn, and acne)
4. Creams, milky lotions, hand creams, and cosmetic oils (for prevention of chapping and roughness of the skin; for prevention of prickly heat, frostbite, razorburn, and acne; for prevention of spots and freckles due to sunburn)
5. Shaving agents (for prevention of razorburn; for protection of the skin for a smoother shave)
6. Sunburn prevention agents (for prevention of chapping due to sunburn and snow burn; for prevention of sunburn and snow burn; for prevention of spots and freckles due to sunburn)
7. Packs (for prevention of chapping and roughness of the skin; for prevention of acne, prevention of spots, and freckles due to sunburn)
8. Medicated soaps (including face cleaning agents, soaps that are mainly bactericides and soaps mainly containing antiinflammatory agents for cleaning, sterilizing, and disinfecting the skin; for prevention of body odor, perspiration odor, and acne; for cleaning of the skin, prevention of acne, razorburn, and chapping)

Active Ingredients for Use in Quasi-Drug Products. The MHW issues lists of designated ingredients of quasidrugs by category. The active ingredients are defined by name, permitted levels, and specification.

Comprehensive Licensing of Cosmetics by Category

Both quasidrugs and cosmetics are subject to premarketing registration, and the MHW determines the category of a particular product formulation at the time of registration. This is customarily based on the active ingredients, the name of the product, and the claims that are made.

This system has been progressively simplified to the point that currently cosmetics are classified into eleven different categories as follows (the definitions

are those of the Comprehensive Licensing Standards of Cosmetic Ingredients by Category (CLS) 1999 [15]:

1. Cleansing Preparations—cosmetic products exclusively used for cleaning
2. Hair Care Preparations—exclusively used on the hair and scalp
3. Treatment Preparations—used for keeping the skin healthy
4. Makeup Preparations—mainly used for makeup effect
5. Fragrance Preparations—liquid fragrance products, powdered fragrance products, and other fragrance products aimed at providing scent. These products fall under the classification of "perfumes."
6. Suntan and Sunscreen Preparations—exclusively used for tanning or sunscreening
7. Nail Makeup Preparations—exclusively used for protecting nail, or for makeup effect on the nail, or for removing nail enamel
8. Eyeliner Preparations—used for makeup effect on the eyelids by using them along the hairline or eyelashes
9. Lip Preparations—exclusively used for makeup effect on the lips or for protecting lips
10. Oral Preparations—used for cleansing the mouth or preventing halitosis and the like
11. Bath Preparations—used for cleansing the body and for enjoying fragrance and the like. These products are used by placing them in a bathtub or by similar action.

The list of categories and the raw materials that are permitted for use in cosmetic products are published in the Comprehensive Licensing Standards of Cosmetic Ingredients by Category (CLS) [15]. In recent years this has been revised and republished annually. Entries in the CLS consist of the name of a raw material, followed by an indication as to which category of cosmetic product it may be used in, together with a maximum level (if defined). Almost 3,000 materials are listed in the 1999 edition of the CLS. The chemical names of raw materials used in the CLS are not always the same as those used in the *International Cosmetic Ingredient Dictionary* [9]; however, the CTFA publishes a book that lists the Japanese names and their equivalents [16].

Specifications of Raw Materials.

Ingredients permitted for use in cosmetic products must conform to an official specification; the source of this specification is listed in the CLS for each ingredient and is based on one of the following reference works:

1. Japanese Pharmacopoeia
2. Japanese Standards of Food Additives
3. The Japanese Standards of Cosmetic Ingredients (JCSI)

4. Ingredients other than those listed in JCSI and to which the MHW assigned specifications of cosmetic ingredients (the Japanese Cosmetic Ingredients Codex)
5. The Standard for Denaturation of Alcohol for Industrial Use
6. The Officially Designated Coal-tar Colors

REGISTRATION OF COSMETIC PRODUCTS

Before a cosmetic product may be marketed in Japan it must be registered with the MHW. If a product is classified as a cosmetic according to the criteria above, then there are basically two types of product registration.

1. When a product conforms to all the criteria laid down in the CLS, that is, it contains only those ingredients listed for use in the category, and within the maximum concentration (if specified), a simple "Todokede" application is required. This is carried out at Prefecture level and usually takes only one day.
2. When a product does not conform to all the criteria laid down in the CLS, that is, it contains:
   a. ingredients not listed for use in the cosmetic category, but with prior use in other categories
   b. a listed ingredient at a concentration higher than the maximum specified for the category
   c. a new ingredient not currently listed in the CLS,

then a more complex "Shonin" application is required. This type of application is handled centrally by the MHW, and it takes up to three months to obtain a registration, depending on the degree of novelty.

Data Requirements for Cosmetic Product Registration

For both product regulations, the manufacturer (importer) is required to provide details of the manufacturing facility, the technical qualifications of the responsible person (normally required to be a pharmacist), and the quantitative formulation. Companies must have the facilities to ensure the quality of the finished product and to this end must either have their own laboratories or use a contract facility.

The layout of the documents containing technical information for the application for registration is prescribed, and data must be submitted in the correct format. Series formulations such as, for example, lipsticks, may be submitted as one formulation with ranges for the variable ingredients. Quantitative formulations must be presented using the Japanese names of the ingredients; it is not sufficient to use the names used in the *International Cosmetic Ingredient Dictionary* [9]. In addition to the main ingredients, it is necessary to provide details of those ingredients that must appear on the product label (described later), and such ingredients that appear as components of mixtures of raw materials ("carry-over" ingredients).

Table 7.1 Safety Data Requirements for Application of Cosmetic Products Containing New Ingredients (in Japan)

Data required	Raw material	Product
	(x indicates required)	
Origin and background of discovery	x	
Use in foreign countries	x	x
Characteristics and comparison with other cosmetic products, including data on similar materials, purpose of use in the product, and assessment of level used in the product.	x	x
Determination of structure	x	
Physical and chemical properties	x	
Acute toxicity studies	x	See note 1
Primary skin irritation test	x	
Repeat skin irritation test	x	
Skin sensitization test	x	
Phototoxicity test	x See note 2	
Photosensitization test	x See note 2	
Ophthalmic irritation test	x	x see note 3
Mutagenicity test	x	
Human patch test	x	x See note 4

Notes to Table 7.1.

1. Where the oral LD_{50} value of the ingredient is $\leq$ 2 g/kg, the test is required. Whenever a finished product is assessed to be safe on the basis of the level used, testing of finished product is not required.
2. If spectrophotometry establishes that the material does not absorb in the ultraviolet region, these tests may be omitted.
3. If no irritant effects on the cornea and iris are observed, and the product has a low potential to enter the eye, this test may be omitted.
4. This test may be omitted for products that are washed off after use

Safety Assessment of Raw Materials and Finished Products. To support the registration of a cosmetic product, it is necessary to provide quality and safety information about the ingredients and/or the finished product. The extent to which these data are required depends on the classification of the particular application, as outlined in the two types of registration noted earlier.

The above applies generally to all raw materials, but for materials classified, for example, as bactericides, preservatives, antioxidants, sequestrants, UV absorbers, and coal-tar colors, additional studies required are

a. Subacute toxicity studies
b. Chronic toxicity studies
c. Reproductive toxicity studies
d. Studies on absorption, distribution, metabolism, and excretion

Thus it is clear that while it is relatively straightforward to obtain approval for a new raw material that is, for example, a plant-derived oil or extract, it is much more difficult to obtain approval for the use of a new preservative. Experience of foreign companies in Japan with regard to applications for materials typical of the latter group suggests that the time required for approval is long.

Data from studies conducted outside of Japan are acceptable provided that evidence for adherence to internationally accepted standards of Good Laboratory Practice is available. Foreign test data on cosmetic products designed to be left on the face or mucous membranes should be accompanied by patch test data from studies conducted in Japan.

Ingredient Regulations

Preservatives. There is no separate list of approved preservatives. Permitted materials are included in the CLS in which the Japanese name and the maximum concentration by cosmetic product category are specified. However, the Japanese regulations do not allow the use of formaldehyde or preservative materials that are formaldehyde donors, with the result that quite a few commonly used preservative materials are not suitable for use in product formulations destined for the Japanese market. Furthermore, as part of its ongoing surveillance program, the enforcement authorities regularly sample products from the shelves of retail stores and test for prohibited materials. Often raw materials such as plant extracts used as components of product formulations contain preservatives, and manufacturers should ensure that they know what these materials are.

Colors. Coloring materials are listed in the CLS and have specific Japanese names. The CTFA *Color Handbook* provides a cross-reference to the nomenclature used in the United States and in the European Union [6]. Colors are required to meet the specifications laid down in the MHW Ordinance No. 30, 1966 on coal-tar colors permitted for use in drugs and the like.

COSMETIC PRODUCT LABELING

The following information must appear on the label of the immediate container of a cosmetic product or on the outer container or wrapper. The reference to the "wrapper" is due to cosmetic products on the Japanese market having both

an outer container and a further clear packaging film. If the labeling of the immediate container is not legible through the wrapper, then the labeling must appear on both. The information on the label must be in the official Japanese language and must be accurately described and legible.

(i) Product name—The name of the product and the category of cosmetic (i.e., function) must be indicated. There are placement and type size requirements
(ii) Name and address of the licensed manufacturer or importer
(iii) Instructions for use
(iv) Warnings—There are specified warning phrases for certain product categories (cosmetics intended for use by children, shampoos, beauty masks, sunscreens, and so forth)
(v) Declaration of contents—For products with a content of not more than 10 g or 10 ml, this may be omitted
(vi) Country of origin
(vii) Ingredients listing (in certain cases only; full ingredient listing is not required)
(viii) Batch code
(ix) Expiration date (shelf life)—This is not required for products that have a shelf life of more than three years after the date of manufacture or importation

Small Containers. In the case of cosmetics in immediate containers or wrappers with a capacity not exceeding 2 ml, or in immediate containers made of glass or similar material with a capacity of more than 2 ml and less than 10 ml, on which the required information is directly printed, the batch code and expirartion date may appear on the outer container or wrapper only, and the name and address of the manufacturer or importer may be abbreviated.

Labeling of Ingredients. There is no requirement for full ingredient labeling. Certain ingredients have been designated by the MHW to require labeling; these are ingredients that consumers may wish to avoid if they have a particular allergy. The list comprises the following (known as "Shitei seibun" ingredients) (see Table 1.2).

Imported Products. The information required to be labeled in the Japanese language may be added to the product on importation by application of what is known as the "Sekinin Seal." This is a label that may be applied after customs clearance but before the product is offered for retail sale.

Registration of Manufacturers and Importers. Companies wishing to manufacture cosmetic products in Japan or wishing to import from foreign countries must obtain a license from the authorities. Applications are made to the office of the Prefectural Authority in which the applicant resides, which then conducts inspections of buildings and facilities of the manufacturing plant or business office. Following inspection the Prefectural Authority forwards the application

Table 7.2 Cosmetic Ingredients That Must Be Listed on the Label[a,b]

Alkyldiaminoethylglycine hydrochloride
Alkylisoquinolinium bromide
Alkyltrimethylammonium chloride
Benzalkonium chloride
Benzethonium chloride
Benzoic acid and its salts
Benzyl alcohol
Benzyl nicotinate
Butylhydroxyanisol
Cantharides tincture
Capsicum tincture
Catechol
Cetanol
Cetostearyl alcohol
Cetyltrimethylammonium bromide
Cetyltrimethylammonium chloride
Cetylpyridinium chloride
Chloramine T
Chlorocresol
Chlorphenesin
Chlorobutanol
Chlorhexidine gluconate
Chlorhexidine hydrochloride
5-Chloro-2-methyl-4-isothiazolin-3-one
Chlorxylenol
Cinoxate
Cresol
Dehydroacetic acid and its salts
Dibutylhydroxytoluene
Diethanolamine
Diisopropanolamine
Diphenhydramine hydrochloride
Distearyldimethylammonium chloride
Domiphen bromide
Edetic acid and its salts
Ginger tincture
Guaiazulene
Guaiazulene sodium sulfonate
Halocarban
Hard lanolin
Hexachlorophene
Hormones
Hydrogenated lanolin alcohol
2-(2-Hydroxy-5-methylphenyl)benzotriazole
Ichthammol
Isopropyl lanolin fatty acid
Isopropylmethylphenol
Isopropyl myristate
Lanolin
Lanolin alcohol
Lanolin alcohol acetate
Lauryl sulfates
Lauryltrimethylammonium chloride
Liquid lanolin
2-Methyl-4-isothiazolin-3-one
Lysozyme chloride
Natural rubber latex
Orthophenylphenol
Oxybenzone
Paraaminobenzoic acid ester
Parachlorophenol
Parahydroxybenzoic acid ester
Phenol
Phenyl salicylate
Polyethylene glycol (mean mol wt not more than 600)
Polyethylene glycol lanolin fatty acid
Polyoxyethylene lanolin
Polyoxyethylene lanolin alcohol
Polyoxyethylene lanolin alcohol acetate
Polyoxyethylene laurylether sulfates
Propylene glycol
Propyl gallate
Pyrogallol
Reduced lanolin
Resorcin
Rosin
Salicylic acid and its salts
Shellac
Sodium cetylsulfate
Sodium *N*-lauroyl sarcosinate
Sorbic acid and its salts
Stearyl alcohol
Stearyldimethylbenzylammonium chloride
Stearyltrimethylammonium chloride
Straight-chain sodium alkylbenzenesulfonate
Thiram
Thymol

continued overleaf

Table 7.2 *continued*

dl-α-Tocopherol	Trichlorocarbanilide
dl-α-Tocopherol acetate	Undecylenic acid and its salts
Tragacanth	Undecylenic acid monoethanolamide
Triisopropanolamine	Vanillylamide nonylate
Triethanolamine	Zinc paraphenolsulfonate
Triclosan	

[a]The names listed in this table may not entirely conform to INCI nomenclature.
[b]For some of these ingredients, the MHW allows variations and abbreviations of some of these names and has published lists of such variations.

to the MHW for examination and subsequent licensing. The following factors are taken into account for licensing purposes:

(i) The manufacturing facilities
(ii) The qualifications of the applicant
(iii) The qualifications and suitability of the person designated as the technical supervisor. Licenses are granted for a period of three years.

Summary

The Japanese system of cosmetic product regulation is considerably different from those of the other two major trading blocs of the world, the United States and the European Union. In order to formulate and market cosmetic products in Japan it is necessary to take account of the restrictions imposed on the choice of raw materials and to allow for the process of registration. The wise formulator will seek advice at a very early stage in the development process if a product is conceivably destined for the Japanese market in order to avoid costly reformulation work at a late stage in the development process.

As noted earlier, the system of cosmetic regulation is under review by the Japanese government. The indications are that it may be changed to resemble more closely the regulation of cosmetics in the United States and in the European Union. It is anticipated that the prior approval of raw materials by the MHW will cease, at least for use in cosmetic products, but that some registration of the product formulation will continue. Currently, these changes are expected to occur early in the year 2001.

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CHAPTER 8

Intellectual Property Issues: Patents and Trade Secrets

With the arrival of the twenty-first century, there is a trend among investment circles to measure a corporation's performance by the value of its intangible assets, such as research and development and intellectual properties (patents, trademarks, copyrights, and trade secrets). With the internationalization of trade, there is also a trend among countries to harmonize laws governing the protection of intellectual properties. For the cosmetic industry, this means that obtaining and maintaining protection of intangible corporate assets will be increasingly important both domestically and internationally. For researchers, formulators, inventors, and manufacturers, this means that certain decisions should be made, and precautionary steps taken, including seeking advice of patent counsel at the start of a research and development project and on an ongoing basis to maximize protection of valuable products and processes.

The protection of intellectual properties is multifaceted, subject to complex, ever-changing legal interpretations, and has many pitfalls. This overview focuses only on patent and trade secret issues. The comments in this presentation are not intended to constitute legal advice or be relied upon in lieu of direct professional advice of counsel.

When a product or process is to be developed, or an existing one is being improved, some of the following issues should be addressed. Is the product or process patentable? Should the process be patented or maintained a trade secret? Does the manufacture, use, sale, offer for sale, or importation of the product infringe on some domestic patent, or if it is to be exported, does it infringe on a foreign patent in the country to which it is exported?

PATENTS VS. TRADE SECRETS

Generally, patents and trade secrets are recognized as being mutually exclusive. A patent requires disclosure of information in exchange for the exclusive rights that are attached to a patent over a limited term. In contrast, a trade secret requires that the information be and remain a secret. Once a patent application or a patent is published, the information disclosed can no longer be a trade secret, and after a patent expires, the information goes into public domain. In principle, trade secrets have an indefinite life as long as they remain secret.

A trade secret can be, for example, a product formula, a proprietary ingredient, or a process for making a product that, by not being known to others, gives the owner of the trade secret a competitive or economic advantage in the market. Unfortunately, trade secrets are vulnerable to being lost or misappropriated. Trade secret status does not protect against independent development or reverse engineering by someone who is not under any confidentiality obligation to the owner of the trade secret. For example, the availability of sophisticated instrumentation and the requirement for cosmetic ingredient labeling may make a cosmetic formulation readily analyzed and matched. If a decision is made to keep an otherwise patentable invention a trade secret, there is also a risk that a later independent inventor may obtain a valid patent enforceable against the earlier inventor. Moreover, delaying a decision to obtain a patent on an otherwise patentable invention by maintaining it as a trade secret may result in precluding a patent from being obtained.

In some countries, trade secrets may be protected under specific statutory laws protecting industrial property, rules against unfair competition, or under criminal law. In the United States, for example, civil causes of action and remedies for misappropriation of trade secrets are available in most states. Misappropriation of trade secrets can also be a federal crime under the Economic Espionage Act of 1996 (18 U.S.C. 1831), which has a scope broad enough to reach violations committed outside the territorial boundaries of the United States if the offender is (1) a U.S. citizen, a permanent resident alien, or U.S. corporation, or (2) has committed an act in furtherance of the offense in the United States.

In order to claim trade secret protection, however, certain measures must be taken to maintain and prove secrecy. Legal counsel, therefore, should be consulted in setting up a secrecy-maintenance program that satisfies the requirements in the state or country in which protection is sought.

WHY PATENT?

Patents have a limited enforceable term, and once the term expires, the information becomes public domain. However, during its enforceable life, a patent gives the patent owner a competitive advantage by way of an exclusive right

to control the unauthorized manufacture, use, sale, and offer for sale of the invention. In most industrialized countries, the life of a patent on a product or process is determined by a number of factors, including the filing date of the patent application and payment of fees to maintain the patent in force, and, under certain conditions, the enforceable term may vary. Therefore, advice of patent counsel should be sought to determine the status of a patent that may be of interest, or which may present a problem.

Worldwide Patent Systems

Global competition is leading countries toward harmonization of patent laws and the possible formation of a worldwide patent system. For example, both the United States and Japan have made changes in their patent laws to implement changes under the agreement on Trade-Related Aspects of Intellectual Property Law (TRIPs) resulting from the Uruguay Round of Multilateral Trade Negotiations signed on April 15, 1994.

Patent protection can be applied for on a country-by-country basis, or under a centralized filing procedure available under two major international treaties: the European Patent Convention (EPC) representing western European countries, and the Patent Cooperation Treaty (PCT), which, as of December 1998, had 98 member countries representing Asia, Africa, Caribbean, Eurasia, Europe, Pacific Rim, South America, and North America. Among other things, these two treaties allow inventors to claim priority based on the filing date of a domestic patent and delay filing costs for national patent protection, which can be substantial while assessing the commercial value of the invention.

For national patent protection, an invention must satisfy the requirements for novelty, inventiveness, and industrial utility of each individual country. Presently the U.S. Patent and Trademark Office, the European Patent Office, and the Japanese Patent Office account for about 90% of all patents throughout the world, so only the U.S., European, and Japanese patent systems are briefly reviewed.

United States of America. Two major categories of U.S. patents exist that are relevant to the cosmetic industry; that is, utility patents and design patents. Utility patents are granted for the following statutory classes of new and useful inventions: compositions of matter (e.g., chemical compositions, including mixtures of ingredients and new chemical compounds, or combinations such as a hair shampoo or skin care lotion, etc.); processes or methods (e.g., chemical, mechanical, or electrical procedures, such as a method for making a cosmetic product or raw material or a method for using a cosmetic composition or raw material); articles of manufacture (e.g., man-made products such as a hair accessory or comb); and machines (e.g., mechanisms with moving parts such as a hair dryer).

Since June 8, 1995, applications for U.S. utility patents can be filed as either provisional or nonprovisional applications. Provisional applications, however, never materialize into a patent unless they are converted to nonprovisional applications within 12 months of filing. The benefits and disadvantages of filing provisionals should be discussed with patent counsel. All pending U.S. patent applications are maintained secret until a patent is granted.

The term of utility patents issuing from nonprovisional applications will vary depending on their filing date, among other factors. Utility patents based on applications filed on or after June 8, 1995, have a term of 20 years measured from the earliest effective filing date of the application. Patents based on applications filed before June 8, 1995, or which were in force on that date, have a term that is either 17 years from issuance, or 20 years from filing, whichever is longer. However, under certain conditions, the patent term may have been extended (e.g., because of certain administrative delays) or shortened (e.g., because of dependency on a priority date of an earlier related application). Also, all utility patents based on applications filed on or after December 12, 1980, are subject to payment of maintenance fees every four years from issuance to avoid lapsing.

Design patents are granted for a new, original, and ornamental design for an article of manufacture. Design patents can protect a product's packaging, such as lipstick cases and bottle shapes, or a product's shape, such as hair grooming devices or shape of a soap bar, for example. Design patents, regardless of their filing date have a term of fourteen years from date of grant and are not subject to maintenance fees.

What Is Patentable?

Under Title 35 of the United States Code, sections 101 *et seq* for an invention to be patentable:

1. It must be useful (Section 101). Cosmetic products and processes, and chemicals used in synthesizing a product having an end use, are generally recognized as useful.
2. It must be new (Section 102) in an absolute sense; that is, the invention must be novel or different from anything known before. Patentable novelty and commercial novelty are not necessarily synonymous. Under statutory Section 102, an invention is *not* new—

    a) If it was known or used by others in this country, or patented, or described in a publication anywhere in the world before the date of the invention (i.e., before the date of conception);
    b) If it was patented or described in a printed publication anywhere or was in public use or on sale in the United States for more than one year before the

patent was applied for (Caution: consumer tests and offers for sale can start this clock running in some cases);
c) If it is abandoned (i.e., start on invention and then lose interest);
d) If the applicant is granted a foreign patent on an application filed more than one year before filing the U.S. application;
e) If the invention was publicly disclosed by someone else in a patent granted on an application filed in the United States or on an international application filed by someone else before the applicant's date of invention;
f) If the applicant is not the inventor of the subject matter of the patent; and
g) If the same invention was made by someone else who had not abandoned, suppressed, or concealed it (a trade secret, e.g., may be judged to be concealment).

3. It is not obvious (Section 103), that is, not readily apparent to a person having ordinary skill in the art in view of the prior technology (prior art). Prior art can be any publication anywhere in the world, including published applications and patents, which in some cases, may even be an inventor's own work; so timing is critical. Unpublished information, such as a true trade secret, is not considered prior art, and so as discussed earlier, a patent can be issued which negates an otherwise patentable trade secret.

The United States follows a first-to-invent rule, so interference proceedings are sometimes instituted to determine which applicant was the first to conceive and diligently reduce the invention to practice. Special rules determine the benefit of priority accorded to provisional applications and to dates of inventions made abroad in NAFTA countries under the North American Free Trade Agreement Implementation Act and World Trade Organization member countries under the Uruguay Round Agreements Act. Good record keeping, therefore, becomes important as evidence.

Europe Patent Convention

The European Patent Convention (EPC) is an important regional patent system. Under the EPC system, a single patent application can be filed with the European Patent Office (EPO) directly or through the provisions of an international PCT application to obtain a European patent. The full European patent application (or international PCT application) is published 18 months from the first filing date. Europe follows a first-to-file rule for priority.

European applications are subject to a formal examination only by the EPO covering the patentability requirements of complete novelty (i.e., absolute—never disclosed before anywhere), genuine inventive step (i.e., not an obvious progression based on existing knowledge), and industrial application. Once a patent grant is officially indicated, the European application is published for opposition. If the granted claims are believed to be invalid, the

European patent grant can be opposed within nine months of its publication by an opposer who can present documents to support this belief. In a successful opposition, the European patent may be revoked or the scope of the claims narrowed.

A European patent issuing from a European application is potentially enforceable in up to 19 contracting states that make up the European region (Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, Netherlands, Portugal, Spain, Sweden, Switzerland, and the United Kingdom). The European patent, however, will only take effect in those states that the applicant designates for protection and in which the patent is validated post-grant by meeting national filing formalities. A European patent has a term of 20 years from date of filing and is subject to annuity payments to each validated country.

Japan. The Japanese patent system is evolving. On July 1, 1995, the Japanese Industrial Property Laws were amended to implement the TRIPS Agreement provided for in the agreement establishing the World Trade Organization. Among other things, the amendments extended the patent term to 20 years from the filing date, extended patentable subject matter to "any inventions," expanded the scope of patent rights, and, effective January 1, 1996, abolished the pre-grant opposition system and introduced a post-grant opposition system. Japan follows a first-to-file rule (Article 39) for priority and an absolute novelty standard. Publication of the invention anywhere in the world, prior to filing the application in Japan precludes the grant of a patent (Article 29 sets out the standards for novelty). Further modifications to the Japanese patent system are planned to bolster its global economic and social development.

INFRINGEMENT ISSUES

Infringement may range from unknowing or accidental to deliberate or reckless disregard of a patentee's rights. As a general rule, the law imposes an affirmative duty of care on a potential infringer with actual notice of another's patent to obtain competent legal advice before engaging in any activity that could infringe another's patent rights. For the formulator and manufacturer, this means that before committing extensive resources toward developing a new product or process, and certainly before marketing a competitive match product, the existence of extant patents that actually or may cover the product or process under development may need to be checked to avoid infringement. For example, the following issues should be addressed: does a patent cover one or more specific ingredients, individually or in combination with other ingredients or does a patent cover the use of a specific ingredient or composition for

a specific cosmetic purpose, or does a patent cover the method of making or using the formulation, or will infringement occur if an ingredient is purchased from a different supplier?

The claims (i.e., the numbered statements that appear at the end of a patent) are what actually define the metes and bounds of the invention and determine the scope of protection to be given. Only the subject matter of the claims of a valid, enforceable patent can be infringed. An expired patent, that is, at the end of its term or if maintaining fees are unpaid, becomes public domain and cannot be infringed. However, before assuming that a patent has actually expired, advice of patent counsel should be sought.

Infringement can be direct or indirect. Direct infringement takes place when each claimed component or element of the invention is literally copied without authorization from the patent owner. For example, if a patented skin exfoliant lotion contains a specific novel skin exfoliant ingredient "A" and a competitor manufacturer makes, sells, or offers to sell a shampoo containing the identical skin exfoliant ingredient "A," direct or literal infringement can occur. Indirect infringement takes place when a competitor encourages or induces others to copy the patented invention or contributes to infringement by selling a component that is a material part of the invention, knowing that it is adapted for use in the invention (e.g., selling skin exfoliant ingredient "A" specifically for use in a skin exfoliant lotion). Even if direct infringement is not found, infringement may still occur if direct equivalency is found. Judicial interpretations of what constitutes equivalency and the determination of infringement issues are not clear-cut, so at the start of a project, advice of patent counsel should be sought to avoid and minimize potential infringement.

Checking for conflicting patents should be a collaborative team effort between research and marketing. The marketing department can best identify competitors and products that may have patents in markets of importance to the company. The research department can best identify information about ingredients, formulations, applications, and processes from state-of-the-art trade and research publications. Patent counsel can also advise on or conduct searches for patents in relevant fields.

Product labels, product bulletins, advertisements, and sales bulletins of a competitive product that may be of interest should be carefully checked for listed patent numbers or for the statement "patents applied for." The terms "patent pending" or "patent applied for" cannot be used unless a patent application is actually filed, so the possible issuance of a patent should be periodically checked. The patent files of the U.S. Patent and Trademark Office can be manually searched in the search room of the patent office in Washington, D.C., or electronically searched. A number of electronic database search services are available, some at no cost and some at varying pay-as-you-go costs in

which patents, published applications, or other publications can be searched. If foreign markets are of interest, or if a product is going to be made or sold outside the United States, a search for foreign patent filings can alert the formulator or manufacturer to potential problems where patent applications may be pending.

Patents are only enforceable in and by the courts of the country in which they are obtained. In the United States, a utility patent can have any number of claims and each claim can be a separate enforceable invention against an infringer, whereas design patents have one claim and only protect the ornamental features of an article, not its utilitarian features. In the United States, if an unauthorized (unlicensed) competitor makes, uses, sells, offers to sell, or imports a patented invention, or actively encourages others to do so, or sells, offers to sell, or imports a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process constituting a material part of the invention, knowing it to be especially made or especially adapted for use in an infringement of the patent and not a staple article or commodity of commerce suitable for substantial noninfringing use, it risks being sued for infringement by the patent owner. If the patent owner sues and wins, it can force the infringer to stop using the invention and pay for damages, which can be substantial.

In principle, a published European patent application confers upon the applicant a provisional protection similar to the rights conferred by the granted patent from the date of its first publication. Whether provisional protection may be retroactively claimed after the European patent is granted will depend on the national laws of the contracting state in which it has been validated and under which the determination of infringement is made. European patents are enforceable by the courts of each state, which the applicant designates just as if it had been issued by that individual state, but if patent invalidity is found in one of the states, this finding does not affect the validity of the patent in the remaining states. Thus an infringer potentially could be subject to patent litigation in each state in which infringement occurs, unless cross-border enforcement under the Brussels Convention becomes a generally accepted practice.

Where protection of new or improved products or processes is at issue, all relevant information obtained by marketing and research and facts known to them should be conveyed to patent counsel for evaluation of patentable subject matter or, alternatively, determination of whether potential or actual infringement might occur or be avoided by appropriate modification of the formula or process. Obtaining an objective competent, written opinion of independent counsel is a significant factor in determining whether infringement, should

it occur, was willful and to ensure due diligence in avoiding activities that infringe the patent rights of others.

RECOMMENDED READING

1. Pamphlets on basic facts and general information about U.S. patents are available from the U.S. Dept. of Commerce, U.S. Patent and Trademark Office, Washington, D.C. 20231, and accessible via the PTO Web site at http://www.uspto.gov.
2. Pamphlets on basic facts and general information about European patents are available from the European Patent Institute Secretariat, P.O. Box 260112, D-80058, Munich, Germany, and accessible via their Internet home page http://www.epo.co.at/epo/epi.
3. Kenney D., Cosmetic Chemistry in the Courtroom, *Cosmet. Toiletries*, (1986) **101**(10), pp 36–49.
4. Kenney D., In Closing: Protecting Intellectual Property, *Cosmet. Toiletries*, (1997) **112**(10), p 118.
5. Kanare H., *Writing the Laboratory Notebook*, published by the American Chemical Society, Washington D.C. (1985).
6. Schaal E., You and Your Patent Lawyer, *Chem. Eng. J.*, pp. 143–144, 1978.

PART THREE

Common Ingredients and Processes

The nine chapters comprising Part Three address cosmetic components and processes that can be used in all types of formulations. These ingredients, concepts, and preparative procedures are general and are not limited to specific cosmetic product compositions.

CHAPTER 9
Surfactants

INTRODUCTION

Surfactants, or surface-active agents, or tensides form a large group of organic substances that have the ability to modify the interface between two immiscible phases. The most commonly cited example is a surfactant's ability to lower the interfacial tension between air and an aqueous surfactant solution. This phenomenon is quite specific and should not be confused with the concept of spreading oil on "troubled waters" or the phenomenon of Newton's rings in which an additional insoluble phase is added to the system. The description of interfacial phenomena and the concepts of surface tension and spreading behavior have been studied since antiquity. These investigations have contributed immeasurably to our understanding of physical phenomena, and the results of these studies are included in all elementary physics texts.

An amphiphilic surfactant molecule is described generally as consisting of a hydrophobic tail and a hydrophilic head and is commonly depicted as a ball (head) attached to a stick (tail) (Fig. 9.1).

THE GIBBS ABSORPTION EQUATION

The solubility of an amphiphilic molecule depends on the ratio of the hydrophilic to the hydrophobic portion. Each molecular segment is

Figure 9.1. Sketch of a surfactant in ball and stick presentation with X indicating a counter ion

preferentially soluble (or remains) in a hydrophilic (polar) or hydrophobic (nonpolar) solvent. If two different immiscible solvent phases are available, the amphiphile is located at the interface in such a way that the hydrophobic portion is in contact with the hydrophobic solvent and vice versa. For this reason, amphiphiles tend to occupy the interface between two phases—such an arrangement lowers the free energy required for dissolution of the amphiphile. A simple illustration follows before the thermodynamics of the amphiphile at an interface are examined further. In a dilute aqueous solution of sodium laurate, the hydrophobic $C_{11}H_{23}-$tail is held in solution by the $-COONa$ hydrophile, even though the tail is forced to contact a hydrophilic (aqueous) environment. If the soap solution is now placed in contact with an air/vapor interface, these hydrophobic tails have the opportunity to extend into the air or vapor phase, which tends to lower the surface tension. The driving force for this arrangement of the soap molecules is so powerful that the concentration of the amphiphile in the surface layer exceeds that within the bulk solution. These oversimplified conditions gave rise in the 1900s to Willard Gibbs' thermodynamic derivation of Γ_2, the surface excess concentration of an adsorbed species:

$$\Gamma_2 = -1/RT \ (d\gamma/d\ln c)$$

where γ is the surface or interfacial tension, R is the gas constant, T the temperature, and c is the solute concentration. The Gibbs adsorption equation and the surfactant concentration at any interface account for the diverse functions performed by surfactants, including all of the following:

Cleaning
Wetting
Emulsification
Solubilization
Dispersion
Foaming

Some additional functions include:

Penetration Enhancement
Antimicrobial Activity

Practicing formulators must understand and work with the basic principles controlling surfactants' behavior. The Gibbs equation is fundamental and teaches how surfactants behave whenever two or more phases are present. In the discussion that follows, some of the cosmetically useful functions of surfactants will be noted. The physicochemical characteristics that contribute

to functionality are discussed first, and details of surfactant chemistry are discussed later.

THE PHYSICAL CHARACTERISTICS OF SURFACTANTS

MICELLE FORMATION

The orientation of amphiphiles at interfaces provides a ready explanation for micelle formation and associated phenomena in surfactant systems. As explained earlier, the hydrophobe of sodium laurate in aqueous solution is surrounded by hydrophilic water molecules. In dilute solutions these molecules may be driven to the (air) surface by entropic forces. If the concentration of sodium laurate is raised and if space at the air surface is limited, two or more hydrophobic tails may bond to each other hydrophobically, creating a hydrocarbon core surrounded by hydrophilic carboxylate segments that can contact the surrounding water solvent. The hydrophobic aggregation of amphiphiles is identified as micellization. Although some premicellar aggregates may form, the formation of micelles requires a minimal concentration of the amphiphile, the critical micelle concentration (CMC).

Micellization was not contemplated in the original Gibbs adsorption equation, which attempted to explain how an increase in amphiphile concentration results in lowering of the surface tension γ. The existence of micelles was seriously questioned in the early years of the twentieth century, but is fully accepted today since it accounts so elegantly for the sudden alteration of many physical properties as the CMC is reached (Fig. 9.2). The most important message from Figure 9.2 is the fact that an increase in amphiphile concentration beyond the CMC cannot lower the surface or interfacial tension beyond that found at the CMC. At higher concentration, the amphiphile generally forms additional micelles, which do not alter surface tension; alternatively the shape or size of the micelle (and the aggregation number) may increase.

Micelle formation has a profound effect on the performance and safety of amphiphiles in cosmetic use. Only some general rules can be provided here, in Table 9.1. For more detailed data, readers are urged to consult References 1 and 2. Micellization is generally viewed as an equilibrium process between monomeric surfactant molecules (S) and micellized surfactant (S_n), in which n identifies the aggregation number, that is, the number of surfactant molecules forming the micelle.

$$n\ S \leftrightarrow S_n \quad \text{or}$$

$$K_n = [S_n]/[S]^n$$

At or near the CMC, the free energy of micellization per mole of surfactant is simply

$$\Delta G_m^{\circ} = \mathrm{RT} \ln \mathrm{CMC}$$

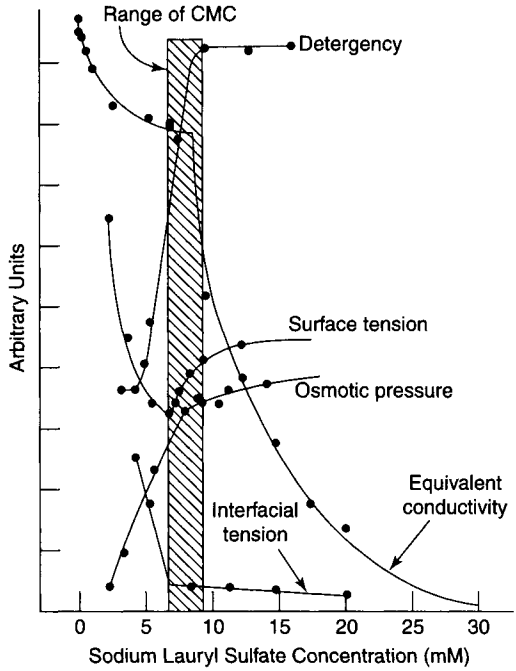

Figure 9.2. The discontinuity at the critical micelle concentration (CMC) of several physical properties in an aqueous sodium lauryl sulfate solution (Modified from Preston, W.C., J. Phys. Coll. Chem., 1948, **52**, *84) This classic presentation describes the behavior of a specific surfactant but is illustrative of amphiphilic behavior in general*

Table 9.1 Features of Surfactant Micelle Formation

Common micelle shapes	Spheres (rare); Lamellae (usually as bilayers); Rods (at relatively high concentrations); Ellipsoids; Disks
Aggregation number	The number of molecules required to form a micelle
	Nonionics $\gg$ Quaternaries $\cong$ Anionics
	Increases with length of hydrophobe
	Increased by increase in electrolyte level
	Lowered by elevated temperature in case of anionics
	Increased by elevated temperature in case of nonionics, especially at cloud point
	Lowered by presence of water-soluble organic solvents
Effects on CMC	Increased by unsaturation in hydrophobe
	At CMC concentration of nonionic much lower than that of ionic surfactants
	CMC lowered in aqueous system by presence of electrolytes

Table 9.2 Packing Parameters (P) and Predicted Aggregation Structures

P	Surfactant type	Aggregation structure
<0.33	Single chain hydrophobe with large hydrophile	Spherical/ellipsoid micelles
0.33 to 0.5	Single chain hydrophobe with small hydrophile; ionics in electrolytes or nonionics	Large cylindrical or rod-shaped micelles
0.5 to 1.0	Double flexible chain with large hydrophile	Vesicles or bilayers
≈ 1.0	Double inflexible chain with small hydrophile	Planar bilayers (membranes)
>1.0	Double chain large bulky hydrophobes with small hydrophile	Inverted micelles

because $S \approx S_n$. The process of micellization requires a positive entropic contribution.

A few additional features of micelle formation require brief mention. Surfactants, including many that occur naturally, can spontaneously associate into a variety of *associative structures*. The nature of these structures depends on the geometry of the associating amphiphiles. Israelachvili [3] showed that a (computable) critical packing parameter (P) controls how surfactants associate with each other. P is computed as

$$P = v/a_o l_c$$

in which v is the volume of the hydrophobic tail, a_o is the minimum interfacial area covered by the hydrophilic portion of the molecule, and l_c is the length of the hydrophobic tail extended in a fluid environment. Some of the structures described in Israelachvili's book are identified in Table 9.2. The Gibbs adsorption isotherm and micelle formation control the useful (as well as some undesirable) functions of amphiphiles. Users of surfactants of any type should always reflect on the effect of the Gibbs equation and of micellization on the product.

MIXED MICELLE FORMATION

In the presence of two or more micelle-forming surfactants, micelle formation is generally enhanced, that is, can occur at CMCs below those of the participant amphiphiles. The relative concentrations and the presence of other substances, such as solvents, salts and the like, influence the nature of the formed micelles.

The formation of mixed micelles has been suggested as a rationale for the reduction in skin irritation when a somewhat irritating anionic cleansing surfactant is combined with a nonionic polyoxyethylene-based amphiphile.

It has been proposed that the level of the skin-penetrating irritant anionic is reduced by micellization into a mixed micelle formed with the nonionic. Similarly, mixed micelle formation may also account for the reduction in the antimicrobial activity of quaternaries in the presence of nonionic surfactants because of micellization.

MICELLAR CATALYSIS

The discussion of how micelle formation affects the performance of cosmetics requires some brief comments on micellar catalysis, with the aid of an example. Chemically, alkyl sulfates are quite unstable to acid hydrolysis. It may be surprising then that an alkylsulfate molecule in a micelle is hydrolyzed faster than a monomeric alkylsulfate. The described catalysis is positive and can also occur in systems containing mixed anionic and nonionic amphiphiles. In pharmaceutical research, efforts to stabilize easily hydrolyzed drugs by negative micellar catalysis have received much attention. As a general rule, it appears that it is difficult to predict what type of micellar catalysis (positive or negative) should be expected from micellization.

SURFACTANT LIQUID CRYSTALS

When a surfactant—usually at high concentration—is crytallized from a solvent, the solvent may become an integral part of the structure. Surfactant liquid crystals are not commonly found in cosmetics except in the structures that may surround emulsified oil droplets. They are discussed briefly in connection with macroemulsions (in Chapter 10).

SURFACTANT ADSORPTION

So far, this introduction to the physical chemistry of amphiphiles has addressed only the adsorption of surfactants to a gas or liquid interface or self-aggregation. Actually, surfactants tend to attach themselves to all types of surfaces and to colloids or polymers present in solution. Some of these macromolecular adsorbers exhibit some surfactant-like properties, even though they are used in cosmetics primarily as thickeners or skin or hair conditioners. The formation of surfactant polymer complexes occurs stepwise, that is, one surfactant molecule at a time, until all reactive sites on the polymer have been occupied. Equilibria should be expected because the adsorbed surfactant species is present both on the polymer and in solution. The nature of the adsorptive process is likely to be dependent on temperature, solvents, ionic strength, pH, and the presence of other species. Only limited space will be devoted to a general description.

NONIONIC POLYMERS AND SURFACTANTS

Adsorption of surfactant on nonionic polymers is controlled by hydrophobic bonding. The results of such adsorption may modify the polymeric substrate's structure. For example, hydrophobic bonding of an ionized surfactant may create electrical charges on the polymer, which may result in critical changes.

IONIC POLYMERS AND SURFACTANTS

In these interactions, a charged surfactant may react by coulombic attraction of opposite charges and by hydrophobic (van der Waals) interactions. Clearly, the first step is likely to involve neutralization of opposite charges. This in turn may be followed by hydrophobic bonding of the surfactant to a previously bound charged surfactant. These phenomena have resulted in some remarkable changes in natural substrates, most of which are negatively charged. Microorganisms as a rule carry a negative charge, which may be neutralized by exposure of the microbial species to a nonlethal dose of a positively charged quaternary surfactant. As a result, the species in this stage (electric neutral) is not likely to move in an electrophoretic system. If, however, some additional quaternary is bound hydrophobically, the microbe's original negative charge is changed to a positive charge, as demonstrated by electrophoretic studies. Such astounding changes in surface charges may occur on soluble or insoluble proteins and may result in surprising effects on skin permeation and related phenomena. It is important for cosmetic formulators to remain wary of all types of interactions between surfactants and various natural substrates.

ADSORPTION AT SOLID-LIQUID INTERFACES

The microbial or skin interface briefly discussed earlier is an example of an adsorption model in which the concentration of the adsorbed species is probably higher on the substrate than in solution. The model controlling this adsorption should be analogous to the model described by the Gibbs adsorption equation. Specifically, cleansing, wetting, and suspending functions require oriented adsorption on a solid substrate. In cosmetics, this adsorption frequently occurs on polar charged surfaces (skin, hair, etc.). One of the significant effects of amphiphile adsorption has already been described earlier (using the electrophoretic behavior of microbiota as an example). In cosmetic practice, the so-called conditioning, that is, a modification of the surface characteristics of the treated substrate, is extremely significant and will be described in connection with the products that perform this function.

Other features of amphiphile adsorption result in spreading, wetting, and capillary flow. The thermodynamics of these phenomena are explained by the almost 200-year-old Young's equation, which depends on the assessment of

contact angles. The contact angle, normally identified as Θ, can be measured when a drop of a liquid (with or without amphiphile) is placed on a solid or a liquid surface. If the drop wets the surface, $\Theta = 0°$; but if the liquid does not spread, $\Theta > 0°$. The relationship between the contact angle and the interfacial tensions is given by Young's equation:

$$\gamma_{12} \cos \Theta = \gamma_2 - \gamma_1$$

in which the γs identify the interfacial tensions of the various interfaces. The free energy change resulting from the spreading of liquid 2 on the surface of 1 is identified as the spreading coefficient S:

$$S_{2/1} = \gamma_1 - \gamma_2 - \gamma_{12}$$

A rigorous derivation of these interactions was provided by Adamson [1]. The spreading coefficient is positive if the liquid 2 spreads on the surface, especially if liquid 2 is modified by the presence of a surface tension lowering amphiphile.

The wetting of solids by an amphiphile solution also depends on the nature of the solid. Some so-called low-energy surfaces are wetted quite easily, while high-energy surfaces are more difficult to wet. This characteristic of solids can be established by determination of the critical surface tension of wetting, which is defined as the surface tension of a liquid that just spreads on the surface of a solid, that is, the point at which $\cos \Theta = 1$. The critical surface tension of polytetrafluoroethylene is quite low; to wet this solid, a surface tension of less than about 18 m N/m will be required. By contrast, a liquid exhibiting a surface tension of about 45 m N/m can be expected to wet a Nylon® surface. The effect of surfactants on wetting processes and spreading is significant for a wide variety of cosmetic functions. The condition generally encountered is one in which the presence of an amphiphile enhances wetting. For example, the presence of a surfactant facilitates the wetting of pigments and talc during processing and the removal of oily soil from a biological substrate (skin or hair) by preferential wetting of the substrate.

FOAM FORMATION

In the creation of foams, air or a gas is dispersed in a continuous liquid medium. The routinely encountered system may be viewed as an emulsion of air in an aqueous medium (see Chapter 10). The generation of foam in cosmetic processing is an undesirable side effect resulting from the lowering of surface tension by the amphiphile. In foams, air bubbles are surrounded by thin layers of liquid films. Thinning of these films by drainage generally precedes foam breakage [4]. Formulators of products designed for cleansing

hair or skin normally prefer the formation of dense cushioning foams because consumers find this type of foam desirable. Actually, foam contributes little to soil removal, but the creation of stable foams in consumer products requires the inclusion of substances that may not be readily removed by rinsing and thus contribute to soil. For many years shampoo formulators have utilized alkanolamides of various types for foam stabilizers.

CHEMISTRY OF SURFACTANTS

The selection of a surfactant for use in a cosmetic product is complicated and depends on the product's function. Six major functions have already been identified earlier, and the *INCI Dictionary* [5] divides the approximately 2,000 commercially available surfactants into six functional categories:

Surfactants, Cleansing Agents
Surfactants, Emulsifying Agents
Surfactants, Foam Boosters
Surfactant-Hydrotropes
Surfactant-Solubilizing Agents
Surfactant-Suspending Agents

The *INCI Dictionary* [5] also classifies surfactants by chemical class, and the examination of the dictionary makes it apparent that some chemical classes may perform more than one function. The most practical chemical classification creates four large classes on the basis of the charge on the hydrophilic head of the amphiphile:

Amphoteric
Anionic
Cationic
Nonionic

By far the largest of these four groups consists of the nonionics, surfactants that carry no charge in an aqueous environment. The second largest group includes anionics, surfactants all of which carry a negative charge in aqueous environments. A third group is identified as cationic since it carries a positive charge. Finally, a fourth much smaller group carries both a positive *and* a negative charge and is identified as amphoteric.

Each of these classes is further divided by indentifying the chemical function of the hydrophobic head. The nomenclature of surfactants is designed to convey chemical information to the layperson and to professionals and to facilitate ingredient labeling. It is impossible to include a full description

of each chemical class. Instead only a few of the chemically distinct classes will be briefly discussed. The chemical structures of amphiphiles have been reproduced in many readily available publications. In light of this, structural details of surfactants are not included in this volume. Readers who require this type of information should consult Reference 2, 5, or 6.

AMPHOTERICS

Cosmetically useful amphoteric surfactants are either

Alkylamido Alkyl Amines or
Alkyl Substituted Amino Acids.

Many authoritative texts identify alkylbetaines as amphoterics. Alkylbetaines rarely exist as zwitterionic materials and carry a tetrasubstituted N-atom. They exist as quaternaries at all pHs and will therefore be discussed with other quaternaries.

Alkylamido Alkyl Amines

Alkylamido alkyl amines are prepared by condensing a fatty acid (or a precursor) with aminoethyl ethanolamine to form a cyclic 2-alkyl hydroxyethyl imidazoline. This cyclic amine is subsequently hydrolyzed during alkylation with chloroacetic acid or ethylacrylate. The commercially available alkylamido amines exist as salts or as free acids, and are listed in the *INCI Dictionary* [5]. These water-soluble substances are compatible with most other chemical classes of surfactants. They can reduce the irritant qualities of anionics and act as foam boosters and are considered substantive to hair. Their detersive properties are poor, and they are not used as emulsifiers. Depending on the purity, most of them contain large quantities of α–or β–hydroxyacids. They are subject to hydrolytic cleavage.

Alkyl Substituted Amino Acids

Alkyl substituted amino acids are prepared by alkylation of synthetic or natural amino acids. They exhibit good stability in cosmetic systems. Many of them foam copiously and are substantive to hair. A complete listing is provided in the *INCI Dictionary* under Alkyl Substituted Amino Acids [5].

ANIONICS

All members of this large class of surfactants carry a negative charge on the hydrophilic head. As a group, anionics are not compatible with cationic amphiphiles.

The subsequent discussion includes the following chemical classes:

Acylated Amino Acids and Peptides
Carboxylic Acids
  Lactylates
Sulfonic Acids
  Taurates
  Isethionates
  Alkylaryl Sulfonates
  Olefin Sulfonates
  Sulfosuccinates
Sulfuric Acid Derivatives
  Alkyl Sulfates
  Alkyl Ether Sulfates
Phosphoric Acid Derivatives

Acylated Amino Acids and Peptides

Acylated amino acids and peptides are prepared by acylation (usually with a fatty acid) of reactive amino groups of amino acids and proteins. The acylation of peptides is generally limited to partially hydrolyzed proteins, but the level of hydrolysis is rarely specified. Acylation may occur at nonamino sites, for example, serine or hydroxyproline residues. The resulting products are acidic, and neutralization of the remaining peptide carboxyl groups is required. These substances foam well and are believed to be nonirritating. They are used in skin cleansers and reportedly exhibit substantivity to protein substrates.

Produced by the acylation of N-methyl glycine, *sarcosinates* belong to this chemical class. They are stronger acids than the fatty acids from which they are derived. They form well-tolerated salts that exhibit water solubility at pHs between 4.5 and 6.0. They are, therefore, used successfully in mildly acidic skin cleansers.

Carboxylic Acids

Carboxylic acids include the fatty acids commonly obtained from the hydrolysis of lipid triglycerides, alkoxylated carboxylic acids, and lactylates. Fatty acids at pHs below 6 to 7 are not ionized. They still have some surfactant properties and can form w/o emulsions in organic solvents. By convention, fatty (or other long-chain) acids are classified as anionic. By analogy, un-ionized I°, II°, or III° alkylamines at elevated pH are generally identified as cationic.

The number of synthetically produced carboxylic acids is small. Specific fatty acids can be obtained by chemical or physical means from hydrolyzed lipids. The free alkanoic acids are of little use in cosmetics, but their water-soluble salts, the soaps, are among the most useful amphiphiles, even though their pHs are well above 7. Salts of alkanoic acids with fewer than 10 carbon

atoms in the chain do not foam well and exhibit no detersive properties. Alkali salts of stearic acid of commerce (a blend of about 55% hexadecanoic and 45% octadecanoic acids) are relatively insoluble and do not produce as much foam as dodecanoates and tetradecanoates. Most stearic acid is obtained by hydrogenation of soybean fatty acids.

Soaps are the most widely used skin cleansing agents in the world and are good emulsifiers. They find extensive use in shaving soaps in which they are blended to produce optimal foam and cushioning. Sodium stearate solutions in alcohol gel upon cooling and are used in deodorant and related stick formulations. Soap solubility is adversely affected by the presence of di- and trivalent alkaline earth and metal ions. Magnesium stearate and zinc laurate are used as lubricating solids and find use in powder technology and as binders.

For a comprehensive listing, the INCI tabulations of Fatty Acids and of Soaps should be consulted [5].

A second type of carboxylic acid is formed by oxidation (or reaction with chloroacetic acid) of the terminal hydroxyl groups of nonionic alkoxylated alcohols. The members of this group, exemplified by laureth-6 carboxylic acid, are strong acids and exist as free acids or as sodium salts. The free acids find use in cosmetics as emulsifiers, while the sodium salts also exhibit some detersive qualities. They have been shown to reduce the irritant qualities of other anionics and are considered mild amphiphiles. In the *INCI Dictionary*, these substances are included in the listings of Carboxylic Acids and of Organic Salts [5].

Lactylates are the esters produced when lactide or lactic acid is esterified by a fatty acid. As a group, the lactylates are widely used good emulsifiers. They are considered substantive to hair and skin. A related food grade emulsifier is formed by esterification of tartaric acid. In the *INCI Dictionary*, the lactylates are included among the Organic Salts, since most of them are marketed as calcium or sodium salts [5].

Sulfonic Acids

Sulfonic acids are represented by five subclasses; all of them possess the extremely stable C–S bond. For a comprehensive listing, the INCI tabulations of Sulfonic Acids and of Alkylaryl Sulfonates should be consulted [5].

Taurates are the acylation products of taurine or N-methyl taurine. Only the neutralized forms are stable in aqueous solution. They foam well and find use in bubble baths and cleansing products.

Isethionates are the esters of isethionic acid and fatty acids. Like the taurates, free isethionic acids are subject to self-hydrolysis. The salts are important and relatively mild constituents of liquid and solid (syndet bars) skin cleansing products.

Alkylaryl Sulfonates are prepared by sulfonation of alkyl substituted benzenes or diphenyl ethers. Alkylaryl sulfonates with long alkyl chains (nine or more C-atoms) have excellent detersive properties and foam well. They are, nevertheless, not widely used in cosmetic cleansers since they can leave a dry and unpleasant feel on the skin. Those that carry only short-chain (methyl) substituents on the aromatic ring are useful hydrotropes because they increase the water solubility of other surfactants, especially in the presence of salts.

Olefin Sulfonates are the complex mixtures formed when an α-olefin is sulfonated. The major constituent of the commercially available substances is probably the salt of a terminally sulfonated olefin. Olefin sulfonates foam well and can be used in acidic skin and hair cleansing compositions. It is important to select grades that are free of the irritating sulfones.

Sulfosuccinates are derived from the mono- or diesters, or amides formed from maleic anhydride and an alcohol or amine. The initially formed unsaturated ester or amide is then converted to a sulfosuccinate by reaction with a sulfite. Ester or amide formation may occur on one or both carboxyl groups. Solubility characteristics and utility vary widely, depending on the nature of the ester- or amide-forming substituents. Sulfosuccinates are used in cosmetic cleansing agents. They are mild and reportedly decrease the irritative properties of other surfactants.

Miscellaneous sulfonic acids include the *acylglyceride sulfonates* and the *alkylether sulfonates*. The former have been used in dentifrices, and the latter, in which the terminal $-OH$ group is replaced by $-SO_3^-$, find use as nonirritating cleansing agents.

Sulfuric Acid Esters

This group consists of the alkyl sulfates and the alkyl ether sulfates. Both of these groups contain the hydrolyzable C–O–S bond, which limits their utility to products having a near neutral pH. They are half esters of sulfuric acids. Only the neutralized sulfates are available since the acid form is subject to rapid self-hydrolysis.

Alkyl Sulfates are obtained by sulfation of primary fatty or synthetic alcohols. Secondary alcohols yield sulfates that are not useful in cosmetic applications. The hydrophobes that provide the most important alkyl sulfates have an alkyl chain length of about 12 to 14 C-atoms. These alcohols include naturally derived lauryl, Ziegler, or Oxo alcohols. Sulfation is carried out with sulfur trioxide or with chlorosulfonic or sulfuric acid. Immediately after sulfation has been completed, the reaction product must be neutralized before it is exposed to water. The water solubility of alkyl sulfates decreases with

increasing molecular weight of the alcohol and depends on the neutralizing cation. Although alkyl sulfates are frequently categorized as potential irritants, they remain among the most useful cleansing agents for cosmetic practitioners. Prolonged patch testing of alkyl sulfates can elicit strong responses. Frequent short-term applications followed by water rinsing is much less prone to elicit adverse reactions.

Alkyl sulfates are widely used in shampoos and skin cleansers and as emulsifiers. For safe use in products that are allowed to remain (dry) on the skin, the concentration of this amphiphile should be minimized. A complete list of these substances appears in the *INCI Dictionary* under Alkyl Sulfates [5].

Alkyl Ether Sulfates are the sulfuric acid esters of ethoxylated alcohols. Their preparation is similar to that of the alkyl sulfates. The alkoxylated alcohols include ethoxylated alkyl phenols, oxo alcohols, and some fatty alcohols. The degree of ethoxylation is variable but is generally less than about 6. As expected, the water solubility of these sulfates is much higher than that of the alkyl sulfates. This group of surfactants is used like the alkyl sulfates in cleansing products. Most authorities consider the ether sulfates milder than the alkyl sulfates. In the *INCI Dictionary*, these compounds are tabulated as Alkyl Ether Sulfates [5].

Phosphoric Acid Esters

The amphiphilic surfactants in this class are mono- or diesters of phosphoric acid and an (ethoxylated) alcohol. The nonesterified proton(s) of the phosphoric acid is generally neutralized in the derivatives used in cosmetics. The esters are formed by reaction of the alcohol with P_2O_5 or polyphosphoric acid. The resultant neutralized esters are less sensitive to low pH than the sulfates. They are widely believed to be much milder than similar sulfates and are believed to be nonirritating on skin.

Phospholipids form a second group of phosphate-derived surfactants that is widely distributed in nature. These substances, also called phosphatides, are esters of a fatty diglyceride with phosphoric acid. Esterification of one of the remaining protons on the phosphate with choline leads to the zwitterionic lecithin. Esterification with a neutral alcohol, such as inositol, yields a slightly acidic molecule. Phospholipids play an important physiological role and are used as food and as drug emulsifiers. Phosphatides have been found useful in the formation of vesicular structures known as liposomes.

CATIONIC SURFACTANTS

A surfactant is categorized as cationic if its hydrophilic head carries a positive charge. This group of surfactants includes a variety of amines since

neutralization of the amino group with an acid yields a positively charged ampholyte. Extensive listings can be found in Reference 5. The category of cationics includes the following classes:

Amines
Alkylimidazolines
Alkoxylated Amines
Quaternary Ammonium Compounds

Alkylamines

Alkylamines do not find extensive use in cosmetics. Even slightly acidic alkylamines at pHs about 3 contain some free (un-ionized) amine that may contribute to off-odors and are widely regarded as potential irritants. The salts of some amines with an interrupted alkyl chain, for example, cocamidopropyl dimethylamine, are occasionally used as emulsifiers.

Alkylimidazolines

Imidazoline compounds are formed by the reaction of aminoethyl ethanolamine with various fatty acid derivatives. They exhibit questionable stability and are used primarily as intermediate in the synthesis of the amphoteric alkylamido alkylamines.

Alkoxylated Amines

Alkoxylated amines are formed by reaction of ethylene oxide with the H-atoms of I^{o} and II^{o} alkylamines. This reaction increases the water solubility of the amine and reduces its volatility. These types of surfactants find use as emulsifiers in acidic systems. They can also provide some hair conditioning since these molecules can bond to acidic group on hair.

Quaternaries

Quaternaries in which the nitrogen carries four substituents are the most important cationics used in cosmetics. Tetraalkylammonium salts such as dialkyl dimethyl ammonium chloride, as typified by ditallow dimonium chloride, are important skin and hair conditioning agents. Similarly, stearalkonium chloride, in which one of the alkyl groups is a benzyl group, has been a crucial ingredient in the development of the so-called cream rinses. Replacement of the long-chain (stearyl) group by a blend of shorter alkyl chains results in the powerful antimicrobial benzalkonium chloride, in which the alkyl groups range from C_{10} to C_{14}. Another important class of antimicrobials is formed when the aromatic N in a heterocyclic pyridine nucleus is alkylated to form, for example, cetylpyridinium chloride. As a general rule, quaternaries with a short (C_{10} to C_{14}) alkyl group are antimicrobial agents, while those with two

alkyl groups or one long (C_{18} or longer) alkyl group are used primarily as conditioning agents.

Betaines form another group of conditioning quaternaries. These molecules are formed by the alkylation of a tertiary amine, for example, lauramidopropyl dimethylamine, with chloroacetic acid. This compound and related substances possess quaternary N-atoms regardless of pH. They are quaternaries, and the positive charge on the N-atom may be neutralized by an extraneous anion or in a very narrow pH range by the ionized carboxyl group, forming a zwitterion. Some authorities believe that the presence of free amine may account for the occasionally observed adverse skin effects.

Many formulators avoid compounding leave-on products containing quaternaries because the more water-soluble quaternaries are considered irritating, at least in the eye. The blanket rejection of quaternaries for skin conditioning and skin care is not justified. The classic cream rinses—when properly used—have elicited no skin irritation, and skin care products based on dialkyl dimethyl quaternaries have been used safely for years.

NONIONIC SURFACTANTS

Nonionic surfactants are amphiphiles that possess no charges at pHs normally encountered in cosmetics. Their water solubility characteristics depend on the presence of polar head groups, primarily hydroxyl or ether substituents. Many nonionic amphiphiles owe most of their hydrophilic characteristics to the presence of multiple hydroxyl functions in the head. However, the most common hydrophiles are polyoxyethylene groupings derived from polymerization of ethylene oxide. It is commonly believed that those polymeric ethers are chemically inert. In fact, however, these ethers and those derived from propylene oxide are subject to peroxide formation on carbon atoms α to the oxygen ether atoms. This phenomenon has been known for many years and was explained by Donbrow around 1975. For a more recent review of this chemistry, readers may wish to peruse the chapter on chemical instability in Reference 2. For an assessment of the potential for adverse effects from the presence of these oxidation products, readers are referred to Chapter 10, Reference 18. Users of ethoxylated raw materials are advised to examine ether-derived raw material for the presence of potential irritants.

The water solubility of nonionic polyethoxylated derivatives is frequently attributed to the formation of H-bonds of the polyether oxygen with the surrounding water. These hydrogen bonds have poor thermal stability, especially in the presence of salts. As a result, heating of a nonionic amphiphile in water reduces both its solubility and its hydrophilic properties. The cloud

point (the temperature at which clouding becomes noticeable) of nonionics is a characteristic that is useful for quality control purposes. The change in hydrophilicity plays a significant role in phase inversion temperature (PIT) emulsification, as discussed in Chapter 10. The group of cosmetically useful nonionics includes five major subclasses.

Alcohols
Alkanolamides
Amine Oxides
Esters
Ethers

Alcohols

Alcohols with amphiphilic properties are usually monofunctional primary alcohols. They were originally obtained by reduction of fatty acids released from saponification of fats and oils. Currently, a number of industrial processes are used for making long-chain alcohols by a variety of reactions; the most significant ones include the Ziegler process, the Oxo process, and the Guerbet reaction. The branched Guerbet alcohols are not used as amphiphiles, but the other types can be used as auxiliary surfactants in emulsificiation and in detersive products. They are considered innocuous and chemically stable in cosmetics.

Alkanolamides

Alkanolamides are the amides formed from various alkanolamines and fatty acids. The most commonly used amines are monoethanolamine and diethanolamine. The N-alkylation of pyrrolidone leads to a cyclic amide that possesses no hydroxyl group.

The preparation of alkanolamides can be performed by condensation of 1 mole of a fatty acid (or a derivative) with 1 mole of the alkanolamine, yielding a super amide; the use of 2 moles of the alkanolamine yields the Kritchevsky condensate. The commercial processes result in a variety of impurities.

These alkanolamides have been used for years as foam boosters and viscosity increasing additives in shampoos. They are rarely used as emulsifiers. The discovery that commercial alkanolamides may contain nitrosamines has resulted in regulatory action in some countries and has reduced usage in consumer products. The source of the nitrosating species is obscure, and there is no published information on the presence of nitrosamines in alkanolamides prepared by ethoxylation of fatty acid amides. It is, therefore, instructive to consider the multitude of components that may be formed during the synthesis of a 1:1 alkanolamide. The commonly identified diethanolamide of the fatty acid is likely to be contaminated with the mono- or diester formed by the

OH groups of the amine and may contain amine soap and esteramides. High levels of ethoxylation yield water-soluble PEG-X acylamides. These amides are lime soap dispersants and can be used as emulsifiers in low pH systems, in permanent wave neutralizers, and in antiperspirants. These ethoxylated amides exhibit good stability in typical cosmetic preparations and are considered safe.

Amine Oxides

Amine oxides form a large group of water-soluble cosmetic solubilizers and detergents. They are prepared by oxidation of tertiary amines, primarily of alkyl dimethylamines and less commonly of N-alkyl morpholines. Commercially available amine oxides are generally contaminated with unreacted tertiary amine, which may account for their inclusion as cationics by some authorities. Amine oxides are stable and innocuous amphiphiles in cosmetic usage. In support of this, it is noteworthy that amine oxides have been used in commerical hand dishwashing products. Cocamidopropylamine oxide (INCI name) is used as a lime soap dispersant and foam booster in cosmetic preparations. This substance, prepared from cocamidopropyl dimethylamine, reportedly reduces skin irritation commonly attributed to the use of alkyl sulfates.

Esters

Esters are the most frequently used amphiphiles in cosmetics. The esters briefly discussed in this section can be used in all types of cosmetic preparations if ester hydrolysis (by acids, bases, or enzymes) remains minimal. If ester hydrolysis should present a stability hazard, formulators seek out the use of nonionic ethers to overcome this problem. To facilitate this brief discussion of nonionic esters, they are divided into several important groups:

Glycerides
Ethoxylated Glycerides
Polyglyceryl Esters
Sorbitan Esters
Carbohydrate Esters
Ethoxylated Carboxylic Acids
Phosphoric Acid Triesters

Glycerides found in nature are normally triesters of glycerin with diverse fatty acids. They are oils or waxes and do not function as amphiphiles. Even the diesters exhibit only limited surfactant-like properties. However, the monoesters are useful emulsifying agents despite their insolubility in water. Glyceryl stearate is an important pharmaceutical emulsifier and is described in many pharmacopoeias. Monoglycerides can be synthesized from glycerin and the fatty acid or frequently by transesterifiation of a triglyceride with glycerin. The utility of these substances is further enhanced by modification with small

amounts of more hydrophilic amphiphiles, thus creating the so-called self-emulsifiying grades.

In another modification, the monoacylated glycerine is further acylated with a more hydrophilic acid (citric or tartaric), creating a wide variety of useful and safe amphiphiles that can be used in foods for human consumption.

Ethoxylated Glycerides are a relatively recent addition to the group of surfactant esters. Treatment of a triglyceride with ethylene oxide can be controlled to create some of the most complex nonionic ester blends in existence. A typical example is olive oil PEG-6 esters, prepared by ethoxylation of olive oil. Such a blend may contain all kinds of mono-, di-, and triglycerides, each of which may be ethoxylated. The terminal group on the ethoxyl chain may be acylated. These surfactant blends can be used as skin conditioning agents (at low ethoxylation) or as emulsifiers (at higher ethoxylation).

Polyglyceryl Esters, a group of interesting amphiphiles, are formed when a preformed polyglyceryl ether is esterified with typical fatty acids. For example, polyglyceryl-10 trilaurate results when the ether formed by the dehydration of 10 moles of glycerin (straight, branched, or cyclic) is esterified with 3 moles of lauric acid. The opportunities to create various amphiphiles is almost endless.

Sorbitan Esters, derived from sorbitol, are among the most popular drug and cosmetic emulsifiers. The acylation of sorbitol is commonly conducted in an acidic system that effects cyclization of the hexahydric alcohol to a variety of cyclic ethers, the sorbitans. Although the *INCI Dictionary* identifies some acylated sorbitol derivatives, these materials are probably sorbitan derivatives. The monoacylated (1,4) sorbitans, for example, sorbitan laurate, are widely used w/o emulsifiers in cosmetic, drugs, and foods. The more highly acylated sorbitan esters are quite hydrophobic and of limited value as amphiphiles.

Ethoxylation of a sorbitan monoacylate effects some rather unexpected changes, similar to the changes occurring during ethoxylation of glycerides. The major component in the resulting mixture has been identified as the acylated ethoxylated sorbitan in which the I^{o} alcohol carries the ethoxylated fatty acid ester. The reaction is commonly carried out with 20 moles of ETO per mole of sorbitan monoacylate, yielding the well-known and widely used polysorbates. The synthetic route may vary from manufacturer to manufacturer, and the endproduct may contain a wide variety of isomers.

Carbohydrate Esters are derived from mono- and di-saccharides by acylation with a wide variety of fatty acids at one or more hydroxyl sites. The properties

of these sugar esters resemble those of the polyglyceryl acylates, and—as is common in these systems—the hydrophile or lipophile characteristics depend on the level of acylation. As a group, these esters formed by the reaction between two edible raw materials are believed to be safe in cosmetic use.

Ethoxylated Carboxylic Acids are normally formed by ethoxylation of fatty acids. The extent of ethoxylation can be quite short or very long. (Readers should note that the reaction of 1 mole of acid with 1 mole of ethylene oxide yields an ethylene glycol monoester.) Esters of this type can also be prepared by esterification of an acid with a preformed polyethylene glycol (PEG). In addition, diesters can be synthesized by reacting a preformed PEG with two moles of the fatty acid. The nature of various potential endproducts depends on the length of the PEG and the C-skeleton of the carboxylic acid.

Phosphoric Acid Triesters are nonionic, and their hydrophilicity depends on ethoxylation of the esterifying alcohol. Thus trioleth-8 phosphates can act as an amphiphile in emulsification, while trioleyl phosphate reacts as a neutral lipid.

Ethers

Ethers are nonionic amphiphiles that carry only polyether group and one or more hydroxyl group. They can be divided into four major groups:

Ethoxylated Alcohols
Ethoxylated (Propoxylated) Polysiloxanes
Ethoxylated Polypropylene Oxide Ethers
Alkyl Glycosides

Ethoxylated Alcohols result when a synthetic or natural alkanol is subjected to ethoxylation. The HLB of the resulting ethers depends on the degree of ethoxylation and the precise nature of the alcohol, which may include phenols, sterols, or other hydrophobic alkanols. Ethoxylated alcohols are identified in INC nomenclature by the suffix *-eth* followed by a number. For example, ceteth-20 identifies a cetyl alcohol derivative with an average of 20 moles of ethylene oxide. This average may have a wide range; in fact, the ethylene oxide level of exactly 20 in commercial ceteth-20 may account for only a small percentage of the total. Ethoxylated alcohols are widely used in cosmetics as emulsifiers and solubilizers.

Ethoxylated Polypropylene Oxide ethers result from ethoxylation of a polyoxypropylene hydrophobe at both ends. These typical block polymers are known are poloxamers. The reverse types of compounds with a polyoxyethylene core and polyoxypropylene side chains are called meroxapols. Propylene

and ethylene oxides can also be polymerized in blends that create hydrophobic or hydrophilic substances, depending on the ratio. As a rule—but not always—hydrophobic alcohols may be reacted with a few moles of propylene oxide before ethoxylation. A typical example is PPG-5 ceteth-20, which is best described as the ethoxylated PPG-5 ether of cetyl alcohol. It is apparent that the types of ethers available to the cosmetic formulator can vary widely and that only precise nomenclature can reflect the exact composition.

Ethoxylated or Propoxylated Polysiloxanes create formidable nomenclature complications. Known generally as dimethicone copolyols, these polymers routinely include a $Si-C_3H_5OH$ monomer that is ethoxylated and/or propoxylated. The levels and the order of ether formation are not disclosed, and compounders who use these very useful amphiphiles are forced to obtain details from their supplier. Dimethicone copolyols are a relatively new class of emulsifiers in which hydrophilicity is combined with the general spreading characteristics of polysiloxanes.

Alkyl Glucosides form another group of nonionic ethers. They are the reaction products of a hydrophobic alcohol with glucose to form an acetal. Under the reaction conditions a small amount of a polymeric glucose derivative is formed. The alkyl group in these acetals rarely is longer than C_{12}. These substances are used in liquid skin and hair cleaning preparations. They foam copiously and are well tolerated.

Table 9.3 Patch Test Performance of Different Surfactants (from Ref. 7)

Surfactant tested	Conc (mM)	TEWL ($g/m^2/h$)	Laser Doppler (A.u. C.)	Erythema (day 2 upon patch removal)
Water Control	—	7	14	2
Cocamidopropyl Betaine	286	13	19	21
Lauryl Glucoside	238	8	19	13
C_{12-15} Pareth Sulfate	120	20	56	38
Sodium Lauryl Sulfate	65	58	68	58
Sodium Cocoyl Isethionate	148	31	57	31
Disodium Laureth Sulfosuccinate	181	12	17	10
Cocamide DEA	323	11	26	21
Sodium Cocoamphoacetate	274	10	28	21

SAFE USE OF SURFACTANTS

Many erudite scientific papers on the safe use of surfactants on the skin surface have been published. The number of amphiphiles that have been studied in detail is miniscule in light of the thousands of surfactant molecules available. Very little effort has been made to assess potentially damaging impurities in commercial amphiphiles. Nonionics are commonly considered to be the least damaging to human skin. Nonionic ethyleneoxide ethers are notoriously impure, and generalizations about the safety of nonionics should be accepted with caution. Anionic sulfates and soaps can elicit serious skin responses when examined via closed patch tests. In normal use, exposure to cleansing amphiphiles is relatively short and causes very little objectively visible damage. Still, users voice subjective complaints about skin tightness, a phenomenon that is not fully explained. Cationics are substantive to proteinaceous tissue and are not readily removed by rinsing. Their retention by the skin may play a role in their germicidal activity.

Surfactants have the reputation of enhancing drug permeation through skin. Penetration enhancement requires prolonged skin contact and seems to be related to the surfactant's ability to alter the skin's barrier lipids. Very little is known about this type of interaction. On the other hand, once the barrier has been modified, the integument may allow all types of undesirable substances access to the body. As a general rule, low molecular weight amphiphiles possessing both some water and lipid solubility are likely permeation promoters; their use is best reduced to a minimum unless skin permeation is desired.

Before closing this discussion of surfactants, it is appropriate to provide some guidance to the relative innocuousness of surfactants. A rational assessment is almost impossible since the scientific literature has been plagued by contradictory observations and perhaps by questionable interpretations. There is excellent evidence that the irritancy of different amphiphiles under occlusion can vary, especially if modern sensitive methods of measurement are included. Judgment via erythema, the time-honored approach by most investigators, needs careful assessment. The production of erythema can be due to the generation of cytokines in the epidermis or simply due to permeation of an irritant into the dermis, where it may elicit some toxic response. Recently published data based on TEWL and laser Doppler flowmeter results after 48-hour Finn Chamber testing are in reasonable accord with the findings of other investigators [7]. Some of the data from this study are shown in Table 9.3. The adjustments in test concentration were made to induce some adverse responses without excessive skin damage.

The tested surfactants were commercial samples, and no effort at purification was attempted. The response to the isethionate is surprising since this group is generally viewed as quite mild.

Formulators should always try to reduce the level of amphiphiles to preclude irritation. During the development of products that remain on the skin it seems wise to avoid or at least reduce the level of better-known irritants such as alkyl sulfates. The compounder normally has more leeway in the use of surfactants whenever the time of skin contact is short (less than about 5 minutes) and if the product temperature is kept low. Skin manipulation, that is, rubbing or inunction, is likely to enhance adverse reactions. Finally, agents that are likely to alter the barrier—and this includes diverse substances that upon penetration are retained in the intercellular lipid—and are skin penetration enhancers are best avoided.

In a recent publication, Tavakkol et al. indicated that assessment of the irritant potential of detergents and surfactants on human skin is fraught with inconsistencies [8]. They examined the problem of skin irritation on hairless mouse skin using histological techniques and TEWL. Treatments were carried out twice daily, five times a week for 15 weeks with 100 µl of 5% sodium lauryl sulfate (positive control) or 5% aqueous solution of a commercial soap bar, a syndet bar, or a liquid soap, and followed by water rinsing. This regimen appeared to cause little visible or histologically detectable damage to the skin [8]. These results support the argument that testing under (simulated) use conditions may be more meaningful for the assessment of skin irritation than standard patch testing [9].

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CHAPTER 10
Cosmetic Emulsification

INTRODUCTION

The opaque characteristics of cosmetic emulsions provide consumers with a visual signal that these products are gentle and beneficial to the skin, while clear products, by contrast, may be viewed as less desirable. This consumer bias has no scientific support: clear water is innocuous, and the expressed clear vegetable oils used for millennia for inunction are well tolerated. Some of the chemicals required for stabilizing milky or creamy emulsions may actually cause undesirable skin effects. To the formulator, the creation of an opaque cosmetic emulsion presents a real challenge because emulsions exhibit only a limited shelf life. Opaque emulsions are difficult and costly to prepare, and are not robust to adverse conditions. Their long-term instability—demanded by the laws of thermodynamics—requires constant monitoring. Despite the publication of many papers and books on emulsions (foods, drugs, and cosmetics), very few individuals know exactly how to prepare these temporarily stable homogeneous blends of two almost immiscible components.

The use of pure lipids on the skin is likely to leave a greasy and tacky finish. Accordingly, dilution with an inert and safe "solvent" is required. The solvent of choice is water, but water does not form a homogeneous mixture with any lipid in the absence of an emulsifier. Consumer demand for a dry finish on the skin, cost of diluent, and safety considerations combine to make aqueous emulsions a desirable topical vehicle.

SOME DEFINITIONS

Cosmetic emulsions can be defined simply as blends of one or more lipids with an aqueous phase in the presence of acceptable emulsion stabilizers. The lipid is generally fluid at or near room temperature, but there are no theoretical

restrictions on the physical nature of the lipid. When a small amount of lipid is added to water and the mixture is shaken, the lipid remains suspended briefly in spherical form (to minimize the interfacial energy between the water and the oil). The oil droplets will agglomerate and separate into a continuous phase, again under the influence of interfacial energy. Stabilization of the oil droplets during shaking or mixing results from the presence of *emulsifiers* and other *auxiliaries*. Processing and the use of other ingredients are the principal requirements for creating diverse emulsions. The emulsions may be opaque, translucent, or transparent, depending on the size of the droplets making up the internal phase.

An emulsion is identified as *water-in-oil* (W/O) if the oil is the *external* or *continuous* phase. By contrast, an *oil-in-water* (O/W) emulsion is one in which the oil represents the *emulsified (internal, disperse, discontinuous)* phase. Emulsifiers (described in Chapter 9) are the materials that make it possible to disperse the internal phase in the form of fine *droplets* (or *globules*) in the external phase. The opaque (or coarse) emulsions identified so far are often referred to as *macroemulsions*. Such emulsions (O/W or W/O) reflect visible light and appear white. The particles of the internal phase of macroemulsions are polydisperse; thus not all of them reflect light identically.

In clear or transparent emulsions, the globules of the internal phase are too small to reflect visible light. Such emulsions are, therefore, often referred to as *microemulsions*.

An additonal complication has arisen through the creation of *submicron emulsions*. These emulsions appear opaque to the human eye, but their particle size is less heterogeneous than that in macroemulsions and might be small enough to allow sterile filtration. Submicron emulsions are formed from coarser emulsions by high-pressure homogenization and filtration.

NATURE OF EMULSIONS

Emulsification processes depend on the use of effective emulsifiers, which make the oil phase and the aqueous phase more compatible. The presence of an emulsifier at or near the interface lowers interfacial tension, and the rate of separation into two phases is decreased signficantly. Emulsifiers, however, cannot overcome the thermodynamic instability (tendency to separate) of macroemulsions; instead, they can only *postpone* the ultimate fate of separation. Processing techniques and auxiliaries can delay separation sufficiently to make such unstable preparations marketable.

The only types of emulsion that are thermodynamically stable are microemulsions. In contrast to macroemulsions, the globule size of microemulsions is only about one-fifth of the wavelength of visible light (i.e.,

about 100 nm or less). For purposes of orientation, some particle size ranges are shown below:

Solutions	<5 nm
Micelles	5–10 nm
Swollen micelles and microemulsions	5–100 nm
Submicron emulsions	100–300 nm
Polymeric latices	150–1000 nm
Emulsions and suspensions	>1000 nm

The exact nature of microemulsions remains controversial. It is best, therefore, to define them operationally by their optical clarity. These emulsions are energetically at a minimum and form and re-form spontaneously within a given temperature range. Schulman originally relied on the formation of clear emulsions through addition of a cosurfactant (usually an intermediate chain length alcohol) to a coarse microemulsion. The formation of a clear dispersion is similar to that of forming a swollen micelle. In this interpretation, the solubilized substance is believed to be trapped inside a micellized surfactant or surfactant mixture. An entirely different explanation of the nature of transparent emulsions relies on the existence of irregular bicontinuous structures in these oil or water or surfactant or cosurfactant blends. More details concerning this controversy and additional descriptions of microemulsions can be found in Attwood's article [1].

Another feature of microemulsions is the requirement for larger amounts of emulsifiers to achieve the desired visual clarity than those required for macroemulsions or submicron emulsions. The relationships between temperature, emulsifier concentration, and the type of emulsion (macro *vs.* micro) formed can be clarified by reference to the so-called Kahlweit fish [2] (Fig. 10.1).

Finally, readers should understand the concept of multiple emulsions. In recent years, formulators have learned how to compound oil-in-water-in-oil (O/W/O) or the reverse, water-in-oil-in-water (W/O/W), emulsions. Their stability depends on the absence of diffusive processes and is limited. At the moment, these types of emulsions are attractive primarily for drug administration, although they may actually occur as intermediates during conventional emulsion preparations. Multiple emulsions will not be covered in detail here, but more information can be found in Reference 3.

EMULSION FORMATION

OVERVIEW

The first step in forming an emulsion is subdivison of the internal phase within the continuous phase, that is, the creation of a dispersion. The lowering

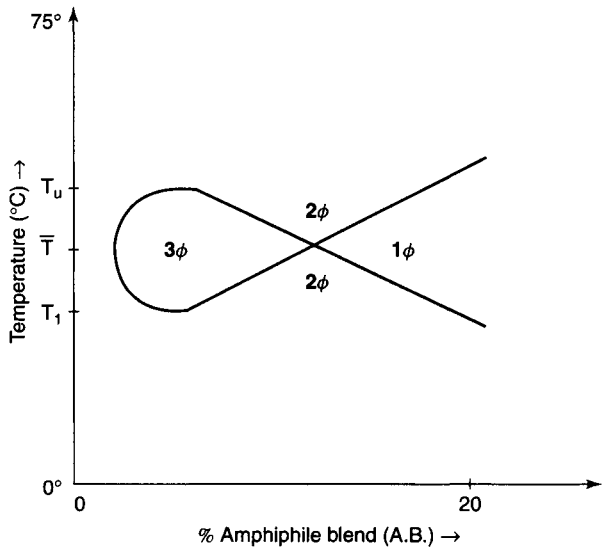

Figure 10.1. Kahlweit fish: Schematic phase diagram of a mixture of water and oil containing varying levels (%) of a nonionic amphiphile blend (A.B.). To the left (at low A.B.) a two-phase (2Φ) W/O macroemulsion forms above T_u; a two-phase (2Φ) O/W macroemulsion exists below T_l. At or near T (the phase inversion temperature) one finds a three-phase (3Φ) system. At a temperature between T_u and T_l, a cross-point is reached at T where A.B. is just sufficiently high to form a single-phase (1Φ) microemulsion system. A lamellar mesophase may exist at still higher A.B., especially below T. (For further discussion consult Ref. 2)

of particle size of the internal phase during the dispersion process causes a large increase in the contact area of the two phases with an accompanying rise in the interfacial free energy. Lowering of the interfacial tension in modern emulsion practice depends on an emulsifier or on a blend to maintain the dispersion of the internal phase.

The emulsifier(s) is added to the system at the time of dispersion. The emulsifier(s) is an amphiphile that is absorbed at the interfaces of two essentially immiscible phases, as described in Chapter 9. The location of the emulsifier on the surface of a droplet of the internal phase is defined by the alignment of the hydrophilic and hydrophobic segments of the molecule to create a palisade-like covering of the interface. In a conventional O/W emulsion, the emulsifier's hydrophobic end contacts or is dissolved in the oil phase, while the hydrophilic end of the molecule preferentially contacts the hydrophilic continuous phase.

As a rule, the type of dispersion demanded in cosmetic emulsions cannot be achieved without some mechanical force. The energy required is supplied by agitators or similiar devices over a period of time. It is the emulsifier's additional

function to prevent coalescence of the internal phase, while the agitation device creates new interfacial areas. In the absence of agitation, formulators would have to depend on the emulsifier to create the desired level of dispersion.

To create an acceptable cosmetic emulsion, stabilizers (coemulsifiers or auxiliaries) must be incorporated to prolong the shelf life of the emulsion; an effective preservative system must be selected to prevent microbiological spoilage; and finally, other chemicals to control, for example, oxidative damage, the pH, and any other unwanted changes are required.

AGITATION

The breakup of the internal phase into small particles requires the expenditure of a considerable amount of energy. Stirring, homogenization, and other processes are used by formulators to create small particles of the dispersed phase. However, experienced compounders know that excessive agitation after completion of emulsification can lead to instability.

The shear and turbulence generated by the mechanical agitator produce only a temporary dispersion. As noted already, coalescence must be slowed down through the use of emulsifiers or gums. The level and time of agitation required depend on the amount of the mixture, its viscosity, and the phase ratio. During the period of agitation, initially formed large droplets should be further reduced in size. If the emulsifier level is too low, if the wrong emulsifier is used, or if the temperature conditions are inappropriate, coalescence will occur despite the continuing input of agitation.

This book cannot hope to acquaint the reader with the intricacies and varieties of mechanical devices designed for use in the scale-up and production of cosmetic emulsions. For specific details, it is best to consult manufacturers of these devices. It is important to remember that equipment used successfully in the laboratory might not function equally as well during scale-up or in production. In addition, the time required and the heating and cooling cycles require control.

If the chemical blend employed is correctly compounded and if temperature conditions are proper, stirring with an impeller mounted on a shaft should result in emulsion formation. The propeller is normally top-mounted for routine laboratory development work. More vigorous agitation, required for more viscous preparations, is achieved by the use of a turbine-type mixer. Paddle blades, counter-rotating blades, or planetary types of mixers may also be used in the laboratory. The more sophisticated types of mixers are routinely used in production and may include scraper blades if heat transfer should interfere with uniformity, especially during the cooling cycle. As explained later, most emulsions are prepared at elevated temperatures, and cooling to room temperature is an essential step.

HOMOGENIZERS

After the initial emulsion is formed by simple agitation, further reduction in particle size can be achieved by passing the product through a homogenizer, a colloid mill, or an ultrasonic device.

FOAMING

Foaming during the preparation of emulsions results from the lowering of surface tension due to the presence of the emulsifier. The formation of stable foams, especially in viscous systems, is very troublesome. For this reason, the incorporation of air during agitation should be minimized. The use of closed systems and of vacuum processing are widely practiced. Some substances (long-chain alcohols and silicones) tend to accelerate foam collapse, but their use may affect the character of the emulsion.

Despite a general recommendation to work with suppliers on up-to-date emulsification and heat exchange equipment, readers might find it useful to consult some existing printed broader reviews [4].

CHEMICAL AND PHYSICAL NATURE OF THE EMULSIFIER

The chemical and physical characteristics of cosmetic emulsifiers are quite variable, as documented by the long list of Surfactant-Emulsifiers in the *INCI Dictionary* [5]. The major features of these amphiphilic compounds were discussed in Chapter 9. Table 10.1 is included to identify some of the characteristics of useful cosmetic emulsifiers.

Regardless of chosen type, emulsifiers are selected to aid in the emulsification and stabilization process by several mechanisms. The first of these is the formation of an *electrical double layer* on the globule's surface. The presence of an ionizing (anionic or cationic) surfactant is a prerequisite for creating such a double layer. The presence of an electrical charge on the surface of a dispersed particle tends to repel a like electrical charge on an adjacent particle.

The second effect is the *lowering of the interfacial tension*, known also as thermodynamic stabilization. Its significance has already been discussed in connection with the Gibbs equation in Chapter 9. This mechanism probably plays an important role in the formation and stabilization of both O/W and W/O emulsions.

In recent years investigators have placed a great deal of emphasis on the *formation of a third phase*, that is, a rigid interfacial film on the globule surface (the third effect). This film is widely believed to consist of a liquid crystalline phase that surrounds each emulsified droplet [6]. The exact nature of these structures (lamellar gel phases, lyotropic hexagonal phases, or lamellar liquid crystalline phases) may vary from emulsion to emulsion. The third phase in

Table 10.1 Common Types of Surfactants Used in Cosmetic Emulsions

Surfactant chemical class	Typical generic example
Anionics	
Carboxylic acids	Soaps
Carboxylic acid esters	Lactylates, PEG* Alkyl carboxylates
Sulfuric acid esters	Alkyl sulfates, Sulfated monoglycerides
Sulfonic acids	Sulfosuccinate esters, Acyl isethionates
Amino acid amides	Sarcosinates, Acylated peptides
Cationics	
Amines	PEG* Alkyl amine
Quaternaries	Tetraalkyl ammonium salts
Amphoterics	
Phosphates	Phospholipids
Amine derivatives	N-Alkyl amino acids, Alkylamido alkylamines
Nonionics	
Alcohols	Fatty alcohols
Ethers	Alkoxylated fatty alcohols, PEG-Phenol Ethers
Esters	Alkoxylated fatty acids, Acyl sorbitans, and PEG-Derivatives, Acyl glycerides
Amides	PEG* Alkyl amides
Polymers	PEG*/PPG** Block polymers, PEG*-Silicone Derivatives, Alkyl-substituted polyvinyl polymers

*PEG—Polyoxyethylene
**PPG—Polyoxypropylene

most cosmetic emulsions consists primarily of liquid crystals surrounding the emulsified globule. Optical microscopy in polarized light is the primary tool for detecting the presence of these structures in emulsions; another tool is interfacial rheometry. The third phase probably stabilizes emulsions against coalescence by altering the van der Waals potential between approaching droplets. A liquid crystalline phase is quite viscous, resists compression by forming relatively thick ($\approx$1 μm) films, and exhibits pseudoplastic rheology. The liquid crystals responsible for stabilization are systems containing primarily emulsifiers, some of the dispersed phase lipid, and water.

Despite the important contributions of electrical charges to emulsion stability, most skin care cosmetic emulsions rely on uncharged emulsifiers (nonionics) The choice of nonionics is supported by their assumed safety by comparison to anionic or cationic emulsifiers. In addition, nonionics as a

group can tolerate salts. Cationics are generally considered poor emulsifiers by comparison to other surfactant classes.

The key to preparing a reasonably stable emulsion is avoidance of droplet coalescence. In a standard O/W emulsion, the specific gravity of the dispersed phase is lower that that of the surrounding continuous phase. Immediately after emulsion formation (when agitation is stopped), the oil globules can be expected to rise. Such rising (also called creaming) is unattractive but can be reduced by increasing the viscosity of the external phase (as postulated by the 100-year-old Stokes equation). Rising may still occur slowly, but the emulsion can be reconstituted by modest shaking. On the other hand, the proximity of globules in an emulsion that has risen may lead to flocculation, a phenomenon in which the emulsified globules adhere to each other. A flocculated emulsion then becomes subject to coalescence, in which two or more droplets may merge to form one large globule. Such coalescence is retarded by electrical repulsion or by the presence of the so-called third phase. Once these emulsion-stabilizing phenomena are overcome, the globules can become so large that they cannot be readily redispersed by shaking. An emulsion in this condition is commonly identified as oiled out. The stabilizing electrical double layer concept is attributed to Derjaguin, Landau, Vervey, and Overbeek (DLVO), and it and the energetics of coalescence were reviewed by Friberg et al. [6]. Friberg's chapter also described means for avoiding droplet coalescence through addition of polymers to the continuous phase.

HYDROPHILE/LIPOPHILE BALANCE (HLB)

Despite the creation of some elaborate schemes for assessing the utility of emulsifiers for the formulation of cosmetics and related emulsions, emulsifier selection remains an art based on trial and error. The number of available nonionic emulsifiers is very large, while the list of ionized emulsifiers—including soaps—is much more limited. Some of the more widely used nonionics are identified in Table 10.2, which lists them in order of increasing HLB.

The HLB concept was developed by Griffin around the 1960s to compare the efficacy of *ethoxylated* emulsifiers. Griffin reasoned that the ratio of the hydrophobic portion to the hydrophilic portion of the emulsifier molecule controls its water solubility and its efficacy as an emulsifier. He computed the HLB value from the following simple equation:

$$\text{HLB} = \frac{\text{Weight of the Polyoxyethylene Portion}}{\text{Molecular Weight of Surfactant}} \times 20$$

Thus a molecule consisting only of polyoxyethylene has an HLB of 20, a highly questionable outcome: PEG-4 or PEG-100 may act as solvents, but

Table 10.2 Cosmetic Emulsifiers[a]

Chemical designation*	HLB	Water dispersibility
Ethylene glycol distearate	1.5	No dispersion
Sorbitan tristearate	2.1	
Propylene glycol stearate	3.4	
Sorbitan sesquioleate	3.7	
Glyceryl stearate (non-self-emulsifiable)	3.8	Poor dispersion
Propylene glycol laurate	4.5	
Sorbitan stearate	4.7	
Diethylene glycol stearate	4.7	
Glyceryl stearate (self-emulsifiable)	5.5	
Diethylene glycol laurate	6.1	Milky dispersion (not stable)
Sorbitan palmitate	6.7	
Sucrose dioleate	7.1	
PEG-4 oleate	8.0	
Laureth-4	9.5	Milky dispersion (stable)
Polysorbate 61	9.6	
Ceteth-8	10.3	
Polysorbate 65	10.5	Translucent to clear
PEG-8 oleate	11.4	
PEG-8 stearate	11.6	
Nonoxynol-9	13.0	
PEG-8 laurate	13.1	Clear solution
Polysorbate 21	13.3	
Polysorbate 80	15.0	
Oleth-20	15-4	
Polysorbate 40	15.6	
Ceteth-20	15.7	
PEG-40 stearate	16.9	
Sodium oleate	18.0	
PEG-100 stearate	18.8	
Potassium oleate	20.0	
Sodium lauryl sulfate	Approx. 40	

*INCI nomenclature

a) A much more comprehensive list of useful cosmetic emulsifiers can be found in the *INCI Dictionary* [5].

they are not amphiphilic emulsifiers. Griffin extended his HLB approach to include some ionic surfactants, as shown in Table 10.2. In practice, the best emulsification for most systems is provided by mixed emulsifiers, and most O/W cosmetic emulsions require HLBs ranging from about 10 to 15. Although commercial ethoxylated emulsifiers are mixtures, formulators blend a relatively

low HLB surfactant with a high HLB surfactant for optimal results. An HLB of about 13 can be reached by blending 30 parts of PEG-4 oleate (HLB 8.0) with 70 parts of polysorbate 80 (HLB 15.0):

$$13 \simeq 0.3 \times 8.0 + 0.7 \times 15.0$$

The common HLB range of about 10 to 15 mentioned above depends on the nature of the emulsified oil phase (Table 10.3). Formulators have learned that each lipid requires a somewhat different HLB for formation of a nonionic O/W emulsion. Stearyl alcohol, for example, requires a high HLB of about 15, while cottonseed oil requires a relatively low HLB of about 10; mineral oils and petrolatum can be emulsified at an HLB of about 12. In cosmetic practice, these variations are at best guidelines since the oil phase in a typical cosmetic may include mixtures of lipids. A much lower HLB (about 4–5) is required for the preparation of a W/O emulsion.

The HLB system is used widely, and Griffin's contribution to emulsification was invaluable. The HLB concept cannot answer the question of how much emulsifier is required, nor can it clarify the emulsification differences between a polyoxyethylene ester and a polyoxyethylene ether having the same HLB. The HLB principle also fails to explain why a purified polyoxyethylene alkyl ether of a lower molecular weight does not yield as stable an emulsion as a similar ether having a higher molecular weight, although both emulsifiers have identical HLBs. It is wise to remember Schott's [7] admonitions that:

a. The HLB is not a universal parameter.
b. There is no correlation between the HLB and a given physical property.
c. The (Griffin) definition of HLB lumps together different surfactant molecules and disregards the nature of the lipophilic moiety.
d. The HLB is useful only as a first approximation.

Schott also noted a monotonic relationship between the log of the O/W partition coeffcient ($K_{O/W}$) and the solubility parameter (δ_O). Despite its limitations, the use of the HLB and its extensions via solubility parameters or phase inversion temperature have been an invaluable aid to emulsion formulators for years. Table 10.2 includes water dispersibility as a third column, showing that the HLB increases with increasing water solubility. Thus a nonionic surfactant's unknown HLB can be estimated within a few units by its water solubility or by the appearance of its aqueous dispersion at or near room temperature.

Elaborate procedures for determining the HLB have been devised. Some of these techniques are noted in Table 10.4.

Table 10.3 HLB Required by Lipids to Form O/W Emulsions

Material	Required HLB
Acetylated lanolin	14
Ascorbyl palmitate	6
C12-15 Alkyl benzoate	13
Caprylic/capric triglyceride	5
Carnauba wax	15
Castor oil	14
Cocoa butter	6
Coconut oil	5
Corn oil	6
Cottonseed oil	5–6
Cyclomethicone	7–8
Dimethicone	9
Isocetyl alcohol	11–12
Isopropyl myristate	11–12
Isopropyl palmitate	11–12
Isostearic acid	15–16
Jojoba oil	6–5
Lanolin	9
Mineral oil (light, naphthenic)	11–12
Mineral oil (light, paraffinic)	10–11
Mink oil	5
Oleic acid	17
Paraffin	10
Petrolatum	7–8
Soybean oil	6
Stearyl alcohol	15–16

Table 10.4 Methods for the Determination of HLB Values

Method	Reference
Computational	Davies, J.T. Proc. 2nd Int. Congress Surface Activity, London, **1**, 426, 1957; Schott, H., *J. Pharm. Sci.*, 1990, **79**, 87.
Relationship to PIT	Shinoda, H., and Kuneida, H. In *Encyclopedia of Emulsion Technology*, (P. Becher, ed.), p. 337, Marcel Dekker, New York, 1983.
Calorimetry	Racz, I., and Orban, E., *J. Coll. Sci.*, **20**, 99, 1965; Rowe, et al., *Int. J. Pharm.*, 1992, **79**, 251.
Phenol Index	Marszall, L., *Fette Seifen Anstrichm.*, 1980, **82**, 210.
GLC	Becher, P., and Birkmeier, R.L. *J. Am. Oil Chem. Soc.*, 1964, **41**, 169.
Solubility Parameter	Bearbower, A., and Hill, M.W., *Amer. Perf. Cosmet.*, 1972, **87**, VI, 85–89.
H-NMR	Rabaron, A., et al., *Int. J. Pharm.*, 1993, **99**, 26–36.

ASSOCIATIVE THICKENERS

Associative thickeners are conventional hydrophilic polymers modified by hydrophobic moieties such as long-chain alkyl groups [8]. The related viscosity-enhancing polymers are customarily used to increase emulsion stability by interfering with settling and rising of dispersed phases, as described by Stokes. Associative thickeners resemble polyacrylate-type carbomers, but some (hydrophobic) alkyl substituents are introduced before or after polymerization. The resulting polymers still gel upon neutralization in the aqueous portion of the emulsion. In addition, the hydrophobic segments on the polymer backbone associate with the emulsion's lipid phase. Adjustment of the level of hydrophobic monomers modifies these and similar polymers derived from other vinyl derivatives.

A typical associative nonionic thickening "gum" is cetyl hydroxyethylcellulose. A better-known synthetic example is the anionic alkylacrylate crosspolymer. To act as an O/W emulsifier, the associative thickener must bond to the emulsion's internal phase through dipole-dipole interactions, hydrogen bonding, and hydrophobic interactions. It is almost certain that such bonding occurs; in addition, the hydrophilic portion of these polymers is anchored in a thickened aqueous phase. It is entirely feasible to use a differently designed polymeric molecule as a W/O emulsifier. In this case, the hydrophobic polymer will be soluble in the continuous lipid phase, and water is then emulsified due to the presence of hydrophilic segments of the polymer.

EMULSION PREPARATION

Cosmetic emulsification depends on the use of emulsifiers selected by the formulator. This choice is based on the formulator's experience, the nature of the oil constituents, the composition of the aqueous phase, and the desired characteristics of the product (for example, high, intermediate, or low viscosity). The preparation of cosmetic macroemulsions is rarely a simple process. On the other hand, formulators have learned that macroemulsions of short-term stability may form spontaneously if a lipid is combined with a relatively high level of emulsifiers. Typical examples are the so-called self-emulsifying bath oils. These clear solutions of oils and emulsifiers disperse to form milky emulsions when they are added to the bathwater. Even clear dispersions, that is, microemulsions, can result when oils, water, and emulsifiers are blended in carefully selected concentrations. As a rule, microemulsions form spontaneously with little or no agitation, and the order to addition of the components is not critical.

In contrast, the preparation of a macroemulsion (O/W or W/O) requires a controlled mixing sequence, a level of agitation, and heating. The subsequent

use of mechanical equipment to yield the desired emulsion is often necessary. Multiphase (or semisolid) O/W emulsions represent a special type of emulsion in which gel phases form a complex network in the continuous aqueous phase to hold the various phases in place.

For reasons of safety and cost, it is recommended that the level of emulsifier in a cosmetic product be kept as low as possible. A comprehensive listing of Surfactants-Emulsifying Agents is provided in the *INCI Dictionary* [5]. It has already been noted that higher molecular weight emulsifiers are generally more efficient that those having a lower molecular weight when the HLBs are the same. Other aspects of good emulsion practice will become apparent from the followng discussion, which describes four types of emulsions: O/W emulsions, multiphase O/W (semisolid) emulsions, W/O emulsions, and microemulsions.

O/W EMULSIONS

This discussion of O/W emulsions includes a description of phase inversion temperature (PIT) and of auxiliaries that enhance the stability of this and other emulsion types. In *classic O/W emulsification* the oil phase and the aqueous phase were prepared separately and then combined with agitation. In a typical procedure, the oil-soluble emulsifiers are blended with the oil phase and warmed to form a clear homogeneous melt at a temperature above the melting point of the highest melting wax. The aqueous phase may include all types of water-soluble components, including any water-soluble surfactants or thickening agents, and is heated to the same temperature as the oil phase. To form an O/W emulsion, the oil phase is added slowly with agitation to the aqueous phase. The reverse type of addition is customarily reserved for W/O emulsions. After addition is complete, the temperature is allowed to drop while agitation is continued. Heat-sensitive components, for example, fragrances or preservatives, are added at lower temperatures. Stirring is usually stopped at about 35 °C and is rarely continued to below 25 °C. At any time during this process, the (warm) emulsion might be especially processed to help reduce the droplet size of the internal phase. Homogenizers, ultrasonifiers, and colloid mills are widely used in cosmetic and pharmaceutical processing, even though this extra step is not always required.

In the preparation of laboratory samples the rate of cooling is not carefully monitored, but in large-scale production, controlled cooling may be rquired. The creation of a macroemulsion of acceptable stability depends to a large extent on achieving a homogeneous blend of a finely divided internal phase. Formulators spend much effort to create systems of low and uniform particle size and to avoid formation of large, generally unstable, emulsion globules.

Phase Inversion Temperature

The differences between the previously described classic techniques for emulsification and modern practices are minor but are of critical importance. Heating of the phases is still practiced, but most emulsion practitioners prefer to exceed the so-called phase inversion temperature (PIT). It has been known for some years that soap stabilized O/W hydrocarbon emulsions form in hot systems but upon cooling invert to form W/O emulsions. Information on the temperature-dependent cloud point of nonionics helped to establish the rationale for the phenomeon of inversion of nonionic macroemulsions. Water-soluble nonionic emulsifiers tend to become cloudy upon heating. At the cloud point, that is, the temperature above which the system is cloudy, the hydrogen bonding of water to the surfactant's hydrophilic portion is weakened. The surfactant becomes less water-soluble, and its emulsifying properties change drastically.

Shinoda provided some theoretical insight into what happens at the PIT [9]. At ambient temperatures a nonionic emulsion prepared with a polyoxyethylene-type emulsifier may contain some micellized surfactant, some oil-swollen surfactant micelles, and some emulsified oil. Raising the temperature alters the HLB of the surfactant, making it more hydrophobic (or lowering its HLB). Micellar stability decreases, and the size of any emulsified oil droplets increases. Ultimately, at some still higher temperature, the PIT, the emulsion separates into an aqueous phase, a surfactant phase, and an oil phase. If the temperature is raised still further, the system, originally an O/W emulsion at lower temperature, inverts to become a W/O emulsion. At the PIT the hydrophilic properties of the emulsifier(s) are in balance, and this temperature is sometimes called the HLB temperature. It becomes apparent now why the surfactant placement (into the oil or the water phase) during PIT emulsification can be neglected because the three-phase system at the PIT equilibrates during cooling.

The features of what occurs at the PIT in emulsion formation is best explained by examination of the well-known Kahlweit diagram (Fig. 10.1) and the accompanying caption. The PIT, which has a small range, separates the O/W macroemulsion system (below T_L) from that of the W/O macroemulsion (above T_U). In the PIT range, three phases are formed at low levels of emulsifier concentration. At high surfactant levels, the systems may form a single-phase microemulsion or lamellar structures.

Conditions for such a distinct separation may not exist in all combinations. Microemulsions, for example, may break up and exist only within a specific temperature range. In other systems one may never find a microemulsion. The phenomenon of the PIT can occur over a broad range of O:W ratios. Maintaining an emulsified system at the PIT can be expected to cause significant

phase separation. A more practical example has been described and explained by investigators in Germany [10,11].

Computational techniques for selection of emulsifiers based on an assessment of a "mixed" oil phase have achieved prominence in recent years. An additional feature of PIT emulsification is its use in low energy emulsion production [12].

Emulsification by the PIT procedure generally succeeds in yielding low viscosity and low particle size emulsions. They commonly exhibit a bluish haze when they are spread thinly on a transparent or reflecting surface. Even more viscous O/W emulsions can show this phenomenon, which results from the small droplet size of the dispersed phase. These droplets are small enough to undergo Brownian movement and are not "stationary." In accordance with the principles of Stokes' law, their mobility is a function of the difference in specific gravities of the dispersed and the continuous phases. In a typical low viscosity emulsion, rising of the internal phase can lead to unsightly creaming even if no globule coalescence occurs. Creaming can be reduced by the addition of polymeric viscosity increasing substances to the continuous aqueous phase.

Auxiliary Emulsifiers

Auxiliary emulsifiers are used to improve the stability of all types of emulsions, not only those of the O/W type. The auxiliary emulsifier may be a finely divided solid, such as a viscosity-enhancing water-swellable clay, or a variety of water swelling organic polymers.

Polar and nonpolar solids, for example, clays, pigments, insoluble hydroxides, carbon, and even some high-melting lipids (glyceryl tribehenate) can be used as auxiliary emulsifiers. By far the most important inorganic stabilizers are water-swellable clays, such as aluminum silicates, bentonite, and related smectite clays. Hydration of these clays is not part of the emulsifcation process. Instead they are hydrated separately and then added to the emulsion. Products modified with clays exhibit pseudoplastic viscosity, that is, are shear thinning. Barium sulfate in the presence of sodium laurate is useful for O/W emulsions at high pH, while this solid favors W/O emulsification in the presence of SLS. The principles accounting for emulsion stabilization by inert solids were reviewed briefly by Friberg et al. [6]. Water-soluble natural gums that increase viscosity have been used as emulsion auxiliaries for many years. Most of them are plant-derived polysaccharides and are safe for ingestion. A few examples are listed in Table 10.5. The popularity of some of these raw materials in cosmetics is decreasing because they tend to leave a tacky film on the skin.

It has been assumed for many years that these gums' primary effect in emulsions is a viscosity increase of the continuous phase. Recent publications

Table 10.5 Some Hydrocolloid and Synthetic Emulsions Stabilizers*

Acrylates/C10–30 Alkyl acrylate crosspolymer
Alginates
C1–5 Alkyl galactomannan
Carrageenan
Carbomer
Cellulosics
Gelatin
Gum arabic
Gum guar
Gum karaya
Locust bean gum
Quince seed sum
PVP/Decene copolymer
PVM/MA decadiene crosspolymer
Xanthan gum

*More comprehensive listings will be found in the *INCI Dictionary* under the headings of Gums, hydrophilic colloids, and derivatives and of Viscosity increasing agents, aqueous [5].

suggest that their adsorption on the surface of emulsified droplets is likely to inhibit droplet coalescence [6].

Finally, a number of synthetic polymers, including associative thickeners, have become available to the formulator (Table 10.5). Their use is particularly attractive since these polymers can be tailored to provide both hydrophilic and hydrophobic segments. Carbomers, polymers of acrylic acid cross-linked by divinyl derivatives, are hydrated separately, then added to the emulsion, and finally neutralized to form the viscosity-enhancing polyionic polymer.

The (frequently) anionic synthetic auxiliary emulsifiers listed in Table 10.5 have helped in the formulation of some of the most stable emulsions in the cosmetic industry. They decrease the movement of dispersed oil globules because of increased viscosity of the continuous phase, and they protect the internal discontinuous phase against coalescence by a mechanism of adsorption because of hydrophobic bonding.

MULTIPHASE O/W EMULSIONS

In the classic and generally viscous skin care emulsions, the internal oil phase may not be dispersed in minute droplets. Brownian movement may

be significantly curtailed, and stabilization differs from that postulated for the conventional, mobile, droplet-based O/W emulsions [13].

The nature of these types of semisolid O/W emulsion was originally explained by Junginger [13]. These creams were based on soaps (Fig. 10.2), but in current practice nonionic emulsifiers (sometimes containing alkyl sulfates) are used. Mixtures of components that yield creams when blended (with heating) with water are commercially available as emulsifying waxes and are described in various pharmacopoeias. A typical mixture may yield a preparation, such as the following:

PEG-20 glyceryl stearate	5.0%
Cetearyl alcohol	10.0
Mineral oil	7.5
Petrolatum	17.5
Glycerin	8.5
Water, demineralized	51.5

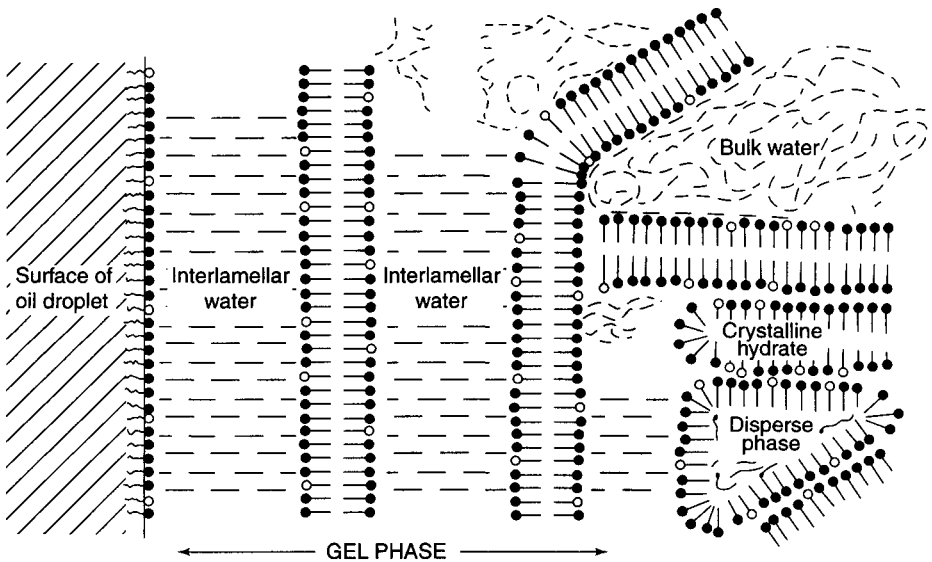

Figure 10.2. Schematic of a multiphase O/W emulsion. The gel phase consists of mixed crystal bilayers of fatty acids (—○) and their TEA soaps (—●). The mixed crystal bilayers may exist simply as hydrates. Bulk water (upper right), bulk oil (left side), or a disperse phase (lower right) may exist depending on the basic composition or presence of other components. [Reproduced by permission from the J. Soc. Cosmet. Chem., 1990, **41**, *9].*

The structure of this product requires the presence of a lamellar gel phase, as explained in the caption of Figure 10.2. The bilayer lamellae within this gel phase are formed by a hydrophobic emulsifier (soap plus free fatty acids, cetearyl alcohol, glyceryl stearate) with a small amount of hydrophilic emulsifier (PEG-20 glyceryl stearate or sodium lauryl sulfate). The hydrophobic tails of these substances contact the emulsion's oil phase, while the hydrophilic heads are attached to the interlamellar water. In addition, the figure shows the presence of bulk water, of a disperse phase and of a crystalline hydrate of a folded monolayer. The mixed crystal bilayers of cetearyl alcohol and hydrophilic PEG-20 glyceryl stearate extend into the water layer. However, above a water level of about 60 percent, the gel structure becomes unstable. The stability of the emulsion system depends on the rigidity of the mixed crystal bilayer, the transition temperature, and the water content. Failure of the gel phase—whatever the adverse storage conditions—can be expected to result in emulsion instability. The interlamellarly fixed water (shown in Fig. 10.2) is separated from bulk water by a permeable membrane consisting of mixed crystals of an amphiphilic phase; thus water movement to bulk water is likely. Similarly, there may be movement of disperse phase to or from the droplet (phase).

In practice, mechanical action on creams of this type can destabilize these emulsions. Therefore agitation is routinely stopped at or near about 35 °C during the cooling cycle of emulsification. High-shear pumping of such products after cooling may also be destructive. It is customary, therefore, to enhance emulsion stability with the aid of thickening agents.

W/O EMULSIONS

In contrast to O/W emulsions, these emulsions require use of an emulsifier with a lower HLB of about 5 to 7. In addition, the oil:water phase ratio should favor oil to ensure formation of a continuous oil phase. The principles of emulsification are the same as those described for O/W preparations except that the aqueous phase is added to the oil phase if the classic emulsification procedure is followed. The PIT process seems impractical for those W/O emulsions that are expected to exhibit stability at or above room tremperature. A little reflection shows that one would have to start with a very cold O/W emulsion and warm it beyond the inversion temperature to change it into a desired W/O emulsion.

In O/W emulsions, the internal oil phase constitutes less than about 30% of the total to avoid a greasy after-finish. The reverse is true in W/O emulsions in which a higher water content lowers greasiness. The water droplets formed during the agitation step are stabilized against coalescence by the viscosity of the oil phase and by contact of the hydrophilic portions of the emulsifier

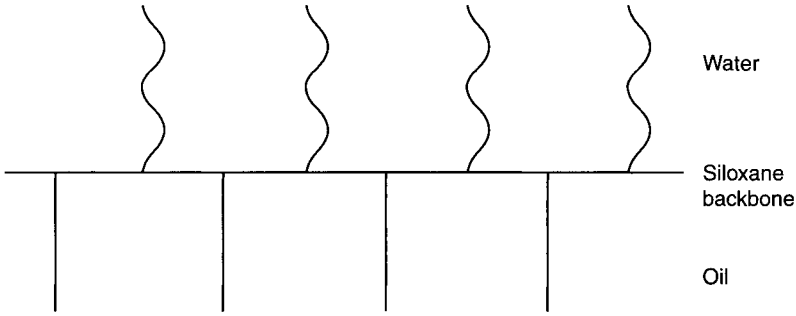

Figure 10.3. Schematic of configuration of cetyldimethicone copolyol at a hypothetical water-oil interface. Hydrophilic side chains contact the water phase; the lipophilic side chains contact the oil phase. [Reproduced by permission of the Int. Fed. Soc. Cosmet. Chemists from IFSCC Monograph No. 4].

with the disperse phase. Blends of emulsifiers for O/W emulsions may include water-soluble substances and water-insoluble amphiphiles. However, for the preparation of W/O emulsions, the emulsifiers are almost exclusively oil-soluble. A list of low molecular weight W/O emulsifiers might include, in addition to the low HLB (less than about 8.0) nonionics (Table 10.2), polyglyceryl-3 distearate, glyceryl oleate, and cetearyl alcohol. Lanolin has been used for many years as a W/O emulsifier.

The consistency and stability of W/O emulsions depend almost exclusively on the viscosity characteristics of the continuous oil phase. As a result, stable W/O emulsions that could tolerate freezing and storage up to about 40 °C were rare because of wide variations of viscosity of the continuous phase. Currently, associative thickeners of different types have been found useful for creating W/O emulsions. In these associative thickeners, the backbone may be a dimethicone copolyol that has been modified by copolymerization with an alkyl silane. At a water–oil interface these molecules, for example, laurylmethicone copolyol, tend to spread out (which is typical for most polysiloxanes) and position themselves, as shown in Figure 10.3. The adsorption efficacy of these hydrophobically modified silicone polyols on a water-oil interface is about 20 times that of sorbitan oleate, making them remarkably effective W/O emulsifiers.

MICROEMULSIONS

The term *microemulsion* in cosmetics identifies a clear-appearing system containing at least two immiscible (mutally insoluble) components. Clear emulsions may be W/O or O/W, but only the latter have gained prominence in the drug and pharmaceutical industries. Transparent cosmetics and OTC topical drugs

play significant roles in commerce, but the mechanism for their purported efficacy remains obscure. Investigators of these systems distinguished several types on the basis of method of preparation and of appearance [14,15]. The previously mentioned Kahlweit fish (Fig. 10.1) is useful for distinguishing between macro- and microemulsions and identifies the area of existence of essentially clear microemulsions: low levels of oil phase; high levels of surfactant; and a relatively narrow temperature range. The definition of microemulsions as transparent is reasonably specific, but vagueness concerning the physical nature of microemulsions persists. *Transparent emulsion, micellar solution, solubilized system,* and *swollen micelle* are typical descriptive terms that are intended to convey supplemental information on the nature of microemulsions. Currently, two concepts dominate the field; microemulsions are viewed as liquid-in-liquid disperse systems with constantly shifting domains; alternatively, they are described as micellar systems. For the practicing cosmetic chemist, microemulsions are systems comprising water, oil, and amphiphile(s), which to the human eye are optically isotropic and which are thermodynamically stable. Although their clarity may exist only within a narrow range of temperatures, any cloudiness disappears when the microemulsion is returned to its original temperature. Microemulsions may exist only in a narrow range of temperatures, and many exhibit critical limits of concentration. These problems were noted in numerous publications [15–17].

At this time it appears that the "clear" and "transparent" single-phase microemulsions with their temperature and concentration limitations form a distinct and separate group from so-called ultrafine emulsions. In contrast to monophasic microemulsions, ultrafine emulsions may exhibit some haziness and are thermodynamically unstable. Nevertheless, they include particle sizes that are in the range of those in single-phase emulsions. The ultrafine emulsions contain lower levels of emulsifiers than single-phase emulsions, but their formation often requires use of specialized high-pressure equipment such as microfluidizers.

In ultrafine emulsions, the comminuted particles of the lipid phase form a core that is surrounded by the molecules of the emulsifier blend. The emulsifiers need not dissolve the lipid phase. Ostwald ripening of these particles can occur, creating larger particles that may rise or sink. In contrast, the oil phase in a single-phase microemulsion is likely to be dissolved in the micellar core of surfactants. Any disturbance by collision or other events is immediately repaired (restored to clarity) by redissolution within the micellar core.

STABILITY OF EMULSIONS

The chemical and physical stability of all types of cosmetics, including emulsions, is discussed in a later chapter. Macroemulsions, regardless of their type,

exist only temporarily and are—by the laws of physics—unstable. Nevertheless, cosmetic formulators make elaborate efforts to prolong the life of their creation. For this purpose, they employ emulsifiers to reduce interfacial tension, they seek out means for enhancing electrical or mechanical barriers to coalescence, they expend much energy on the reduction of particle size of the internal phase, and they carefully manipulate the viscosity of the system to keep the internal phase from coalescing and moving. Despite these efforts, the emulsion's stability is only transitory, and macroemulsions begin the process of destabilization soon after manufacture.

The goal of formulators should be to delay emulsion breakdown sufficiently to meet the product needs of the market during the short interval of temporary physical stability. The length of this interval should be predetermined by the marketer.

Basing an emulsion's stability on meeting a rigid set of complex laboratory standards may not necessarily provide a useful answer to the formulator. Instead it may be more pertinent to establish consumer acceptance of the product after short exposure to adverse conditions, such as a shipping test or stationary cycling within a limited range of temperatures. Based on only the most rudimentary understanding of the PIT and temperature-dependent viscosity changes, it is unlikely that one acceptably robust formula can meet the requirements for marketing in (cold) temperate climates or in the tropics.

SPECIAL CONSIDERATIONS

Like all cosmetic products, emulsions cannot be marketed safely unless they meet rigid stability criteria. Some of these criteria are particularily difficult to achieve and deserve special comments.

1. Emulsions as a group are intimate mixtures of water with diverse organic substances and are subject to microbial contamination. Preservation by various means is required, as detailed in Chapter 14, and the adequacy of preservation should be examined periodically,

2. The need for the use of antioxidants depends on the nature and the quality of the emulsion's ingredients. Oxidative degradation during long-term storage occurs rarely and is commonly reduced in accordance with the concepts presented in Chapter 12, "Antioxidants". Conditions after use of an emulsion on the skin present an additional criterion for the formulator. Any emulsion meeting normal safety assessment and which is removed by water rinsing is unlikely to cause any skin irritation. However, emulsions used for skin treatment and which remain on the skin and may be reapplied *ad lib* need closer monitoring.

3. Many amphiphilic emulsifiers may modify the epidermal barrier function and facilitate access of a variety of noxious substances. The incidence of this type of penetration enhancement can be materially reduced through the use of nonpenetrating high molecular weight associative emulsifiers. Surfactants or emulsifiers are not likely to persist as micelles after loss of water. However, they may permeate slowly to the epidermal lipid bilayers and change diffusion and barrier properties. The intuitive assumption that a "clear" emulsion is a more effective delivery vehicle than a macroemulsion may not be valid. Instead the concentration of the emulsifier blend in a microemulsion is likely to decrease the barrier properties of epidermal lipids.

4. A much more insidious effect could be attributed to the use of all polyoxyethylene derivatives. When these types of ingredients are left on the skin after drying of the emulsion, they are subject to photooxidation. As noted in Chapter 9, "Surfactants", the formed peroxides give rise to aldehyde and acidic components. Fortunately, the predominantly formed aldehyde, formaldehyde, is volatile and has not been associated with any dermatitic responses. Questions about the benign nature of polysorbates and ethoxylated ethers have recently been raised by Bergh and her coworkers [18], but no general conclusions can be drawn at this time.

5. Active delivery with the aid of emulsions remains an elusive enigma. As noted in the introduction, technologists view emulsions as systems that allow topical administration of actives in dilute form. The active may be a mixture of emollient or occlusive lipids, a drug substance, or a related therapeutic entity. The differences between macroemulsions and microemulsions and between O/W and W/O preparations are likely to disappear shortly after inunction when most of the emulsion's volatiles (primarily water) evaporate. At this point, the active is no longer emulsified, and the residue on the skin is a blend of all types of emulsion components. Permeation to lower strata of the epidermis does not occur via emulsified globules but by diffusion of individual molecules, possibly through tortuous and narrow channels. The delivery of actives from a microemulsion remains a problem in the case of flavorants, fragrances, or drugs. Head space analyses of volatiles from a solubilized solution shows that solubilization interferes with volatility.

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CHAPTER 11
Rheological Additives

What Is Rheology?

Consumers know rheology. They know how they want their hand lotions to flow, and they know how they don't want them to flow. They expect their nail polish to brush on smoothly, and they don't expect their shampoos to run out of their hands like water. All these expectations are built upon the knowledge of flow properties. It may not be a technical knowledge, but it can surely influence their buying patterns. Since repeat sales are important to the viability of any product, it is up to the cosmetic scientists to create the proper rheology, or flow properties, in their cosmetics. To do this, the cosmetic scientist must be aware of a whole class of compounds identified here as "rheological additives."

There are a number of ways that formulators can influence the rheology of their products. Increasing the viscosity of a system can be achieved through inclusion of waxes or fatty acids; surfactant systems can be thickened by the simple addition of salts, whereas alcohols and glycols can sometimes be used to decrease the viscosity. There are times, though, when these measures do not provide the necessary properties, and another type of additive must be used. Natural gums and extracts, modified naturals, synthetic additives, clays, and silicas all have characteristic rheological effects that go beyond just "thickening." These additives can also be used to suspend pigments or active ingredients, control flow, increase emulsion stability, and promote penetration, lubricity, slip, and thermal stability. By familiarizing themselves with rheology and by using rheological additives, cosmetic scientists can better predict how their formulas will react under different conditions of use and—more importantly—how the products will be perceived by the consumer.

COSMETIC RHEOLOGY

The science of rheology is becoming increasingly important as cosmetic products are becoming more technically advanced. To better understand the mechanisms behind properties such as viscosity, shelf life, and suspension

and flow, familiarity with some rheological concepts is necessary. Rheology is completely defined as the science of "how materials deform and flow under the influence of external forces." The external force applied over a certain area is typically called a "shear stress" and is measured in units of Newton/meter^2, or Pascal (Pa). When the shear stress is applied, the force exerted causes movement of the material. The material closest to the force moves the fastest, and the material furthest away moves the slowest, setting up a velocity gradient. This velocity gradient is called "shear rate" and is measured in (meter/second)/meter, or simply reciprocal seconds (1/s.). The ratio of the force applied to the movement achieved (shear stress/shear rate) is the definition of "viscosity." Water has a lower viscosity than honey, since one achieves more movement of water for a particular amount of force than of honey. Viscosity is measured in Pascal seconds (Pas) in the International System of Units, or traditionally in poise (P), where 1 Pascal second = 10 Poise, and 1 Millipascal second (mPas) = 1 Centipoise (cP) [Table 11.1].

All fluids are characterized by their response to shear; the viscosity of Newtonian fluids remains constant even when sheared, while non-Newtonian fluids respond to a shearing force by exhibiting a change in their viscosities. Water and mineral oil are typical examples of Newtonian fluids, as are many shampoos. In Figure 11.1, curve A illustrates the relationship between viscosity and rate of shear for a Newtonian fluid. In some instances, a certain force must be applied before any shear (or flow) takes place at all; such materials are said to be non-Newtonian and exhibit "plastic" behavior, as shown in curve B. The amount of force that must be applied before any flow takes place is called the "yield value." Understanding what a yield value is helps us accept the fact that honey is actually more viscous than mayonnaise, even though mayonnaise may sometimes appear thicker. Honey will flow out of a jar if the jar is tipped, and mayonnaise will not. Mayonnaise exhibits plastic flow with a high yield value (85 Pa) that keeps it in place against gravitational force, while honey has no yield value at all and will eventually flow out of the jar. Yet if you try to stir both materials, you can feel much more "resistance to flow" or "viscosity" in the jar of honey.

Table 11.1 Typical Viscosities

	Pascal second (Pas)	Poise (P)	mPas or cP
Water	0.001	0.01	1
Oil	0.01	0.1	10
Glycerin	1	10	1,000
Honey	10	100	10,000

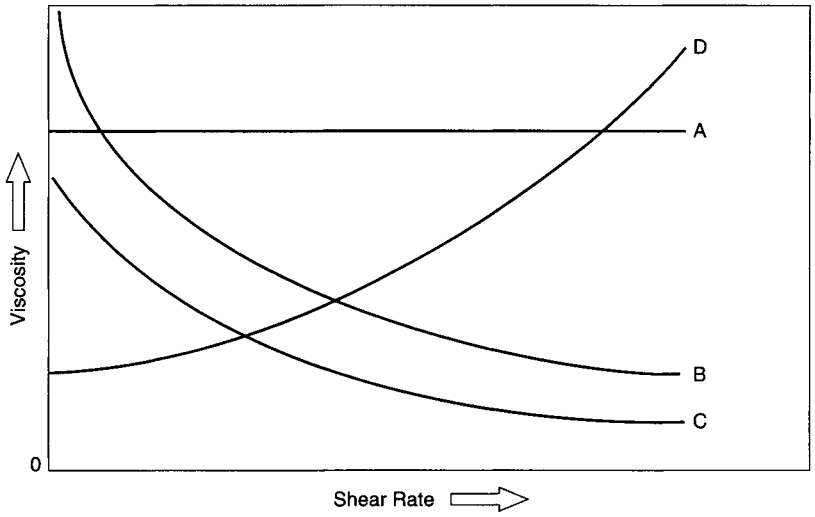

Figure 11.1. Response of viscosity to shear; A = Newtonian; B = plastic; C = pseudoplastic; D = dilatent

Many fluids do not possess a yield value but merely exhibit a decrease of viscosity as the rate of shear increases from zero. These are referred to as "pseudoplastic" materials, depicted as curve C. Many colloidal gums and polymer systems form pseudoplastic water gels; as a result, the creams, lotions, or hair gels made from these ingredients are often pseudoplastic.

Dilatent materials "firm up" as the rate of shear increases, shown as curve D. Though this kind of flow is rarely encountered in cosmetic systems, it may occur in heavily pigmented concentrates.

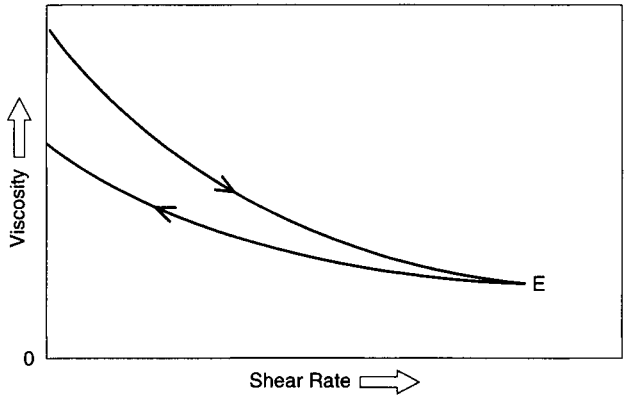

Figure 11.2. Response of viscosity to shear in a thixotropic system

The non-Newtonian systems discussed so far will recover their original viscosities very quickly when the shearing force is removed. Thixotropic materials react differently, as shown in Figure 11.2, in curve E. They exhibit a "shear thinning" effect similar to pseudoplastics, but when the shear is removed or reduced, their viscosities are rebuilt much more slowly. The shear thinning "up" curve differs from the shear thickening "down" curve, and the system is reported to exhibit hysteresis. Depending on the other characteristics of the system, full viscosity build-up can take anywhere from mere seconds to days. A thixotropic product remains thick when stored on the shelf but becomes thin when shaken or applied. Besides the extra stability benefits derived from being thick when not being used, these materials can exhibit better penetration and spreadability when they are thinned down during the shear of application. This time-dependent type of flow is often seen in emulsions, mascaras, and nail polish, and can be intensified by clay-based additives.

Many systems cannot be fully defined by the simple rheologies described so far. There are often "elastic" and "viscous" components of systems combining to create a "visco-elastic" flow. Truly viscous materials will completely use up all deformation forces, while truly elastic materials will store the deformation forces and later fully release them. Characterizing viscoelastic systems requires sophisticated rheometers and usually involves plotting the system's complex modulus, (G^*) made up of the storage modulus (G') or elastic component and the loss modulus (G'') or viscous component. By studying the effects of extremely fine oscillation on the shear stress response, the elastic response and the viscous response can be separated and individually defined.

INSTRUMENTATION FOR RHEOLOGICAL MEASUREMENTS

Measurement of rheological properties can be done in a number of ways. Methods can be as simple as a comparison to fluids of known viscosities or timing of the rate of flow through a defined orifice. The more complex rheometers are computer-controlled and designed for studying preparations over a very wide range of shear rates automatically to provide a "rheological profile" under many different conditions. In the middle of these two extremes is probably the most widely used instrument for measuring rheology in the cosmetic industry, the Brookfield viscometer. The principle behind this instrument is that viscosity can be measured by submerging a spindle into the fluid and by recording the amount of drag or resistance observed when the spindle is rotated. Shear rate is varied by changing the speed of rotation, and shear stress is varied by changing the size or contact area of the spindle. The Brookfield viscometer is easy to use, reliable, and relatively inexpensive. It can be used to measure a range of viscosities from water-thin fluids to thick creams, with the help of a wide range of spindles and a helipath attachment. The drawback of

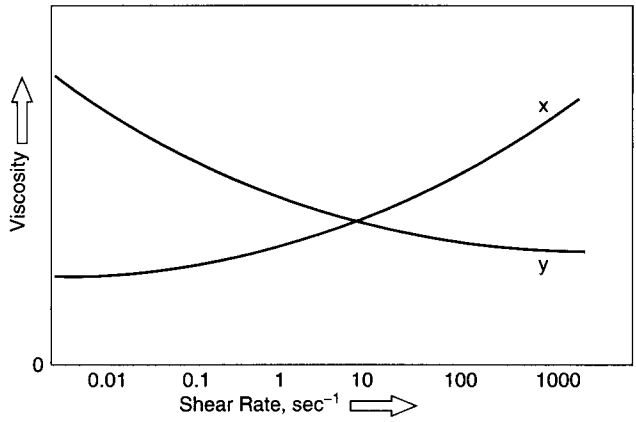

Figure 11.3. Demonstration of why single point viscosity measurements might not be useful. See text for explanatory comments.

this machine is that the range of shear rates that it can test is quite limited. For developmental work and fine-tuning of formulations, testing a broader range of shear rates is often necessary.

The range of shear rates encountered in the cosmetic industry is very wide. Pigment settling occurs in the neighborhood of 10^{-4} sec^{-1}; pouring a lotion from a bottle occurs at about 10 sec^{-1}; and the shear rate that a formulation is exposed to when dispensed from an aerosol is approximately 10^4 sec^{-1}.

Figure 11.3 shows viscosity profiles for two formulas. When tested in the mid-shear rate range of 10 reciprocal seconds, the two formulas have identical viscosities. At higher shear rates, formula X is much thicker than formula Y, and at lower shear rates, formula X is much thinner than formula Y. It is very important, therefore, to know what shear rate range is used whenever viscosity measurements are made or discussed. The description of the viscosity may not be enough to fully characterize a product if a simple viscometer with restricted capabilities is used. It may be necessary to view the whole range of shear rates, from very low to very high. To do this, a more complex rheometer must be used. A rheometer (like the ones from Haake, Bohlin or CarrieMed) will be able to automatically ramp up and down through a continuous progression of changing shear rates and plot not only the data but also a shear profile of the product. This profile may run from 10^{-5} sec^{-1} all the way up to 10^5 sec^{-1}. This type of machine can also automatically adjust the temperature or the time it takes to run the full profile.

RHEOLOGICAL EFFECTS IN THE LABORATORY

Cosmetic scientists must be aware of rheological effects encountered during the formulation stage. A suspending agent may need to be added whenever a

solid ingredient is included that must be uniformly dispersed throughout the formula. Suspending agents are rheological additives since they change the rheology of the fluid, making it more difficult for the solid particles to flow through. Many suspending agents form a loosely bound structure within the liquid, and the solids become trapped or supported. If the weight of the solid exceeds the strength of the supporting structure, the solid will settle. This is the reason why fine particles suspend more easily than very large ones. Antiperspirants and nail polishes both depend on suspending agents to help distribution of active ingredients and pigments. If it were not for the use of rheological additives, insoluble aluminum salts in antiperspirants would very quickly settle to the bottom and form hard, nondispersible cakes. Nail polish without rheological additives would allow the various colored pigments included to form layers of sediment at the bottom, according to their densities. Even lipsticks benefit from suspending agents. When a lipstick is manufactured, it is held in a molten state until it is poured into molds. When melted, it is critical that the pigments stay in uniform suspension; otherwise, some lipsticks of the batch may contain more pigment or color than others. After injecting the hot lipstick mass into a mold, it is also important that the pigment does not settle into the tip of the stick, or the lipstick's appearance will suffer.

Emulsion technology is another key area for the use of rheological additives. Stabilizing emulsions against phase separation can be accomplished with two different rheological approaches: adding a rheological additive to the external phase or adding it to the internal phase. The first approach is the one most frequently used. By choosing an additive that either increases the viscosity of the external phase or introduces a yield value to that phase, the formulator can slow down the flow of the internal phase through the external one. Formulators can also adjust the rheology of the emulsion by incorporating a rheological additive into the internal phase. The stabilizing effect here is caused by making the internal phase more "deformation resistant." Using an oil-in-water emulsion as an example, a viscosity-increasing additive in the oil phase will make the oil droplets more resistant to deformation as they flow past each other. The harder they are to deform, the harder it will be for the oil phase to flow through the aqueous phase, thereby increasing the time required for creaming, phase separation, or coalescence.

The formulation chemist must also think about the level of shear to which the formula will be subjected in the laboratory or in the plant environment. If any rheological additives in the formula are shear-sensitive, such as large polymers or silicas, then the intended rheology is affected by breakdown of the structure; in the case of additives that thrive on shear, such as clay, viscosity may build up. Encapsulated active ingredients or fragrances are also shear-sensitive. When sheared, their encapsulation may break down and not provide

the intended time release or protection from the incompatible components. For these reasons, it is important that formulation chemists understand the rate of shear generated by different kinds of machinery. Propeller mixers are relatively slow and the velocity gradient between the mixer and the walls of the container is so low that this type of equipment is usually considered very low shear. Dispersers used for pigment concentrates and rotor stators usually travel at much higher speeds and, coupled with the higher viscosities of concentrated batches, will provide much higher rates of shear than propeller or paddle blades. Dispersers can be considered medium shear pieces of equipment.

Homogenizers, colloid mills, and triple roller mills generate the highest shear rates usually encountered in cosmetic equipment, since they move material quickly and force it to travel through small openings, thus providing very high shear stresses with high velocity gradients. By being aware of the processing and packaging equipment and the ranges of shear rates they may deliver, a formulating scientist should be able to avoid many potentially damaging situations for his product.

Another factor that affects rheology is the temperature of the product during storage and use. If a viscosity-increasing rheological additive is significantly affected by heat, and if it is used, for example, in a sunscreen product, chances are that the customer will not find the expected rheology when the product is used after exposure in the hot sun for several hours on the beach. Lipsticks must also retain their shape and functionality when left in a purse in a very hot car on a summer day. Though the wax base itself may soften, it should not be allowed to flow into an unusable mass. Careful consideration of temperature sensitivity should be given during initial formulation studies.

RHEOLOGICAL EFFECTS IN MANUFACTURING

Manufacturing and Process Development departments must be concerned with the rheological behavior of the batch if they are to decide how to produce it, move it through their plant, and package it. If a batch has a high yield value, the amount of product left clinging to the sides of a kettle can be reduced if side sweep blades are used. If a batch's viscosity is so high that it is interfering with the efficiency of mixing, it may be necessary to add the rheological additive later in the process or treat it in such a way as to minimize the viscosity increase until the rest of the batch is uniformly mixed. Through the use of rheological additives that do not build viscosity until neutralized, activated, or sheared, the processing departments have much more flexibility in how they can handle the batch. It is much easier to mix or transport thin materials than thick ones.

As described for formulators, process engineers must also be aware of the shear levels generated by their equipment and be alert to changes that can be caused by shear. Changing kettle configuration, types of mixing blades, or

timing of a batch or pumping materials from one section of the plant to another can all have significant effects on formulations. If rheological characteristics are destroyed by long, slow mixing times or the laminar flow encountered inside long stretches of piping, it may be possible to regenerate the structure at the end of the process by passing the batch through a high shear piece of equipment before packaging. By working with the formulator, the engineers can get an idea of how best to handle a process.

In-process testing can also be affected by the rheological response of the formula. If a sample is taken and its viscosity tested at an elevated temperature, one typically observes a lower value than that obtained on a room temperature sample. Products that contain waxes or polyethylenes can show different viscosities depending on the cooling rates of the samples, since structure formation can be affected. If one tries to measure the viscosity of a thixotropic material without control of the length of time before testing, one may get results that are not reproducible since the time on the viscosity recovery curve is not controlled. For all these reasons, the collection of in-process samples should not be taken lightly if the batch is to be considered under control.

RHEOLOGICAL EFFECTS DURING STABILITY TESTING

As with in-process testing, product stability tests must be carefully controlled if they are to be meaningful. Physical stress tests such as aging, thermal stress, freeze-thaw cycling, vibration, or centrifugation must be examined in ways that make sense for a particular product. Predictive tests at elevated temperatures can be useful, but to be reproducible the product must be cooled down to the same temperature each time it is tested. Much information can be gained by working at room temperature, but if the temperature of the laboratory changes significantly during the night or on weekends, then a much safer bet is to place the sample in a temperature-controlled water bath at 25 °C. It should also be remembered that the internal temperature of the sample is what is usually measured by a Brookfield viscometer spindle. If enough time was not allowed for equilibration, then the inside of the sample could be warmer than the outside, and large samples would take longer to cool than smaller ones.

Thixotropic products can be particularly sensitive during stability testing. Since these products regain their viscosities over time and since the level of viscosity drop will be dependent upon the amount of shear, all thixotropic tested materials should have the same shear history; otherwise, enough time must pass to allow the product to reach its rebuilt viscosity. Therefore, if a product is stirred or shaken before viscosity testing, it should be done in a reproducible way, and the product should always be given the same amount of recovery time before testing.

Centrifugation or vibration testing can be misleading and should not be carried to an extreme. Though positive results in these tests may be reassuring, negative results should not always be looked at as the kiss of death. Most products are exposed to a certain amount of vibration in delivery trucks or trains and should be able to withstand some vibration without causing too much of a change. Even vibration at elevated temperatures will be encountered and should be tested. The question of "how much is too much" will always be open for debate. The forces of centrifugation, on the other hand, are not routinely encountered by products and should not be used as the sole criterion for acceptance or rejection of a product. Centrifugation is often used to give a formulator a quick test for emulsion creaming or phase separation. Since both of these phenomena are caused when the internal phase passes through the external phase, an indication that the phases do not move significantly, relative to one another, can be reassuring to a formulator. If creaming or phase separation does occur during centrifugation, the formulator can only be sure that at a certain "G" force (which may be very unrealistic for any products not taken up into space) a separation will occur. Since most products will never experience higher gravity forces, this kind of testing should only be used as a positive confirmation of good stability, not as a sole criterion for rejection.

RHEOLOGICAL ADDITIVES

The category of rheological additives can be split into two distinct areas: additives that can be used to modify water and additives that can be used to modify liquids other than water. As shown in Table 11.2, rheological change in aqueous systems can be accomplished by the addition of natural gums, clays, cellulosics, polyethylene glycols, and polymers. Anhydrous systems are more

Table 11.2 Rheological Additives Classification*

Water-based systems	Anhydrous systems
Natural gums	Organoclays
Cellulosics	Polyethylenes
Clays	Trihydroxystearin
Polyethylene glycols	Al/Mg hydroxide stearate
Polymers	Silicas

*Comprehensive listings of rheological additives can be found in the *INCI Dictionary* (latest edition) under the headings of Viscosity Controlling Agents and Suspending Agents. As a group, the viscosity-enhancing additives find extensive use in foods and drugs. The chapter on polymeric pharmaceutical excipients [1] provides insights into the regulations covering these materials and some of their chemistry.

often modified by the use of organoclays, polyethylenes, trihydroxystearin, aluminum/magnesium hydroxy stearates, and silicas. Though this basic classification system can be useful, it should be remembered that many cosmetic systems contain both water and oil phases and can therefore use rheological additives from either group, depending on the need.

The category of rheological additives for water-based systems includes a number of natural and modified polysaccharides, better known as natural gums. Natural products have fallen out of favor with formulating chemists over the years due to the innate variability of these products and the increased development of new rheological additives, though consumer interest in "natural" products has helped to keep some of them around. Natural gums may be able to fulfil a particular need more efficiently than synthetic gums. When those cases arise, formulators can still call on carrageenan, guar, karaya, tragacanth, and xanthan gums to give them a variety of rheologies and viscosities as well as some salt and pH tolerance, depending on the ingredient chosen. As with many other additives for water-based systems, these gums are basically used as rheological modifiers in the water phase of emulsions. Synergistic effects can also be achieved by the combination of some of the natural gums with clay products, such as the use of xanthan or guar gum with aluminum magnesium silicate.

Cellulose is another naturally occurring polysaccharide, and through chemical modifications it accounts for a family of rheological additives that includes cellulose gum, hydroxyethylcellulose, methylcellulose, and hydroxypropylcellulose. Due to the modifications, some of the derivatives display excellent salt tolerance, surfactant compatibility, or film-forming properties, which make them particularly useful in certain shampoos, hair care products, and shaving products.

Clays for rheological effects are available in four primary types: bentonites, hectorites, synthetic hectorites, and magnesium aluminum silicates. Bentonites are based on aluminum silicates, while hectorites are based on magnesium silicates. The different chemistries and the differences in the natural formations of these clays account for the different properties. Hectorites tend to build a higher amount of viscosity than the other additives, based on their smaller particle size and larger surface area. These materials typically produce pseudoplastic rheology in water-based systems and are used primarily for viscosity enhancement, flow control, and emulsion stability.

Polyethylene glycols (PEGs), consist of variable molecular weight polymers of ethylene oxide. These materials are soluble not only in water but also in alcohols and glycols; they are used as thickeners, humectants, and lubricants in creams and lotions, and as co-gelling aids for antiperspirant sticks. The higher

the molecular weight, the more effective the polymer is in providing viscosity. PEGs below a molecular weight of 700 are liquid at room temperature.

Synthetic polymers are used extensively in cosmetics to build pseudoplastic viscosity, create clear gels, and stabilize emulsions. The main base used for most cosmetic polymers is acrylic acid, and the polymer is described as a homopolymer (made entirely of one kind of polymer), copolymer (combinations of more than one type of polymer), or cross-polymer (copolymers with a cross-linking agent). These materials are supplied in a tightly coiled acid form and become effective only when uncoiled by neutralization with a base. Their effectiveness comes from both long-chain entanglement and hydrogen bonding; they are typically used at concentrations ranging from 0.1% to 0.5%. Salt sensitivity and the inability to withstand high levels of shear are the two limitations formulators must bear in mind. The carbomers and variations based on similar chemistry have become the most widely used polymers in cosmetics, and are available in a variety of grades from a number of suppliers.

Organoclays are reaction products of hydrophilic clays with long-chain quaternary compounds, for example, quaternium-18 hectorite. The quaternary ammonium compound provides compatibility with nonaqueous liquids, allowing the primary clay rheology to be expressed in nonaqueous systems such as oils, esters, and silicones through a hydrogen bonding structure between platelets. The organoclays are the rheological additives of choice in nail lacquers, antiperspirant roll-ons, aerosols, and waterproof mascaras, due to their thickening and suspending abilities. To be fully dispersed, organoclay powders need chemical activation and very high shear, though they are available as gels in fully activated and sheared forms in a number of cosmetic oils for users that do not have high shear capability. Organoclay gels are unaffected by high temperature or high shear processing, though laminar flow can reduce the viscosity of the overall system.

Polyethylenes and their variants are used for their thickening and suspending properties in anhydrous systems such as lipsticks, antiperspirant sticks, and mascaras. They improve water resistance, form films, improve heat stability, and can form clear gels when quickly cooled, allowing the formation of a fine thixotropic crystal structure. To achieve good properties, the additive needs to be heated to 80 °C or higher, depending on the grade of polyethylene.

Trihydroxystearin is a castor oil–derived rheological additive that provides a high degree of thixotropy and viscosity. It is used to help stiffen lipsticks and antiperspirant sticks, thicken emulsions, and, together with organoclays, control the flow and recovery time in mascaras. Heat and shear under carefully controlled conditions are necessary for full rheological development.

Aluminum magnesium hydroxide stearate is a complex of the hydroxide and stearic acid, which can form gels in a number of cosmetic oils. It can suspend

pigments and some other active ingredients and can increase the temperature stability of the formula.

Silicas, or silicon dioxides, build their thixotropic structures in oil systems through a network of long chains and hydrogen bonds. These very fine particulates are either porous or not, depending on their manufacturing process. The liquid process (hydrated silicas) yields a very porous material that can absorb oils, while the vapor or "fumed" process yields a higher surface area and a significantly reduced bulk density. Silicas are used for viscosity building, for creating thixotropy, and for providing suspension properties. Care must be taken to avoid high shear processing after the addition of a silica, since it can destroy the hydrogen-bonded network.

The decision of which rheological additive to use in a certain situation is up to the formulator. As in many cases, the final answer can be reached by several different paths. By being cognizant of the different rheological additives available and the advantages and drawbacks of each one, a formulator will be able to narrow the search but might not always be able to identify the best available additive for the job. Though there are some additives that are used more often in certain products than others, that alone should not be considered as a determining factor when formulating. The type of rheology required, the temperature requirements, compatibility with other formulation ingredients, ultimate formula pH, the need for clarity, and available processing equipment must enter into the decision. The best way for a formulator to avoid the pitfall of developing basically the same type of formula time and again is to strive to continue learning and experimenting with new rheological additives as they are introduced.

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CHAPTER 12
Antioxidants

INTRODUCTION

This chapter introduces the reader to the mechanisms by which ambient oxygen can react with cosmetic products or with biological constituents. This is followed by a description of cosmetic antioxidants and related substances that are used to prevent some of the undesirable oxidative reactions. Finally, this chapter provides a few recommendations to formulators to help them to prevent undesirable oxidation reactions.

Antioxidants are used in cosmetics, pharmaceuticals, and food, and on the skin surface to eliminate or at least to minimize the undesirable reactions resulting from oxidation. It is widely and erroneously believed that atmospheric oxygen acts as an oxidizing agent for fatty materials and related substances. Oxygen in air exists in the so-called triplet state, $^3O_2$, which contains two unpaired electrons with parallel spins in the same electronic orbital; two-electron reactions of this molecule are prohibited by the Pauly exclusion principle, and $^3O_2$ is quite unreactive and benign unless its reactions are catalyzed by transition metals. Nevertheless, it is well established that oxygen is consumed during the reactions of lipids and that the end products contain oxygen. For many years the malodorous substances formed have been markers for rancidity. In addition, these oxidative reactions have been shown to interfere with the stability of active (drug) constituents and with general product integrity. It is important for formulators to understand how ambient oxygen can react with cosmetic ingredients and how to prevent these reactions.

MECHANISM OF TYPE I OXIDATIVE REACTIONS

In the so-called type I reaction, a substrate's energy level may be raised by (ultraviolet) light or some other energy transfer reaction [1]. Such high energy molecules can form a free radical directly by homolytic scission, which releases a hydrogen atom. Alternatively, an extraneous high energy molecule

can acquire a hydrogen atom from the substrate, leaving a free radical. Formulators wishing to avoid type I reactions should eliminate the common causes of de novo free radical formation by reducing exposure of the oxidizable substrate (RH_2)[a] light, heat, and metallic contaminants. Formulators should also guard against the inadvertent contamination by hydroperoxides, which might be present in commercially available lipids and a variety of bleached cosmetic ingredients. Hydroperoxides of varying stabilities may be formed during photooxidation (described under type II reaction).

The initiating free radical formation described above is the precursor to autooxidation and starts a chain process.

$$\text{Initiation: } RH_2 \rightarrow RH^{\cdot} + H^{\cdot} \quad (1)$$

Before studying the reactions of the initiating radical $RH^{\cdot}$, it is essential to examine the lipid species most likely to form $RH^{\cdot}$. As a general rule, alkanes and aromatic rings rarely form free radicals. However, the site of one or more double bonds is the most probable locale of attack. In the case of (Z)-9-octadecenoic acid (oleic), C-atoms 8, 9, 10, and 11 are almost equally likely to become the sites for a free radical; in the case of (ZZ)-9, 12-octadecadienoic acid (linoleic), the primary free radical sites are found on C9 and C13. Although some isomerization reactions may occur, the identified C-atoms are the most likely sites for peroxide formation during the subsequent propagation step.

In the absence of oxygen, the radicals $RH^{\cdot}$ and $H^{\cdot}$ may react with each other to re-form the original substrate without any chemical oxidation. In the presence of $^3O_2$, however, $RH^{\cdot}$ may form a peroxide radical, as shown below:

$$\text{Propagation: } RH^{\cdot} + O_2 \rightarrow RHOO^{\cdot} \quad (2)$$

$$RHOO^{\cdot} + RH_2 \rightarrow RHOOH + RH^{\cdot} \quad (3)$$

During the propagation reactions, peroxide free radicals, $RHOO^{\cdot}$, and hydroperoxides, RHOOH, are formed. These reactions may continue indefinitely until all of the RH_2 or all of the oxygen is used up, or until the chain reaction is terminated. The peroxide species are not stable; they can oxidize other substances in the formula or can self-destruct to aldehydes and other unwanted species. As a rule, the propagation reaction shown in Equation 2 is very fast, while the propagation reaction shown in Equation 3 is quite slow.

The free radical reactions are finally terminated either by the reactions of two free radicals with each other to form nonradical products or by the formation

[a] The radical forming compound is identified as RH_2 because the substance formed after homolytic fission is likely to contain one or more covalently bound hydrogen atoms.

of a long-lived radical and its dimer.

$$\text{Termination: } 2\ \text{RHOO}^{\cdot} \rightarrow \text{nonradical products} \quad (4)$$

$$2\text{RH}^{\cdot} \rightarrow \text{RH}{-}\text{RH} \quad (5)$$

$$\text{RH}^{\cdot} + \text{TH} \rightarrow \text{RH}_2 + \text{T}^{\cdot} \quad (6)$$

In Equation 6, termination is effected through the antioxidant tocopherol (TH), which forms the relatively long-lived tocopheroxyl ($T^{\cdot}$) radical.

A few additional points are included below to provide further information on typical autooxidation reactions. The most reactive species are those with the highest number of unconjugated double bonds. Hydroperoxides can rearrange, and atmospheric $^3O_2$ may exchange with hydroperoxide oxygens. The breakdown products of the hydroperoxide species may include a variety of unexpected compounds. Their chemistry may be complex and their mechanism of formation obscure, but formulators should try to use ingredients that are unlikely to form these substances.

Although reactions between ambient oxygen ($^3O_2$, triplet ground state) and most organic molecules in the singlet ground state are spin forbidden, such reactions are often thermodynamically favored [2]. Thus some one or two-electron transfers to $^3O_2$ are possible, as shown below:

$$\text{RH}_2 + \text{O}_2 \rightarrow \text{RH}^{\cdot} + \text{O}_2^{\cdot -} + \text{H}^{+} \quad 1\ \text{electron} \quad (7)$$

$$\text{RH}_2 + \text{O}_2 \rightarrow \text{R} + \text{H}_2\text{O}_2 \quad 2\ \text{electron} \quad (8)$$

Cosmetic raw materials can form the initiating $RH^{\cdot}$ radical; biomolecules (RH_2) undergoing these reactions include ascorbate and cysteine, which convert oxygen to superoxide (Equation 7) or hydrogen peroxide (Equation 8). Transition metals, for example, copper or iron, tend to relieve the spin restrictions. These metal catalyzed reactions must be included here, although they are not triggered by energy-induced H abstraction.

Purists differentiate between true autooxidation reactions as described by reactions 1, 2, and 3, which require only abstraction of a hydrogen atom at the beginning, and transition metal-initiated catalysis. It can be stopped by preventive antioxidants as exemplified by oxygen- or peroxide-consuming reducing agents. Alternatively, the chain propagation reactions 2 and 3 can be inhibited by chain breaking antioxidants, as shown in reaction 6. The one-electron oxidation facilitated by the presence of transition metals shown in reaction 7 creates a free radical ($RH^{\cdot}$) and superoxide ($O_2^{\cdot -}$). Metal inactivation or chelation by EDTA, desferrioximine, phytates, and the like is preventive widely practiced antioxidation. Superoxide is a powerful oxidant, while the other free radical, $RH^{\cdot}$, can enter the propagation reaction (Eqn. 2).

MECHANISM OF TYPE II OXIDATIVE REACTIONS

In these types of reactions, $^3O_2$ is attacked by an energetically activated sensitizer to form singlet oxygen, $^1O_2$, as the primary product [1,3]. The chemical sensitizers discussed here have the ability to absorb ultraviolet light. Frequently the sensitizers are synthetic dyes such as methylene blue or eosine; other sensitizers include chlorophyll, flavins, porphyrins, and melanin. The sensitized molecule must dispose of the absorbed energy, sometimes by decomposition or fluorescence, or by more complicated processes. The most benign of these is the emission of heat, and this is the preferred mode for the absorbing molecules used as sunscreens in cosmetics. Nevertheless, the reaction with $^3O_2$ is an ever-present possibility, with resulting $^1O_2$ formation. As explained by Laustriat [3], $^1O_2$ differs from $^3O_2$ by spin inversion. The formed $^1O_2$ may return to its ground state, $^3O_2$, by emission of energy, by emission of heat, by quenching, or through photooxidation. Quenching occurs through energy transfer to a molecule by intersystem crossing. β-Carotene is the best known naturally occurring quencher of $^1O_2$ in the human body, but its use in cosmetics is limited by its intense orange color. True photooxidation occurs when $^1O_2$ encounters an oxidizable substrate. Upon contact, $^1O_2$ can form an oxetane or a hydroperoxide with an isolated double bond or with conjugated double bonds.

In practice, both type I and type II reactions can occur simultaneously. Cosmetic formulators cannot routinely differentiate between these two reactions, especially since the species formed are likely to interact. The most destructive of these species is the hydroxyl radical that is formed by reduction of hydrogen peroxide in the presence of ferrous ion (Fenton reaction). It is noted that photosensitization need not involve photooxidation. In the absence of oxygen, photosensitized molecules may undergo a series of nonoxidative (sometimes degradative) reactions. The better-known reactions of this type include the photoaddition of psoralens to nucleotides and the formation of pyrimidine dimers upon solar irradiation.

Autooxidation and photooxidation create a complex series of reactive oxygen species (ROS) that can attack cosmetic products before and after they are topically applied [4,5]. In addition, ROS can attack and damage all types of biological components. The ROS include the following substances:

Organic Peroxides	RHOOH
Superoxide	O_2^-
Hydrogen Peroxide	H_2O_2
Hydroxyl Radical	$HO\cdot$
Singlet Oxygen	$^1O_2$

Cosmetic chemists should make efforts to avoid ROS generation in their compositions and on the skin. Most ROS can interact with each other. Some of the more important reactions that have been reported are shown below:

$$O_2^{\cdot -} + H^+ \rightarrow HO_2^{\cdot} \quad (9)$$

$$2O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2 + {}^3O_2 \quad (10)$$

$$O_2^{\cdot -} + H_2O_2 \rightarrow OH^{\cdot} + OH^- + {}^3O_2 \text{(Haber/Weiss)} \quad (11)$$

$$O_2^{\cdot -} + Fe^{+++} \rightarrow {}^3O_2 + Fe^{++} \text{(Haber/Weiss)} \quad (12)$$

$$H_2O_2 + Fe^{++} \rightarrow Fe^{+++} + OH^{\cdot} + OH^- \text{(Fenton)} \quad (13)$$

Both Equations 9 and 10 are pH dependent; Equation 10 is the reaction catalyzed by superoxide dismutase. Equations 11 and 12 are attributed to Haber and Weiss, and the better known Fenton reaction (Eqn. 13), a modification of the Haber/Weiss reaction, is particularly important in in vivo systems.

USE OF ANTIOXIDANTS

In cosmetics antioxidants are routinely employed in order to inhibit the oxidative deterioration of ingredients and to avoid skin damage from diverse photooxidative reactions. Several groups of chemicals have been found to be useful, and brief descriptions follow. Although concerned primarily with the use of antioxidants in foods, the comprehensive recent review by Halliwell et al. is recommended to researchers seeking additional information [6].

PHENOLIC ANTIOXIDANTS

The preferred phenolic antioxidants are normally classified as hindered phenols (ϕ–OH) because the most effective ones carry one or more *t*-butyl groups on the aromatic ring. These substances cannot inhibit the abstraction of a hydrogen atom from the organic material subject to oxidation, but they interfere with chain propagation by forming a relatively stable phenolic radical ($\phi O^{\cdot}$) and restoring the attacked molecule to its normal state:

$$RH_2 \rightarrow RH^{\cdot} + H^{\cdot}$$

$$\phi - OH \quad RH^{\cdot} + \phi - OH \rightarrow RH_2 + \phi - O^{\cdot}$$

In effect the $\phi - OH$ competes with ambient O_2 to prevent formation of a lipid peroxide. In the absence of this competition, the propagation reaction, starting with a single $R{\cdot}H^{\cdot}$ molecule, can provide as many as 1,000 $RHOO^{\cdot}$ molecules (Eqn. 2), depending on the amount of available oxygen.

$\phi - OH$s can also react with other reactive oxygen species, such as superoxide, hydrogen peroxide, hydroxyl radicals, lipid peroxide (LOOH), and lipid

peroxyl radicals ($LOO\cdot$). It is not surprising, therefore, that phenolic antioxidants have become the preferred choice of formulators.

One of the features of the antioxidant phenol is the presence of an intact phenolic hydroxyl group. Thus the esters of antioxidant phenols, for example, tocopheryl acetate, are not effective free radical scavengers. Tocopheryl acetate in vitro cannot perform a protective function, although it may do so in vivo due to the presence of nonspecific esterases in the body. This problem has not been fully clarified [7]. It is generally not possible to include α-tocopherol (Formula 1, Fig. 12.1) in finished cosmetic products because its conversion to tocoquinone (Formula 3, Fig. 12.1) by oxidation causes severe discoloration. Nevertheless, some investigators have claimed that tocopheryl acetate can protect skin against UVB damage. These results have been explained occasionally by assuming that tocopheryl acetate acts as a UVB absorber or has the ability to scavenge singlet oxygen.

Table 12.1 Selected Phenolic Radical Scavenger Antioxidants

Arbutin	*t*-Butyl hydroquinone
BHA	Tocopherol (and some derivatives)
BHT	Nordihydroguaiaretic acid
Kojic acid	Rosmarinic acid
Hydroxyanisole	Trolox
Hydroquinone	Gossypol

In cosmetic practice, BHA, BHT, and *t*-butyl hydroquinone are used primarily for the protection of finished products. The levels required to protect vegetable or animal lipids in cosmetics rarely exceeds 0.05% by weight; because of its cost and instability as the free phenol, α-tocopherol or one of its esters is used primarily for the protection of lipids in the skin. Tocopheryl acetate can penetrate the epidermis and may be converted to free tocopherol, and concentrations for this use may be as high as 0.5%. Justification for the use of vitamin E in skin care products is provided by the observations of Thiele et al. [8]; during tape stripping of human stratum corneum they noted a steady drop in tocopherol content as the skin surface is approached. They also showed that UVB irradiation (at 0.75 MED) caused a significant drop of α-tocopherol in the top layers of the stratum corneum.

The resonance stabilized tocopheroxyl radical, shown in Formula 2 (Fig. 12.1), results from radical scavenging by tocopherol and may also be formed by UVB irradiation. The tocopheroxyl radical may be formed in tocopherol-containing lipids in mammalian species and is physiologically

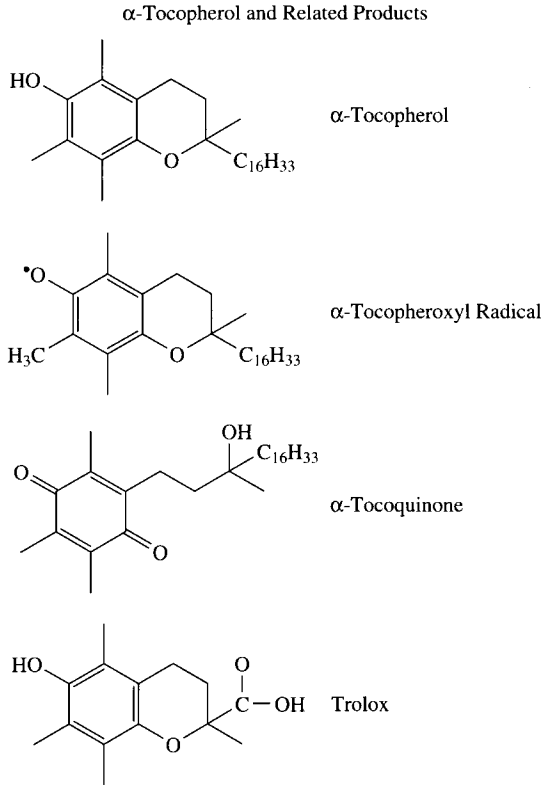

Figure 12.1. α-Tocopherol and related products

recycled with the aid of ascorbic acid. Tocopherol is water-insoluble; therefore, Trolox (Fig. 12.1), a water-soluble analog, is currently under study.

Useful phenolic antioxidants occur in a variety of plants (Chapter 15). For example, rosmarinic acid is found in *Rosmarinus officinalis*, while nordihydroguaiaretic acid occurs in *Larria divericata*. Thus the use of plant parts or essential oils may result in antioxidant protection in diverse cosmetic products. The most effective antioxidants in the spice group are rosemary, sage, and thyme. Not all plant-derived phenolic antioxidants are used in cosmetics; gossypol, for example, is reportedly toxic to animal species.

FLAVONOIDS

Polyphenolic flavonoids as a family of plant-derived organic compounds represent some of the most common and active naturally occurring antioxidants. They are water-soluble and occur in nature as glycones, usually glucosides

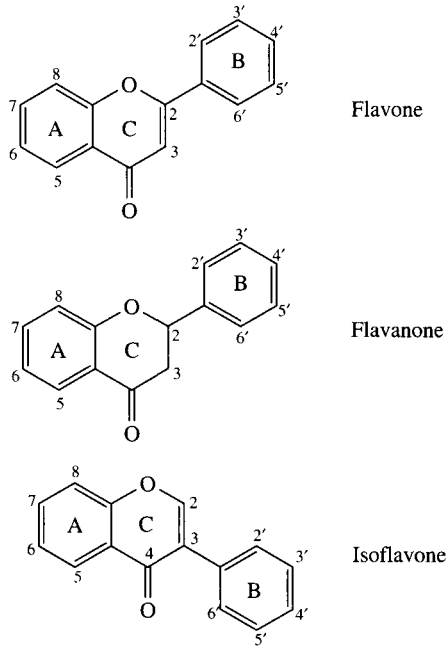

Figure 12.2. Common Flavonoid Structures (A and B rings carry one or more -OH substitution)

or rutinosides. In contrast to most of the previously discussed phenolic chain breakers, the flavonoids function in aqueous systems. In modern cosmetics they are rarely introduced as pure substances but rather as components in impure mixtures of plant-derived ingredients (Chapter 15).

The group of flavonoids includes a wide variety of structurally diverse compounds, all of which possess a phenolically substituted 1,2-benzopyran skeleton (Fig. 12.2). The heterocyclic ("C") ring in many flavonoids may carry a keto substitution in the 4-position; the so-called "B" ring occupies either the 2- or 3-position. The number of −OH substitutions may be as high as 8. Anthocyanidins in which the "C" ring contains two double bonds carry a positive charge.

Details about the chemical structures of flavonoids were assembled by Lien et al. [9], who tried to relate antioxidant activity to structure, especially the

Table 12.2 Selected Antioxidant Flavonoids in Cosmetics

Class/name	Common plant source
Flavanol	
Epicatechin	Acacia catechu* or
Catechin	Camellia sinensis* or
Epigallocatechin	Melaleuca alterniifolia*
Epicatechin gallate	
Epigallocatechin gallate	
Flavonol	
Diosmin	Diosma crenata*
Kaempferol	Cucurbitaceae*
Quercetin*	Rhododendron spp.*
Myricetin	Myriaceae
Flavone	
Apigenin	Carum petroselinum*; Apium graveolans*
Flavanone	
Naringin	Citrus paradisi*
Hesperidine*	Citrus sinensis*
Anthocyanidin	
Malvidin	Primula spp.*
Cyanidin	Centaurea cyanus*
Isoflavone	
Genistein	Prunus spp.*

*An asterisk after a name indicates a listing in the *INCI Dictionary*.

location and number of OH– group. Table 12.2 is a listing of some antioxidant flavonoids that might be found in cosmetics. It is apparent that the antioxidant flavonoids are phenols that can form stable radicals. In addition, evidence has been accumulated showing that flavonoids as a group can chelate heavy metals (iron), thus decreasing their prooxidant effect. A few references are cited for readers who require additional information [10,11].

The use of flavonoids as antioxidants is relatively costly. Thus they are selectively used to protect cosmetic formulations, although their natural origin makes them attractive in all types of skin care products. On the other hand, information documenting their efficacy to protect against oxidative or UV light–triggered skin damage might be considered apocryphal. The evidence for antioxidant activity, especially in living systems, relies on data developed by internists and nutritional scientists. It is widely believed that the epigallocatechins are more effective antioxidants than the tocopherols [10].

PHENOLIC ACIDS

Some hydroxylated benzoic acids, phenylacetic acids, and phenylacrylic acids are important food and cosmetic antioxidants. A partial list of some of these substances follows:

Selected Phenolic Acid Antioxidants Used in Cosmetics

Name	Identity/Structure
Protocatechuic Acid	3,4 dihydroxybenzoic acid
Resorcylic Acid	3,5 dihydroxybenzoic acid
Gallic Acid (and Methyl and Propyl Esters)	See *INCI Dictionary*
Caffeic Acid	See *INCI Dictionary*
Ferulic Acid (and esters)	See *INCI Dictionary*
Chlorogenic acid	See *INCI Dictionary*

The antioxidants derived from cinnamic acid are of particular interest since they can undergo *cis-trans* isomerization under the influence of UV irradiation.

MISCELLANEOUS ANTIOXIDANTS

The relatively short list of alternate antioxidants includes some substances that react with oxygen. Some of the listed sulfur-containing substances may act as radical scavengers, while the most interesting ingredient in this list, ascorbic acid, (Table 12.3), acts primarily as an oxygen scavenger. This vitamin is rarely used for the protection of finished cosmetics since it is easily oxidized

Table 12.3 Miscellaneous Antioxidants

Name	Principal activity
Ascorbic acid (and derivatives)	Oxygen scavenger, radical scavenger
Ascorbyl palmitate	Oxygen scavenger, radical scavenger
Carotenoids	Singlet oxygen scavenger
Cysteine hydrochloride	Oxygen scavenger
Dithiothreitol	Oxygen scavenger
Glutathione	Oxygen scavenger, reducing agent
Thioglycolic acid (and derivatives)	Oxygen scavenger
Thiodipropionic acid (and derivates)	Radical scavenger (?)
α-Lipoic acid	Hydroxyl radical scavenger Singlet oxygen scavenger
Xanthines (caffein, uric acid)	Hydroxyl radical scavenger (?)
Enzymes Superoxide dismutase Catalase	Destroy ROS

by air, with formation of color bodies. As noted earlier, ascorbic acid in vivo recycles tocopheroxyl radicals to tocopherol:

$$\text{Ascorbate } H^- + TO^{\cdot} \rightarrow \text{Ascorbyl radical}^{\cdot} + TOH$$

In cosmetics, ascorbic acid (as a salt or in ester form) is employed as a topical antioxidant despite its oxidative instability and tendency to discolor. The presence of significant levels of ascorbic acid on the skin surface is well documented, although the utility of topical ascorbic acid as a photoprotectant or aging preventive is less well documented. Despite these questions, it is commonly asserted by experts in the field that ascorbate and tocopherol function together to protect membrane lipids [4]. It is also noted that magnesium ascorbyl phosphate and tocopherol have been claimed to form a synergistic antioxidant system.

The tabulation of miscellaneous antioxidants includes some that might not be useful in cosmetics. The –SH-containing substances are generally unstable because they form hydrogen sulfide. The list also excludes sulfites, which may induce respiratory problems in human. In any case, sulfites are not antioxidants in the true sense; they react with oxygen, thus reducing its concentration in closed systems. The list also excludes several plant-derived phospholipids that are identified as antioxidants by some authorities. It has been established that most commercially available forms of lecithins deteriorate upon exposure to air. One may safely assume that the successful antioxidant studies of some phospholipids were conducted with grades that contained some natural antioxidants such as tocopherol.

The observation that xanthines act as antioxidants is supported by a mechanism in which the purine forms an oxygen-centered radical with the extremely aggressive hydroxyl radical [12].

The history of β-carotene as a systemic antioxidant is controversial, especially since this substance seems to act as a prooxidant in in vitro studies [13]. The photochemistry and the photooxidation of carotenoids as a group are not well understood, although the photoinstability of all-*trans* retinoic acid is established.

Justification for and problems associated with the use of antioxidants in humans were comprehensively reviewed by Fuchs in 1998 [5]. This review is an excellent source of information for those interested in the prevention of photodamage on skin.

RECOMMENDATIONS

Formulators must recognize that photooxidative (type II) reactions are much faster than autooxidative (type I) reactions. In addition, the classic chain breaking

antioxidants cannot prevent type II reactions; but their presence might inhibit free radical propagation after initiation by photooxidative processes.

Before any unsaturated or polyunsaturated material is used in a formulation, the compounder should always determine that use of the unsaturated ingredient is warranted. Compounders should also attempt to eliminate substances that are likely to induce singlet oxygen formation on the skin surface.

To be on the safe side, it is wise not to introduce bleached ingredients into products unless they are known to be free of oxidizing species. Raw materials should be stored in a dark, cool environment with minimal exposure to oxygen and light. The presence of tramp transition metals should not be tolerated, although chelation may be of some help on occasion.

Rancid odors in (raw material) lipids are a warning that oxidative reactions may have occurred. Analytical procedures for assessing the oxidative status of lipids and surfactants are available in pharmacopeial and analytical compendia. The peroxide value (POV) is a most useful tool for determining raw material acceptability. In the case of finished products, the POV can be used as a guide to long-term stability.

The presence of aldehydes in lipids or lipid-derived raw materials is evidence of oxidative damage. Another sign of past oxidative attack is the presence of conjugated double bonds. The formulator must decide whether the levels of oxidatively generated side products make an ingredient unsuitable for use in a cosmetic.

The conditions for the formation of ROS in products and after product use on the skin were identified previously; formulators and production personnel must use good judgment to avoid or minimize these conditions and attempt to avoid the use of ingredients that might form undesirable products through (photo)oxidative reactions on the skin. In practice, it is possible to reduce the incorporation of air into products during manufacture and to deliver a product free of ROS. Nevertheless, problems can still arise during use by consumers and because of light exposure.

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CHAPTER 13
Moisturizers and Humectants

Humectants are hygroscopic substances that are used in cosmetic formulations to retard moisture loss from products during storage and skin application. Many humectants also function as skin moisturizers and are used in skin and hair preparations to raise the water content of these tissues.

For many years, formulators depended on humectants to keep products from drying out and to facilitate product application to the skin. Today, however, humectants are used predominantly in cosmetics for skin moisturization. This shift in performance for some rather pedestrian components is not surprising, since moisturization of skin has become a powerful claim for the efficacy of diverse types of cosmetics.

SKIN MOISTURIZATION

The technology to increase the water content of skin or of its appendages has revolutionized skin care in the past quarter century. Prior to this period, skin care products were formulated primarily with various lipids since it was widely believed that fats and oils helped to make skin soft and supple. During the 1950s, Irving Blank reported the then unexpected results of his study with callus, which showed that water was the plasticizer of choice for this tissue. This revolutionary observation was shortly thereafter found to be equally applicable to skin softening. Today moisturization, that is, hydration, of skin has become one of the cardinal concepts in skin care. It is noted here in passing that skin benefits have been attributed to aqueous glycerin preparations for many years before Blank's work and continue to be. It is surprising that workers in the field, nevertheless, failed to recognize the significance of water for maintaining skin health until well after World War II.

If adequate water levels in the skin are not maintained, the skin becomes brittle (less flexible) and flaky (scaly), and might appear wrinkled. Today formulators, skin scientists, and the public are aware of the merits of moisturization. The levels of water that are required for achieving these benefits remain poorly defined. On a priori grounds, one might argue that the water levels found in healthy skin, that is, skin that does not show any of the noted stigmata, should suffice. Unfortunately, the water content of keratinocytes in the basal layer (about 70%) decreases slowly in the stratum granulosum (about 65%), and then more rapidly (to about 35%) in the lower layers of the stratum corneum. As the stratum corneum matures, its water level drops more slowly until it reaches the desquamating layers (about 15–20%) [1]. Thus the adequate levels of water are difficult to define, especially since the outermost layers of the stratum corneum are in equilibrium with the variable ambient relative humidity.

Skin dryness or the dry skin syndrome is poorly defined. Sometimes it is clearly associated with overt clinical symptoms; sometimes it depends on personal perception; but it is almost never defined on the basis of a specific skin or stratum corneum water content. Thus the modalities for relieving skin dryness can vary widely.

There is an entirely different way of creating various water levels in the epidermis. Soaking of skin in water causes swelling and can raise the "free" or bulk water level to as much as 500% of epidermal dry weight. Most of this water is rapidly lost on air exposure, primarily by evaporation. At this point, the epidermis may contain about 38% of "loosely bound" water. Much of this water is lost to the environment or as a result of physiological processes. Finally, approximately 5% of water is "tightly bound" and is not readily exchanged or lost.

The water content of skin also varies widely from site to site: palm $\gg$ forehead $>$ back and abdomen $>$ forearm, and upper arm. The appearance of wrinkles on the skin of the aged gave rise to the notion that aged skin is "drier" than the skin of young adults. If dryness of stratum corneum of the aged were the result of its water content, old skin should contain significantly less water than the skin of young adults. This is not the case, based on a review by Wilhelm and Maibach [2] of earlier work by several investigators. There is no striking relationship between water content and age, thus refuting the dryness (lack of water) claims of antiwrinkling skin care products for the skin of the elderly. They [2] reported that transepidermal water loss (TEWL) on the forearm drops modestly with advancing age, from about 4.0 $g/m^2/h$ at age 10 to about 3.0 $g/m^2/h$ at age 70, and concluded that the water content of the corneum decreases only slightly with age. This conclusion is based primarily on the reported variable results of the changes of TEWL with advancing age.

TEWL, formerly known as insensible perspiration, is the amount of water escaping from an area of skin during a specified period of time. TEWL is commonly believed to be due to the permeation of water through the epidermis by various diffusion processes. The measurement may also include water lost from appendageal structures, for example, eccrine ducts, if the humidity and temperature are not carefully controlled. Reliance on TEWL for assessing the skin's moisture content might not be entirely valid, even though the data are supported by electrical and rheological measurements. It is more likely that TEWL reflects the corneal barrier quality.

In contrast to the review of Wilhelm and Maibach [2], a more recent review of similar data suggests that few substantive data can be found in the literature to support the notion that aged skin contains less water than young skin [3]. There is also no evidence that the water content of photoaged skin differs from that of chronologically aged skin. The relationship of wrinkling of skin, water content of skin, and water loss from the skin still awaits a rational explanation before moisturization of skin as a means for wrinkle removal can be assessed scientifically. The question of the exact location of water molecules in the stratum corneum has not been answered, and the nature of the water in the stratum corneum, that is, absorbed or as liquid water or vapor, or both, has not been ascertained.

In order to reach the skin surface, water molecules need to find a path through or around the lipid bilayers between the corneal cells. Passage of water molecules is facilitated by barrier damage of the stratum corneum and by low ambient relative humidity. TEWL is restricted by occlusion, that is, covering the skin with a water-impermeable film, or by the addition of substances to the stratum corneum that lower the fugacity of water. Cosmetic formulators who wish to increase the water content of stratum corneum exert much effort to keep water in the skin through use of occlusive agents, or through moisturizers that tend to reduce the volatility of water. In the following discussion, an attempt will be made to explain how skin (regardless of age) can benefit from cosmetic treatment.

Performance on skin of moisturizing preparations regardless of composition may be assessed clinically or instrumentally. Among the techniques that have achieved prominence are mechanical, optical, and electrical procedures [4]. Clinically, dermatologists may rely on microphotography, erythema, and scaling. The ongoing refinement of these techniques has resulted in a competitive numbers game in which marginal differences are exploited, while the consuming public may fail to perceive notable differences in efficacy.

Dry skin—regardless of its causes or its symptoms—is not repaired by the casual application of a moisturizing product to the top of the stratum corneum. It is more likely that continued use of moisturizing products creates

an environment that encourages physiological repair of some undefined—at this writing—skin damage. The length of time required for repair of xerosis by product usage may be more critical to the consumer than exaggerated claims for the level of moisturizers incorporated into the product. The causes of dry skin may be variable: in winter skin, that is, that produced by a dry and cold environment, the epidermis fails to retain sufficient water, which in normal circumstances is constantly replenished from the dermis. In aging skin, metabolic or circulatory problems may modestly reduce the skin's water content. To date, it has not been established whether both winter skin and aged skin respond identically to moisturizing therapy.

SKIN MOISTURIZATION WITH OCCLUSIVE AGENTS

By restricting the escape of water vapor from the skin, occlusive treatments trap water in the uppermost layers of the skin. The covering of skin with water-impermeable lipids has been practiced since antiquity. The evaporative processes on the skin are only partially inhibited by occlusion with substances such as petrolatum or triglycerides since they fail to provide a 100% effective evaporative block, because of imperfections on the skin. The use of water vapor–impermeable plastic films, for example, Saran® wrap, on large portions of the body surface may interfere with the evaporative heat exchange processes on the skin surface. An abbreviated list of occlusive agents used in cosmetic and pharmaceutical practice is provided in Table 13.1. However, the list excludes a large number of emollient lipids that are considered by some authorities to be occlusive.

As a rule, the required levels of occlusive agents on the skin are quite high. Most of them are unctuous and tacky and must be formulated with considerable care. Emulsification of occlusive agents or combination with hygroscopic agents materially reduces their occlusivity. The presence of emulsifiers or humectants in the film may interfere with retention of moisture by occlusivity.

Investigators who wish to create an emulsion that upon drying forms an occlusive film are advised to establish occlusivity with the aid of TEWL measurements: immediately after application of an emulsion to the skin, TEWL spikes upward until most of the preparation's water has evaporated. The nonvolatile emulsion residue remains on the skin surface for some time, but the TEWL returns to normal 20 minutes after treatment with an ordinary cream, a lipid-rich cream, or even petrolatum [4]. Lodén [4] also reviewed the results in which hand and body lotions were used by hundreds of subjects for several weeks, but this and similar discussions fail to describe the exact composition of the studied products [5]. The use of petrolatum on the skin eliminates or at least reduces the evaporative flux of water from the skin surface. This phenomenon

Table 13.1 Selected Occlusive Agents

Arachidyl behenate
C30-40 Alkyl dimethicone
Cholesteryl oleate
Dimethicone
Glycol distearate
Hydrogenated rice bran wax
Octyl dodecyl stearate
Paraffin
Petrolatum
Polyethylene
Tripalmitolein

A more comprehensive listing of Skin Conditioning Agents—Occlusive may be found in the *INCI Dictionary*.

could result in unphysiologically high levels of water in the stratum corneum as long as a high level of occlusion is maintained. During this state, normal processes on the epidermis may be affected. Persistent high water content in the stratum corneum has been reported to reduce barrier repair, at least in solvent extracted neonatal rat corneum. The modest level of occlusion and the removal of the occluding lipid during washing or by abrasion are likely to preclude serious side effects. Continuous daily inunction with an occlusive product is known to repair obvious skin damage (clinical scaling, itching, and erythema) and allows repair of the epidermal barrier by the normal physiological processes. As mentioned earlier, the hyperhydration of the corneum layer is reduced rapidly to normal by evaporation after removal of the occluding film.

Petrolatum is the most studied occlusive agent in cosmetics and pharmaceuticals. It is a complex mixture of hydrocarbons derived from petrolatum. It is unctuous and leaves an oily or greasy residue on the skin. The debate concerning its ability to penetrate into human stratum corneum has not been settled. The other occlusive agents in Table 13.1 are relatively hard solids that cannot be used topically in their native state. They are, therefore, modified with less occlusive substances or are used in emulsions.

The discussion of moisturization by occlusion has so far not addressed some important attributes of skin treatment with an occlusive agent. One of the overlooked benefits from occlusion is acceleration of wound healing. Moisture in the skin seems to stimulate the repair of wounds, probably by enhancing epidermal proliferative processes. Today these observations are used in surgical coverings. Another more questionable benefit is the enhancement of

skin penetration by drugs. A huge number of publications support the concept that drug permeation through skin is enhanced by occlusive coverings. The precise mechanism for this phenomenon is not critical. Since cosmetics are coverings on the skin, they can facilitate transdermal adsorption. This effect is not always desirable, and formulators must strike a balance between transdermal drug permeation and retention of actives on the skin. Transdermal penetration may interfere with cosmetic practices: for example, it is not wise to enhance transdermal permeation of sunscreening agents; a UV absorber in the dermis, for example, cannot protect the epidermis.

An interesting observation was reported by Held et al., following repeated use of a (commercial) occlusive moisturizer on the forearms of healthy volunteers (6). The product was applied three times daily for four weeks. The evaluation at the end of the treatment period included patch testing with a 0.3% sodium lauryl sulfate solution. On days 14, 28, and 30 skin capacitance and TEWL measurements were made. Skin capacitance on the treated arm was elevated over that of the control arm. TEWL on the treated site did not differ significantly from that on the untreated site. However, on day 30 (2 days after SLS patching), the moisturizer-treated site showed much higher TEWL than the untreated site. These results are unexpected but suggest that the benefits of moisturizer treatment may not extend to deliberately irritated skin.

SKIN MOISTURIZATION WITH HUMECTANTS

The assertion that a humectant in or on the skin can absorb water from the environment and deliver it to the constituents of the skin has rarely been challenged. Actually, this concept violates some laws of physics and has no foundation in fact. Humectants absorb or release water vapor, depending on the relative humidity of the environment. The source of this absorbed water can be the atmosphere or the biological substrate (skin). Thus conditions exist in which a humectant might actually deprive skin of water. Once a humectant has sorbed water, the activity coefficient of water is lowered. Unless the water in skin tissue has a lower activity coefficient than that in the surrounding humectant-water blend, water molecules will not be transferred to the skin. Recognition of these facts establishes that in moisturization with a humectant it is not the water molecules per se but the aqueous humectant blend that plasticizes the skin.

The type of plasticization attributed to hygroscopic substances had its beginning in the studies dealing with the so-called Natural Moisturizing Factor (NMF). NMF in the presence of moisture has the ability to keep stratum corneum flexible. The identification of some of the constituents of NMF gave rise to the use of structurally similar ingredients in skin care (Tables 13.2

Table 13.2 Composition of Natural Moisturizing Factor

	%
Amino acids	40.0
PCA	12.0
Lactate	12.0
Urea	7.0
Na^+, Ca^{++}, K^+, Mg^{++}, PO_4^{---}, Cl^-	18.5
NH_3, Uric acid, Glucosamine, Creatine	1.5
Unidentified	About 10.0

Table 13.3 Selected Hygroscopic Agents

Acetamide MEA	Maltitol
Collagen (and hydrolysates)	Mannitol
Glucamine	Methyl gluceth-20
Glucose	PCA (and salts)
Glucuronic acid	PEG-10 Propylene glycol
Glutamic acid	Polyamino sugar condensate
Glycerin	Saccharide hydrolysate
Histidine	Saccharide isomerate
Honey	Sorbitol
Hydrogenated honey	Sucrose
Hydrogenated starch hydrolysate	Urea
Lactic acid (and salts)	Xylitol
Lactose	

The *INCI Dictionary* should be consulted for a more comprehensive listing under the headings of Skin-Conditioning Agents—Humectant and of Humectants.

and 13.3). The most interesting humectant in NMF is PCA, a degradation product of glutamic acid. It has recently been discovered that the NMF mixture is an enzymatic degradation product of filaggrin, as reviewed by Rawlings et al. [7].

In recent years, cosmetic formulators have utilized a number of hydrophilic polymers as humectants. The high molecular weight of these substances precludes their penetration into the epidermis, and it is likely that these film-formers are retained in the top layers of the stratum corneum and can provide smoothness and slip. Some of these substances are listed in Table 13.4.

Rawlings and coworkers [7] provide some cogent reasons for careful selection of humectant-type moisturizers: above all, they must not interfere with the enzyme-controlled normal desquamatory processes. The degradation of

Table 13.4 Selected Hydrophilic Polymers Commonly Used as Skin Moisturizers

Alginic acid (and salts)
Betaglucan
Chitosan (and salts)
Collagen (and hydrolysates)
Dextran
Glycosaminoglycans
Hyaluronic acid (and derivatives)

desmosomes requires a series of enzymes and the presence of water. Any effort to modify the water content (moisturization) of stratum corneum with a humectant must also consider the impact of the agent on hydrolytic processes. Evidently glycerin does not interfere with the complex intracorneal processes described in detail in Rawling et al.'s review [7].

Some recently published animal studies [8] demonstrate that environmental conditions such as extremely low or high relative humidity influence not only epidermal structure and function but also barrier repair processes. Thus the thickness of the epidermis (and of stratum corneum) is increased by low humidity. A dry environment also increases lamellar body secretion, corneal lipid content, and barrier recovery. It is a noteworthy manifestation of homeostasis that human skin responds with high levels of TEWL—as noted earlier in the case of hyperhydration—and attempts to lower TEWL under drying (low humidity) conditions.

The skin's ability to respond to the environment seems to be a function of the effectiveness of the lipid barrier and the presence of an adequate level of NMF. If NMF is low, an externally applied (moisturizing) humectant seems to act as a suitable replacement.

CONCLUDING COMMENTS ON SKIN MOISTURIZATION

Moisturization of skin should result in objectively observable benefits. The consumer has a right to expect increased skin flexibility, reduced scaling, decreased roughness, and some smoothening effect from the use of any moisturizing product. Many of the moisturizing agents included in Table 13.4 are not humectants. Nevertheless, their application to the skin from aqueous systems creates an environment in the corneum that retards rapid loss of water from the skin surface. It is not possible to predict exactly how the aqueous blend of product-derived moisturizer(s) and natural NMF controls TEWL, that is, loss of water under different environmental conditions (relative humidity,

temperature, air movement, etc.). The humectants most commonly used in cosmetics (glycerin, propylene glycol, sorbitol, and butylene glycol) are known to lower the vapor pressure of water, as shown by measurements of the relative humidity above their aqueous solution (Table 13.5). These skin moisturizers are rarely used at concentrations exceeding about 25%, which lowers the relative humidity only slightly from 100% (pure water) to about 90–95%. Evaporative water loss from the product or sorption of water (from the skin or the atmosphere) may yield humectant concentrations on the skin that differ materially from those in the product. Humectants do not penetrate appreciably into the epidermis but remain on or near the skin's surface. At this time, the level of a given humectant in different layers of the corneum has not been correlated with its concentration in the product.

A number of test procedures for establishing moisturizing efficacy are available. It is beyond the scope of this text to describe the many methods that have been employed. Readers requiring this information should consult Chapter 34 and some of the following references: *Bioengineering of the Skin: Water and the Stratum Corneum*, edited by Eisner, P., Berardesca, E., and Maibach, H. I, CRC Press, 1994; Ref. 3; Tagami, H., Quantitative measurements of water concentration of the stratum corneum in vivo by high-frequency current, *Acta Derm. Venereol.* (Stockh), 1994, Suppl. **185**, 29–33; Ozawa, T., and Takahashi, M., *Skin Hydration: Recent Advances, ibid.*, p. 26–28; Martinsen, O.G., et al., Electrical methods for skin moisture assessment, *Skin Pharmacol.*, 1995; **8**, 237–245, Franconi, F., et al., Measurement of epidermal moisture content by magnetic resonance imaging; assessment of a hydration creme, *Brit. J. Dermatol.* **132**, 913–917, 1995.

Some of the reported procedures need careful monitoring. Use of an ionizable humectant may complicate electrical measurements. Capacitance data may be affected by the application of diverse substances to the skin. Moisturization of hair, which has become popular, may be acceptable up to a certain water content level; moisturization beyond that limit results in curl relaxation

Table 13.5 Relative Humidity Above Solutions of Different Humectants

% Humectant	Glycerin	Sorbitol	Propylene glycol	Butylene glycol	Sodium lactate
10	97	99	98	97	96
20	95	97	94	96	93
30	92	95	93	94	86
40	87	93	87	91	76
60	72	84	78	79	35
80	48	58	54	59	22

and loss of style retention. Moisturization of lip tissue represents a special problem. Lips are constantly exposed to water but still crack and flake. No good explanation for the mechanism by which humectant moisturizers work is available, although the benefits projected from occlusion appear reasonable.

The application of humectants to the skin generally enhances TEWL. UV light exposure and washing with soap also increase TEWL. Glycerin, one of the preferred humectant moisturizers, has been reported to improve the intracorneal protective barrier function [9]. As noted throughout, humectants are generally believed to perform their benefits as a result of their physicochemical effect on water content, regardless of their location in the stratum corneum. These polar molecules may gain access to portions of the stratum corneum via polar (aqueous) microchannels within the corneal lipid bilayer or may reside within the protein of the keratinocytes.

The best documented scientific data on skin moisturization support the conclusion that xerotic or dry skin can benefit from repeated application of occlusive or humectant moisturizing ingredients over a period of time. The major benefits include reduced flaking and itching and increased flexibility. These benefits are often attributed to increased water levels in different skin strata. It appears reasonable to attribute the reported changes in skin condition to the presence of ingredients or the enhancement of biological processes that restore the intracorneal barrier and improve the water retention by the stratum corneum. Formulators must always keep in mind that the health of human epidermis may be affected by (1) the intracorneal lipid layer, its formation, hydrolysis, and oxidation, (2) the uncertainties of the enzyme-dependent synthesis of NMF, and (3) climatic changes. Data supporting the concept that the skin's water ecology plays *the* dominant role in skin health are not available at this time.

HUMECTANT USE TO PREVENT WATER LOSS FROM PRODUCTS

The ability of humectants to maintain the water level of products was formerly an important reason for humectant use. Packaging innovations in recent years, as exemplified by use of water-impermeable plastic laminates or of captive caps, have materially reduced the importance of this application of humectants. It is discussed here only because of its historical importance.

The use of humectants in products may also affect water evaporation during application, and this is an important reason for their use. By retarding the loss of water and by their lubricating effect, cosmetic humectants facilitate the spreading of products on the skin.

Another ancillary attribute of humectants is their ability to act as solvents that help to keep products homogeneous during application. Glycerin and

sorbitol are relatively poor solvents for cosmetic lipids, but propylene glycol exhibits some compatibility with nonpolar ingredients. Propylene glycol has also been reported to act as a synergist for some preservatives, and this effect may also be related to solubility.

Formulators, especially those using lipophilic drugs, must examine all aspects of the inclusion of a humectant as a product moisturizer. The desired effects of the product also affect skin; elevation of water levels in the epidermis may enhance drug penetration; if the humectant should permeate into the lipid layers between the corneal cells, it may modify the barrier properties of the skin.

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CHAPTER 14
Preservation

INTRODUCTION

Many of the materials used in the manufacture of cosmetics, drugs, and toiletries are susceptible to microbial contamination and degradation. In this chapter, sources of contamination and use of preservatives for controlling microbial growth in products will be discussed.

There has been an increasing awareness of the problems of microbial spoilage of aqueous cosmetic and toiletry products, and this has increased the importance of the role of the microbiologist in product formulation. Although the primary emphasis of product development is on aesthetic appeal and/or functionality of the product, adequate preservation is considered essential to prevent product spoilage and health hazards because of microbial contamination.

Normally healthy individuals have considerable resistance to infection by bacteria and fungi commonly found on their skin and in their usual environment, but in susceptible individuals, for example the newborn, the very old, those in ill health or receiving drug therapy, there is an increased probability of infection. It should be remembered that a product may contain growing bacteria, even though there is no visible evidence of this. Application of a contaminated product to the skin may cause an infection, particularly if the skin is broken or damaged.

Even though microorganisms are ubiquitous and the body is continually exposed to them, products should not constitute any greater microbial hazard than that presented by the normal environment. Cosmetics and toiletries are not necessarily intended to be sterile; however, aqueous products in multiple-use containers must be adequately preserved so that they are self-sterilizing. In addition, appropriate packaging is necessary to help prevent contamination from the environment and during use by consumers.

Preservatives are added to aqueous products to prevent spoilage, that is, to prolong the shelf life of the product, and to protect the consumer from the possibility of infection. It is recognized that products may require protection

from contamination during manufacture, although preservation must never be used to correct defects because of inadequate compliance with good manufacturing practices (GMPs). It is also recognized that cosmetic products may be subjected to consumer abuse, possibly more so than pharmaceutical products. Although products cannot be protected against extremes of abuse, such as the use of saliva in the application of eye makeup, or leaving the cap off a bottle of shampoo during use in the shower, the manufacturer should anticipate misuse when the product is formulated.

Adequately preserved aqueous products must be preserved and/or packaged so that they do not become contaminated from the time of manufacture until they are used by the consumer. To ensure this, the microbiologist must be involved with selection of the preservative system of a product from the beginning of formulation work. The preservative system chosen must be evaluated by preservative efficacy testing and realistic use or abuse tests during product development to ensure that the preservative system is adequate and that the product is able to resist contamination by bacteria, yeasts, and molds during actual use.

MICROBIAL METABOLISM AND GROWTH

Microbial growth is the orderly increase in all components of the population. Bacterial growth results in an increase in biomass and an increase in the number of cells making up the population. In general, bacteria are considered to be unicellular organisms that grow by binary fission, which means that each cell divides to form two cells. Molds are fungi that grow and form a mycelium as a result of branching and intertwining of individual hyphae. Yeasts are fungi that generally are unicellular and frequently reproduce by budding. Budding is a process by which the buds (new cells) are formed and "pinched off" from the original yeast cell.

Microbial growth requires suitable physical requirements including suitable temperature, suitable pH of the growth medium (i.e., product or raw material), freedom from harmful hydrostatic pressure, freedom from harmful radiation, and suitable osmotic pressure or water activity (a_w). The a_w is an expression of the relative humidity of the headspace over the product. Microbial growth also requires suitable chemical requirements including water, nutrients (i.e., sources of carbon, nitrogen, phosphorus, sulfur), minerals, oxygen (i.e., proper oxidation or reduction potential), organic growth factors, and freedom from inhibitory chemicals (i.e., antibiotics, preservatives, or sanitizers).

Bacteria, yeasts, and molds are widely distributed in nature and are able to utilize a wide range of materials as substrates for energy and growth. They are able to grow in raw materials and finished aqueous products when physical

and chemical conditions permit. When they grow, microorganisms can cause rapid and profound changes in their immediate environment with accompanying changes in the physical characteristics of a product (i.e., change in pH, viscosity, odor, flavor, color, etc.). The synthesis of new cells or fungal mycelia involves many complex chemical reactions occurring in a remarkably short period of time. Microorganisms carry out these reactions by means of enzymes. Some of the basic enzymatic reactions that can occur are as follows:

Hydrolysis	The addition of H_2O to the molecule. The next step in molecular breakdown is often thus facilitated so that molecules are split at the hydrolyzed link.
Dehydration	The removal of H_2O from one or more molecules.
Oxidation	The removal of hydrogen or the addition of oxygen to the molecule; also a process that involves an increase in the number of positive charges on an atom, or a decrease in a number of negative charges.
Reduction	The removal of oxygen or the addition of hydrogen; the reverse reactions to those of oxidation.
Decarboxylation	The removal of CO_2
Deamination	The removal of $-NH_2$
Phosphorylation	The esterification of the molecule with phosphoric acid. This is usually accomplished by the transfer of the phosphate from some substance other than phosphoric acid itself.
Dephosphorylation	The removal or hydrolysis of phosphoric acid from phosphorylated compounds.

The growth of different kinds of microorganisms in a product results in formation of a large variety of end products. In mixed populations, there is, of course, a certain amount of competition for essential nutrients between the different organisms. Those that can convert the materials in the environment satisfactorily survive, while those that live with difficulty die out, providing a further source of convertible substrate for those that remain. In utilizing the substrate, the metabolic processes of some organisms result in the formation of acid end products that have a limiting effect on growth, and in some cases the changes brought about are sufficient to inhibit further growth. Most organisms are, however, capable of carrying out neutralizing reactions and in this way some degree of stabilization of the environment can be achieved.

Microorganisms can grow from a few cells/ml to over 10^6 cells/ml in less than 24 hours when growth conditions (water availablity, nutrients, pH,

oxidation or reduction potential, and temperature) are optimal. The speed with which microorganisms can propagate, and the variety of reactions that they can perform, indicate how necessary it is to inhibit their growth in products whose physical characteristics must remain unchanged during long periods of storage and use in the hands of the consumer.

Although the growth of molds in products may be evident by the formation of a film of mycelia on the top or sides of the product in containers, often microbial growth is detectable only by the changes in the physical characteristics of products. Microbial metabolism may cause the formation of gas, which may be seen as bubbles or frothing in liquid preparations, and the production of undesirable odors. In addition, microorganisms may cause cracking of emulsions, alteration in rheological properties, or loss of texture in topical preparations. It is also possible that microbial contamination may be detected as an allergic reaction to the application of foreign protein to the skin from a contaminated product.

The time required for these effects to occur depends on how suitable conditions are for microbial growth. Chemical preservatives are used to minimize the possibility of microbial growth in aqueous products. Inadequate preservation may become evident by frequent contamination of new batches of product, by the Phoenix phenomenon (i.e., the situation that occurs when initial testing fails to detect contamination while later testing reveals the presence of viable microorganisms), and by reports of contamination that occur during consumer use of the product. Contamination may be the result of microbial adaptation to the product and its preservative system. The process of adaptation may involve gradual alteration of pH by the organism to a level at which growth can take place, or the induction of enzymes that are able to utilize product components as substrates for growth. Metabolic adaptation may also involve altered gene action that results in the development of increased resistance to, or metabolism of, the preservative. *Pseudomonas* species have been found to develop resistance to parabens and benzalkonium chloride used as preservatives in detergent-containing products. In both products the *Pseudomonas* was found to metabolize the detergent. Product contamination by the mold *Cladosporium resinae* was reported to be caused by the hydrolysis of the preservative (methylparaben) to *p*-hydroxybenzoic acid.

SOURCES OF CONTAMINATION

RAW MATERIALS

If the raw materials used in manufacturing of cosmetics are heavily contaminated, it is likely that the finished product will be similarly contaminated, and

any preservative system present will be unnecessarily strained. This can be avoided by careful monitoring of raw materials.

The water used in product manufacture is the most frequent source of microbial contamination, often supporting large numbers of microorganisms (i.e., $>10^6$ cfu/ml). Municipal water contains low numbers of organisms, usually <300 cfu/ml. Softened, distilled, or, in particular, deionized water is capable of supporting the growth of some bacteria (especially pseudomonads), and numbers can rise to 10^6–10^7 cfu/ml when water is stored. Many cases of product contamination have been traced to heavy contamination in the beds of ion exchangers or water storage tanks.

Fats, waxes, and refined oils do not contain sufficient water to support microbial growth, so they contain relatively few organisms. Natural materials such as gums and herbs are exposed to environmental contamination and/or aqueous processing, so they are heavily contaminated by a variety of yeasts, molds, and bacteria. The natural gums, tragacanth, karaya, and acacia, were heavily contaminated before sanitary processes were put into place to help control microbial contamination and growth. Synthetic gums generally contain few, if any, viable microorganisms. Other naturally occurring materials such as talc, kaolin, chalk, and rice starch may contain bacteria, particularly those that are capable of forming spores. Spores often are difficult to kill and "carry over" into finished products; thus use of raw materials with appropriate microbial limits helps prevent unnecessary contamination of finished products.

The containers of raw materials—drums, sacks, cartons, and so forth —may also be a source of contamination prior to manufacture. Manufacturers must use a risk assessment to determine the likelihood of contamination of incoming raw materials and set up a sampling or testing program to monitor raw materials. Highly suspect materials that may support microbial growth, such as deionized water, should be sampled several times a week to ensure that they continue to meet appropriate levels of microorganisms (i.e., <100 cfu/ml and no *Pseudomonas aeruginosa*). Each lot of botanicals and materials that may have been exposed to water at some stage during processing (i.e., starch, protein powders, extracts) should be tested to see if it meets microbial specifications. Anhydrous materials (mineral oil, esters, lipids, waxes) may be sampled and tested "once for the record" to verify that materials from a particular manufacturer present no unacceptable risk of contamination.

ENVIRONMENT

Another possible source of contamination is the air, which contains mainly mold and bacterial spores, and skin microflora (primarily micrococci). Environmental control is facilitated by covering of containers and reduction of

air currents over open product streams. Although there may be some seasonal variation in the types and numbers of microorganisms recovered from the plant environment, routine monitoring of the air and selected surface sites within the production area is advised so that deviations from normal standards of cleanliness may be detected and brought back into control.

EQUIPMENT

During manufacture, the product can easily become contaminated by organisms that accumulate in the plant as a result of faulty or inadequate cleansing. Pieces of equipment with inaccessible joints, pipes, and pumps are often difficult to clean properly, and washing with detergent solutions may only result in dilution of the product to form stagnant foci in which bacteria and fungi thrive. Equipment should be designed to facilitate easy cleaning and disinfection, and inaccessible grooves and dead ends in all items that come into contact with the product should be avoided wherever possible.

Disinfection with 150–200 ppm of hypochlorite will sanitize clean metal and glass in two minutes and sterilize in 10 minutes. The corrosive nature of this treatment is a disadvantage. Hot water, or preferably live steam, has been recommended as the best disinfecting agent. Detergent sanitizers containing quaternary ammonium compounds or detergent iodine mixtures are also useful, but it is essential to remove product residues from the equipment and to rinse thoroughly with hot water before utilizing any of the above disinfection procedures since many are inactivated by residues of organic material. Air locks in the equipment may also prevent certain parts from coming into contact with the cleaning and sterilizing fluids and should be avoided.

The need for good housekeeping procedures cannot be stressed too strongly. The education of plant operators is of paramount importance so that they appreciate the necessity of performing plant cleaning operations properly. Two 15-minute exposures to a sanitizing agent (i.e., live steam), or two 5-minute exposures to 200 ppm hypochlorite solution will not provide the same kill of some microorganisms as one 30-minute treatment with live steam, or a 10-minute treatment with the hypochlorite solution. Procedures must be validated, and personnel must be trained to follow established procedures.

It is believed that one of the most common causes of house organisms and product contamination is failure to eliminate water residues from equipment after cleaning and sanitization. It is imperative that equipment be drained thoroughly and dried if it is not to be put into service in less than six hours. Validated cleaning procedures should ensure that no aqueous residues remain at the bottom of tanks, in pipe elbows, transfer lines, pumps, and fillers.

Microbiological testing must be done as part of the validation of the cleaning and sanitization procedures. RODAC plates and/or swabbing techniques may be used for this purpose together with sampling of the final rinse fluid after sanitization to determine the microbial load on the internal surfaces.

Bacteria grow in dilute product residues and become adapted to the product preservatives. These adapted bacteria then contaminate the next batch of product when it passes through this equipment. This results in contamination of an entire lot of new product.

PACKAGING MATERIALS

Since most products are exposed to further contamination during the filling of containers, cleaning and disinfection of filling equipment is also important. Containers and closures should be dust-free and microbiologically clean. This can be achieved by a filtered air blast, which is probably more effective than the use of detergent and water. Air lines must be checked to ensure that they do not contaminate the packaging components. Caps and liners are notorious for allowing molds to develop, and much of the growth on the surface of cosmetic creams is directly attributable to cap linings. Quite frequently creams containing preservatives, which are otherwise adequately preserved, break down following the introduction of large numbers of fungal spores from a cap lining. These organisms germinate initially in the microfilm of water on the lining and spread gradually to areas of slight separation around the edge of the cream. Many toilet preparations, in addition to having a long shelf life, may be in use by the consumer for many months, so that spoilage does not become apparent until the contents are more than half used. Products packed in wide-mouthed jars, and flexible bottles that draw air back into them, are more liable to contamination than those packed in collapsible tubes and bottles with small orifices.

As plastic materials are not subject to biodegradation, use of such materials instead of cellulosic materials should be associated with a reduction in microbial spoilage. Unlike paper, cardboard, and cork, plastics generally present no microbiological problems; however, they are porous to oxygen and carbon dioxide and encourage water condensation and spoilage by microorganisms that may be present.

PERSONNEL

Probably the greatest microbial hazard to the product during manufacture or packaging is from the operators. Operators should be properly instructed to appreciate that they are a potential source of contamination and they should

be trained to maintain high standards of personal hygiene and cleanliness. The wearing of protective overgarments is advisable.

MICROBIAL GROWTH IN PRODUCTS

A number of factors determine whether microorganisms will survive and grow in a product and hence these influence the need for preservation. Some of the more important are examined below.

WATER CONTENT

Because microorganisms depend on water for the synthesis of cellular components, the physical and chemical characteristics of the water phase in an emulsion, for example, are dominant factors in determining whether growth occurs. In single-phase, nonemulsion products, however, the amount of growth that will occur is determined by factors such as the pH, a_w, surface tension (surfactant type and concentration), and oxygen tension of the system.

In general, emulsions with a continuous water phase are more susceptible to bacterial attack than those with a continuous oil phase, although bacteria have frequently been isolated from inadequately preserved w/o emulsions. Microorganisms require aqueous environments for growth; however, some bacteria and fungi can survive for extended periods of time in hydrocarbons free of any separate aqueous phase. In addition, supposedly anhydrous cosmetic products may support the growth of contaminating microorganisms if moisture has entered the products, either via the user or through condensation. In emulsions, microbial growth occurs in the aqueous phase and at the water-oil interface. For example, microorganisms at the o/w interface may degrade triglycerides and other lipids in emulsions. Fatty acids and glycerol are liberated by the hydrolysis of triglycerides, and these components can then be metabolized for microbial growth. The availability of moisture (i.e., high enough a_w) will have a significant effect on the magnitude of growth, especially for bacteria such as *Pseudomonas aeruginosa*, which cannot grow when the a_w is <0.97.

NUTRIENTS

The nutritive value of the aqueous phase for the organisms present in a product will contribute to the amount of growth that will occur, and the presence of carbohydrates, proteins, and phospholipids will increase the need for adequate preservation. Sorbitol, glycerol, and even surface-active agents (particularly the nonionics) when present at low concentrations can be metabolized by microorganisms. Many organisms are able to hydrolyze the ester linkages of certain

nonionic surfactants, which allows them to grow. The rate of growth is dependent on the number of organisms in the inoculum and the physicochemical characteristics of the product (pH, a_w, availability of oxygen, etc.).

Anionic surfactants are also capable of acting as sources of energy for microorganisms. Their chemical structure controls their susceptibility to attack and certain bacteria are capable of oxidizing terminal methyl groups to carboxyl groups. Although there are reports that indicate that the alkyl sulfates, sulfonated fatty acids, amides and esters, and the low molecular weight polyethylene glycol derivatives are rapidly broken down, alkyl aryl sulfonates, alkyl phenoxypolyoxyethanols, and high molecular weight polyethylene glycol derivatives reportedly are attacked more slowly. Interpretation of these data must be done with caution because most commercially available surfactants are aqueous and contain preservative systems that may have affected the ability of microorganisms to use them as substrates for growth.

Many vegetable gums utilized as thickeners can be used as nutrients by microorganisms. Polysaccharides may be attacked by extracellular enzymes and thus depolymerized. Starch may be degraded by amylases and carboxymethylcelluloses by cellulases. It has been reported that methyl and ethyl celluloses are more resistant to microbial attack than many other cellulose derivatives.

pH VALUE

Microbial growth generally occurs best around neutral pH (5–8), and the growth of many types of organisms is impaired as the pH decreases below pH 5 or increases above pH 9. The pH value of a product will affect the degree of ionization of utilizable materials, influence the electrical charge at the bacterial and fungal cell walls, modify enzyme production or activity, and hence regulate the availability of nutrients and the ease with which they are assimilated by the microbial cell. The growth tolerance limits for pH differ widely for various microorganisms, so the pH of a product itself should not be considered to be the only factor contributing to self-sterilization of a product. Gram-negative bacteria including *Pseudomonas* species, which are extremely common contaminants of toilet preparations, can exist over as wide a pH range as 3–11. Although many fungi grow most prolifically at acid pH, they have been known to survive on vanishing creams at pH 9.

OSMOTIC PRESSURE/WATER ACTIVITY

The semipermeable membranes that surround all microbial cells can be ruptured by changes in osmotic pressure, and changes in osmotic pressure lead to membrane shrinkage and dehydration of the organism. The available water,

which may be described by osmotic pressure or a_w, can have a limiting effect on growth. Concentrations of 40–50% glycerin and sorbitol are inhibitory to nearly all bacteria and fungi of interest in cosmetic products. Thus very concentrated products are likely to be self-preserving, which means that their physicochemical composition does not permit growth. However, dilution of these products may make them susceptible to growth and spoilage because dilution makes more water available (increases the a_w). Shampoos that are frequently sold to professional hairdressers as concentrates for dilution before use are often not susceptible to bacterial degradation until they are diluted with water.

SURFACE TENSION AND OXYGEN TENSION

Although low concentrations of surfactants may be used as substrates for growth, surface tension is itself a factor influencing growth. Many Gram-negative bacteria, and the coliforms in particular, grow well in the presence of surfactants, while most Gram-positive organisms do not grow well at surface tension levels much below 50 dyn/cm (0.05 N/m). Gram-negative organisms such as pseudomonads and coliforms may flourish in shampoos and are common contaminants of the aqueous phases of inadequately preserved emulsions. Cationic surfactants are toxic to many organisms, anionics to a few, and nonionics to hardly any; thus surface tension per se will not be the only limiting factor but will have an effect in association with the presence or absence of toxic groups in the surfactant molecules and the product preservative system.

Microorganisms that contribute to product spoilage often are aerobic and depend on the availability of oxygen for their metabolism. The oxygen tension in most products, with perhaps the exception of those in pressurized packs, will almost invariably provide sufficient oxygen for the growth of microorganisms provided that all other factors are favorable.

TEMPERATURE

The susceptibility to microbial attack will vary with the temperature of storage, so that a cosmetic kept at room temperature will be liable to spoilage by different organisms from those that flourish in a product kept in a hot environment (e.g., one left in the sun or in a hot car). Bacteria that cause problems in cosmetics and toiletry products generally grow well at 30–37 °C, whereas yeasts and molds grow best at 20–25 °C.

CLINICAL SIGNIFICANCE OF CONTAMINATION

Several surveys have been conducted to determine the type of microorganisms found and extent of contamination in used and unused cosmetics. The data in Table 14.1 summarize the types of microorganisms in used and unused cosmetics and toiletries. Table 14.2 lists some of the genera of microorganisms that have been isolated from cosmetics and toiletries. Gram-negative bacteria, especially *Pseudomonas* spp., have been the most frequently isolated organisms in unused cosmetics. Used cosmetics are most frequently contaminated with microorganisms commonly found on the skin, including staphylococci, diphtheroids, and micrococci; however, fungi and yeasts are also encountered. While it is appreciated that contaminated cosmetics may lose their aesthetic appeal, less is known about the potential danger of these contaminants to the consumer. Hand creams and lotions are extensively used in hospitals. Often patients are more likely to be susceptible to infections than healthy individuals, so the microbial state of these cosmetics may have important implications. An example of this was the septicemia outbreak caused by *Klebsiella pneumoniae* in a hospital intensive care unit, in which the source of infection was found to be a dispensing bottle of contaminated lanolin hand cream. A follow-up survey in another hospital examined 26 brands of hand cream, used and unused, and disclosed that four brands contained a variety of Gram-negative bacteria. It was suggested that the increase in numbers of Gram-negative infections in this hospital was related to the use of contaminated products.

Table 14.1 Contamination of Used and Unused Cosmetics and Toiletries by Microorganisms

Products	Microorganisms most frequently isolated
Unused cosmetics and toiletries	Gram-negative rods, especially pseudomonads and *Burkholderia cepacia*, spore-forming bacilli, Gram-positive cocci and diphtheroids.
Used cosmetics and toiletries	Gram-negative rods, including *Pseudomonas aeruginosa*, Gram-positive cocci, especially staphylococci and micrococci, yeasts (*Candida parapsilosis*) and molds (*Cladosporium* spp.)

Table 14.2 Some Microorganisms Isolated from Cosmetic and Toiletry Preparations

Bacteria	Yeasts	Molds (Fungi)
Gram-positive:		
Bacillus (spore-former)	*Candida*	*Alternaria*
Micrococcus	*Monilia*	*Aspergillus*
Sarcina	*Torula*	*Cladosporium*
Staphylococcus	*Zygosaccharomyces*	*Fusarium*
Streptococcus		*Geotrichum* (machinery mold)
		Penicillium
		Rhizopus
Gram-negative:		
Acinetobacter		*Thamnidium*
Alcaligenes		*Trichothecium*
Burkhoderia		
Enterobacter		
Escherichia		
Klebsiella		
Proteus		
Pseudomonas		
Serratia		

There is evidence implicating use of contaminated cosmetics in the production or persistence of eye infections. Ocular cosmetics become contaminated with resident bacterial flora from the skin and eyes, and there have been reports of contamination by yeasts and saprophytic molds. These organisms may grow in the cosmetics and be inoculated in high numbers into the outer eye. A correlation between organisms found in the outer eye and those found in the cosmetics of the user has been shown. Several cases of staphylococcal blepharitis or conjunctivitis were correlated with contaminated cosmetics, such as mascaras, and many of the conditions improved when use of the contaminated products was discontinued. Although new eye cosmetics are rarely contaminated with microorganisms, contamination during use appears to be an ongoing problem. This creates the opportunity for improved preservative systems to ensure that products are better able to resist contamination during use and/or creative packaging to prevent contamination during use of the product. Fortunately, manufacturers are now more aware of microbial problems, and the incidence of contaminated unused products is much lower than prior to 1980.

The virulence factors of microorganisms include toxins, enzymes, lipopolysaccharide (LPS; endotoxin), and other products that affect mammalian cellular physiology and immune function. Microorganisms

growing on skin and mucous membranes may produce undesirable changes, including inflammation and immunomodulation. The "flesh-eating bacteria" phenomenon occurs when the skin immune system (SIS) overreacts to superantigens produced by *Streptococcus pyogenes* during infections of the skin. *Staphylococcus aureus* produces a number of virulence factors, including toxic shock toxin 1, which causes toxic shock syndrome (TSS). TSS has caused death in several women who wore tampons for extended periods. *Pseudomonas aeruginosa* produces proteolytic enzymes and lipases that help it invade tissues. The exotoxin A produced by this organism prevents protein synthesis so that infected cells cannot make enzymes to modify metabolism and stop the spread of this organism in the body.

PRODUCT PRESERVATION

PRESERVATIVE REQUIREMENTS

The "ideal" preservative that is both safe and effective in all kinds of cosmetic and toiletry preparations is like the Holy Grail—it has not been found. This means that the composition of each new product must be studied in detail before selecting a suitable preservative. In order to avoid preservative failure, a careful analysis must be made of the factors in the product that are likely to favor the growth of microorganisms, the ingredients that are likely to be contaminated before use, and also those that are likely to influence adversely the efficiency of whatever preservative is ultimately selected. The essential requirements of a preservative are:

(i) freedom from toxic, irritant, or sensitizing effects at the concentrations used on the skin, mucous membranes, and in the case of orally administered products, on the gastrointestinal system;
(ii) stability to heat and prolonged storage;
(iii) freedom from incompatibility with other ingredients in the formula and with the packaging material, that could result in loss of antimicrobial action.

Other requirements are that the preservative should be active at low concentrations; retain its effectiveness over a wide pH range; be effective against a wide range of microorganisms; be readily soluble at its effective concentration; have no odor or color; be nonvolatile; retain its activity in the presence of metallic salts of aluminium, zinc, and iron; and not be corrosive to metal tubes or rubber packaging components.

Table 14.3 lists preservatives used frequently in cosmetics and toilet preparations. A thorough knowledge of the factors that can influence the efficiency

Table 14.3 Preservatives Frequently Used in Cosmetic and Toiletry Formulations (in alphabetical order)

2-Bromo-2-nitropropane-1,3-diol
5-Bromo-5-nitro-1,3-dioxane
Benzalkonium chloride
Benzethonium chloride
Benzoic acid (sodium benzoate)
Benzyl alcohol
Boric acid
Butylparaben
Captan
Chlorhexidine acetate
Chlorhexidine digluconate
Chlorhexidine dihydrochloride
Chloroacetamide
Chloroxylenol
Chlorphenesin
Dehydroacetic acid (sodium dehydroacetate)
Dichlorobenzyl alcohol
Dimethoxane
DMDM Hydantoin
Ethylparaben
Formalin
Glutaraldehyde
Hexamidine isethionate
Imidazolidinyl urea
Iodopropynyl butylcarbamate
Isobutylparaben
Isopropylparaben
Methenamine
Methylchloroisothiazalinone and methylisothiazolinone
Methyldibromoglutaronitrile
Methylparaben
p-Chloro-*m*-cresol
Phenoxyethanol
Phenethyl alcohol
Phenyl mercuric acetate
Polymethoxy bicyclic oxazolidine
Propylparaben
Quaternium-15
Salicylic acid
Sodium bisulfite
Sodium borate
Sodium hydroxymethylglucinate
Sodium sulfite
Sorbic acid

Table 14.4 Advantages and Disadvantages of Different Classes of Preservatives

Class of Preservative	Advantages	Disadvantages
Acids: Benzoic, Sorbic, Dehydroacetic	More active against yeasts and molds; Some activity against bacteria	pH-dependent because of dissociation: benzoic effective below pH 4; sorbic effective below pH 4.5; dehydroacetic effective below pH 6; Poor activity against pseudomonads
Paraben Esters: Methylparaben Propylparben Ethylparaben Butylparaben	Active against Gram-positive bacteria, yeasts and molds; relatively nonirritating at use concentrations	Inactivated by nonionics and cationics; more effective at acid pH
Quaternary Ammonium Compounds: Benzalkonium chloride Cetylpyridinium chloride Benzethonium chloride	Primarily active against Gram-positive bacteria; some activity against Gram-negative bacteria; most active above pH 7	Incompatible with anionics and proteins; poor activity against pseudomonads
Formaldehyde donors: 2-bromo-2-nitropropane-1,3-diol (BNPD) Glutaraldehyde Quaternium-15 Imidazolidinyl urea Diazolidinyl urea DMDM Hydantoin	Broad spectrum of antimicrobial activity; relatively inexpensive; retain activity in presence of surfactants and wide pH range (except BNPD, which is not stable above pH 6)	Some are incompatible with proteins; irritant; not permitted in some countries
Alcohols: Ethyl alcohol Benzyl alcohol 2,4-dichloro benzyl alcohol	Broad spectrum	High concentrations (>15%) of ethyl alcohol are required for antimicrobial action; ethyl alcohol is volatile (may evaporate from products over time); alcohols may be inactivated by nonionics
Organic mercurials: Phenyl mercuric salts	Broad spectrum of antimicrobial action; stable	High toxicity and irritancy; restrictions on use (e.g., eye area cosmetics in U.S.); inactivated by proteins and anionics; may be inactivated by nonionics

Table 14.4 *(Continued)*

Class of Preservative	Advantages	Disadvantages
Miscellaneous: Mixture of chloromethyl-isothiazolinone and Methylisothiazolinone	Broad spectrum of antimicrobial action at low concentrations	Inactivated at high pH; may be inactivated by proteins
Phenoxyethanol	Weak antimicrobial action; most active against Gram-negative bacteria	Inactivated by highly ethoxylated compounds

in a particular system is required before selection of preservatives for a particular formula. Table 14.4 indicates the advantages and disadvantages of some of the established groups of preservatives.

FACTORS INFLUENCING THE EFFECTIVENESS OF PRESERVATIVES

Concentration of Preservative

There are no hard and fast rules about the optimum concentrations at which various preservatives should be used because each product (formula, package and consumer use) is different. Some products, by virtue of the concentration of materials in their aqueous phase, are virtually self-preserving without any addition of preservatives being necessary, whereas others may provide a nutritious environment for the growth of microorganisms and thus require fairly high concentrations of preservatives.

Effective concentrations of preservatives range from as little as 0.001% in the case of organic mercurial compounds to 0.5% or even 1% of such materials as the weak acids, depending on pH and composition of the product.

The availability of the preservative to the microorganisms it is required to inhibit is probably more significant than the overall concentration. "Availability" in this context can be defined in accordance with the mechanism of action of the particular preservative; it may depend on the degree of adsorption (if the preservative acts by adsorbing to the bacterial cell wall or envelope), the permeability across the cell envelope (if this is the mechanism), or the flux across cell membranes (if diffusion rate is important). The availability of the preservative is also influenced by the distribution or partition of the preservative between phases of the product. Partitioning properties of preservatives are discussed later in the chapter.

The advantages in using preservatives in combination rather than using single preservatives include: (1) broadening the antimicrobial spectrum of

activity; (2) using a lower concentration of each of the preservatives, thus avoiding problems of toxicity or insolubility; (3) reducing the probability of survival of an organism resistant to one of the preservatives, provided that the other preservative(s) in the system act by a different mechanism; (4) improving the antimicrobial activity of the combination that may be greater than the additive effects of the individual preservatives—synergism.

Frequently the *p*-hydroxybenzoic acid esters are used in combination, the methyl ester in the aqueous phase of an emulsion and the propyl ester in the oil phase. Addition of the preservative to the oil phase is not so much to prevent the multiplication of organisms in this phase, because growth occurs in the oil phase, but is intended to prevent diffusion or partition of the methyl ester from the aqueous phase into the oil phase. Also, it is believed that the presence of propyl ester in the oil phase will tend to stabilize the distribution between the phases. Bactericidal activity often is governed by the concentration of preservative in the aqueous phase.

The parabens have been used in combination with other preservatives, for example, phenoxyethanol. Combinations of parabens and phenoxyethanol have a wider spectrum of antimicrobial activity than any of the separate components, and it has been shown that methylparaben and phenoxyethanol have synergistic antimicrobial action against fluorescent pseudomonads. Synergism has also been found to occur with combinations of benzalkonium chloride or chlorhexidine with some aromatic alcohols.

Dissociation and pH

Formulations of cosmetics and toiletries encompass a wide pH range since microorganisms of one sort or another are capable of growing between pH 2 and pH 11. Ideally, a preservative should be effective over this range. In practice, many preservatives are pH-dependent, the majority of them (e.g., methylparaben) being more active in the acidic than in the alkaline range. Some preservatives with a wide pH profile have the disadvantage of being chemically highly reactive compounds (e.g., formaldehyde and formaldehyde donors) that react with other components of the formulation. The pH may also have an effect on the microbial cell surface and may affect the partitioning of an antimicrobial agent between the cell and the product.

For many preservatives, the most pronounced effect of pH on activity is on the antimicrobial agent itself. Many weak acids are used as preservatives. Their activity depends on the amount of undissociated acid, which in turn depends on the dissociation constant and pH of the system. It has been suggested that anions of acids may be inactive as a result of repulsion from the negatively charged microbial cell wall. Benzoic acid is an excellent preservative in its undissociated form, but its antimicrobial action is strongly pH-dependent so

that approximately 60 times as much benzoic acid is required at pH 6 as at pH 3. Dehydroacetic acid enolizes to give a weak acid with a very low dissociation constant. It retains activity at higher pH values than most other organic acids, which is an important reason why it is frequently used.

Phenolic preservatives, which include the parabens, behave as weak acids and consequently are less dramatically affected by pH than stronger acids. For example, methylparaben at pH 8.5 is approximately 50% undissociated. The relationships between pH and effectiveness of a range of preservatives have been studied. When the pH of the environment is below the pK_a, changes of pH are of little consequence, but higher concentrations of the preservative are required to produce the same antimicrobial action as the pH is increased above the pK_a.

Other preservatives, for example, cationics, are active only in the ionized form. The activity of cetrimide increases with pH as a result of increased cellular uptake. Quaternary ammonium compounds are active at alkaline pH, but activity is progressively lost at lower pH values. The activity of some preservatives is pH-dependent by virtue of chemical instability. For example, 2-nitro-2-bromo-propanediol loses activity as a result of degradation above pH 7 more rapidly than at pH 4. On the other hand, hexamethylene tetramine is stable and inactive above pH 7 because it relies on chemical breakdown with the production of formaldehyde for antimicrobial action.

In order to utilize a preservative economically and effectively, it is necessary to know whether there is a correlation between pH and activity. A great deal of money may be saved by use of preservatives that are most effective under the pH conditions prevailing in their products.

Partition Coefficient

The preservation of formulations containing oil and water is complicated by the ability of preservatives to distribute themselves between these two phases. Since microorganisms grow only in the aqueous phase, it is important that the preservative does not distribute itself in such a way as to leave an ineffective concentration in this phase. Ideally, a preservative should have high water solubility and low oil solubility, that is, have a low oil-water partition coefficient. For simple systems where no emulsifier is present, the concentration of the preservative in the aqueous phase (C_w) can be calculated from the following equation:

$$C_w = \frac{C(\varphi + 1)}{(K_w^o \varphi + 1)}$$

in which C is the total preservative concentration, φ is the oil-water ratio, and K_w^o is the oil-water partition coefficient. The concentration of preservative in the aqueous phase is influenced by the oil-water ratio. As a general rule, when

$K_w^o < 1$ the aqueous concentration is increased by increasing the proportion of oil, and when $K_w^o > 1$ an increase in the proportion of oil decreases the aqueous concentration.

The partition coefficient itself varies with pH and the nature of the oil. Some oils are predominantly hydrocarbon, whereas others, for example, vegetable oils, contain oxygen atoms. Preservatives such as chlorinated phenols form hydrogen bonds with the latter type of oil, giving them a high partition coefficient and thus rendering the preservative unsuitable for systems containing this type of oil. However, chlorinated phenols are suitable preservatives for formulations based on oils that are predominantly hydrocarbon.

Various workers have shown that the addition of propylene glycol to the water phase of an emulsion reduces the partition coefficient and thus makes more preservative available in the water phase. Propylene glycol has been found to be effective at 16% in many cosmetic products, and its antimicrobial properties are believed to be three or four times greater than those of an equivalent amount of glycerin. Propylene glycol does not appear to act solely by virtue of its osmotic effect, and it also appears to be antimicrobial to some microorganisms at high concentrations.

For systems containing oil and water phases and an emulsifying agent, the preservative concentration in the aqueous phase may be further reduced by binding or solubilization of the preservative by the surfactant. A voluminous literature exists on the inactivation of preservatives by surfactants, particularly the nonionics, and some aspects of inactivation are dealt with in a subsequent section of this chapter.

Susceptibility of Organisms to Preservative

Several nonionic surfactants, notably polysorbate 80, ceteth-20, and PEG-8 laurate, have been found capable of exerting a "protective" effect on microorganisms. It was shown that polysorbate 80 protected *Escherichia coli* from the lethal effects of *p*-chloro-*m*-xylenol by preventing in part the leakage of the cell contents, as indicated by the release of radiolabeled glutamate, which had previously been added to culture media in which the organisms were grown. Many reports show that polysorbate 80 and various polyethylene glycol esters protect Gram-negative organisms from the inhibitory effects of chemical preservatives.

Interactions Between Ingredients and Preservatives

Apart from chemical incompatibility between the ingredients used in products and the preservatives, physical factors, such as solubilization, adsorption, or bonding with active sites, can render preservatives inactive in otherwise chemically compatible systems.

Surface-active Agents. Certain cationic surfactants have strong antimicrobial properties, and their effect is additive when they are used in combination with other antiseptics or preservatives. The antimicrobial effectiveness of cationics varies according to the length of the hydrophobic chain, the most effective compounds having an alkyl chain length of about 12 to 14 carbon atoms. Soaps and anionic surfactants exert mild antimicrobial influences at high concentrations but tend to support the growth of Gram-negative bacteria and fungi at low concentrations.

The preservation of emulsions stabilized with either soap or anionic surface-active agents has not, in general, presented many problems, because when these agents are used as emulsifiers in creams, the concentration of surfactant in the aqueous phase is tolerably high and usually presents an environment that is hostile to the growth of microorganisms. Nevertheless, these materials decrease the activity of many preservatives to some extent, and this is the result of solubilization of the preservatives in the surfactant micelles. Below the critical micelle concentration (CMC) of a soap or anionic detergent solution, preservatives and antiseptics tend to be potentiated in their action, whereas their activity is diminished above the CMC (see Chapter 9).

Nonionic surfactants are now widely used as emulsifiers for creams and also as solubilizers for perfumes in nonemulsified products. The relationship between these materials and preservatives is thus of great importance. Nonionic surface-active agents inactivate preservatives to a far greater extent than soaps and anionic or cationic detergents and, unlike the other surfactants, most nonionics have no growth-inhibiting properties, thus increasing the necessity for adequate preservation of systems that contain them. They have no denaturing effect on bacterial proteins, and many can be utilized by bacteria and fungi as sources of energy. For this reason alone the absence of an effective preservative in nonionic-containing products often becomes unpleasantly apparent in a remarkably short time. However, some nonionic surfactants, notably the more hydrophobic octyl and nonyl phenols, have been shown to possess growth-inhibitory properties. Combinations of polyoxyethylene octyl and nonyl phenols and some antibacterials, for example 2-nitro-2-bromo-propanediol, produced synergism.

Many publications have dealt with the incompatibility of nonionic surfactants and preservatives. The hydrophile-lipophile balance (HLB) of nonionic surfactants influences their effect on preservative efficiency. The more oil-soluble nonionics, having HLB values of about 3–6, which are often used in water-in-oil emulsions, have a greater inactivating effect on commonly used preservatives than those with higher HLB values.

The mechanism of the interaction between nonionic surfactants and preservatives has attracted a great deal of attention, and there is evidence to support

the view that the interaction is attributable in part to micellar solubilization of preservatives by nonionic surfactants and also to complex formation. Complexes can be formed by hydrogen bonding between the phenolic hydroxyl group in certain preservatives and the oxygen atoms in the ether group of the ethylene oxide adducts. This mechanism cannot, however, account entirely for nonionic preservative interactions because a high degree of hydrogen bonding, and consequently inactivation, would be expected when cellulose gum and tragacanth gum are present, but these materials do not inactivate preservatives to the same extent as the high molecular weight polyethylene glycol ester.

In aqueous solutions of polyethylene glycol, it was found that, except for very high concentrations, the activity of cetylpyridinium chloride is reduced by the presence of the glycol (although not as much as predicted by binding data). Since polyethylene glycol does not form micelles, it was suggested that the interaction may be due to an attraction between the electron-deficient pyridinium ring of the antibacterial agent and the electron-rich polyether linkages of the glycol.

Nonionic surfactants form micelles in aqueous solutions at very low concentrations and for this reason, when used either as emulsifiers or solubilizers, will always be present at concentrations well above their CMC. The hydrophile-lipophile characteristics of the preservative will influence its relationship with the nonionic. To be effective, preservatives must be in solution and "available" in the aqueous phase of a product. The more lipophilic preservatives appear to be bound to a greater extent than the more water-soluble compounds. Thus propylparaben was found to have a far greater affinity for polysorbate 80 than methylparaben. At 5% polysorbate 80, 22% of the methyl paraben existed as free preservative, whereas only 4.5% of the propylparaben existed in a free state under equivalent conditions. Preservatives that appear to be much less affected by the presence of nonionic surfactants are formaldehyde, sorbic acid, benzoic acid, and dehydroacetic acid.

Studies have shown that the bactericidal properties of some quaternary ammonium compounds in dispersed systems correspond to the concentration of free preservative in the aqueous phase. Attempts have been made to describe the systems mathematically in order that the quantity of preservative required to produce effective preservation in surfactant solutions or emulsions may be calculated. In a solubilized system, micelles act as reservoirs for the preservative. Any loss of preservative from the aqueous phase—for example, because of interaction with microorganisms, product ingredients, or packaging—will lead to an adjustment of preservative concentration in the other phases until the equilibrium is reestablished. Consideration has been given to calculating the capacity of aqueous systems; however, since these systems are complex and many variable factors are involved, the concentration of preservative given by

mathematical considerations can be regarded only as a starting concentration that must be subjected to microbiological evaluation within the product.

Hydrophilic polymers, including high molecular weight PEGs, tragacanth gum, methylcellulose, cellulose gum, and PVP, have only a marginal effect in reducing the efficiency of the majority of preservatives. Quaternary ammonium compounds lose activity in the presence of lanolin and methylcellulose. Table 14.5 summarizes some early work showing the degree of binding or loss of preservative by various other cosmetic ingredients.

Several workers have reported that addition of certain substances to the aqueous phase of emulsions can minimize the inactivating effect of nonionic surfactants on preservatives. Materials such as propylene glycol, glycerin, and hexylene glycol change the partition coefficient of the preservative between the phase of the emulsion, thus making more preservative available in the aqueous phase. Ethyl alcohol, propanediol and butylene glycol have also been reported as being useful for this purpose.

Influence of Solid Particles on Preservatives. A large number of different insoluble solids are used in cosmetic and toilet preparations. These include talc, kaolin, titanium dioxide, tartaric acid, zinc oxide, and chalk, and the insoluble solids used to color creams and the natural and synthetic pigments, all of which present surfaces on which adsorption of preservative will occur. The extent of this adsorption depends on the nature of the solid, the type of preservative, and the pH of the system. For any particular solid, knowledge of the surface electrical charge under particular conditions in the product, the total surface area presented to the aqueous phase, and any ion exchange

Table 14.5 Ratio of Total to Free Preservative in Presence of Surfactant and Polymers

Preservative	Polysorbate 80		PEG-40 Stearate		PEG 75		Methylcellulose	
	2%	5%	2%	5%	2%	5%	2%	5%
Methylparaben	2.5	4.5	2.0	3.0	1.2	1.5	1.05	1.25
Ethylparaben	5.0	11.0	3.0	5.0	1.3	1.6	—	—
Propylparaben	12.5	27.0	6.0	13.5	1.4	1.7	—	—
Butylparaben	30.0	63.0	18.0	40.0	—	—	—	—
Phenol	1.6	2.5	—	—	1.2	1.25	—	—
Sorbic acid	1.8	2.9	1.7	2.7	1.1	1.2	—	—
Cetylpyridinium Chloride	38.0	60.0	—	—	—	—	—	—
Benzalkonium Chloride	3.0	5.5	—	—	—	—	—	—

mechanisms that might operate should enable reasonable predictions to be made about the quantity of preservative lost to the surface.

Surfactants adsorb onto solid surfaces so that the order of addition of ingredients during manufacture can influence preservative adsorption. If the preservative is dissolved in a slurry carrying the suspended solid particles, greater adsorption will occur than if it is added after the particle surfaces have become coated with surfactant.

The activity of a preservative may be reduced by interaction with, or loss through, the container or closure. Interaction of preservatives with rubber has been well documented. Phenolic and quaternary ammonium compounds have been reputed to react with polyurethane. Parabens, benzoic, sorbic, and salicylic acids are taken up by nylon, polyvinylchloride, and polyethylene. Preservative efficacy testing should be done during stability testing of products to demonstrate continued adequacy of preservation for the expected shelf life of the product.

SELECTION OF A PRESERVATIVE

PRESERVATIVE SYSTEM

Contemporary cosmetic and toiletry formulations may contain natural or synthetic lipids, botanicals, alpha-hydroxy acids, enzymes, gums, fragrances, surfactants, conditioners, chemical preservatives, and so forth. The preservative system of a product involves more than compounds with known antibacterial activity because factors such as pH, a_w, nutrient availability, surfactant type and concentration, sequestering agents, alcohols, and so forth, determine the extent to which preservative action is manifested in a given formula.

It is evident that some materials will contribute to the preservative system and others will interfere with it. Selection of chemical preservatives should be done after considering the following:

1. Check ingredients for the likelihood of contamination (e.g., water, materials of natural origin, packaging, etc.).
2. Consider the levels of materials that might provide sources of energy for microbial growth (e.g., glycerin sorbitol, and so forth, at concentrations below 5%; nonionic surfactants at almost any useful concentration; soaps and anionic surfactants at concentrations below about 15%; and materials known to be good substrates for microorganisms—proteins, carbohydrates, cellulose derivations, and natural gums).
3. Determine the pH of the aqueous phase of the product before attempting to use any of the preservatives that depend strongly on being in an undissociated form for their activity. Consider changing the pH to provide enhanced antimicrobial activity.

4. Depending on the ratios of water and oil present in the formula, estimate whether certain preservatives will be partitioned between the two phases, possibly leaving insufficient levels in solution in the aqueous phase to be effective. Decide whether any of the materials in solution in the aqueous phase are likely to reduce the partition coefficient (e.g., propylene glycol and hexylene glycol) and thus tend to help the effectiveness of the preservative or, alternatively, increase the partition coefficient (e.g., surface-active agents), thus reducing its effectiveness. Consider the possibility of adding agents that will alter the partition coefficient or the CMC; for example, urea increases the CMC of nonionic surfactants, thus reducing the number of micelles and the degree of preservative inactivation.
5. As a guide, estimate the approximate ratio of total to free preservative in the presence of macromolecules in the formulation, and multiply the normally effective concentration by the appropriate factor (see Table 14.5).
6. Choose the least toxic of the possible preservatives for preservative efficacy testing.

When developing a new formula, consider both preservatives that are well known and allowed in many countries (Table 14.6), and other preservatives and/or preservative systems that may have application in a particular formula because of the type of packaging, intended use, or special preservative requirements (i.e., spectrum of antimicrobial activity, low cost, low toxicity, compatibility or stability, etc.) Where possible, "preservative-free" or self-preserving formulas should be considered (see p. 299). Globalization of products requires that they be suitable for registration in many countries. Several chemical preservatives are approved for use by the European Union (E.U.), by the Japan Ministry of Health and Welfare, and by the Cosmetic Ingredient Review (CIR). The CIR is an interagency body established by the Cosmetic, Toiletry and Fragrance Association to review raw materials and to

Table 14.6 Selected Preservatives Allowed in the United States, European Union and Japan

Preservative	Maximum Allowable Level
Paraben Esters (methylparaben, propylparaben, ethylparaben, butylparaben, isopropylparaben, isobutylparaben)	0.8%
Benzyl alcohol	1.0%
Phenoxyethanol	1.0%
Chlorhexidine	0.3%
Chlorphenesin	0.3% (E.U.); 0.05% (Japan)
Dehydroacetic acid	0.6% (E.U.); 0.5% (Japan)
Sorbic acid	0.6% (E.U.); 0.5% (Japan)

publish recommendations stating safe use up to a maximum concentration. Some chemical preservatives that may be considered for global use are listed in Table 14.6.

PRESERVATIVE EFFICACY TESTING

Preservative efficacy testing, or "challenge testing," is performed on aqueous cosmetic and pharmaceutical products to determine the minimum effective concentration of antimicrobial preservatives required for adequate preservation. Products are satisfactorily preserved if they meet appropriate acceptance criteria.

Preservative Efficacy Test Methods

Compendial methods of preservative efficacy testing used in different countries include the United States Pharmacopoeia (USP), British Pharmacopoeia (BP), and European Pharmacopoeia (EP) methods. There are trade association methods, such as the Cosmetic, Toiletry and Fragrance Association (CTFA) method, and rapid procedures such as the linear regression method. All of these methods have a number of similarities, including test organisms used, recovery systems, and the method of performing aerobic plate counts (APCs). Preservative efficacy tests typically are performed by adding 0.1 ml of a saline suspension of organisms to 50 g of a product sample to give an initial count of about 10^6 cfu/ml. The samples are mixed by shaking or stirring, and aliquots are withdrawn at various times (typically initially 4 or 6 hours, 24 hours, 7 days, 14 days, 21 days, and 28 days), and colony counts are made to determine the remaining cfu/ml of each test organism at each time point. The number of organisms remaining (cfu/ml at a particular time) is used to determine whether the product preservative system meets acceptance criteria, which are expressed in the number of log-reductions at a particular time (e.g., reduction from 10^6 to 10^3 cfu/ml at 7 days) or the decimal reduction time (D-value). The D-value is the time required for killing 90% of the population of test organisms (a 1 log reduction) and is determined by calculating the negative reciprocal of the slope of the survival curve. The survival curve for each test organism is constructed by plotting the log number of viable microorganisms recovered from the inoculated sample as a function of the time at which that sample was taken.

Types of Organisms Used in Preservative Efficacy Testing

In general, compendial (USP, EP), CTFA, and the linear regression method use the same basic test organisms, which include: *S. aureus* ATCC 6538, *P. aeruginosa* ATCC 9027, *E. coli* ATCC 8739, *Candida albicans* ATCC 10231, and *Aspergillus niger* ATCC 16404. Use of these test microorganisms provides a range of morphological and physiological types of organisms

that can be reasonably expected to be encountered in the manufacturing environment and during use by consumers. Some laboratories use additional microorganisms to ensure that their products are adequately protected from these microorganisms.

Rechallenge Testing

The rationale for rechallenge testing—the use of repeated inoculations—is that it represents the repeated contamination of a product that may occur during use. Repeated inoculation with specific test organisms shows the number of challenges a product can withstand before the preservative system fails for that organism. An alternative to rechallenge testing is to increase the inoculum. Testing 10 times with 10^6 organisms/ml has been shown to give the same results as testing once with 10^7 organisms/ml, up to the point at which the preservative system is overwhelmed.

Acceptance Criteria

Unlike the USP, EP, and CTFA methods, which determine the percentage of the original population present after 2, 3, 7 and/or 14 days, the linear regression method determines the D-values. The slowest rates of killing allowed for bacteria used in preservative efficacy testing (i.e., the largest D-values) are D-values of $\leq$112, $\leq$56, $\leq$16, $\leq$4, and $\leq$28 hours for the USP, CTFA, EP, pathogens (linear regression method), and nonpathogens (linear regression method), respectively. Larger D-values indicate a slower rate of killing than smaller D-values; it is evident that the USP criteria are the most lenient. It has been reported that the maximum permissible D-values for unadapted Gram-negative bacteria were around 30 hours. This means that Gram-negative bacteria routinely used in preservative efficacy testing persisted or grew if they were not killed with initial D-values of $\leq$30 hours.

The EP method allows use of "B" criteria where the "A" criteria cannot be attained (i.e., for reasons of an increased risk of adverse reactions). The "B" criteria require a 3 log (99.9%) reduction in bacteria and a 1 log (90%) reduction in fungi by 14 days and no increase in bacteria or fungi at 28 days. These criteria ($\leq$112 hours for bacteria) are quite lenient. Formulas that approach the maximum allowable limits for USP, CTFA, and EP "B" criteria should be used with caution for products in multiple-use containers unless precautions in manufacturing and packaging prevent contamination.

Preservation of Products During Use

The required D-value concept is useful for evaluating the effect of formula, packaging, and consumer use or abuse on product preservation. Three variables that determine whether a product can become contaminated are the preservative system of the formula, the packaging factor, and the consumer use or abuse

factor. Manufacturers should consider home use tests of the product to determine whether it remains uncontaminated during use. Maintenance of preservative efficacy (as indicated by testing samples of product returned after a period of use) and an APC of <10 cfu/g (for aqueous products) indicates that the product preservative system is satisfactory in the packaging used and in the manner used.

GLOBAL PRESERVATIVE SYSTEMS

Chemical preservatives have been used successfully in cosmetics and toiletries to prevent the growth of bacteria, yeasts, and molds. The *INCI Dictionary* lists many preservatives; Annex VI of the European Cosmetics Directive lists preservatives and acceptable use levels; and the Ministry of Health has published a list of ingredients and concentrations allowed for use in Japan. The Ministry of Health considered information on formaldehyde donors for several years before permitting their use, with stringent restrictions. Companies currently are marketing combinations of existing preservatives for application with broader spectrum of activity or synergistic activity in cosmetic products because mixtures of preservatives often are more effective against different microorganisms than the individual preservatives.

Globally marketed products must contain preservatives at levels acceptable in markets around the world. Although manufacturers are able to use conventional preservative systems for domestic products, they are finding that levels of chemical preservatives used in some formulations do not meet registration requirements in other countries. Removal of the regulated chemicals, such as the formaldehyde donors, often makes it difficult to have the formula meet appropriate acceptance criteria to ensure adequacy of preservation during manufacturing and use by the consumer.

Self-Preserving Products. There has been a trend in recent years to formulate products that respond to the (perceived) consumer need for natural cosmetics. These products contain "natural ingredients," and they may be fragrance-free and "preservative-free." Preservative-free means without chemical preservatives. In the E.U., this term means without chemicals listed as preservatives in Annex VI of the Cosmetics Directive. Generally, multiple-use aqueous consumer products in their current containers will be inadequately preserved by simply removing preservatives from the formula. It is possible to provide preservative-free products if they are sterilized and packaged or stored appropriately.

The term "self-preserving" is more appropriate than "preservative-free" for most aqueous cosmetic and toiletry products in multiple-use containers because these products have a preservative system that kills microorganisms and/or prevents their growth. Self-preserving products may be formulated by applying the principles of preservation, including use low or high pH, low

a_w, chelating agents, surfactants that have antimicrobial action, and packaging that protects the formula from contamination. Self-preserving products reduce and/or eliminate the need for chemical preservatives and allow the development of global formulas without violation of rules relating to the use of chemical preservatives. It is believed that the use of preservative-free or self-preserving formulas may be a convenient way of globalization of products.

The regulatory controls of preservatives not only vary from country to country but also are subject to modification with limited publicity. Manufacturers and formulators must, therefore, keep informed on the changing environment for the use of preservatives.

SAFETY OF PRESERVATIVES

Preservatives are biocides, which means that they are molecules designed to interfere with cellular integrity or metabolism. Although preservatives may be more toxic to microorganisms than to humans, they may cause irritation, contact sensitization, or other toxicity problems. It is always advisable to use the lowest effective concentration.

If preservative efficacy testing reveals that several times the usual concentration is required to achieve the desired antimicrobial action (because of increased partitioning into the nonaqueous phase, physicochemical binding, or factors influencing dissociation), the preservative's toxicity at the required use level should be considered before proceeding. Although a preservative may be partially bound in a product and the remaining fraction in the aqueous phase may represent no more than is safely used in other formulas, the ratio of bound to free preservative is unlikely to remain unchanged when the product is actually in use. From a toxicity point of view, the total amount is more important than only that fraction which is acting as a preservative in the particular vehicle. Application of the product to the skin disturbs the preservative's original equilibrium between the various phases of the product and may result in liberation of previously bound preservative. Evaporation of water will increase the concentration of the preservative available to the skin and may result in primary irritation or, in some cases, sensitization.

Generally, there is no sharp dividing line between a toxic and a nontoxic concentration of preservative in a formulation. Instead there is a reasonably continuous spectrum of toxicity, ranging from the very low concentrations at which a few people may show an adverse reaction, to the high levels in which both primary irritant and allergic responses will be more numerous. The toxicology of the paraben esters has been throughly studied, and no primary irritation following their use at concentrations up to about 0.3% has been reported. Levels of between 5% and 10% have been used in powders, ointments, and solutions to treat athlete's foot and, even at these levels, adverse

reactions have not been numerous. When contact sensitization is suspected, it is often necessary to use higher concentrations of the preservative than those normally employed in products in order to identify true skin allergies in standard 48-hour patch test. Sorbic and benzoic acid have also been used in products at concentrations far in excess of those required for normal preservation. Benzoic acid appears to have a reasonably clear bill of health, but sorbic acid has caused primary irritation characterized by erythema and itching, even when used at concentrations below 0.5%. The incidence of sensitization to sorbic acid is fairly low, and it is generally believed that concentrations of about 0.2% are unlikely to constitute a safety hazard. There are relatively few reports on adverse effects caused by dehydroacetic acid, and it has been used widely as a food preservative. It is not affected much by the presence of nonionic emulsifiers, so it appears that it merits more consideration as a preservative for cosmetics and toiletries. The organic mercury compounds are, of course, recognized poisons. Although they present a toxicity hazard to those who handle them in concentrated form in factories, they apparently have been used safely at concentrations below 0.01% for a number of years. In the United States, the Food and Drug Administration has ruled that mercurial preservatives should not be used in cosmetics, except in the case of eye-area cosmetics, because the mercury compounds (up to a limit of 50 ppm) are very effective in preventing *Pseudomonas* contamination. *Pseudomonas* infection of the eye can lead to serious injury or blindness.

The quaternary ammonium compounds have been extensively tested for skin irritation and sensitizing properties. At concentrations below 0.1%, most of those commonly used as preservatives appear to cause little or no irritation; higher concentrations can cause erythema and drying of the skin. Cases of sensitization to cetrimonium chloride at concentrations of about 1% have been reported. The substantivity to the human skin of quaternaries has caused concern about plant safety.

The toxic thresholds of preservatives depends not only on the concentrations at which they are used but also on the vehicle. A certain concentration of a particular preservative may be quite harmless in one system while the same level might evoke adverse skin responses in another because of the presence of substances that increase its penetration through the skin. Formaldehyde and formaldehyde-releasing preservatives have been identified as dermatitis-causing ingredients in cosmetics on the basis of patch tests under the aegis of the North American Contact Dermatitis Task Force. In the same publication (*J. Am. Acad. Dermatol.*, 1985, **13**, 1062) propylene glycol was also found to cause dermatitis. These results are significant but do not warrant any conclusions about the safe use of chemical preservatives in finished preparations. Thus the need for safety evaluation of each final formulation is clear.

CURRENT REGULATIONS AND GUIDELINES RELATING TO MICROBIAL QUALITY OF COSMETICS

GOOD MANUFACTURING PRACTICES

The U.S. Food and Drug Administration has published current GMP regulations for drug products and GMP guildelines for cosmetics. The GMP regulations establish general requirements for a functioning quality assurance system for manufacturing drug products. Successful implementation of the GMP regulations requires the establishment of a Quality Control Unit that is responsible for ensuring compliance with GMPs and has the authority to effect changes in procedures, specifications, lab methods, and so forth. Microbiological aspects of GMPs involve working with manufacturing personnel to maintain plant sanitation; providing information for microbiological risk assessment of raw materials; and performing microbiological tests on raw materials, in-process materials, and finished products to ensure that they meet appropriate acceptance criteria. The GMPs provide a set of guidelines to follow to help ensure that products are made with proper controls. The Council of Europe published Guidelines for Good Manufacturing Practice of Cosmetic Products (GMPC). The objective of the GMPCs are to prevent quality defects and to provide a model for member states. Annex VI of the E.U. Cosmetic Directive lists permitted preservatives, their maximum concentrations, and conditions of use.

MICROBIAL LIMITS ON FINISHED PRODUCTS

Finished products are tested to demonstrate that they meet microbial limit guidelines—that they are free from unacceptable levels of contamination. The CTFA microbiological limit guideline for cosmetics recommends the following specific criteria:

Baby products—not more than 500 microorganisms per g or ml
Products about the eye—not more than 500 microorganisms per g or ml
All other products—not more than 1,000 microorganisms per g or ml
No product shall have a microbial content recognized as harmful to the user as recovered by standard plate count procedures

In 1998, the Scientific Committee for Cosmetic Products and Non-Food-Products Intended for Consumers released new microbiology guidelines. Category 1 products are those intended for children under three years, eye area, and mucous membranes; Category 2 products are other cosmetic products. The new guidelines are:

Category 1—total viable count—not more than 100 cfu/g or ml
Category 2—total viable count—not more than 1,000 cfu/g or ml

The new Category 1 guidelines are more rigorous than the CTFA guidelines for baby and eye-area cosmetics. Both CTFA and EC guidelines may be suitable for anhydrous products, in which the unavailability of water prevents microbial growth, provided that these products do not contain [opportunistic] pathogens. Manufacturers should recognize that these are finished product guidelines, and they apply to products after they have been released to the trade. Freshly made and aged aqueous products should meet microbial limits of APC <10/g or ml unless the physicochemical conditions of the product (i.e., including low a_w, low or high pH, high alcohol concentration, etc.) prevent microbial growth.

INTERNATIONAL COUNCIL ON HARMONIZATION

In the past, countries have approached regulation of cosmetics and drugs by themselves. In recent years, European Union (E.U.) countries have been involved with reaching consensus or "harmonization" (i.e., standardization) of test methods used by different E.U. countries so that they do not become an issue for registration and marketing of products throughout Europe and the rest of the world.

There are scientific positions concerning what a particular country wants for its consumer products; however, there are also political considerations ranging from policies and/or guidelines to regulations that either facilitate or restrict trade. Significant progress is being made in Europe, Southeast Asia, Australia, and the United States to implement International Council on Harmonization (ICH) guidelines. The ICH has made significant progress in recent years in getting alignment of countries around the world to agree on guidelines for stability testing. The United States and other countries are in the process of adopting many guidelines set forth by the ICH. However, differences in microbiological test methods and acceptance criteria have not been resolved; therefore, global harmonization still appears to be several years away.

SUMMARY

The goal of product preservation is to prevent microbial growth that could cause product deterioration and make the product injurious to consumers. Preservative efficacy testing is performed to determine the minimum effective concentration of preservative(s) required to ensure that the product is safe and stable. There is a need for standardization of test methods and acceptance criteria, and we are seeing movement in this direction as countries become aligned with ICH guidelines. Compendial and trade association acceptance criteria should be used with caution for formulas that kill Gram-negative bacteria at rates approaching the maximum allowable limits of these methods.

Globalization of products forces manufacturers to modify conventional preservative systems to use allowed chemical preservatives at concentrations regulated by governments. This has created the opportunity for use of self-preserving products, which have advantages of reducing and/or eliminating chemical preservatives that are potential sources of skin irritation and contact sensitization; meeting the demands of consumers who want natural products; encouraging the use of contamination-resistant packaging; and eliminating regulatory issues surrounding the use of chemical preservatives. Not all current formulas may be changed into preservative-free or self-preserving products in their current form, and opportunities exist for innovators to apply the principles of preservation to the development of preservative-free and/or self-preserving products.

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CHAPTER 15
Use of Botanicals in Cosmetics

INTRODUCTION

From the very beginnings of time man has used botanical materials for the beautification and care of the skin. It would be impossible to write about every commercially available botanical extract employed in cosmetics and skin care today. However, it is possible to provide a survey of the types of materials that are available and to help the formulator to explore the potential of nature's bounty.

BOTANICALS AS NATURAL PRODUCTS

We must first define what we mean by "natural," and though this term is not legally defined, an undisputable description would be "any material that is harvested, mined, or collected, and which may have subsequently been washed, decolorized, distilled, fractionated, ground, milled, separated, or concentrated in order to leave a chemical or chemicals that existed in the original source material." As an additional consideration one might include "the modification of natural plant derived substances by the action of microorganisms, enzymes, or yeasts in order to modify or increase the yield of the desired material by this process." A classic example is the production of ethanol by the action of yeast on carbohydrates.

The definition of "naturally derived" would identify the use of a botanical raw material as the starting point in a chemical process to produce a new chemical or chemicals that in themselves may not exist in nature or in the starting material. An example of this would be the sulfation and ethoxylation of a blend of reduced fatty acids obtained from coconut oil to produce sodium laureth sulfate.

The definition of "nature identical" refers to a substance that has been produced synthetically, usually not from a botanical starting material, to produce a substance that is identical to the naturally occurring one. An example of this would be natural α-tocopherol (from wheat) as opposed to that made from petrochemical starting materials. Another example would be the synthesis of α-bisabolol (a component naturally occurring in chamomile). The nature identical materials are considerably cheaper than the natural products; the former often occur as racemic mixtures, whereas the natural form commonly exists in a specific chiral form.

AVAILABLE SOURCES

Terrestrial and marine plants provide many important raw materials for use in food, in construction, and for specialty products used in cosmetic and drugs [1]. It is beyond the scope of this publication to describe all plant-derived cosmetic raw materials. Thus the many lipids, proteins, and carbohydrates that are gathered by diverse methods and have been used for a long time as bulk components in cosmetics will be covered only in passing. Instead this chapter is intended to emphasize the utility of specialty botanical ingredients that have attracted consumer interest and acceptance in recent years.

These components of cosmetics are sometimes introduced into cosmetics almost as they are found in nature, with minimal purification. Typical examples are wood powder, wheat (*Triticum vulgare*) gluten, cucumber (*Cucumis sativus*) juice, or olive (*Olea Europaea*) oil. Some of these bulk ingredients are used in cosmetics without regard to their minor and often unidentified constituents.

The emphasis in this discussion is on plant constituents that are believed to benefit human skin and to contribute to attractiveness. For these purposes an effort is made to isolate (or extract) some selected constituent(s) from the bulk raw material. For example, olive (*Olea Europaea*) oil unsaponifiables is a minor constituent of olive oil with a modest content of plant sterols. Further rectification may yield pure grades of tocopherols.

Consumers recognize the value of purified plant constituents in cosmetics, and their desires are generally met by cosmetic marketers through use of extracts and the like in finished products. Extracts and similar concoctions of plant parts provide the formulator with readily usable ingredients that are free of all types of undesirable impurities normally found in harvested plant materials, for example, leaves, roots, or fruits [2].

EXTRACTS

The methods and the solvents used for the preparation of extracts differ only marginally from pharmacopoeia to pharmacopoeia. Botanical extracts

are concentrated preparations of vegetable matter obtained by removal of the desired constituents of the respective plants with suitable menstrua, by evaporation of all or nearly all of the solvent, and by adjustment of the residual masses or powders to the prescribed standards. In some cases, the matter to be extracted may undergo a preliminary treatment, for example, inactivation of enzymes, grinding, or defatting. Extracts are prepared by maceration, percolation, or other suitable validated methods using ethanol or another suitable solvent. After extraction, unwanted matter is removed, if necessary.

Liquid Extracts

Liquid extracts may be prepared by the methods described earlier using only solvents of suitable concentration, or water, or by dissolving a soft or dry extract in one of these solvents and, if necessary, filtering; whatever their method of preparation, the extracts obtained have comparable compositions. A slight sediment may form on standing, and that is acceptable as long as the composition is not changed significantly. Liquid extracts may contain suitable antimicrobial preservatives.

Soft Extracts

Soft extracts are preparations of an intermediate consistency, between liquid and dry extracts. They are obtained by partial evaporation of the solvent used for preparation. Soft extracts generally have a dry residue of not less than 70% by mass. They may contain suitable antimicrobial preservatives.

Dry Extracts

Dry extracts are solid preparations obtained after removal of the solvent(s) used for their production. Dry extracts generally have a dry residue of not less than 95%. Standardized dry extracts are adjusted to the defined content of constituents, using suitable inert materials or a dry extract of the vegetable matter used for the preparation. Where applicable, the monograph for a dry extract prescribes a limit test for the presence of the solvents used for extraction.

The plant material used for extraction should meet some minimal requirements. Above all, it must conform to reasonable standards of identity. The user of a commercially available extract may demand information on the plant raw materials, as noted below:

- Where it was grown, since the weather can affect the chemical composition of the plant.
- Which part was used in the extraction, that, is the leaf, flower, whole herb, stems, roots, rhizomes, fruits (seeds), the bark, or the sap. The chemical composition varies according to the part of the plant used.
- Whether the fresh or dried plant was used.
- Whether there are any possible adulterants present, either from "weeds" growing alongside the plant or cheaper material that was added to lower costs.

- Whether the species of plant has been validated.
- When it was harvested, for example, that the plant was ripe.
- How it was harvested.
- How it was processed, that is, whether it is the aqueous or oil-soluble fractions that contain the active constituents.
- How much of the plant was used to produce the final product. It is worthless to use an extract of unknown concentration and one should always work in fresh plant equivalents. If the extract was made from dried plant material, then as a rule of thumb, multiply the figure by a factor of eight.
- The age of the plant material and how it was stored.

PLANT-DERIVED RAW MATERIALS USED IN COSMETICS

Some of the most widely used botanical substances are briefly described in this section. As noted before, many of these materials are bulk commodities, while others represent extracts prepared primarily for use by the cosmetic and allied industries.

LIPID PLANT CONSTITUENTS

There is much confusion in the identification of plant lipids as waxes, butters, or oils. Waxes are hard solids at room temperatures, but the differences between butters and oils are fuzzy. The terms are frequently used interchangeably. The identification clearly depends on the solidification point of the plant lipid, which in turn varies as a result of the exact lipid composition. Some of the lipids described in this section may have distinctive (and sometimes desirable) odors.

The oils and butters as a rule are based on blends of triglycerides; they are emollients or occlusive moisturizers that may leave the skin with a greasy finish. Their consistency is temperature-dependent. Natural waxes provide an alternative to synthetic waxes obtained from the petrochemical industry. All plants having the name *cerifera* have been used traditionally as sources of wax and used ethnobotanically as a source of fuel for lighting, that is, as candles or torches.

The following list of botanical lipids is presented in alphabetical order and is not exhaustive. Chapter 16 provides some additional data on the chemistry of some of the most important oils.

Apricot (*Prunus armeniaca*) Kernel Oil performs similar in all respects to sweet almond oil.

Avocado (*Persea gratissima*) Wax is now becoming commercially available. This wax, also known as avocado oil, has been popular for skin care despite its potential to become rancid. It is reportedly skin-substantive and contains high levels of phytosterols.

Bayberry (*Myrica cerifera*) Wax is a wax with a slightly green tinge that can be used as an alternative to ozokerite.

Black Currant (*Ribes nigrum*) Seed Oil is a seed oil with excellent emolliency on the skin and a rich source of γ-linolenic acid.

Borage (*Borago officinalis*) Seed Oil, another rich source of γ-linolenic acid, provides excellent emolliency on the skin.

Brazil Nut (*Bertholettia excelsa*) Oil is reportedly skin-substantive and rich in natural phytosterols. It lost its popularity because of fears of inducing nut allergies.

Camellia Sinesis (*Thea sinensis*) Oil is a light, fast-absorbing, nontacky oil that is ideally suited for emulsions and as a component of massage oils; it has a very low odor and is almost colorless.

Candelilla (*Euphorbia cerifera*) Wax resembles carnauba in all respects but has a lower melting point.

Carnauba (*Copernicia cerifera*) Wax is a high melting point wax most commonly used in lipsticks. It can be emulsified when it is combined with lower melting point waxes or oils as cosolvents.

Castor (*Ricinus communis*) Oil is one of the stalwarts of lipstick formulation since it creates the highest gloss of all natural oils when applied to the skin. It is occlusive, water-repellent, tacky, and very protective to the skin. This oil is a major component of zinc and castor oil cream for the prevention of diaper rash and appears in nearly all pharmacopoeias.

Cocoa (*Theobroma cacao*) Butter is a low-melting lipid used primarily in suppositories.

Coconut (*Cocos nucifera*) Oil is widely available as coconut butter and as the wax for use in skin care products.

Cotton (*Gossypium herbaceum*) Seed Oil, a water-white oil, has a relatively nongreasy application and is rapidly absorbed into the skin.

Dog Rose (*Rosa rubiginosa*) Seed Oil, an exceptional oil, has been extensively examined for its healing and cicatrizing properties.

Evening Primrose (*Oenothera biennis*) Seed Oil is the most popular and most traditional source of γ-linolenic acid. It has been used in a pharmaceutical product for atopic eczema.

Grape (*Vitis vinifera*) Seed Oil is a light, fast-penetrating oil with excellent odor and color.

Jojoba (*Buxus chinensis*) Wax, a liquid wax, is a well-known and popular lubricant.

Illipe (*Bassia latifolia*) Butter; Shea (*Butyrospermum parkii*) Butter; and Mango (*Mangifera indica*) Seed Oil are triglycerides that have found acceptance in various cosmetic products.

Lavender (*Lavandula angustifolia*) Wax, Jasmine (*Jasminium officinale*) Wax, and Orange (*Citrus aurantium*) Wax are available commercially but are relatively expensive. They are produced from the sludge left behind after distillation of the essential oils from the flowers of these plants and will lend a fragrance to the final product.

Palm (*Elaeis guineensis*) Oil is available as the oil and as the related palm (*Elaeis guineensis*) kernel oil.

Peanut (*Arachis hypogaea*) Oil is a highly regarded oil and is frequently used in suntan preparations because of its purported UV absorbance and good adhesion to the skin. It was also used in baby care products and in pharmaceutical preparations because of its substantive protection of the skin. Today it is less popular because of concern of skin allergies.

Rice (*Oryza sativa*) Wax is an attractive white wax with occlusive properties that has become commercially available in recent years.

Sunflower (*Helianthus annuus*) Seed Wax has recently come onto the market and can be used as a substitute for ceresin.

Sweet Almond (*Prunus amygdalus dulcis*) Oil is a long-established and traditional emollient that appears in some of the earliest pharmacopoeias. It exists as an almost odorless, water-white oil that has good skin penetration and is not oily on application.

Wheat (*Triticum vulgare*) Germ Oil is a relatively light, nontacky oil and is one of the best natural sources of tocopherol.

NONLIPID PLANT CONSTITUENTS

This discussion of plant-derived substances includes ingredients that may perform diverse functions on the skin.

Moisturizing Agents

Skin moisturization is particularly critical, and glycerin certainly belongs to the above-defined class of naturally derived substances. In addition, petrochemically produced glycerin belongs to the class of nature identical materials. Sorbitol is reputed to act as a moisturizer for skin. It is a sugar alcohol isomeric with mannitol and galactitol. It is most commonly found in ripe mountain ash or rowan berries (the name sorbitol is derived from its Latin name, *Sorbus aucuparia*), cherries, plums, pears, and apples.

Some formulators might prefer to use ground fruits or juices and add them directly to the products as moisturizers. The plant materials might include:

- cucumber (*Cucumis sativus*)
- banana (*Musa sapientum*)

- oatmeal (*Avena sativa*)
- strawberry (*Fragaria vesca*)

Others might prefer to use the leaf sap of a plant like aloe vera (*Aloe barbadensis*), which will be discussed in this section.

Emulsifiers

The availability of effective plant-derived emulsifiers is limited. The only anionic emulsifiers are soaps obtained by reacting natural fatty acids with various alkalies.

The zwitterionic emulsifier lecithin obtained from soy beans (*Glycine soja*) differs from other phospholipids because of its amphoteric nature (see Chapter 9). It is a widely used emulsifier in viscous food products. Where used for more fluid emulsions, reconstitution by shaking may be required. The zwitterionic betaine (trimethylgycine) is widely distributed in plant species but exhibits no amphiphilic properties.

No nonionic emulsifiers exist in the plant kingdom.

Thickeners

Nature is a prolific provider of thickeners and, though none of them are as versatile as carbomer, one can create viscosity increases ranging from slight thickening to gel formation for a face mask.

One of the most recent to reach the commercial market is a branched polysaccharide (galactoarabinan) that has been extracted from larch (*Larix occidentalis*); the properties are said to be similar to those of guar gum. Most cellulose gums are naturally derived as an unwanted part of the wood pulp process to produce paper.

A much more comprehensive list can be found in the *INCI Dictionary* under Gums, Hydrophilic Colloids and Derivatives, and under Carbohydrates.

These gums are used as viscosity-increasing agents in emulsions, skin care products, and hair holding preparations. As a group they suffer from a tendency to leave a tacky finish, especially at high humidities.

Table 15.1 Partial List of Carbohydrate Gums Used in Cosmetics

Name	Source
Locust bean gum	Ceratonia siliqua
Alginic acid	Phaeophyceae
Guar gum	Cyanopsis tetragonoloba
Karaya gum	Sterculea urens
Tragacanth gum	Astragalus gummifer
Gum arabic	Acacia spp.

Preservatives

The list of plant-derived preservatives is extremely limited. Benzoic acid and benzyl alcohol both occur in plants. They are also on the permitted list of preservatives, and the synthetically prepared copies are "nature identical" preservatives. Similarly, sorbic acid occurs in nature, particularly in mountain ash berries (*Sorbus Aucuparia*). The salts find use in foods and cosmetics.

Naringenin, derived from grapefruit seed and present in all Citrus spp., was used as a preservative, although never identified in the literature.

Hinokitiol, which has recently become available, reportedly exhibits antimicrobial activity. It was originally found in *Chamaecyparis obtuse* extract. Hinikitiol (β-thujaplicin) is widely viewed as an antioxidant and reportedly can prevent apoptosis of keratinocytes after UVB exposure [3].

Finally, 4-hydroxybenzoic acid is commonly found in a variety of plant materials, such as barley, strawberries, black currants, peaches, carrots, and grapes. It is probably one of the most widely distributed aromatic organic acids in the plant kingdom. The esters are also well represented, for example in *Rubus* spp., which reportedly also contain benzoic and sorbic acids.

Antioxidants

Protection of skin health through antioxidant and antiinflammatory activities plays an important role in claims made for cosmetic benefits. Plant derived antioxidants have been used for years to protect foodstuffs, and in most recent years they have assumed a role in skin protection against environmental damage (see Chapter 12). The most important botanical skin protectant antioxidants are tabulated below in Table 15.2. Many of these occur in nature; they have also been modified by various means, and some are available in nature identical synthetic forms. Table 15.2 excludes carotenoids, although some of them, for example, β-carotene, are singlet oxygen scavengers.

Chelating Agents

Phytic acid, found in rice (*Oryza sativa*) bran, is a good natural chelating agent. Other botanically derived sequestrants may include cyclodextrins and

Table 15.2 Botanical Antioxidants Used in Skin Protection*

Arbutin	Gallic acid and derivatives
Ascorbic acid and derivatives	Kojic acid
Caffeic acid and derivatives	Nordihyroguaiaretic acid
Camellia sinsensis oil	Rosmarinic acid
Ferulic acid and derivatives	Tea tree (*Melaleuca Altenifolia*) oil
Flavonoids (diverse)	Tocopherols and derivatives

*The *INCI Dictionary* listing of antioxidants includes additional substances

citric acid, and various carboxylic acids derived from monosaccharides, for example, glucaric acid.

Sunscreens and UV Absorbers

Nature produces an abundance of natural sunscreens, since plants may also need protection against excessive ultraviolet radiation [5]. Legislation specifically identifies those materials that may be used as UV sunscreens; surprisingly, none of the natural plant materials is permitted (in the U.K./EEC).

FRAGRANT PLANT CONSTITUENTS (FLAVORANTS AND ESSENTIAL OILS)

The use of plant-derived essential oils for perfuming cosmetic products is ubiquitous. Literally hundreds of fragrant materials derived from nature exist. Most of them are extremely expensive. On their own they might seem rather coarse to the nose of the consumer, who in the past might have expected a more sophisticated smell in their products. However, the growth of aromatherapy has produced a dramatic swing in fragrance acceptance by users, and there is now a place for pure essential oils.

The *INCI Dictionary* includes more than 100 essential oils. Only a few of them can be discussed here. The following examples will provide an idea of the depth and range available. Essential oils used undiluted can be abortifacient, extremely irritant, and severely erythemogenic. They must always be diluted in a carrier before use. An attempt has been made in this discussion to include the traditional folkloric applications for the included essential oils. As a result, the discussion may include undocumented therapeutic claims. If the essential oil is used in aromatherapy, such usage is noted without identification of claimed benefits.

Basil (*Ocimum basilicum*) Oil has been used for alleviating mental fatigue and as a first aid treatment for wasp stings. It may also help to clear rhinitis.

Bergamot (*Citrus aurantium bergamia*) Oil has been used traditionally for acne, boils, cold sores, eczema, insect bites, insect repellent, oily complexion, psoriasis, scabies, varicose veins, ulcers, wounds, thrush, infectious disease, and depression. It is used in aromatherapy. A psoralen-free source of the oil should be used in cosmetics since this material is phototoxic on the skin.

Black Pepper (*Piper nigrum*) Oil is a powerful rubefacient and is used in cases of muscle aches, arthritis, neuralgia, and other related conditions.

Cedarwood (*Cedrus atlantica*) Oil is used for its purifying properties and has been used for the treatment of dandruff, acne, and psoriasis.

Chamomile (*Anthemis nobilis*) Oil [Roman] has been used for insomnia, muscle tension, cuts, scrapes, and bruises. It exhibits antiinflammatory and skin-soothing properties. It is used in aromatherapy.

Cinnamon (*Cinnamomum cassia*) has been used for its antimicrobial and antiseptic properties. It should be diluted before application to the skin.

Clary Sage (*Salvia sclarea*) Oil is antispasmodic and is used in aromatherapy.

Clove (*Eugenia caryophyllus*) Oil is antibacterial, antifungal, and antiseptic; it has been used for dental infections and for the alleviation of dental pain.

Coriander (*Coriandrum sativum*) Oil has antiinflammatory and sedative properties.

Cypress (*Cupressus sempervirens*) Oil has been used in cases of edema, cellulitis, and varicose veins. It is reported to exhibit antimicrobial properties.

Eucalyptus (*Eucalyptus globulus*) Oil is the natural choice for viruses of the respiratory system and for the treatment of catarrh. It is used in products designed to improve breathing by relieving symptoms of congestion.

Fennel (*Foeniculum vulgare*) Oil is antispasmodic, antiseptic, and stimulating to the cardiovascular and respiratory systems.

Geranium (*Pelargonium graveolens*) Oil has been used for centuries for skin care. It has a soothing and healing effect on the skin and has been used in aromatherapy.

Ginger (*Zingiber officinale*) Oil is used as a rubefacient. It relieves arthritis, rheumatism, sprains, muscular aches, and pains, catarrh, congestion, coughs, sinusitis, sore throats, diarrhea, colic, cramps, indigestion, loss of appetite, motion sickness, fever, influenza, chills, and infectious disease.

Grapefruit (*Citrus grandis*) Oil, a most invigorating fragrance that works exceptionally well in shower gels. May have some antibacterial activity.

Jasmine (*Jasminum officinale*) Oil has been shown to enhance creative thought and has been cited as an aphrodisiac. The Hindu name "Moonlight of the Grove" probably alludes to this function; there is evidence that it reduces stress.

Juniper (*Juniperus communis*) Oil is frequently used as a skin detoxifier and cleanser, reducing dermatitis, eczema, and acne. It should be used with care as it is an abortifacient.

Lavender (*Lavendula angustifolia*) Oil is one of the most useful essential oils. It is beneficial for a great number of skin conditions such as burns, rashes, and psoriasis and prevents scarring. It has also been used extensively in geriatric institutions to help with sleeping disorders. It reportedly possesses antispasmodic, sedative, hypotensive, antiinflammatory, analgesic, antiinfectious, cardiotonic, and anticoagulant effects.

Lemon (*Citrus medica limonum*) Oil has been found useful in cases of cellulitis and for increasing lymphatic function. It is used in products for a revitalizing or freshening claim.

Lemongrass (*Cymbopogon schoenanthus*) Oil works well for purification. It acts as a vasodilator and an antiinflammatory.

Melaleuca or Tea Tree (*Melaleuca alternifolia*) Oil is antiinfective, antiparasitic, antiinflammatory, immune-stimulating, decongestant, and analgesic. It has been used in cases of dandruff, pediculosis, acne, and eczema.

Myrrh (*Commiphora myrrha*) Oil has been used for skin conditions such as athlete's foot, chapped and cracked skin, eczema, wounds, and wrinkles.

Olibanum (*Boswellia carterii*) Resin is considered the holy oil in the Middle East and was used religiously for thousands of years. It is well known for its healing powers and repair of damaged skin. It reportedly prevents scarring and tumor formation and stimulates the immune system.

Patchouli (*Pogostemon cablin*) Oil is very beneficial for the skin and may help prevent wrinkles or chapped skin. Reportedly, it is a general tonic and stimulant and helps the digestive system.

Peppermint (*Mentha piperita*) Oil is used for its cooling and refreshing properties.

Rose (*Rosa damascena*) Oil [Turkish] The aroma of this oil is intoxicating and harmonizing. It is stimulating and elevating to the mind, creating a sense of well-being.

Rosemary (*Rosmarinus officinalis*) Oil can benefit problem skin conditions and is especially useful for the treatment of dandruff. It exhibits antibacterial properties and may even help to fight *Candida* infections. It is anticatarrhal, antiinfectious, and antispasmodic, and helps to overcome mental fatigue.

Rosewood (*Aniba rosaeodora*) Oil is less costly than other rose oils (which are expensive). It has a soothing, calming effect to both mind and body. It is a strong antimicrobial agent.

Sage (*Salvia officinalis*) Oil has been used in Europe for skin conditions such as eczema, acne, dandruff, and hair loss. It is used by aromatherapists.

Sandalwood (*Santalum album*) Oil is similar to olibanum. Traditionally, it is used for skin regeneration and to relieve the symptoms of sciatica and lumbago.

Thyme (*Thymus vulgaris*) Oil is used for overcoming fatigue and physical weakness after illness. It is antimicrobial, antifungal, and antiviral.

So-Called Natural Water-Soluble Fragrances

Essential oils can be obtained, for example, by expression or solvent extraction. In an alternate process, odoriferous plant parts are steam distilled. The oil may then be collected by separation from the condensed distillate. The leftover water distillate contains plant components and some volatile oils. This material is normally marketed as a water. Typical flower representatives are cabbage rose (*Rosa centifolia*) flower water, matricaria (*Chamomilla recutita*) water, and peppermint (*Mentha Piperita*) leaf water. A similar distillate is obtained from *Hamamelis virginiana* but is marketed primarily as a hydroalcoholic solution.

NATURAL COLORS

An infinite number of colors is produced by nature; who could not wonder at the bright vibrancy of spring as the dazzling daffodils show their trumpets to herald the coming of summer. Some plants have such spectacular color that their beauty is legendary: the voluminous surge of color from the bougainvillea, the velvet-colored softness of roses, the cool hue of a woodland carpet of bluebells, or the majesty of a cactus in flower over the arid desert.

Despite this potential storehouse of fabulous natural colors, the law is quite specific in identifying those that may be used. However, sometimes a plant containing natural color is used for different beneficial properties, and this can carry the penalty of tinting the product in which it is used illegally.

The list of plants providing color is long, and only a few are discussed below. Leaves, roots, flowers, barks, fruits, and stems can be used, and surprisingly, it is not always the flowers that deliver the strongest colors. A list of a few typical chemical entities and sources is given in Table 15.3. Despite some exceptions, plants produce natural color to attract insects for the purpose of pollination. Once the act of fertilization has been completed, the need for attraction disappears, and the flower dies. The requirement for colors are therefore only transient, and the chemicals responsible for them are generally unstable. Readers are cautioned about the use of plant-derived pigments. Some of them, including compounds safe for food use, are not permitted in cosmetics.

Table 15.3 Selected Pigments from Botanical Sources

Pigment name	Pigment source
Annatto (Bixin)	Annatto (*Bixa orellana*)
Anthocyanin	Grape (*Vitis vinifera*) *[Black]*
	Elder (*Sambucus nigra*)
	Hibiscus (*Hibiscus sabdariffa*)
Beta-carotene	Carrot (*Daucus carotta sativa*)
	Algae (*Algae spp.*)
Betanin (?)	Beet (*Beta vulgaris*)
Capsanthin/capsorubin	Paprika (*Capsicum annuum*)
Chlorophyll	Grass (*Graminae Spp.*)
	Spinach (*Spinacio oleracia*)
	Alfalfa (*Medicago sativa*)
Crocetin	Gardenia (*Gardenia jasminoides*) *[Fruit]*
	Crocus (*Crocus sativus*)
Curcumin	Turmeric (*Curcuma longa*)
Luteolin	Marigold (*Tagetes erecta*)
	Alfalfa (*Medicago sativa*)

The terms *bioflavonoids* and *flavonoids* describe a large series of plant-derived phenolics, most of which have antioxidant potential. Some of these compounds are deeply colored and may be used for their tinctorial attributes. Some members of this group impart color and exhibit other desirable effects; their use for one purpose or the other may require regulatory clearance.

Alizarin (Pigment Red 83, CI 58000) and *Purpurin* (CI 58205 or 754410) are two red chemicals found in the roots and tubers of *Rubia tinctorum*

Amaranth is found in the leaves of *Amaranthus caudatus* extract and in other plants and *A. tricolor* (leaves), *Celosia cristata* (Amaranthaceae) flowers, in leaves of *Atriplex hortense* and *Chenopodium amaranticolor* (Chenopodiaceae) leaves. This substance should not be confused with synthetic amaranth, CI 16185 (Acid Red 27).

Annatto or norbixin (CI 75120) is extracted from the *Bixa orellana* tree seeds; it gives a yellow to deep orange color. Bixin, another chemical found in the plant, is responsible for some of the color.

Anthocyanidins, present in *Hibiscus sabdariffa*, delphinidin or cyanidin, the glucoside hibiscin, and the *Anthocyanins*, especially cyanidine chloride, are bioflavonoids. These colorants are found in cherry, plum, blackberry, black carrot, blueberry, cranberry, grape, elderberry, mulberry, purple corn, rosehips, red cabbage, and red currant.

Apigenin occurs widely in plants and yields a dull, golden yellow. This flavonoid is usually found in Matricaria (*Camomilla recutita*) extract.

Azulene is probably the most famous of all the blue dyes that comes from German chamomile (*Matricaria recutita*), Roman chamomile (*Anthemis nobilis*), yarrow (*Achillea millefolium*), or wormwood (*Artemisia absinthium*). This oil is responsible for the brilliant dark blue color of the essential oils distilled from the fresh flowers. The azulenes are generally recognized as exhibiting antiinflammatory and healing actions.

Betalaines and Betanines are found in beet (*Beta vulgaris*) extract [red]. This extract is known are Beetroot Red. A similar color also occurs with isobetanidin in the flowers of *Mesembryanthemum edule* (Aizoaceae) and *Portulaca grandiflora* (Portulacaceae). A related compound is phytolaccanin, which occurs in the fruits of *Phytolacca americana* (Phytolaccaceae) and in *Portulaca grandiflora* (Portulacaceae). It is a purple pigment. Similar pigments can be isolated from *Carpobrotus acinaciformis, Drosanthemum floribundum, Mesembryanthemum* spp., and *Opuntia bergeriana* and other *Opuntia* spp., (Cactaceae). These natural colorants should not be confused with Pigment Red 53 (CI .115585), sometimes named betanine.

(Blue) Gardenia is obtained from the fruit extract of *Gardenia* spp., modified by reacting with an amino acid. It provides a dull navy blue to a rich azure blue color.

Caramel is produced by heating food grade carbohydrates in the presence of selected accelerators.

Carotenes is the name given to a group of yellow or orange unsaturated colors extracted from such diverse sources as algae, carrots, and palm oil. Related carotenes include *Lycopene*, found in tomatoes, and *Canthaxathin*, found in some edible mushrooms.

Capsanthin/Capsorubin, isolated from paprika oleoresin, and *Xanthophyll*, are present in Marigold (*Tagetes erecta*).

Carthamin is found in the flowers of *Carthamus tinctorius* or safflor (Bastard saffron), yielding the yellow-orange pigment carthamin (CI 75140).

Chlorophyll, extracted from grass and alfalfa, is present in all green plants and has always been a part of the human's diet. It gives a moss green color. It is naturally oil-soluble, and it is also found in green vegetables such as spinach (*Spinacia oleracea)* and the common stinging nettle (*Urtica dioica*). *Chlorophyllin copper* complex is derived from chlorophyll but gives a brighter more intense green color due to the replacement of the naturally occurring magnesium in the chlorophyll by copper. A further modification provides the water-soluble Natural Green 3, CI 75810.

Crocin and Crocetin provide a bright yellow color that has been in use for over 1,000 years. Crocin is extracted from the fruit of *Gardenia jasminoides*. Another color found in the plant is crocetin, commonly found in *Crocus sativus* (styles), better known as saffron. In other *Crocus* spp. the color is often found in the petals. This material has been used for over 2,000 years as a food color; it is identified as Natural Yellow 6, CI 7510.

Curcumin is the pigment of the spice turmeric and will give a range of colors from yellow to deep orange. This has been in use as a food ingredient for over 2,000 years. It also contains a closely related chemical called desmethoxycurcumin, in which one of the methoxy groups is replaced with a hydrogen atom. Curcumin is Natural Yellow 3 (CI 75300).

Indigo is extracted from the fermented leaves of the plant *Indigofera tinctoria*. This produces a blue to mauve indigoid structure, CI 7300. A rich blue color obtained from the fermented leaves of the plant *Isatis* spp. has been used for many years for dyeing fabrics. It has the identical structure as the indigotin found in indigo.

Juglone, obtained from Black Walnut (*Juglans nigra*) shell extract contains a naphthoquinone that stains skin and hair dark brown. This substance is chemically related to lawsone, *q.v.*, and shikonin, *q.v.*

Lawsone, a red to orange color used frequently in hair care, is derived from henna (*Lawsonia alba*) leaves. This color has been used for nearly 5,000 years and was used by the ancient Egyptians for dyeing their hair and nails.

Luteolin is a flavonoid found in *Reseda luteola*, which is common in many parts of central Europe. An infusion of the plant has been used for treating wounds and for chronic skin disorders. It has antiinflammatory and antibacterial properties. This dye is also present in *Genista tinctoria* The glycosides of this flavonoid occur in shepherd's purse (*Capsella bursa-pastoris*) extract.

Phycocyanobilin is an extract from a blue algae, often from *Spirulina* spp. The color is similar to that of blue gardenia. Several phycocyanobilins are the chemical species accounting for this color.

Pratol is another yellow-colored flavonoid found in clover (*Trifolium pratense*) extract.

Santalin, the red dye obtained from red sandalwood (*Pterocarpus santalinum*), is a complex molecule. The extract includes a number of forms of this colorant, all of which give rise to quite intense red colors.

Shikonin and related compounds are found in *Lithospermum erythrorhizone*. Shikonin and alkannin are naphthaquinone dyes, with an intense red color. The water-soluble extract can be used as a natural color and also exhibits an antiinflammatory and calming effect Depending on pH value and solvent system, extracts of *Lithospermum* occur in various colors: below a value of pH 7 the extract is intense red, in the neutral range it is purple; in weakly alkaline medium it is bluish-purple; and at pH 5 approaching 10 it is deep blue.

PLANT ADDITIVES THAT ARE REPUTED TO BENEFIT SKIN

Topically applied plant materials can provide a plethora of useful attributes to a product. The belief that plant materials can alleviate skin conditions and can contribute to skin beauty originated in folkloric medicine. Today phytotherapy is supported by Western dermatology and Chinese medical practice.

The recent discussion by Brown and Dattner demonstrates that various plants may alleviate the symptoms of acne, diaper rash dermatitis, irritant dermatitis, inflammation, atopic dermatitis, psoriasis, herpes simplex, poison ivy, and pruritus [6]. For the more cosmetically oriented investigator, plant extracts provide soothing, toning, and skin-whitening effects.

It has already been mentioned that it is important to add a sufficient amount of plant material to be of benefit. This should be qualified by adding the requirement that one must know what active plant phytochemical is responsible for the desired effect and to ensure that it is present in the purchased plant extract at a standardized level. The plant material of choice is usually added to the cosmetic preparation in the form of an extract.The use of powdered plant

parts is much less common. A few of these plant extracts warrant specific mention:

Clover (*Eugenia caryyophyllus*) has been traditionally used for eczematous skin conditions, especially where the skin is pruritic. It is also useful for boils and pimples.

Comfrey (*Symphytum officinale*) contains allantoin, and the level of this wound-healing substance should be controlled.

Plantain (*Plantago lanceolata*) and other *Plantago* spp. are a source of aucubin, which is soothing, anti-inflammatory and antierythematous. Aucubin is found in the leaves, seeds, roots, and stems of many other plant species.

Sage (*Salvia officinalis*) has been discussed previously under the heading of essential oils. Its skin-firming effects and toning and astringency depend on its tannin content.

German chamomile (*Camomilla recutita*) activity depends on whether an aqueous extract or the essential oil is used. The activity of the aqueous extract resides in the flavonoid level of apigenin and apigenin-7-glucoside. In the case of the oil the α-bisabolol content and the chamazulene content contribute to the soothing, healing, and antiinflammatory beneficial effects.

Aloe vera (*Aloe barbadensis* Miller) activity could be attributed to the trace amount of the cathartic barbaloin and the levels of mannose and mannose-6-phosphate. There is growing evidence, however, that the major material responsible for the beneficial effects of aloe vera is an acetylated polysaccharide, mannan. The benefits attributed to aloe vera gel are soothing of the skin and reduction of erythema. Studies have shown that aloe vera is a remedy for radiation (solar and radiotherapy) burns [7]. It may even be used as a prophylactic against radiation-induced erythema. Topical treatment stimulates fibroblast activity and improves the rate of wound healing.

Witch hazel (*Hamamelis virginiana*) is a source of antiinflammatory healing and antipruritic skin benefits. The extract is commonly fortified with ethanol to enhance the solubility of various constitutents, including hamamelitannin and gallic acid.

CONCLUSIONS

This brief overview of botanical additives demonstrates the potentials for compounding cosmetics with plant-derived materials. The ever-increasing public acceptance of beneficial effects from skin inunction with botanicals creates a market not only for products that may be exclusively plant-derived but also for products relying for claims and benefits on inclusion of botanical constituents.

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CHAPTER 16
Specialty Lipids

INTRODUCTION

Lipids as a group are used in the compounding of cosmetics to serve diverse functions, which may include viscosity control, solvent action, and gloss production. The major thrust of this chapter is limited to the use of lipids as skin treatment agents or protectants. The lipids employed for this last purpose may be hydrocarbons, silicones, synthetics, or a variety of nonvolatile (fixed) oils found in animal or plant tissue.

The use of plant (seed)-derived oils dates back to antiquity. Compounders have used these substances successfully for skin and hair care without detailed knowledge about their composition. Those who were intent on coating the skin for diverse treatment purposes pursued the use of animal- and plant-derived lipids for skin protection and the treatment of chapped, irritated, or scaling skin disorders. Until about 1950 oils and fats were believed to soften skin and make it more pliable. This belief was supported by the sensorial observation of *emolliency*, a term that has never been explained in the scientific literature. An emollient in a skin care product is expected to soften the skin without tackiness and to leave the skin smooth to the touch. This is a purely operational definition of emolliency but in light of current knowledge points to the importance of water in emolliency.

In the years following World War II, Irving Blank and his associates established that soft and pliable stratum corneum requires plasticization with water and that the lipids commonly used did not materially change the rheological behavior of stratum corneum. A few years later investigators established that films of many hydrophobic lipids on the skin could reduce the loss of water from the skin and that they acted as moisturizers by helping to retain water in the skin, water that was normally lost by evaporation. The nature of this process was discussed in some detail in Chapter 13.

For practical cosmetic applications, coating the skin with any one of a number of lipids has become a means for adding water to the stratum corneum without the need for any type of water-soluble moisturizer. Thus "occlusive"

lipids assumed an important role in cosmetic formulations designed to alleviate the dry skin syndrome.

The exact role played by "natural" lipids in skin structure and membranes has been of concern to biologists for many years. The natural lipids on the stratum corneum surface include sebaceous lipids as well as corneal lipids, presumably in a mixture that coats the skin. It cannot surprise anyone that cosmetic formulators and clinicians have attempted to benefit skin conditions and appearance by increasing or decreasing the levels of this surface film. Sebum actually was called an excretory and useless substance some 35 years ago. The more recent data on the composition of sebum suggest that sebum may include indigestible lipids from animal or plant sources. It is also likely that the hydrocarbon fraction of sebum represents compounds not synthesized in the body but absorbed from petroleum sources in the environment.

The recognition that skin surface lipids can arise from two entirely different sources (sebum or intracorneal lipids) forced a complete rethinking about these lipids. The functions of sebum, if any, are limited to lubrication of the emerging hair, although some investigators have vigorously advanced the concept that the free acids in sebum help to create an acidic environment on the skin surface that discourages microbial growth. Actually, the presence of fatty acids on the skin surface is puzzling: fatty acids are widely viewed as potentailly irritating to skin; they may form an antimicrobial acid mantle on the skin, which has just been described briefly; finally, the sebaceous secretion is also the growth medium for malassezia organisms, which form fatty acids from glycerides.

By contrast, the epidermal lipids evolving from the Odland bodies of granular keratinocytes have been endowed with a most critical role in skin health and skin therapy. About 20 years ago, Peter Elias began his work demonstrating an important role for epidermal lipids derived from the lamellar granules (Chapter 1). The major components of these lipids include about 40% sphingolipids, about 75% neutral lipids (mostly sterols, triglycerides, and free fatty acids), and small amounts (about 10%) of some polar lipids (cholesteryl sulfate, phospholipids, and glycerides). The figures do not add up to 100% but are reported here as they appear in the literature. This blend of lipids forms a structured bilayer between the evolving corneal cells, as postulated by Elias and his coworkers [1].

The current consensus of the importance of corneal lipids in skin health and drug permeation is based on the concept that the corneal lipids form a barrier to the ingress of topically applied materials and conversely to the egress of substances out of the skin. Thus deliberate or accidental damage to this barrier may be required to deliver most drugs from topical drug forms. The level of barrier damage needed for drug administration is commonly assessed via transepidermal water loss (TEWL), which is widely viewed as a measure

of barrier intactness. It is commonly agreed that an intact barrier, as assessed by TEWL, also ensures an intact barrier to substances entering or passing through the skin. The absence of any controversy concerning this issue is surprising. TEWL obviously measures the outward passage of water vapor. The inward passage of a nonvolatile drug or cosmetic component requires that the entering molecule must find its way, that is, diffuse, through preexisting lipid or aqueous channels within the stratum corneum. Externally applied substances, including surfactants and some polar lipids, impact the quality of the barrier. It is safe to assert that any cosmetic ingredient applied to skin can modify the quality of the barrier and thus is likely to have some adverse or beneficial effect on the performance of the skin. These findings and observations have encouraged the drug and cosmetic industries to modify the barrier to enhance drug (or active) permeation and to reduce the egress of just one substance, water, which exerts critical effect on skin elasticity. It is not uncommon to read that corneal lipids alone control water passage (in or out) through the stratum corneum. In recent years it has, however, been reported that the degree of cross-linking and hardening of keratinocyte envelopes, especially of involucrin, may play an additional role in TEWL and barrier integrity.

The assessment of the impact of any externally applied substance is difficult, especially if it is a mixture of applied materials. If the mixture is properly formulated, with cosmetic elegance in mind, it should be expected to modify the barrier because the desired nonoily skin finish requires penetration. Hundreds of topically safe lipids and emulsifiers are available to the formulator. These can be combined ad lib by the compounder, but comprehensive evaluations are rarely made available. A few examples are cited later in this chapter to show the need for critical assessment. Investigators sometimes examine the complex interactions that control the events on the skin surface; but as a rule, the fate of a drug or other active is of primary concern.

USE OF LIPIDS ON SKIN

The use of petroleum-derived, animal, or plant lipids on human skin cannot be equated with the structure forming bilayers of epidermal lipids. Externally applied neutral lipids are likely to form an unstructured film on the skin surface. The epidermal lipids, by contrast, surround each keratinocyte or corneal cell and may even be bonded covalently to the cell membrane. This type of palisade-like structure [1] is not duplicated by the (random) inunction of skin with lipids of diverse sources. As a matter of fact, one may need to consider the impact of the applied "foreign" lipids on epidermal lipids if the former are intended to penetrate into the epidermis. Pharmaceutical scientists

carefully select drug molecules that can permeate into and through the skin for topical or systemic therapy. Penetration enhancement for systemic efficacy is achieved by addition to the drug of molecules that facilitate the drug's passage through the skin. As noted earlier, enhanced permeation is a sign of barrier damage. Human skin is designed to keep foreign substances out of the body. Manipulation of the skin to permit entry of a foreign substance into normal skin probably involves deliberate barrier damage. Such damage should be expected to be minimal if the amount of the foreign substance required for activity is small.

PETROLATUM

The pharmaceutical literature includes much information on facilitating drug penetration of skin with the aid of this unctuous nonpenetrating hydrocarbon. Petrolatum on the skin is widely reported to reduce TEWL and to enhance drug permeation. The unpleasant sensation from residual petrolatum on the skin can be reduced by admixture with glycerides (mono-, di-, and tri-) and with a variety of (mostly nonionic) surfactants. These blends may or may not exhibit the desired occlusivity of pure petrolatum. It is also rarely noted that the components of these lipid blends do not permeate epidermis at identical rates. The more rapidly penetrating components, for example, surfactants, may in practice reduce the corneal barrier. If a low molecular weight humectant is included, it cannot be expected to remain uniformly suspended in petrolatum and will in all likelihood reduce petrolatum's occlusivity.

The above is a simplistic analysis of petrolatum's action on the skin. As the number of ingredients increases, one should expect additional complications. For example, the epidermal permeation of any cosmetic active component is controlled by the distribution coefficient between the product and the epidermis.

The reduction in TEWL by a petrolatum layer on the skin [2] is between 40 and 50%, while in vitro the reduction may exceed 90%. The reasons for these differences are not clear, and additional data are reviewed in Reference 3. Lodén's work indicates that petrolatum reduces TEWL instantaneously by about 50%. Removal (with diethylether) after five minutes restores TEWL to base levels (about 5.5 $g/m^2/hr$). If the petrolatum is allowed to remain on the skin for 40 minutes before removal, the TEWL climbs to between 11 and 12 $g/m^2/hr$ within one minute but then continues to decline to base levels during the next 20 minutes. The observed hyperhydration—as evidenced by the high TEWL—is an indication that petrolatum has indeed raised epidermal water levels. Regression studies suggest that prolonged and repeated exposure to petrolatum can benefit dry or scaly epidermis. Petrolatum is not likely to exhibit pharmacological activity, and observed benefits should be attributed to

the sequelae of hyperhydration, which has been shown to accelerate wound healing. No data have been provided to show that cosmetic emulsions of petrolatum provide comparable effects.

Lodén [2] also studied the effects of a high lipid (66% lipid) and of a normal lipid level (27% lipid) emulsion. Within one minute of application, the lipid-rich cream effected an eightfold to ninefold increase (over base level) of TEWL, while the ordinary cream effected a 12-fold increase. These differences are attributable to evaporation of water from the two products. After five minutes exposure and product removal, TEWL on the cream treated sites remained elevated, about 20 $g/m^2/hr$ for the ordinary cream and 12 $g/m^2/hr$ for the high lipid product. These levels of TEWL declined rapidly toward pretreatment levels. Lodén makes the interesting comment that the water in lipid emulsion seems to enter the epidermal tissues.

CERAMIDES

Shortly after the identification of deglycosylated ceramides in human and animal skin [4,5], cosmetic technologists began to examine synthetic alternatives [6]. The ceramides, derived from *erythro*-sphingosine, have been held responsible for the water-holding properties of stratum corneum. Workers throughout the world studied animal-derived ceramides and ceramides synthesized by biotechnologically modified microorganisms, as well as by classic organic synthetic methods. Imokawa's studies showed that optimal activity required the presence of two long alkyl groups bonded to each other through an amide linkage [6,7]. Thus in this type of pseudoceramide the presence of hydroxyl groups in the compounds tested appears to be of secondary importance. Other approaches to create synthetic ceramides are based on the amidation of an amino glyceryl ether with various hydroxy acids. The efficacy of a long-chain alkoxylated alkyl succinic acid, esterified with a long-chain fatty alcohol, without any nitrogen has also been publicized.

The common feature in these and most other attempts to create skin conditioning agents resembling natural ceramides are two long (C_{12} to C_{22}) alkyl chains bound to each other via a relatively short hydrophilic bridge. The two hydrophobic chains are likely to interact hydrophobically with adjacent similar molecules. It is also noteworthy that the (sometimes) hydroxylated alkyl chains in natural ceramides appear to be covalently bonded to the proteins of the corneal cells.

Evidently Imokawa and coworkers are the only investigators who attempted to relate the function of intercellular lipids in stratum corneum to water retention in this tissue [7]. Despite these efforts, questions remain about the utility of ceramides (and pseudoceramides) in skin care. For example, Imokawa notes

that α-methylheptadecyl glyceryl ether (GE) is required for demonstrating the potential of ceramides. He fractionated epidermal lipid chromatographically and then treated human forearm skin with one of these fractions via the following protocol: dry skin was created by extraction with acetone and ether. The site was then treated with one of the epidermal lipid fractions for three days. The (parametric) measurement was based on skin conductance (μmho), as shown below in Table 16.1. In examining these data it should be noted that the same solvent base (with 1% GE) was used in all treatment.

It is significant that the ceramide fraction and the glycolipid fraction increased skin conductance. These data clearly suggest that some skin lipids can modify the capacity of stratum corneum to retain moisture. The striking and unexpected observation that some lipids can play a role in the skin's water ecology still requires confirmation on normal human skin that has not been severely damaged by solvent extraction. It also seems necessary to explain the need for GE in demonstrating efficacy. Despite these unanswered issues, there is evidence that the skin of the elderly may be deficient in ceramides or that the ratio of the ceramides in the aged is modified [8].

Research in this field is ongoing. It was recently reported that in porcine skin 40% ω-OH ceramides are bound via OH to the corneocyte envelope while 60% are bound via the 1-OH group in sphingosine (Abstract 313 May 1999, meeting, Soc. Invest. Dermatol.). Such studies may finally bring to fruition the promise of skin care with ceramides. Some very recent studies of ceramides throw additional light on their contribution to the epidermal barrier. It was reported that vesicles formed from ceramide 3 (≈30 to 50%), cholesterol (≈25%), palmitic acid (≈25%), and cholesteryl sulfate (≈10%) became more resistant to disintegration by a blend of dodecyl betaine and sodium dodecylsulfate when the ceramide 3 level in the vesicle was increased. This is an important in vitro confirmation of the biological activity of ceramides [9].

A more spectacular finding was reported by D. Marzio and her coworkers; the application in vivo of sonicated *Streptococcus thermophilus*—presumably

Table 16.1 Skin Conductance After Extraction and Subsequent Treatment with Epidermal Lipid Fraction

Treatment	Skin conductance (μmho)
None	11.0
Ceramide Fraction	17.1
Cholesterol Fraction	14.0
Free Fatty Acid Fraction	12.2
Glycolipid Fraction	16.9
Solvent Base (Squalane, 99%, plus 1% GE)	11.5

high in sphinogmyelinase—to humans effected an increase in skin ceramide levels after 7 days [10]. Confirmation of this study by other investigators is likely to have a major impact on the cosmetic use of ceramides beyond their previously reported upregulation of the skin water content.

NATURAL GLYCERIDES

The use of triglycerides on human skin for diverse purposes was briefly mentioned at the beginning of this chapter. Today "natural" lipids are much sought after because the public is aware of the presumed safety of edible glycerides containing monounsaturated fatty acids. Cosmetic chemists eagerly examine lipids from a multiplicity of cultivars for their utility in skin care. Oils and fats of high oleic acid content are available and continue to gain acceptance. Some of the plant-derived oils containing 50% of oleic acid are apricot kernel oil, avocado oil, canola oil, hazelnut oil, mango kernel oil, and sweet almond oil.

A much more comprehensive listing of these lipids has appeared in volume 5 of *Bailey's Industrial Oil and Fat Products* [11].

The importance of polyunsaturated fatty acids in skin health has been known for years in connection with the essential fatty acid deficiency syndrome. Formulators are not comfortable with use of unsaturated triglycerides since they readily undergo peroxidation. Nevertheless, black currant seed oil, borage seed oil, evening primrose oil, and kukuinut oil are used for specialty products. Linoleic acid plays a role in the formation of ceramide 1, in which it is esterified to an ω-OH fatty acid. These polyunsaturated fatty acids are competitive inhibitors of the oxidation of arachidonic acid to prostaglandins and can modify inflammatory events in the epidermis [12].

Plant-derived triglycerides are important constituents of all types of cosmetic products. Particularly popular are modifications of these triglycerides by glycerolysis leading to mono- and diglycerides. In addition, di- and triglycerides have been found to react with ethylene oxide, leading to complex substances that are useful emulsifiers and skin conditioning agents. Although the exact composition of, for example, PEG-20 almond glycerides, a polyethylene glycol derivative of the mono- and diglycerides of almond oil, with 20 mols of ethylene oxide is not fully clarified, this and many similar substances are widely used as emollients or emulsifying agents.

Modern consumers and marketing and development personnel view the use of plant natural lipids favorably and as benign. By contrast, the natural lipids derived from animal sources have limited appeal. Thus the distinction between animal and plant lipids assumes an additional dimension based on consumers' dislike of animal tissue. As a result, lard and tallow fatty acids and their

precursor triglycerides are steadily being replaced by lipid fractions exclusively derived from vegetable sources. It is interesting that "natural" plant lipids often must be hydrogenated before they become cosmetically useful ingredients. For example, the stearic acid of commerce is actually a fraction of hydrogenated soy fatty acid.

Triglycerides from natural sources generally include all the extraneous and poorly identified components found in lipids. In modern practice, these lipids may be hydrogenated to preclude oxidative damage. Sometimes these lipids are sophisticated with various antioxidants for the same purpose. Large amounts of these lipids are saponified to yield water-soluble glycerin and soaps. In addition, a complex set of water- and alkali-insoluble natural unsaponifiables is isolated. Only about 15 of these are used as cosmetic ingredients. The unsaponifiables may include a variety of hydrocarbon-like sterol precursors, sterols, and complex alcohols. This portion of most vegetable triglycerides has assumed an important role as cosmetic ingredients. It consists predominantly of mixed phytosterols, especially β-sitosterol. When used on human skin, the unsaponifiables have been claimed to enhance collagen synthesis. When properly formulated into cosmetics, these sterols are also reported to increase the skin's water content. One may safely assume that plant sterols can provide an occlusive coating on the skin.

Under normal conditions, plant oil unsaponifiables should include all lipid-soluble vitamins. Thus the unsaponifiables are good sources of tocopherol and retinol. In addition, they are likely to contain tocotrienol, an important antioxidant. Clearly, unsaponifiables may contain biologically active constituents.

The hydrolysis of triglycerides yields blends of different fatty acids that are useful as soaps and as raw materials for all types of cosmetic ingredients. As mentioned already, an entirely different class of ingredients results from partial glycerolysis of lipids, that is, mono- and diglycerides. Some of these are primary emulsifiers or skin conditioning agents and can react with ethylene oxide to create lubricating skin care agents and emulsifiers.

ANIMAL LIPIDS

The rationale for the use of animal-derived lipids in cosmetics is illustrated by the fate of lanolin and lanolin-derived raw materials. About 30 to 40 years ago, lanolin played a significant role in all types of cosmetics for skin and hair care. The lanolin mix obtained by wool scrubbing was hailed as a water-in-oil emulsifier, as a skin-healing agent, and as a wetting agent for pigments. Occasional reports of sensitization reactions were disputed as statistically insignificant. There was a period not so long ago when a lanolin-free cosmetic product could not be sold. Nevertheless, lanolin's penetration into cosmetic formulation lost some of its popular appeal and suffered a further steep decline

when the presence of pesticides in lanolin became a matter of concern. The study of allergies to lanolin—due evidently to the presence of so-called wool wax alcohols—seems to have ended abruptly because lanolin's use declined materially. Wakelin et al. conducted a recent retrospective (15 years) review of lanolin allergy comprising almost 25,000 patients patch tested with wool wax alcohol. The incidence of hypersensitivity (1.7%) among dermatologic patients was quite low and did not vary during the period studied. It is, nevertheless, remarkable how a skin lubricant used for centuries should become a critical component of cosmetics and then suddenly lose its place in the sun due to public whim.

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CHAPTER 17
Aerosol Technology

INTRODUCTION

This chapter is intended to outline the status of aerosol technology in cosmetic preparations, at the time of this writing, with no attempt to provide details of product formulation. Instead, formulation details are described in various chapters of this book. A listing of cosmetic aerosol products follows; it excludes aerosols intended to deliver over-the-counter (OTC) drugs and other drug products.

The aerosol industry has adopted some terminology from industries unrelated to cosmetics; an effort will be made to acquaint the reader with these concepts.

HISTORY

Aerosols for delivery of personal products had their beginning early in the twentieth century but achieved popular acceptance only about 40 years later. At that time, bug sprays based on refrigerant gases were adapted to cosmetic applications. Starting about 1950, aerosols for cosmetic use experienced

Table 17.1 Cosmetic Aerosol Products

Space sprays (small particles)
Powders
Fragrances
Surface coating (coarse, wet)
Antiperspirants
Hair sprays
Colorants
Foams
Shaving
Mousses
Shampoos

significant growth until in 1978 the use of chlorofluorohydrocarbons for nondrug applications was essentially banned, at the least in the United States. The subsequent introduction of propellants with reduced ozone depletion potential gave some impetus to the marketing of cosmetic aerosols. In recent years, concerns about the introduction of volatile organic compounds (VOC) into the atmosphere have created additional restrictions on the aerosol industry.

DEFINITION

The word *aerosol* is a generic term in colloid chemistry for finely subdivided liquid or solid particles dispersed in and surrounded by a gas. The particles' size should be smaller than about 50 μ and usually is less than 10 μ. The Chemical Specialities Manufacturers Association broadly defines an aerosol product as a self-contained sprayable product in which the propellant force is supplied by a liquefied gas. Scientifically, "aerosol" refers to a suspension of liquid or solid particles in a gas, that is, the result of dispensing a product from a container under pressure. Nevertheless, the commonly used terminology defines aerosols as the delivery system for foams, pastes, powders, and the like from a pressurized container.

PRINCIPLE OF AEROSOL TECHNOLOGY

The concept of dispensing a product from a container under pressure is illustrated in Figure 17.1. Depression of the actuator opens a valve that otherwise seals the contents of the container from the ambient external pressure. The propellant (gas or liquid) expands and forces the product up into the dip tube for dispensing into the surroundings [1].

COMPONENTS OF AN AEROSOL

A finished aerosol product includes the product, the propellant, the container, the valve with attached dip tube, and the actuator. In common practice, the arrangement of these components is that as shown in Figure 17.1.

CONTAINER

Aerosol containers must be designed to contain the product and the propellant, that is, to maintain their shape despite the pressure differential between the inside and the outside. The container must resist deformation even after prolonged contact with the propellant and the product. The materials of choice are tin-plated steel, aluminum, glass, and—in some countries—polyethylene terephthalate.

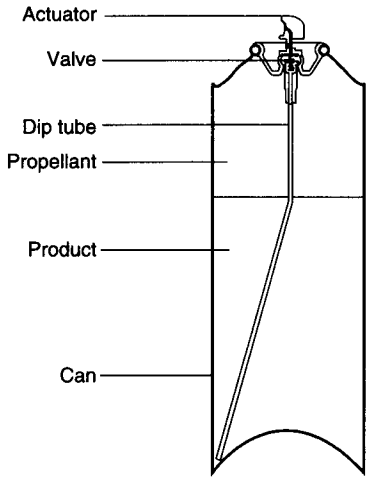

Figure 17.1. Components of an aerosol dispensing system; the propellant in this case is lighter than the product and is not miscible with it. Headspace is not specifically shown.

Three-Piece Tin Plate Steel

For the manufacture of this type of container, steel plate of the desired thickness is coated with tin and then "reflowed" to produce a shiny nonporous coating. Three-piece steel containers are decorated and coated flat before assembly. A variety of organic coatings may be applied to enhance the stability of the metal against corrosion. Such cans are available in different sizes and in varying levels of tin coating.

In the United States steel can dimensions are measured in inches and $\frac{1}{16}$ inches. A can designation of 202 × 509 identifies a can diameter of 2 and $\frac{2}{16}$ inches, and a can height of 5 and $\frac{9}{16}$ inches.

Two-Piece Tin Plate Steel

These cans are manufactured by impact extrusion and wall ironing. As a rule, protection by the tin plating is less reliable than that obtained in three-piece cans.

The choice between the two types of steel can depends largely on the vacuum required for crimping on the valve. The three-piece can has a higher capacity to resist collapse.

Aluminum

Most aluminum cans are produced from 99.5% pure aluminum by impact extrusion. Aluminum cans have aesthetic appeal but have higher costs than tin plate cans. They are frequently subject to corrosion, and there is a lack of effective corrosion inhibitors.

Most experts agree that aluminum cans are better suited for water-based products, for example, shaving foams and mousses, than tin-plated steel cans. Aluminum cans, like tin-plated steel cans, are shatterproof and can withstand a wide range of pressures. Aluminum cans can be provided with outside or inside curls and various shoulders to accommodate a variety of over-caps or spray-through domes. They require corrosion-resistant internal coatings such as organosols (for water-based products), epoxy phenolics, or polyamide imide (for water-alcohol and dimethyl ether–containing formulae).

Regardless of the can type, all metal cans shipped in the United States must conform to regulations concerning buckle pressure and burst pressure. In the United States these regulations are formalized by the Department of Transportation.

The corrosion rate of aluminum cans is dependent on the purity of the metal used in manufacture. For example, the rate of corrosion of a can made from 99.998% pure aluminum is aboaut 1/5000th that of 99.7% pure aluminum.

Glass

Both plastic-coated and uncoated glass are available. Uncoated glass containers must withstand pressures up to 15 to 20 psig at 21 °C. They are useful for fragrances in hydroalcoholic media and employ *n*-butane as propellant. If they are formed from clear glass, they are not useful for products sensitive to ultraviolet light.

Coated glass containers provide ultraviolet light protection and—when fractured—retain glass fragments in the plastic coating. Though safer at higher pressures, the end product pressure should not exceed 40 psig at 38 °C. The thickness of the plasticized or polyvinyl chloride coating is about 0.035″ to 0.055″.

Regardless of coating, glass containers have aesthetic appeal and are rarely plagued by corrosion problems. They are available only with 20 mm openings, which restrict the valve mounting cup to 20 mm, in contrast to the one-inch openings on metal cans.

Polyethylene Terephthalate

In the United States, the use of polyethylene terephthalate (PET) for aerosol constainers is not permitted because the plastic is distorted during the mandatory hot water bath testing. The use of PET bottles is allowed in some other jurisdictions.

VALVE

Without a fully functional valve, a marketable aerosol cannot be prepared. As a result, many types of valves are available for controlling the flow of

product from the filled container. Aerosol valves may be vertical-acting or toggle-acting; they may be metering; and they may deliver liquid foam like a shaving cream or dry antiperspirant spray.

In modern usage, the term *valve* includes the stem, stem gasket, spring, body or housing, dip tube, and the mounting cup (Fig. 17.2). The valve must not only seal the product from contamination from the environment but also preclude loss of the propellant. The stem is commonly made of a rigid plastic (nylon, acetal, or polyester); it is slotted or barbed to hold the actuator. The stem gasket is made of a flexible polymer, such as buna, neoprene, or butyl rubber. The shape of the stem can be varied to allow rapid filling of propellant "through the stem." The spring is 302 or 304 stainless steel, with five to seven spirals. The housing may be provided with a vapor tap that allows dispensing in a position in which the dip tube does not contact the product. The dip tube is commonly prepared from polyethylene or polypropylene and is firmly attached to the housing. Finally, the mounting cup, which is crimped to the aerosol container curl, is made of the same metal as the container. The mounting cup may include a cut gasket or other sealing mechanism to ensure a hermetic seal when the valve is crimped to the container. If the product is dispensed only when the container is inverted, a dip tube may not be required, as, for example,

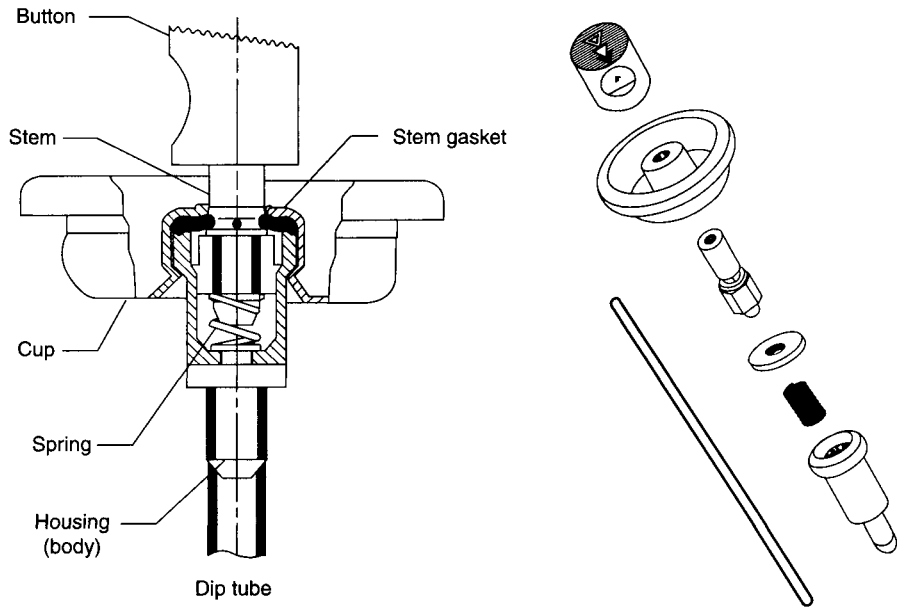

Figure 17.2. Diagrammatic view of a typical aerosol valve, showing the key components (Courtesy of Precision Valve Co., Yonkers, N.Y.)

in some shaving foams. The selection of the stem gasket is critical for proper operation of the aerosol unit. For the sake of compatibility and functionality, the formulator has to make a selection from nitrile, neoprene, buna, butyl, or viton rubber. This choice is as important as the selection of propellants or of product constituents and may require extensive stability testing.

Standard valves are designed to deliver the product at a rate acceptable to the consumer and appropriate to the product. The criterion is the spray (or delivery) rate, which must remain inviolate throughout the life of the product.

Foam valves provide unobstructed product passage through the body and stem orifice.

Powder valves allow smooth passage with no hold-up of solids to interfere with valve operation.

Spray valves for water-based products may require two entrances to the chamber in the valve housing; one of these taps the vapor phase, which admits only propellant vapor, and the other provides access via the dip tube. This type of valve, known as a vapor tap valve, helps to break up particles when the product is actuated. Such valves are sometimes provided with a so-called Aquasol piece, in the valve body; the exiting propellant/product mixture spins the piece, which helps break-up of larger particles.

Vapor tap valves are required for spraying in the upright and inverted positions. Vapor tap valves reduce the product discharge rate and deliver a drier product. Formulators should recognize that such valves increase the discharge of propellant and may modify the spray pattern. It is essential to make certain that there is sufficient propellant in the unit to ensure uninterrupted discharge until empty.

Metering valves include a holding chamber in the valve body for delivery of a predetermined quantity of the product. They are employed primarily for costly perfumes and therapeutic inhalers.

Crimping

Tight attachment of the valve to the container is essential if leakage is to be avoided. Latent leakers are those cans that pass the water bath test but may begin to leak after storage. Successful crimping requires adherence to tight dimensional specifications for different valve cups attached to different cans. The crimp diameter and the crimp height are critical dimensions. A workable set is shown in Table 17.2.

ACTUATOR

The actuator is the final mechanical device required for a functioning aerosol product. As shown in Figure 17.2, the actuator or button fits on the valve stem and is available in a variety of sizes and shapes. It determines whether

Table 17.2 Crimping Dimensions in mm; Allowable Variations Are ±0.13 mm

	3-Piece tin plate can		Aluminum can outside curl		Aluminum can inside curl	
Cup Style	Crimp Diameter	Crimp Height	Crimp Diameter	Crimp Height	Crimp Diameter	Crimp Height
Taperseal tin plate	27.18	4.70	27.30	4.70	27.30	4.70
Tin plate with cut gasket	27.18	4.83	27.18	4.83	27.18	4.83
Tin plate laminate with cut gasket	27.18	5.08	27.18	5.08	27.18	5.08
Aluminum with cut gasket	26.92	4.95	26.92	4.95	26.92	4.95

the product is dispensed as a foam, spray, or steady stream. The terminal (0.025–0.3 mm) orifice in the actuator may range from 0.01 to 0.06 inches. The activator may include an insert that determines the nature and the spreading of the escaping product.

PROPELLANTS

The aerosol propellant provides the energy for driving the product out of the container and through the valve. The propellant may be a liquefied gas, which vaporizes at atmospheric pressures and ambient temperature, or a compressed gas. The propellant level in most aerosols is high, and the propellant may act as a diluent or solvent for components of the formulation. The key requirement for a propellant is the ability to deliver a product at an acceptable rate throughout the life of the product [2]. Pressure loss in the case of compressed gases is not uncommon, and the liquefied gases are more likely to provide reliable product delivery. Table 17.3 lists the propellants currently used in aerosol technology.

HYDROCARBON PROPELLANTS

The once popular chlorofluorocarbon (liquefied gas) propellants were identified a few years ago as ozone-depleting chemicals. They have been banned in the United States since 1978 and are rarely used in other countries.

The liquefied propellants shown in Table 17.3 are odorless and have low levels of toxicity on inhalation. They produce the same constant pressure at any time as long as propellant remains in the container. Hydrocarbons such as propane, *i*-butane, and *n*-butane are FDA-approved food additives.

Table 17.3 Aerosol Propellants

Liquefied Gas Propellants
Hydrocarbons
Propane
i-Butane
n-Butane
i-Pentane
n-Pentane
Ethers
Dimethylether
Hydrofluorocarbons
Difluoroethane
Tetrafluoroethane
Hexafluoroethane
Compressed and Soluble Gas Propellants
Carbon dioxide
Nitrous oxide
Nitrogen
Air

After the ban of chlorofluorocarbons in 1978, hydrocarbons found in crude oil and natural gas fields became the dominant aerosol propellants. They are marketed at levels exceeding 95% after purification by fractional distillation. Major impurities include hexanes, unsaturated hydrocarbons, and some sulfur-containing compounds. Hydrocarbons belong to the group of volatile organic compounds, the VOCs. The vapor pressures of the principal liquefied hydrocarbons at 70 °F (21 °C) are as follows: propane—108 psig (7.6 bars), *i*-butane—31 psig (2.2 bars), *n*-butane—17 psig (1.2 bars). Hydrocarbon propellants have low specific gravities, and the liquids generally float on the product unless they are miscible. They are soluble in many organic solvents and are entirely noncorrosive to contacting metal surfaces. Their flashpoints and explosion limits are low, and they can be blended to achieve various desirable pressures. Hydrocarbon blends exhibiting 46 psig pressure at 70 °F (3.17 bars at 21 °C) are particularly useful and may be prepared by weight as follows:

A. Propane (A 108) 15.1% and *i*-butane (A 31) 84.9%
B. Propane (A 108) 26.0% and *n*-butane (A 17) 74.0%
C. Propane (A 108) 27.3% and *i*-butane (A 31) 28.9% and *n*-butane (A 17) 43.8%

Despite their identical vapor pressures, blend A produces a drier foam shaving cream than blend B; blend C yields intermediate results.

Work with hydrocarbon propellants must be conducted with care, taking into account the following:

The propellants are heavier than air.
Explosion-proof exhaust hoods are required.
Static electricity must be avoided.
Confined areas should be examined for hydrocarbon residues with infrared detectors.

DIMETHYL ETHER

Dimethyl ether (DME) exhibits a vapor pressure of 63 psig (4.34 bar) at 70 °F (21 °C) and is quite soluble in water (35%). DME is flammable and has global warming potential but no ozone depletion potential. Its water solubility makes it particularly attractive for use in high-water systems. It develops a high pressure but is much less flammable than hydrocarbons; nevertheless, the precautions described for handling hydrocarbons should be followed. DME forms azeotropic mixtures with hydrofluorocarbons; such blends are briefly discussed later in this chapter. DME is a solvent for many of the gasket rubbers used in aerosols. Butyl and Viton gaskets are likely to perform well, but swelling tests with specific formulations are required.

DME is not corrosive, but in blends with aqueous systems, attack on metal surfaces exposed to liquid or gas phases is possible. Thus the need for using corrosion inhibitors exists. This is particularly important if a solvent such as ethanol is present. As noted earlier, DME is a VOC as defined by the California Air Resources Board (CARB) and the Environmental Protection Agency (EPA).

HYDROFLUOROCARBONS

Table 17.3 identifies three hydrofluorocarbons (HFC) that are important propellants for the aerosol industry. One of the mysteries surrounding these materials is their numerical nomenclature, which follows some unusual rules. The HFCs are identified by three numbers: the first identifies the number of C-atoms by C-1; the second identifies the number of H-atoms by H+1; the third identifies the number of F-atoms in the compound as F. Thus propellant 227 is derived from propane (2-1 C-atoms), contains one hydrogen atom (1+1H), and seven fluoride atoms. Any letter following these three digits refers to the structure of the molecule.

HFC 152a has no ozone depletion potential and is exempted by the CARB and the EPA from VOC regulations. Structurally it is CH_3CHF_2 with a vapor pressure of 63 psig (4.34 bar) at 70 °F (21 °C). It has a high vapor pressure and

only slight solubility in water. Its use requires containers that can withstand high pressures.

HFC 152a can be blended with DME or the commonly used hydrocarbons to provide a variety of pressures. The pressures developed vary and are best obtained from propellant suppliers. In practice, the blends of pure propellants may form azeotropes, but the pressures developed in diverse products containing surfactants, solvents, and water should be determined experimentally.

HFC 152a is not subject to hydrolysis; can corrosion tests and inhibitors are, nevertheless, required to prevent attack on steel or aluminum containers in the presence of products. HFC 152a is a good propellant for emulsified products and for foams such as hair mousses, lotions, and creams. It yields creamy and firm foams, which are preferred over the foams produced by hydrocarbon propellants. Some supplier-recommended combinations follow:

	Hair Mousse	
Concentrate	92%	92.5%
n-butane	4%	—
HFC 152a	4%	7.5%
Vapor pressure (21 °C)	60 psig (4.1 bar)	72 psig (5.0 bar)
	Shaving Cream	
Concentrate	94%	94%
n-butane	3.6%	—
HFC 152a	2.4%	6%
Vapor pressure (21 °C)	50 psig (3.4 bar)	69 psig (4.8 bar)

Even nonflammable blends may fractionate and should be handled as flammable components. HFC 152a is not an aggressive solvent and is compatible with most valve gaskets; butyl rubber is preferred over buna N or neoprene. HFC 152a exhibits a low order of toxicity.

HFC 134a is a nonflammable propellant exhibiting a pressure of 70 psig or 4.8 bar at 21 °C; its specific gravity is 1.22. Because of its relatively high global warming potential, regulatory agencies discourage its use in personal care aerosol packages. It forms azeotropes with DME and hydrocarbon propellants. Its solubility in water is low. It is currently used as a replacement for chlorofluorocarbon propellants in metered-dose drug inhalants because of its low ozone depletion potential.

HFC 227a has a low ozone depletion potential and a low global warming potential. Its vapor pressure is only 40 psig (2.76 bar) at 21 °C. It too is used in inhalation drug products.

COMPRESSED GASES

The most commonly used gases, CO_2, N_2O, and N_2, are injected as gases into the aerosol product and produce pressures as high as 140 psig at ambient temperatures. The most serious problem with their use is loss during repeated actuations. Liquefied gases produce pressures near 45 to 50 psig and maintain this pressure during discharge up to 100%. In contrast, compressed gases may start at pressures near 100 psig but create a pressure of only 30 to 25 psig after 50% of the product is discharged. They are low-cost, nontoxic, nonflammable propellants with no adverse effects on ozone levels. They cannot be used with vapor tap valves, and CO_2 may have an effect on corrosion. During use the spray rate should be expected to drop.

FILLING

Only three commercial procedures for filling aerosols are practiced: cold filling, under-the-cup filling, and pressure filling. Of these, cold filling is rare as of the time of this writing and will be described only in passing.

COLD FILLING

In this process, the propellant is chilled and can be handled as a liquid. The product (concentrate) is also chilled and metered into the container. Next, the cold propellant is added. Finally, the assembled valve is then crimped on the container. In this filling sequence, the evaporation of some of the propellant before sealing expels most of the air from the open container. Today, EPA/VOC regulations have critically reduced this type of filling. In addition, the costly steps of chilling and transferring cold product and propellant have been replaced by alternative filling procedures.

UNDER-THE-CUP FILLING

In this procedure, the concentrate is filled into the open container at room temperature. Next, the assembled valve is placed loosely on the aperture of the container, and the filling head is lowered to seal around the container. After slightly lifting the valve assembly, a vacuum is drawn on the container head space, and the propellant is injected between the container and the valve unit. Finally, the valve is crimped to the aperture while the filling head recedes. This filling method is practiced primarily in the United States; it is fast, but some loss of propellant is unavoidable.

PRESSURE FILLING

This is the most widely used method of filling aerosol, even though under-the-cup filling remains popular in the United States. The propellant losses are much lower than in under-the-cup filling. The concentrate is added to the container, followed by removal of air from the head space. After crimping of the valve to the container, the propellant is pressure filled through the valve. Variations are sometimes necessary to bypass the button or to attach the button to the filled container.

HOT WATER BATH TESTING

Before or after the filled unit is examined by check weighing, it is passed through a hot water bath (50–55 °C). This exposure is intended to identify and allow removal of leakers by observation of bubbles escaping from the filled unit.

HEAD SPACE

The need for adequate head space in a filled aerosol container arises from the fact that upon warming, the contents of the package must be allowed to expand. If gas is present, this expansion can proceed without creating excessively high pressures. If no gas is present, the expansion of the liquid in a can raises the internal pressure precipitously, resulting in bursting of the package. A sensible head space is about 80% of the container overflow capacity. The computation requires data on the specific gravity of contents (propellant plus concentrate). The volume of the fill is then easily computed. Some minor correction is made for the space occupied by the valve. A level of about 20% of the overflow capacity not occupied by product and propellant is sufficient to allow for expansion during normally expected temperature exposure.

OPERATION

The operation of a typical aerosol product is pictured in Figure 17.3.

ALTERNATE SYSTEMS

Over the years systems have been developed that use principles of pressure dispensing that differ from conventional aerosol technology. The most important of these are attempts to reduce or eliminate the dispensing of propellants into the atmosphere with every actuation. Some of these devices are designed to replace the propellant with a compressed gas. In a second type the use of a

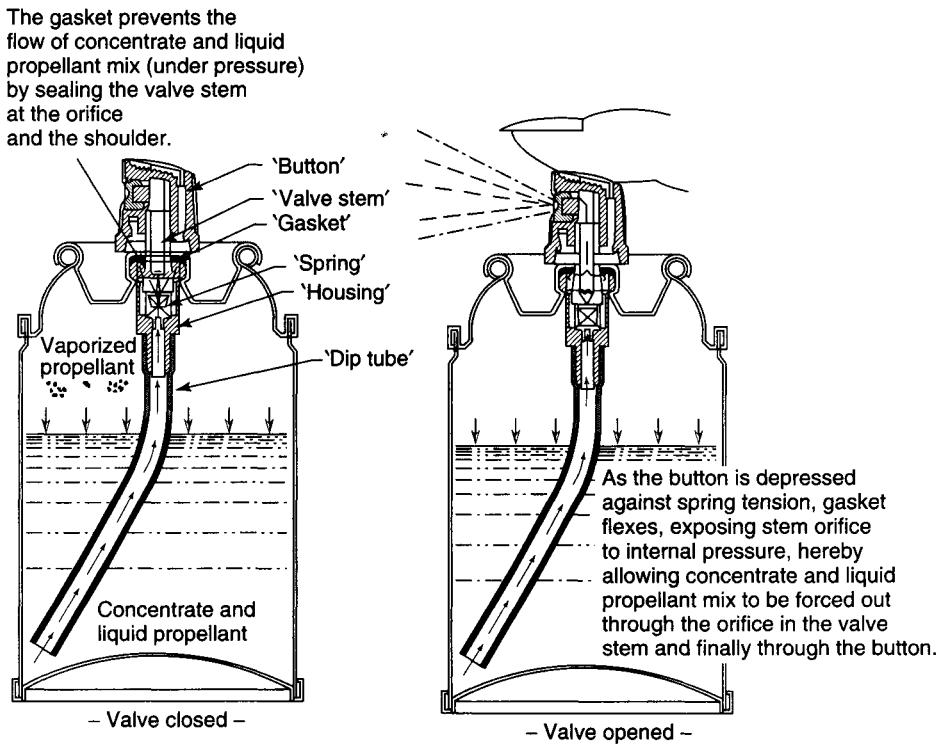

Figure 17.3. Diagram showing the operation of a conventional aerosol product (Courtesy of Precision Valve Co., Yonkers, N.Y.)

propellant is replaced with a pressure-generating device (pump) activated by the consumer.

BAG IN A CAN SYSTEM

This trademarked Advanced Barrier System provides a pouch for the formulation that is completely separated from the propellant system in the unit. The pouch is a laminate of polypropylene (which is in contact with the product), with a central aluminum foil and an outer layer of nylon, and is compatible with aqueous and solvent-based formulations. The propellant, either compressed air or nitrogen, surrounds the bag. When activated, the gas exerts pressure on the pouch for discharge. No propellant gas is released into the atmosphere.

SEPRO CAN SYSTEM

In this system the product is contained in a polyethylene bag that is separated from the propellant system. The driving propellant, which may be a

hydrocarbon liquid, is injected through a plugged hole in the bottom of the can. The propellant is retained in the container after use.

LECHNER SYSTEM

This system relies on a thin flexible aluminium bag that is fitted into an aluminium can. This approach has been employed for hair coloring products and drugs; the aluminium bag prevents permeation. The driving propellant is usually a liquefied hydrocarbon and is injected into a plug on the bottom of the unit. In this case, too, the driving propellant remains in the can.

EP SPRAY SYSTEM

This approach also utilizes a multilayered pouch for the product. The nitrogen or compressed air propellant creates a swirl in the valve, creating unique spray patterns.

PISTON SYSTEM

In this approach a plastic cup-shaped piston forms a barrier that fits inside an aluminum or three-piece steel can. The piston separates a thick viscous product from a hydrocarbon liquid gas that is inserted through a hole in the base of the container. When the actuator is depressed, the propellant raises the piston to effect product discharge. The product has to be viscous enough to prevent seepage between the can well and the piston.

Several systems have been designed to avoid the use of any propellant. Some typical propellant-free dispensing systems are described briefly below.

Atmos Dispensing System. This system consists of a package within a package—a thin-walled durable PET bottle surrounded by a rubber sleeve. As the inner bottle is filled, the rubber sleeve expands to provide a self-pressurized driving force that expels the product when the valve actuator is opened. The viscosity of deliverable products includes liquids, gels, creams, and the like.

PUMP ACTIVATED SYSTEMS

Some dispensing devices combine a pump activator with a container for the product and a valve unit. Devices for dispensing products in droplet form by mechanical agitation are well known. Some more sophisticated approaches are briefly noted here:

Dry Spray Dispenser. The ambient air pumped through the valve into the package provides internal pressure. The dry spray valve includes a vapor tap,

which when actuated helps to atomize more viscous fluids. The components are refillable.

F-Z Finger Pump Foamer. This device pumps a combination of air and liquid through two fine-meshed screens located in the actuator to create a dense foam. The foaming liquids should have low viscosity and may include hair fixatives, facial cleansers, body emollients, tanning products, and shaving creams.

Co-dispensing Systems. A co-dispensing pump assembly separates two components up to the point of discharge. It is constructed to dispense two products at a 10:1 ratio by using a larger outer pump and a smaller inner pump. The containers are fed by two dip tubes. The design is such that the filled assembled package resembles a single-dose dispenser.

STABILITY TESTING

The stability testing of filled aerosols differs from that of other products because corrosion and mechanical failure are responsible for product instabilities. Formulators must make sure that the product is stable and unaffected by storage in the container in the presence of the propellant. In addition, corrosion of the container and swelling of valve components require monitoring. For practical purposes, tests are best conducted on filled units at various conditions. Devices exist that accelerate corrosion by electrical means, but the repeated actuation of filled container reveals all types of defects to the examiner, including product changes. Can corrosion and gasket deterioration may require destruction of stored samples at scheduled intervals. Marketing of newly formulated aerosol products should be delayed until all test requirements have been completed satisfactorily (Chapter 37).

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PART FOUR

Formulation and Performance

Part Four of this edition includes descriptions and compositions of a wide range of cosmetic (and OTC) products together with safety and performance testings.

CHAPTER 18
Skin Care Products

INTRODUCTION

The following introductory comments are intended to describe the basic requirements which govern cosmetic skin care development.

Cosmetics are used daily by healthy people for long periods of time. They must meet certain fundamental conditions, but above all they must be safe during use; it is not acceptable for them to produce side effects. This requirement differentiates critically between cosmetics and pharmaceuticals for external use; only the latter have treatment as their purpose. Efficacy and safety should always be balanced in the development of cosmetics. It is a prerequisite of cosmetics that their activity should be confined to the skin as much as possible. Transport of active ingredients into the circulation has to be restricted to avoid systemic responses. The percutaneous absorption routes by which active ingredients may penetrate the skin must be considered along with their behavior in the skin and the effect of lipid removal.

Structurally, the skin is divided into the epidermis, dermis, and subcutaneous tissue (Chapter 1). The outermost layer of the epidermis, the stratum corneum, has a low moisture content of 10–25%. It acts as a barrier that controls the entry and exit of chemical substances, including pharmaceutical agents, and the evaporation of moisture [1]. The amount of intercellular space in the horny layer is 10–30%, which is much higher than that of ordinary tissue (0.5–1.5%). This intercellular space is filled with an amorphous substance formed from lipids, which play a very important role in the horny layer's barrier function [2,3]. It is generally accepted that there is a direct relationship between the amount of lipid removal and the extent of disruption of the barrier function [4]. Moreover, it has been shown that this intercellular space contributes to the topical absorption of drugs.

Both water-soluble and lipid-soluble substances pass through a poorly understood cell transport system. The two major penetration routes for lipid-soluble substances include one that passes through the intercellular spaces and another that transports them through the corneal cells. It is difficult to distinguish

precisely between the contributions of these two routes, but it is known from horny layer experiments in humans that substances with an octanol/water distribution coefficient of up to 1,000 pass into the cytoplasm and those with a coefficient of over 1,000 enter into the lipids in the intercellular spaces [5].

The skin includes appendages such as sweat glands, sebaceous glands, and hair follicles. The surface area occupied by these appendages is extremely small, but they play an important role in the initial stages of skin penetration. This appendageal route is said to be a major penetration route for ionized and water-soluble substances (including peptides). Illel et al. [6] observed during penetration experiments using hydrocortisone, niflumic acid, and *p*-aminobenzoic acid that the drug flux and water diffusion through hairless skin were two to four times lower than those for normal hirsute skin. Penetration by this appendageal route plays a very important part in the initial absorption of substances, but—with the passage of time—penetration through the horny layer (transepidermal route) increases greatly.

Below the stratum corneum lies the viable epidermis with a large moisture content. Substances pass through this part of the skin by diffusion due to the concentration gradient. Beneath the epidermis is the dermis, which is traversed by capillary vessels and lymphatic ducts. It is here that the active ingredients that have penetrated the skin are transferred to the general body circulation.

The major factors that influence skin absorption are described below. In the following discussion the terms *drug, active*, and *pharmaceutical agent* are used interchangeably.

HYDRATION

Hydration is the condition in which the water content of the skin is above normal. Hydration of the horny layer promotes the penetration of the skin by many substances. The moisture content of the horny layer may be increased to 50–75% by hydration, while the normal amount is only 10–25%. Further, it is reported that the horny layer swells to a thickness more than twice its normal level of 40 μ. Thus the amount of free moisture in the horny layer's intercellular spaces increases, expanding the route for the diffusion of water molecules [7]. As the intercellular spaces become larger, the amount of a substance penetrating the skin increases. The mechanism by which hydration increases skin penetration is not well understood.

TEMPERATURE

It has been reported that a 10 °C rise in temperature increases skin penetration 1.4- to 3-fold. The major reasons for this are a lowering (20–30%) of the activity coefficient of pharmaceutical substances in the skin and an

increase in drug solubility. An increase in diffusion rate and blood flow due to the temperature increase may also play a part. The phase transition from gel to liquid crystal of horny layer lipid hydrocarbon chains following an increase in temperature reduces viscosity and results in an increase in the diffusion rate of substances. Differential scanning calorimetry (DSC) shows that phase transitions of the horny layer take place over a wide temperature range, from 42–70 °C. Within the temperature range of 25–45 °C, increases in the freedom of speed and movement of hydrocarbon chains is observed, and there is a general loosening of the lipid matrix as the temperature increases. The change in the alkyl chains from gel to liquid crystal increases the fluidity of the lipoidal pathway, increasing the permeability coefficient of lipid-soluble substances manifold.

DELIPIDIZATION

The granular layer of the epidermis secretes glycolipids, sterols, and other substances into the intercellular spaces. Subsequent hydrolysis and esterification at this site form sphingolipids, fatty acids, cholesterol, and their esters. These substances loosely fill the intercellular spaces. Though the lipid content of the horny layer is only about 10%, its lipids constitute a major barrier and a pathway to the penetration of lipid-soluble substances. The removal of lipids by means of organic solvents (e.g., acetone, chloroform-methanol, hexane plus methanol) increases the penetration of the skin by substances. Grubauer et al. [4] noted a direct relationship between the disruption of the barrier and the amount of lipid removal.

The foregoing discussion of the biological and physical functions of the skin and skin penetration shows the need for making fine adjustments to cosmetic preparations. The important fundamental requirements for the selection of cosmetic bases include

Chemical stability
Good affinity with the skin
High safety with no skin irritation
Good emolliency and spreading
Drug efficacy unaffected
Ready drug release from the base into the skin

The above are the minimum requirements for cosmetic products. However, if percutaneous absorption is desired in cosmetics, skin penetration by active substances controls the choice of excipients. The formulation of the desired product can then proceed on the basis of the pharmaceutical efficacy with emphasis on the targeted part of skin (horny layer, epidermis, dermis, etc.). For instance, when the pharmaceutical agent is to act only on the skin surface

without absorption, petrolatum and water-soluble substances are the most useful bases. On the other hand, if the agent is to have a certain degree of skin penetration and act on the lower part of the epidermis, lipid-soluble substances, such as plant oils and lanolin or substances exhibiting emulsifying functions, are more effective bases to use. It is extremely difficult to select bases that satisfy all the conditions. For the development of drug-containing cosmetic preparations, studies are required to select a base that satisfies most of the mandatory requirements.

The most important criterion is solubility. The solubility of the active drug in different bases has to be known, and the base must be selected to prevent deterioration in the properties of the cosmetic. Generally, the pharmaceutical agent will have higher activity, and its distribution and absorption in the skin will be better the closer its concentration in the product is to the saturation solubility. It is also important to take into account the rate of evaporation of the base when the cosmetic is on the skin. Evaporation may become a problem in the case of sparingly soluble drugs; in such cases it may be necessary to employ chemical modification (derivatives) to reduce loss in efficacy.

The incorporation of pharmaceutical agents into cosmetics requires sophisticated technology because the properties of the agent should remain unaltered by complex base formulations to protect efficacy and skin absorption [8]. Product forms may be selected on the basis of the solubility of the pharmaceutical agent in question. However, a selection process based on the other physicochemical factors mentioned above is still lacking and will become an important research problem in the future. Novel product forms hold promise; liposomes and other nano-sized microemulsions are now in the process of being developed. Research will be needed to see whether they will provide good product forms for percutaneous absorption.

SKIN CARE AND THE BARRIER FUNCTION

Research on the mechanism of the horny layer's barrier function has been conducted since the mid-1980s employing electron microscopy and molecular biology techniques. Recent reports have suggested that skin care bases may have a beneficial effect on metabolism and homeostasis of epidermis. Investigators have relied on hairless mouse and human skin in this research. The focus has been on the skin's barrier function and the mechanism by which it is maintained, including pathological features of biochemistry and molecular biology. Moreover, the physiological effects of skin care product bases on the skin were demonstrated through use of cell cultures, something that would not have been possible using conventional techniques.

Recently reported barrier function–related research with impact on future development of skin care products will be discussed in the next sections.

EFFECT OF EXTERNALLY APPLIED LIPIDS

The intercellular lipids of the horny layer consist mainly of cholesterol free fatty acids and ceramides. When such lipids are applied to the skin surface, the lipid molecules are thought to penetrate into the horny layer and to be taken up by the epidermal cells; they are then used in the formation of the intercellular lipid structure as cornification proceeds [9]. The stratum corneum's barrier function is disrupted by tape stripping and treatment with acetone or certain surfactants. Its recovery process is influenced differently, depending on the type of lipid or lipids applied to the skin surface.

The results of such experiments have been very interesting. If the lipids are applied singly or two at a time, recovery of the barrier function is delayed [10]. However, recovery of the barrier is promoted by use of a mixture of three types of lipids—especially when the molar ratios are equal—or by mixtures in which linolenic and palmitic acids are present at mole ratios three times those of other constituents [11]. But when the barrier function is disrupted by surfactant, this effect is not consistently observed [12]. For example, when the barrier function is disrupted by N-lauroyl sarcosine (free acid), enhanced recovery is observed, but not if disruption is the result of sodium dodecyl sulfate exposure (Fig. 18.1). In addition, recovery may vary with the age of the animals [13].

It appears that the external application of lipids has varying effects on epidermal functions, depending on the composition of the lipid preparation, the age of the subjects, and the type of damage-causing treatment. It would seem desirable to design the reparative lipid base on the basis of the age of the users, the cosmetic used, and the type of barrier-damaging agent. The pathological changes that occur with changes in barrier function are discussed under Effect of Occlusion.

EFFECT OF IONS AND PH

Cosmetic bases contain large amounts of chemical salts, and in some cases their ions may affect epidermal functions. If the barrier function is disrupted by treatment with acetone, application of calcium and potassium ions inhibits its recovery. Sodium and chloride ions have no effect. The blocking of calmodulin antagonists and calcium and potassium channels has the effect of preventing the inhibition of recovery by calcium and potassium ions [14]. If calcium ions are forced into the epidermis by sonophoresis to increase the calcium ion concentration in the upper epidermis, the extracellular secretion of lamellar granules is suppressed. On the other hand, when a calcium-free solution is

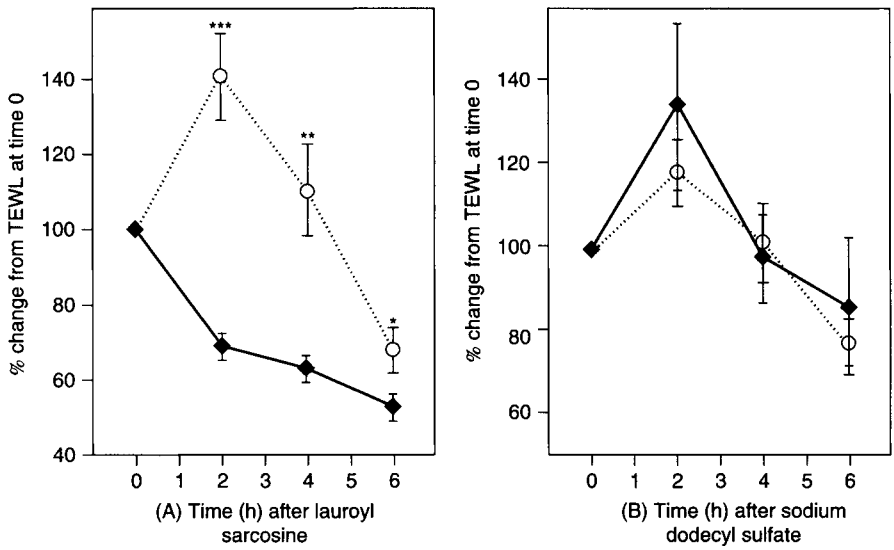

Figure 18.1. Recovery of barrier function after disruption with lauroyl sarcosine (A) and SDS (sodium dodecyl sulfate) (B) through application of lipid mixture (■) (cholesterol: ceramides: linoleate: palmitate—4.3:2.3:1.15:1) or vehicle (○) (propylene glycol:ethanol—7:3). TEWL at time 0 = 1.92 mg/cm/h in A; TEWL = 3.82 mg/cm/h in B. After disruption by acyl sarcosine, application of the lipid mixture promoted barrier restoration, but no enhancement was observed after alkyl sulfate exposure.

forced into the epidermis to decrease the upper epidermis calcium concentration, this has the effect of promoting the extracellular secretion of lamellar granules so that granules accumulate between the granular layer and the horny layer [15]. Calcium concentration increases gradually from the basal layer toward the granular layer, but the gradient disappears abruptly as cornification proceeds [16]. The concentration gradient also disappears with disruption of the barrier function but returns to normal as the barrier recovers. Occlusion after barrier disruption inhibits both barrier function and calcium ion gradient recovery. In a study of essential fatty acids using deficient animals, a study in which a cholesterol synthesis inhibitor was applied and an area of psoriasis (disruption of barrier function) was created on the skin, the calcium ion concentration gradient in the epidermis was consistently abnormal. Calcium ions and the calcium ion concentration evidently play very important roles in the maintenance of the barrier function and thus in regulating the production and release of lamellar granules as well.

Cosmetic bases are generally adjusted to be weakly acidic. This practice stems from the weakly acidic pH of the skin's surface, but slight acidity is also important for maintaining epidermal functions. The pH of the epidermis is related to barrier function maintenance. When the barrier function has been disrupted, the application of a neutral buffer solution (pH 7.4) inhibits its recovery, while a weakly acidic buffer (pH 5.4) does not. Though a mechanism to explain this difference has not yet been found, it is thought to be due to lowered activity of β-glucosylcerebrosidase, an enzyme that plays an important role in barrier formation by hydrolyzing cerebrosides to free ceramides. The optimum pH for this enzyme's activity is weakly acidic; its activity would be reduced if the pH of the epidermis became neutral or basic [17].

The pH of skin care products must therefore be adjusted in order to avoid interference with the biochemistry of diverse epidermal functions and to maintain the efficacy of pharmaceutical agents.

EFFECT OF OCCLUSION

Creams and other skin care products can cause occlusion in the epidermis. The effects of occlusion on the functions and biochemistry of the epidermis have been gradually elucidated.

If the barrier function is disrupted and the skin is then covered with latex or other clinging film to prevent the passage of moisture, a series of processes required for barrier function may be disrupted. For instance, the synthesis of lipids and the production and release of lamellar granules is inhibited, obstructing barrier function recovery [18]. When the occlusion is effected with a material, such as Gore-Tex®, which does not completely prevent the passage of moisture, barrier function recovery is not inhibited. Barrier function disruption increases the production of DNA in the epidermis, the density of epidermal Langerhans cells, and proliferation of other cell types [19]. These changes are completely or partially inhibited when occlusion is effected using a film that does not allow the passage of moisture [20].

However, the increase in cytokine production due to barrier perturbation is not inhibited by occlusion [21]. If untreated skin is subjected to occlusion, the size of the interleukin (IL) pool is reduced, while its release is inhibited with barrier disruption. It has been observed that barrier disruption also promotes the prenilation of epidermis proteins. The investigation of these events, triggered by barrier disruption and the effect of occlusion, has been conducted primarily on rodent skin. Nevertheless, control of the release of the above factors—including cytokines—may thus be extremely important for the development of agents for sensitive skins.

MOISTURE BALANCE

Maintenance of the barrier function is very important in improving the overall skin condition, which can be achieved through the supply of lipids and salts to the skin. It is critical, while doing this, to supply these constituents to an appropriate location and in an appropriate form. These features are also important for the utility of skin care products.

In the case of a topical drug this kind of utility need not be considered, but in the context of cosmetics for skin care utility it is as significant as the efficacy of the pharmaceutical agent. For instance, petrolatum and other hydrocarbon preparations are often applied externally as medicinal products for the simple care of dry skin. Such substances are expected to be very effective for this condition in view of their occlusive effect. However, their utility is poor because of their stickiness. On the other hand, fatty acids and higher alcohols may be very desirable in terms of utility but produce virtually no occlusion when applied alone. Such oily ingredients are, nevertheless, important ingredients for skin care products. Other important ingredients are natural moisturizing factor (NMF) components, such as amino acids, and humectants, such as polyhydric alcohols. The penetration of the horny layer by humectants plays an important role; in fact, they do not penetrate well when applied alone, which is particularly true in the use of ionic ones.

The components of the horny layer include NMF constituents in keratinized cells that can retain moisture. The cells are surrounded with a covering of lipids. The basis of skin care is to maintain this specific structure, and this concept has been embodied in the moisture balance theory [22]. A combination of oily components, humectants, and water in an emulsion should be a most effective form for skin care. In the future it will become increasingly important to design skin care products on the basis of the moisture balance concept as well as of the physiology of the skin barrier function. These issues are discussed later in this chapter.

CREAM SKIN CARE PRODUCTS

TYPES OF SKIN CARE PRODUCTS

There are no limits to the variety of products that can be created for the purpose of skin care. Generally, products such as sunscreens or tinted foundation preparations, include ingredients intended to improve skin condition. This chapter is limited to products for which skin care or skin protection is the primary objective.

There is another approach dividing skin care products by viscosity. The distinction between a skin care lotion and a skin care cream on the basis

of pourability from a container or of a viscosity measurement is, however, ignored in the following discussion.

Skin care products commonly are emulsions or clear or translucent preparations; their texture may vary from fluids to solids. Despite the extraordinarily wide variety of skin care products on the market, consumers prefer emulsified preparations for skin care. As will become apparent subsequently, emulsions are most likely to provide optimal efficacy for skin products. Consumer acceptance of skin care preparations is complicated by the fact that emulsions may be dispensed in jars or squeezable containers (tubes), by pumps or from bottles. Thus, the terms *gel, cream, lotion*, and *milk* describe a continuum of products. What is critical are the components that are included to provide a desirable and efficacious product.

Creams and lotions are emulsions consisting of two immiscible liquids, for example, water and oil, with one of them forming the dispersed phase and the other the continuous medium. The dispersed phase is distributed in the continuous medium in a stable state (see Chapter 10). Creams are semisolids and are the classic types of skin care cosmetics because of their wide range of stability. These semisolid viscous preparations can be formulated to contain oils, humectants, water, and other ingredients. As noted, the viscosity of skin care products can range from a pourable liquid to an unctuous solid; when the viscosity of the emulsion is so low that it flows due to gravity, the product is called a (milky) lotion.

The raw materials used in the preparation of skin care products are so many and so varied that it is impossible to mention them all. There are also many excellent and effective formulations for creating shelf-stable preparations of such materials that it is similarly impossible to identify all of them. Further, as new ingredients—emulsifiers, softening agents, and humectants—are constantly being employed in skin care products, any listing of them would soon be out of date.

Thus the materials and formulations discussed in this section are generally those that have been widely used for a long period of time; they are still highly valued and should be considered as starting products on which the development of new skin care products can be based. Suppliers make continual efforts to develop novel formulations in order to demonstrate the excellence of their products. Cosmetic chemists should not blindly follow such formulae but use them as a reference, study them, and utilize them for the development of their own formulations.

Traditionally cosmetic skin care preparations have been sold by type and by function, that is, according to their advertised mode of application and packaging claims. For this reason consumers have always differentiated emulsion cold creams from emulsion night creams. However, this is not a very

distinctive classification because of overlapping visual appearance, feeling on the skin, ease of spreading, and rub-in characteristics. Thus creams cannot be classified by function alone, and consumers are guided by their own judgments, using the manufacturer's indications of functions, effects, and quality only as a guide.

However, cosmetic chemists should view this problem in terms of physics and chemistry. This includes such aspects as the water to oil ratio, characteristics of the continuous phase, pH of the emulsion, type of softening agent used, and the melting point of the oil phase.

There are some relationships (Table 18.1) between skin care product categories when they are ranked by function (based on the marketer's intended use) and by subjective judgment (based on user's perception). Another way of comparing skin care preparations may be based on the lipid levels of different types of marketed products (Table 18.2). When oil content data are compared directly with the intended use of more than 230 products, a modest relationship between functional descriptions and actual compositions is revealed:

Cleansing and Night Creams oil levels cluster at about 30–60%.

Hand and Body Creams rarely contain more than 20% lipids.

Vanishing Creams generally contain 10–30% of an oil phase.

Lotions and Milks may contain as little as 3% and rarely more than 10% of oil.

SKIN CARE PRODUCT COMPONENTS

Skin care formulations include oily ingredients, water solubles, surfactants, preservatives, chelating agents, perfumes, and active (or pharmaceutical) agents. Creams are either O/W or W/O emulsions with special features resulting from the surfactants and oily ingredients employed. In the case of O/W creams with a high internal phase level, the cream state is due to the high number of the emulsion particles. If the internal phase ratio is low, as, for example, in lotions, the desired viscosity is reached by adding amphiphilic substances, such as higher fatty alcohols and fatty acids, to lower the fluidity of the external phase. The observed thickening is the result of lamellar liquid crystal formation of the amphiphilic alcohol in the presence of a (nonionic) surfactant.

Another means for thickening lotions and stabilizing milky lotions is the use of hydrophilic (water-soluble) gums. Lipophilic surfactants are the emulsifiers used for W/O creams. The oily ingredients used comprise mainly non-polar types. In order to improve stability, it is important to prevent coagulation of the internal (water) phase, requiring careful selection and combination of oils. The most widely used cream and lotion ingredients are shown in Table 18.3. As a result of recent advances in chemical synthesis and refining techniques, novel

Table 18.1 Characteristics of Skin Creams

Functional	Physicochemical	Subjective
Cleansing creams	Medium-to-high oil content	Oily
	Oil-in-water or water-in-oil	Difficult to "rub in"
Cold creams	Low slip-point oil phase	May be stiff and "rich"
Massage creams	Neutral pH	Also popular as lotions
Night creams	May contain surfactants to improve penetration and suspension properties	
Moisturizing creams	Low oil content	Easily spreadable and "rub in" quickly
Foundation creams	Usually oil-in-water	
	Low slip-point oil phase	Available as creams or lotions
Vanishing creams	Neutral to slightly acidic pH	
	May contain emollients and special moisturizing ingredients	
Hand and body protectants	Low-to-medium oil content	Easily spreadable but do not "rub in" with the ease of vanishing creams
	Usually oil-in-water (O/W)	
	Medium slip-point oil phase	Very popular in lotion form
	May have slightly alkaline or acidic pH	
	May contain protective agents, especially silicones and lanolin	
All-purpose creams	Medium oil content	Very often slightly oily but should be easy to spread
	Oil-in-water (O/W) or water-in-oil (W/O)	
Softening lotion	O/W emulsion	Moisturizing
	Low viscosity	Emollient
	Low oil content	Lubricating

lipids, humectants, emulsifiers, and active agents are now used more widely. Some especially important components are discussed in greater detail below.

HUMECTANTS

Investigators have demonstrated repeatedly that water is required for skin softness. The skin is the outermost layer of the body and protects the body from the external environment and at the same time plays an important role in maintaining the level of moisture in the epidermis. Judicious use of humectants

Table 18.2 Formulations of Different Creams

Cream type	Main ingredients		Typical example
	Oil phase Proportion (%)	Emulsifier	Typical products
O/W type	2–20	Higher fatty acid soap Nonionic surfactant Protein-based surfactant Soap + nonionic surfactant Beeswax + sodium borate + nonionic surfactant	Emollient cream Hand and body preparations
	20–85		Emollient cream Massage cream Cleansing cream
W/O type	20–50	Nonionic surfactant Amino acid + nonionic surfactant (amino acid gel emulsification) Organically modified clay mineral Soap or nonionic surfactant	Emollient cream
	50–85		Massage cream Cleansing cream Emollient cream
Anhydrous oily type	100	Oily gelling agent	Liquefying cream (Cleansing cream)

is believed to add water to dry skin, moisturize the skin, and help biological processes within the epidermis (Chapter 13). Typical moisturizers include organic polyols, simple salts such as sodium lactate and sodium pyrrolidone carboxylate, and water-soluble polymers such as polyethylene glycol and hyaluronic acid. Humectants serve several purposes, as noted in Chapter 13.

(1) For moisturizing the skin

- Remain in the skin and horny layer to moisturize them adequately
- Impart a smooth, moist feeling to the skin

(2) For cosmetic formulation

- Contribute to maintenance of emulsion and solubilized systems by retarding moisture losses

Table 18.3 Common Cream Components

Components	Typical raw materials
Oil phase components	Hydrocarbons: squalane, liquid paraffin, petrolatum, solid paraffin, microcystalline wax, ceresin, etc. Fats and oils: olive oil, almond oil, cocoa butter, macadamia nut oil, avocado oil, hardened palm oil, castor oil, sunflower oil, evening primrose oil, synthetic triglycerides, etc. Waxes: beeswax, lanolin, carnauba wax, candelilla wax, jojoba oil, etc. Fatty acids; stearic acid, oleic acid, isostearic acid, myristic acid, palmitic acid, behenic acid, etc. Higher alcohols: stearyl alcohol, behenyl alcohol, hexadecyl alcohol, octyldodecyl alcohol, cholesterol, etc. Synthetic esters: isopropyl myristate, triglycerides, pentaerythrityl tetraesters, cholesteryl ester, etc. Silicones, dimethyl polysiloxane, methylphenyl polysiloxane, cyclomethicone, etc.
Water phase components	Humectants: glycerin, propylene glycol, sorbitol, polyethylene glycol, dipropylene glycol, 1,3-butylene glycol, polyglceryl-2, mannitol, PEG methyl glycoside, biopolymers, PCA, etc. Thickening agents: quince seeds, pectin, cellulose derivatives, xanthan, gum, sodium alginate, carrageenan, carboxyvinyl polymer, etc. Alcohols: ethanol, isopropanol Water
Sufactant (emulsifiers; solubilizers)	Nonionic: glyceryl stearate, PEG sorbitan fatty acid esters, sorbitan fatty acid esters, PEG alkyl ether, PEG-PPG co-block copolymer, PEG-hardened castor oil ester, etc. Anionic: fatty acid soaps, sodium alkyl sulfate, etc.
Others	Perfumes Colorants: permitted colors, pigments Chelating agent: EDTA Preservatives: parabens, sorbic acid, thymol, etc. Antioxidants: butylated hydroxytoluene, vitamin E, etc. Buffers and pH-controlling agents Antimicrobial agents Actives: vitamins, UV absorbers, amino acids, whitening agents, plant extracts, α-hydroxy acids

- Lower freezing point to enhance low temperature stability
- Increase solubility and help retain fragrance
- Control viscosity
- Improve luster
- May enhance bacteriostatic action

The beneficial effects of humectants on the skin and on the product have been studied by many techniques. For example, the hygroscopicity of humectants has been investigated at different relative humidity conditions, with emphasis on those polyols and other humectants in general cosmetic use. (Figs. 18.2 and 18.3). Figure 18.2 shows that highly hygroscopic humectants tend to absorb large amounts of moisture at elevated relative humidities. The overlap of water sorption data at 40% or higher humidities—shown in Figure 18.2—disappears at lower humidities, that is, below about 50% relative humidity (RH) in a range in which dry skin syndromes are common. Figure 18.3 shows that the amounts of moisture absorbed by humectants is relatively low but increases modestly when the relative humidity is raised; such increase varies for different humectants. Some humectants do not absorb much moisture at low humidity but absorb much larger amounts at high RH.

Sodium hyaluronate is a well-known example of a typical glycosaminoglycan, present in the dermis and classified as a moisturizer. This humectant demonstrates little water sorption at 33% RH (≈30%) and at 75% RH (≈40%).

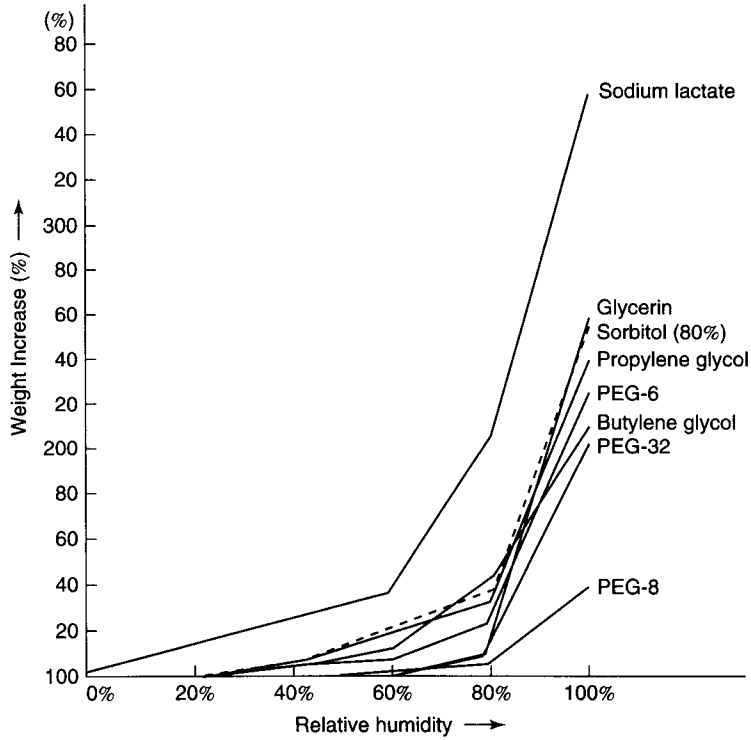

Figure 18.2. Water sorption of humectants at various relative humidities (23 °C)

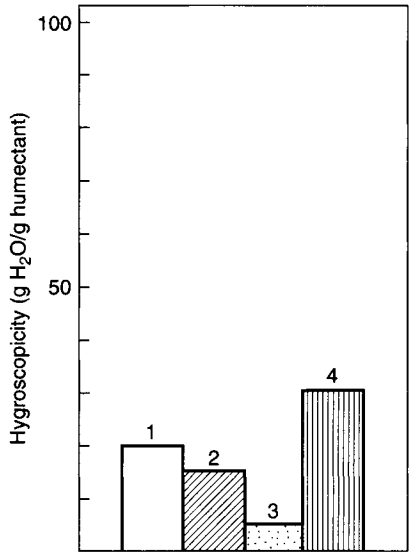

Figure 18.3. Water sorption by selected humectants at 33% relative humidity (1—Sodium PCA; 2—Glycerin; 3—Sorbitol; 4—Sodium Hyaluronate)

The behaviors of NaPCA and hyaluronic acid (H) at different RHs need careful examination. NaPCA tends to absorb large amounts of water (≈100%) at high RH but retains only about 60% when the humidity is lowered to 50% at 25 °C. This is similar to the water retention capacity of glycerin, which is only about 40% at RH 50%. By contrast, H absorbs only about 50% by weight of water at high RH. An aqueous solution of H upon exposure to 50% RH has the ability to retain 200% of water. The assessment of the merits of a skin "moisturizer" probably requires an assessment of how much and how long absorbed moisture is retained at lower RHs.

The lipid components of skin care products contribute to the effects of moisturizers by modifying their tendency to lose water when exposed to low humidities. The horny layer as the outermost layer of the skin is the focus of moisturization. This layer must have a certain moisture retention capacity. The intact horny layer utilizes moisture from within the body and contains water-soluble (humectant) substances known collectively as the natural moisturizing factor (NMF) for retaining this moisture. The horny layer also includes a lipid film that reduces the loss of the NMF [23].

It is thought that the penetration of moisture into the horny layer is regulated by epidermal and sebaceous lipids. Such substances are important factors in moisture retention by the horny layer. Moisturizing (skin care) cosmetic products imitate these functions and are formed by blending water, oil, and

humectant. This is expressed formally in the so-called Moisture Balance Theory (Fig. 18.4), described in detail in Reference 24.

The horny layer is made up of protein—principally keratin—lipids, and water-soluble NMF (Chapter 13). Today it is thought that NMF plays an extremely important role in the horny layer's ability to retain moisture. Amino acids are major constituents of the NMF. If amino acid metabolites such as pyrrolidone carboxylic acid and urea are included, the proportion of NMF accounted for by amino acids rises to 60–70%. Therefore, amino acids are commonly included in skin care products because they are believed to be very important for moisture retention by the horny layer.

The most important point in the design of cosmetic skin care preparations is the combined use of substances of relatively small molecular weight, such as the polyols, pyrrolidone carboxylates, lactic acid, and amino acids, and polymers such as glycosaminoglycans. The smaller organic molecules exhibit high hygroscopicity but equilibriate rapidly with the ambient relative humidity. On the other hand, the polymeric humectants behave differently due to their structure and as a rule are less rapidly influenced by environmental conditions.

When the horny layer absorbs moisture, it becomes flexible. This softness has been measured mechanically, and changes in softness with time can be

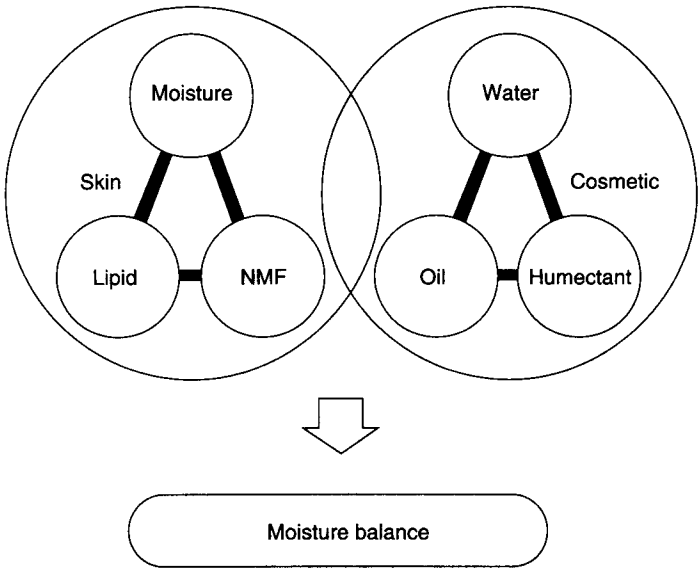

Figure 18.4. Theory of Moisture Balance: Constituents of skin care products are chosen to match components in normal skin [25]. (Reproduced by permission of Elsevier Science B.V.)

assessed readily. Placing a drop of water onto the horny layer softens it; but upon drying it becomes harder than it was initially. Application of a polymeric water-soluble substance such as H to the horny layer also increases the skin's resistance to extension during drying; this is thought to be due to film formation on the skin. By contrast, when a hygroscopic material such as glycerin is used in combination with H, skin softness is maintained longer than with glycerin alone. This has been attributed to the plasticizing action of polyols on polymeric humectants, and this synergistic effect is very dramatic.

The combination of humectants with other ingredients is a crucial aspect of cosmetic skin care preparations. Some important restraints exist: In formulating hand and body preparations intended to overcome the syndromes of winter skin (roughness, scaling, cracking, and erythema) it is best to avoid all components that may contribute to potential irritation. For many years glycerin has been the component of choice, and this humectant's performance should always be examined during development of new formulations. Moisturizers remain on the skin and horny layer as plasticizers. They impart a smooth, moist feeling to the skin and must not interfere with—or enhance—biochemical processes that occur normally in the skin.

OILY INGREDIENTS

A great variety of lipids can be used in skin care products, ranging from solid through semisolid substances to those having greater fluidity (oils). Recent evidence suggests that skin care preparations can be improved by judicious selection of oily constituents.

The oily components of skin care products contribute to the emolliency of the preparation and are selected on the basis of their ability to augment the natural barrier lipids in the stratum corneum (Chapter 16). Emolliency is the ability of the applied product to produce a sensation of suppleness and smoothness to the skin surface and the provision of slip.

The barrier lipids in normal skin reduce the evaporative loss of water from the skin that is the transepidermal water loss (TEWL). The barrier lipids also serve as a barrier to the penetration into the epidermis of externally applied substances, which include drug constituents and moisturizers. The barrier layer is a layer of lamellar lipids filling the intercellular spaces of the horny layers. It is formed when lamellar granules (given various other names such as Odland bodies or cementosomes) originally formed in the spinous layer move to the granular cells and release their content into the intercellular spaces.

There is now much interest in the relationship between the barrier layer and the barrier function [25]. Despite the extensive information concerning the relationship between the NMF and dry skin, there is still insufficient evidence

for establishing the relationship between dry skin and intercellular lipids. Barrier lipids can be lost or damaged by diverse lipid solvents (e.g., acetone) and reportedly by exposure to surface-active agents. Barrier layer damage increases TEWL significantly and allows access of undesirable substances to the skin. Thus restoration or repair of the barrier layer has become a major objective of skin care preparations. The lowered water content of the stratum corneum in cases of barrier damage affects the adhesion of corneal cells to each other and alters the physiological (enzymatic) processes required for forming a healthy nonscaling corneal surface.

Creams containing varying amounts of oil and humectants can be expected to modify moisture retention and the rate at which this moisture may escape through the corneal membrane. In vitro and in vivo studies have been used to examine the occlusivity of skin care products, that is, the extent to which they inhibit the passage of moisture and modify TEWL.

MISCELLANEOUS INGREDIENTS

As a group, skin care products are primarily emulsions, and emulsion stabilizers are found in most preparations, as described in Chapters 10 and 11.

In recent years, the inclusion of botanical extracts, vitamins, antimicrobials, and the like has become an important marketing advantage. Claims based on these additives must be carefully phrased to maintain the product(s) in the cosmetic area. In addition, such claims are rarely based on rigorous scientific evidence of performance. A case in point is the use of different components of green tea for antioxidant purposes on the skin surface. Although these substances exhibit systemic effects upon ingestion, evidence for skin benefits from topical application has not been established.

Some authorities have suggested that a topical vitamin deficiency could be alleviated through the topical application of vitamins in sufficient amounts. Others have asserted that it is rare for such vitamin deficiencies to be serious and that they can be remedied best by oral administration. Topical application of vitamins to rats increases the thickness of the epidermis with an accompanying reduction in the rate of keratinization; but such results were not seen in the epidermis of humans. Even the best vehicle for vitamin administration has been hotly debated. The effects claimed for systemic royal jelly and pollen have also been claimed for topical application. The effects are sometimes attributed to the water-soluble vitamin B complex and its components, pantothenic acid, panthenol, and pantethine. Useful effects on skin have been claimed, although there is no clear evidence that such substances actually are absorbed percutaneously and transported to the site where their action is to be manifested. Nevertheless, vitamin B complexes, panthenol, and pyridoxin derivatives are today widely used in cosmetic products.

The use of ascorbic acid in cosmetic products creates stability problems due to oxidation. Vitamin A and vitamin D are both oil-soluble vitamins and are necessary for skin health. These vitamins are best taken orally to treat any part of the body when there may be a deficiency. Ergocalciferol and cholecalciferol, and vitamin A are sometimes administered together, and vitamins A, E, and D_3 reportedly have synergistic effects when taken in a mixture. Vitamin E is said to promote percutaneous absorption, and biotin may assist cholesterol synthesis. In modern practice, tocopherol and ascorbic acid and derivatives are the preferred antioxidants in skin protectant preparations (Chapter 12). Carotenes of various types also exhibit antioxidant properties but are used primarily for the control of keratinization and in antiwrinkle products.

The so-called vitamin F used in topical preparations has received much attention in the earlier scientific literature; it is currently known as essential fatty acids (EFAs). This blend of unsaturated fatty acids has cured dermal symptoms due to chronic EFA deficiency in a rat model; the problem remains that no EFA deficiency occurs naturally in rats.

Skin care preparations may include hundreds of ingredients that have been claimed to benefit the appearance or health of living skin. Neither their ability to permeate the corneal barrier nor the nature of their pharmacological effects within the skin are rarely critically examined. Table 18.4 lists a few of these cosmetically active ingredients and their sources, for illustrative purposes only.

SKIN CLEANSING PRODUCTS

In order to keep the skin in a healthy and attractive state, it is necessary to cleanse it regularly to remove dirt, sebum, dead cells, and other detritus. The traditional method for removing cleansing creams was by wiping off, but the desire to wash off remnants of cleansing creams created the wash-off type, which is now the major product on the market. In order to reduce residual stickiness after washing, the proportion of solid to semisolid oils in the oil phase is kept low.

WIPE-OFF CREAMS

The combined solvent actions of water and oil can cleanse the skin surface very effectively. With an appropriate formulation of these constituents, cleansing can still be achieved without completely removing the skin's natural lipid film. (This is actually achieved by leaving behind a thin film of an oily softening agent, which gives the skin surface a healthy and soft feeling.) This method is more convenient than use of soap and water. During their usage some cleansing cream is massaged onto the skin surface; as a result, the dirt comes

Table 18.4 Assorted Skin Care Ingredients

Identity	Effect/Character	Source
Algae extract	??	Botanical
Amniotic fluid	Hormone source	Animal
Apricot kernel extract	??	Botanical
Avocado oil unsaponifiables	Phytosterol	Botanical
Betaglucan	Polysaccharide	Animal
Brain lipids	??	Animal
Camellia sinesis extract	Antioxidant	Botanical
Chitosan	Polysaccharide	Animal
Collagen	Protein	Animal
Cucumber (cucumis sativus) juice	??	Botanical
DNA	??	Animal
Echinacea angustifolia	??	Botanical
Ferrous glucoheptonate	Antioxidant	Synthetic
Ginkgo biloba	??	Botanical
Hyaluronic acid	GAG	Animal/Biotechnology
Hydrolyzed silk	Amino acid	Animal
Hydrolyzed yeast	Saccharide	Animal
Inulin	Polysaccharide	Botanical
Nonfat dry colostrum	Protein	Animal
Pyridoxine dicaprylate	Vitamin derivative	Synthetic
Quinic acid	Antioxidant	Botanical
Serum albumin	Protein	Animal
Yogurt	Protein	Animal

off the skin and is incorporated into the emulsion. Then, wiping with a tissue or cotton wool removes any dirt or old cosmetic together with the cleansing cream. Such a cleansing emulsion should include a rich oil phase that spreads easily and that does not penetrate the skin.

Cold creams (this name is due to the cooling effect that these products have on the skin) comprise another group of emulsions that are related to cleansing creams. Cold creams were the first types of emulsion to be featured in scientific papers, and they have a long history dating back to the second century. They are prepared from natural waxes and plant oils (traditionally beeswax and olive oil). At the beginning of the twentieth century, mineral oils replaced such unstable plant oils, thereby establishing the basis for modern cold creams. When sodium borate is added, it reacts with the free fatty acids (lignoceric and cerotic acids) in the natural wax, producing a sodium soap. Although it is now possible to prepare a wide range of different emulsions with alternative emulsifying agents, beeswax–sodium borate emulsions are still popular.

Beeswax has a unique smell and is a natural substance; as a result, the quality and price of beeswax tend to vary. If the amount of sodium borate is slightly less than that required stoichiometrically, a more stable cream with a better texture is produced. Usually the amount of beeswax is 5–15% by weight. In a cold cream, the amount of beeswax that has been neutralized by sodium borate varies from 5–16%. The smaller amount of beeswax (if necessary, other waxes may be added to increase viscosity) produces a softer cream.

Cleansing cream formulae 18.1, 18.2, and 18.3 are all W/O type creams. A modified clay can be used as an alternative to waxes for thickening the continuous oil phase, as shown in Formula 18.3.

The beeswax–sodium borate system is suitable for both W/O and O/W types of emulsions without any additional emulsifying agents. The factors affecting the emulsion type are the ratio of oil to water, the percentage of saponified beeswax, other ingredients (affecting HLB), and the temperature.

Formulae 18.1 and 18.2 Cleansing Cream

	(1) %	(2) %
Beeswax	16.0	12.0
Mineral oil	50.0	—
Sodium borate	0.8	0.5
Cetyl esters	—	12.5
Sesame oil	—	40.0
Water	33.2	35.0
Perfume, preservative	q.s	q.s

Formula 18.3 Cleansing Cream

	%
Beeswax	12.0
Mineral oil	53.0
Quaternium-18 hectorite	0.7
Sodium borate	0.7
Water	33.2
Isopropanol	0.4

Procedure: Combine and melt all the oily components at 70 °C. Dissolve the borate and the clay in the aqueous phase at 70 °C. Combine the phases by stirring the water phase into the oil phase. Add any remaining ingredient(s), pass through a Homomixer®, strain and cool.

In the process of making such preparations, phase inversion may occur. When an O/W emulsion is applied to the skin surface, phase inversion is observed as the water phase begins to evaporate Nonionic emulsifying agents are used to supplement beeswax–sodium borate emulsions in order to enhance emulsion softness and stability. The emulsifying agents that are most often used together with them are sorbitan esters. Formula 18.4 (O/W) and formula 18.5 (W/O) are typical.

Lighter O/W creams with a medium oil content are also used as cleansing creams. Such products are favored by consumers in a number of markets and many of the popular creams are based on the conventional stearic acid–triethanolamine emulsion system or self-emulsifying glyceryl stearate. Formulae 18.6 and 18.7 are typical for such creams.

Waterless wipe-off cleansing creams, commonly known as liquefying creams, consists only of gelled oils and have been made for many years.

WASH-OFF AND TWO-WAY TYPE CLEANSING CREAMS

Wash-off cleansing creams and the two-way types, which can be either wiped or washed off, have recently become the most popular types of cleansing cream in the market. A low content of solid and semisolid oils and a combination of small amounts of fatty acid soap and nonionic surfactant create the two-way type to be either wiped or washed off. Formula 18.9 is typical of this type of product.

Cleansing emulsions that foam upon the addition of water when used on the skin are identified in formulae 18.10 and 18.11 below.

Formula 18.12 represents a soap-free two-way lotion.

Formulae 18.4 and 18.5 Cleansing Cream

	(4) %	(5) %
Beeswax	10.0	10.0
Mineral oil	50.0	20.0
Lanolin	3.1	3.0
Sodium borate	0.7	0.7
Hydrogenated vegetable oil	—	25.0
Antioxidant	—	0.5
Sorbitan sesquioleate	1.0	—
Sorbitan stearate	—	5.0
Polysorbate 60	—	2.0
Water	35.2	33.8
Perfume, preservative	q.s	q.s

Procedure: Similar to method for Formulae 18.1 to 18.3.

Formulae 18.6 and 18.7 W/O Cleansing Cream

	(6) %	(7) %
Mineral oil	29.0	18.0
Stearic acid	13.5	—
Triethanolamine	1.8	—
Glyceryl stearate (SE)	—	15.0
Water	51.9	55.0
Glycerin	2.0	5.0
Sodium alginate	1.8	—
Cetyl alcohol	—	2.0
Spermaceti	—	5.0
Perfume, preservative	q.s	q.s

Procedure: Combine all the water-soluble components in the water at 70 °C. Add to this the homogeneous mixture of the oily constituents with stirring. Pass the preliminary emulsion through a Homomixer®, de-aerate, strain and cool.

Formula 18.8 Waterless Cleansing Creams

	%
Ceresin	8.0
Microcrystalline wax	5.0
Petrolatum	35.0
Liquid paraffin	50.0
Polyethylene, low molecular weight	2.0
Perfume	q.s.

Procedure: Blend all ingredients except the perfume at about 90 °C; then cool to around 60 °C and add the perfume. It is necessary to monitor the solubility of the low molecular weight polyethylene. The stability of the final product can vary greatly depending on the stirring conditions between 90 °C and 70 °C during cooling and after the cream has solidified.

Today wash-off cleansers at low pH are preferred over neutral products. Compositions of this type resemble those described in Chapter 24.

Washable oily gel compositions have recently enjoyed high sales because they are able to remove makeups of the W/O emulsion type. In use they exhibit the characteristic moistness of gels and are easily washed off. Formula 18.13 is a typical example of this product.

Formula 18.9 Cleaning Cream

	%
Stearic acid	2.0
Cetyl alcohol	3.0
Petrolatum	10.0
Mineral oil	38.0
Isopropyl myristate	10.0
Propylene glycol	5.0
Glyceryl stearate	2.5
Polysorbate 60	2.5
Potassium hydroxide	0.1
Preservatives, antioxidant, perfume	q.s
Water	26.9

Procedure: Add the propylene glycol and alkali to the water and heat to 70 °C. Heat the oil components to make a solution, add the surfactants, preservative, antioxidant, and perfume and maintain at 70 °C. Gradually add the oil phase to the water phase with stirring. Pass the emulsion through a Homomixer®, de-aerate, strain and cool.

Formulae 18.10 and 18.11 Cleansing Emulsions

	(10) %	(11) %
Stearic acid	10.0	12.5
Mineral oil	5.0	—
Petrolatum	2.0	—
Cetearyl alcohol	1.5	2.0
Isopropyl myristate	3.0	5.0
Polysorbate 20	2.0	—
Glycerin	6.5	—
Sodium laureth sulfate	5.0	—
Triethanolamine	1.5	—
Polyoxyethylene sorbitan monolaurate	2.0	—
Water	61.5	68.1
Lanolin	—	0.4
Sodium cocoylisethionate	—	12.0
Perfume, preservative	q.s.	q.s.

Procedure: Follow the method shown for Formula 18.12, with appropriate modification.

NIGHT AND MASSAGE CREAMS

Traditionally, the products known as night creams and massage creams have been designed to moisturize the skin when left on it for several hours after

Formula 18.12 Cleaning Lotion

		(%)
Oil component:	Stearyl alcohol	0.5
	Hydrogenated palm oil	3.0
	Mineral oil	35.0
Humectant:	Dipropylene glycol	6.0
	PEG 400	4.0
Surfactants:	Sorbitan sesquioleate	1.6
	Oleth 20	2.4
Thickening agent:	Carbomer (1% aqueous solution)	15.0
Alkali:	Potassium hydroxide	0.1
Preservative, Chelating agent, Perfume		q.s
Water		32.4

Procedure: Add the humectants and chelating agent to the water and heat to 70 °C (water phase). Heat the oil component ingredients together to make a solution, add the surfactants, preservative, and perfume and keep heating to 70 °C. Add this to the water phase, which includes the carbomer and the alkali, to carry out the preliminary emulsification. After making the emulsion particles uniform with a Homomixer®, de-aerate, strain and cool.

Formula 18.13 Washable Gel

	%
Mineral oil	12.0
Triethylhexanoin	50.0
Sorbitol	10.0
PEG 400	5.0
Sodium methyl cocoyl taurate	5.0
Octyl dodeceth-20	10.0
Perfume	q.s
Water	8.0

Procedure: Add the sorbitol and the taurate to the water and heat to 70 °C. Combine all remaining components and heat to 70 °C. Add this gradually to the water phase and pass the emulsion through a Homomixer®, de-aerate, strain and cool to create an almost transparent gel.

application. They therefore contain high levels of oil phase so as not to disappear quickly from the skin surface and thus may contact the user's clothes or bed sheets. Such creams are W/O emulsions and tend to be semisolid or high viscosity items.

The benefits of using night creams and related products have sometimes been exaggerated, even though such creams definitely have a moisturizing effect. This is achieved by formation of a sealing layer on the skin's surface,

which reduces the TEWL. Like many other creams, these products make the skin smooth through their lubricating action and smoothen the jagged edges of the outermost layer of the horny layer cells.

Manufacturers sometimes use the term *nutritive* for such creams, but it is very difficult to justify the use of this term without reference to the ingredients because the cells of the horny layer are dead. Under the prevalent definitions, ingredients like hormones may penetrate the horny layer but may change product positioning from a cosmetic to a pharmaceutical.

Vigorous massaging of the skin reduces the accumulation of superfluous layers of dead epidermal cells and improves the circulation in the epidermis. A major factor in performance is the effect of manipulation on the emulsion, and this will subtly influence the ease of massaging. The design of massage creams is more difficult than that of emollient creams because the former must exhibit not only shear stability but also a cleansing effect.

The term *moisturizing* has been applied to conventional W/O massage creams. Formula 18.14 is typical for such a massage cream. However, recent advances in skin research broadened the concept of moisturizing to include formation of an occlusive layer on the skin surface. Miscellaneous active ingredients can also be added to such creams.

Formula 18.14 W/O Massage Cream

		%
Oil component:	Microcrystalline wax	9.0
	Paraffin	2.0
	Beeswax	3.0
	Petrolatum	5.0
	Hydrogenated lanolin	5.0
	Squalane	34.0
	Hexadecyl adipate	10.0
Humectant:	Propylene glycol	5.0
Surfactant:	Glyceryl oleate	3.5
	Polysorbate 80	1.0
Preservative, Antioxidant:		q.s
Perfume:		q.s
Water:		22.5

Procedure: Heat the oil components to make a solution, add the surfactants, preservative, antioxidant, and perfume and maintain at 70 °C. Add the humectant to the water and heat to 70 °C to make the water phase. As this cream is of the W/O type, gradually add the water phase to the oil phase to carry out the preliminary emulsification. In order to make the emulsion particles uniform, pass through a Homomixer®, de-aerate, strain and cool.

Formula 18.15 Emollient Lotion

		%
Oil component:	Stearic acid	2.0
	Cetyl alcohol	1.5
	Petrolatum	4.0
	Squalane	5.0
	Triethylhexanoin	2.0
Surfactant:	Sorbitan mono-oleate	2.0
Humectant:	Dipropylene glycol	5.0
	PEG 1500	3.0
Alkali:	Triethanolamine	1.0
Preservative, Perfume		q.s
Water:		74.5

Procedure: Add the humectants and alkali to the purified water and heat to 70 °C (water phase). Make a solution of the oil components, add the surfactant, preservative, and perfume and heat to 70 °C (oil phase). Add the oil phase to the water phase and carry out the preliminary emulsification. After making the emulsion particle size uniform with a Homomixer®, de-aerate, strain and cool.

Instead of the fairly heavy massage and night creams exemplified for Formula 18.14, lighter O/W lotions are today preferred by many consumers. A typical example is provided in Formula 18.15.

ANTIWRINKLE CREAM

Dryness of the horny layer is considered a cause of wrinkles, and it has been reported that small wrinkles become more pronounced in winter because of skin desiccation. It has also been reported that the steady use of cosmetics with high moisturizing capabilities tends to normalize the production of NMF and of other components of the horny layer's moisture retention system. At the same time moisturization reduces the small wrinkles at the corners of the eyes. Thus cosmetic formulae with functional humectants can be expected to be very effective in this respect [26].

The formation of wrinkles is closely related to changes in the structure, function, and physical properties of the skin during aging. Such changes are aggravated by exposure to the sun's rays. A wide range of histological and morphological differences has been observed between a skin showing chronic photoaging and a naturally aged skin. Wrinkles may occur on any part of the body such as on the face, especially the forehead, around the eyes, between the eyes, and around the mouth, and on the nape of the neck, and on elbows,

feet, and hands. Usually they begin to appear at around age 30 and increase in number, depth, and area with aging; they may be classified as:

1. Linear wrinkles (commonly called crow's feet around the outer corners of the eye)
2. Glyphic wrinkles (crisscrossing triangular or rectangular wrinkles commonly seen on the cheeks and nape of the neck)
3. Crinkling (fine wrinkles commonly seen on the unexposed skin of elderly people)

Wrinkles of types 1 and 2 reflect photoaging-caused changes, while those of type 3 reflect intrinsic-aging, dependent changes. Wrinkle formation is caused by various internal and external factors. UV light is known to be one cause, but there are also other causes, ranging from environmental stress through dryness to physical and chemical trauma. Wrinkles are thought to be formed by loss of tension and elasticity due to reduced water content of the stratum corneum. Other reasons include thickening of the stratum corneum, atrophy of the epidermis, changes in the amount and quality of dermal collagen and elastic fibers, and deterioration of the three-dimensional structure of the dermis.

Effective antiwrinkling agents include retinoic acid and other forms of vitamin A that have been shown to have a mitigating effect on various histological changes occurring in photoaged skin. However, the effective forms of vitamin A are very susceptible to heat, light, and oxygen; care is required in formulating manufacturing, preservation, and filling of such preparations.

In cosmetic surgery, wrinkles are treated by using concentrated solutions of α-hydroxy acids (usually glycolic acid or lactic acid) as peeling agents to remove epidermis and to promote its reproduction. At this time, there are insufficient data to show that use of such preparations at modest pHs and low concentrations produces observable effects in mitigating photoaging stigmata and in alleviating wrinkles. Eye cream compositions, for example, formula 18.16, are used by consumers to help reduce the appearance of wrinkles (crow's feet).

VANISHING AND EMOLLIENT CREAMS

As the name suggests, creams coming under the heading of vanishing cream are designed to spread easily on the skin and then rapidly vanish into it. In order to disappear quickly into the skin, the oil phase of vanishing creams is formulated from soft esters that hardly leave any visible film on the skin. For the same reason, formulae using little oil are normally selected.

In traditional formulae for vanishing creams, the oil phase consists of high-quality stearic acid. Stearic acid melts at temperatures above body temperature,

Formula 18.16 W/O Eye Cream Formula

		%
Oil component:	Petrolatum	5.0
	Mineral oil	15.0
	Isopropyl myristate	5.0
Humectant:	Propylene glycol	5.0
	Glycerin	10.0
Clay mineral:	Stearalkonium bentonite	1.0
Surfactant:	Glyceryl stearate	2.0
Active agent:	Vitamin A	0.1
Preservative, Antioxidant, Perfume		q.s
Water:		q.s

Procedure: Heat and mix the oil component; then add the modified clay, surfactant, preservative, and perfume and adjust temperature to 70 °C. Agitate to form an oily gel by dispersion and dissolution. Add the humectants to the purified water and bring to 70 °C. Gradually add the water phase to the oily gel with stirring. Pass through a Homomixer®; then de-aerate, strain and cool to 30 °C.

crystallizes appropriately in use, and forms a non-oily film. Such creams have been described as stearic acid suspensions in a stearate soap gel (hydrogel suspension). A typical simple vanishing cream can be made as shown in Formula 18.17.

Although this formula appears to be very simple, stearate creams are actually quite complex, as noted in Chapter 10. The structural characteristics were explored by Junginger [Ref. 13, Chapter 10]. Today the pH of these creams is kept between 6.0 and 6.9, due to the presence of unneutralized fatty acids.

Currently few moisturizing creams resemble traditional vanishing creams. "Rich" types of creams containing large amounts of oil are not very popular at present because light textured creams are the preferred O/W creams. Formula

Formula 18.17 Vanishing Cream

	%
Stearic acid	15.0
Potassium hydroxide	0.7
Glycerin	8.0
Water	76.3
Perfume, preservative	q.s

18.18 and a product based on composition 18.19 are typical examples of such creams. Formula 18.20 and 18.21 are included to illustrate W/O creams.

Until recently, development of stable W/O cream emulsions required raising the viscosity of the external oil phase, which made the product feel oily and sticky during use. Today the development of such techniques as the amino acid gel emulsification technique [27], the organically modified clay mineral

Formula 18.18 O/W Emollient Cream

		(%)
Oil component:	Stearic acid	8.0
	Stearyl alcohol	4.0
	Butyl stearate	6.0
Humectant:	Propylene glycol	5.0
Surfactant:	Glyceryl stearate	2.0
Alkali:	Potassium hydroxide	0.4
Preservative, Antioxidant:		q.s
Perfume:		q.s
Water:		74.6

Procedure: Add the humectant and alkali to the water and heat to 70 °C to make the aqueous phase. Heat the oily ingredients to make a clear solution. Add the surfactants, preservative, antioxidant, and perfume and maintain at 70 °C. Add this to the water phase with stirring. After making the preliminary emulsion pass through a Homomixer®, de-aerate, strain and cool.

Formula 18.19 O/W Emollient Cream

	(%)
Oil component:	6.0
Humectant:	2.0
Surfactant:	4.0
Preservative, Antioxidant, Perfume:	9.0
Water:	10.0
Stearyl alcohol	6.0
Stearic acid	4.0
Hydrogenated lanolin	3.0
Squalane	2.0
Octyldodecanol	q.s
1,3-butylene glycol	q.s
PEG 1500	
Ceteth-25	
Glyceryl stearate	

Procedure: Same as for Formula 18.18.

Formula 18.20 W/O Emollient Cream

		(%)
Oil component:	Mineral oil	30.0
	Microcrystalline wax	2.0
	Petrolatum	5.0
Surfactant:	Polyglyceryl-2 dioleate	5.0
Preservative, Perfume:		q.s
Water phase (1):	L-Sodium glutamate	1.6
	L-Serine	0.4
	Water	13.0
Water phase (2):	Propylene glycol	3.0
	Water	40.0

Procedure: Make a solution of the amino acids in the water phase (1) at 50 °C and, with stirring, gradually add it to the dioleate surfactant, also heated to 50 °C to make an emulsion compound (amino acid gel). Next, make a solution of the oil components at 70 °C and evenly disperse the emulsion compound in it. Then, heat water phase (2) ingredients to 70 °C and add this to the dispersion with thorough stirring. Pass through a Homomixer®, de-aerate, strain and cool to 30 °C.

Formula 18.21 W/O Emollient Cream

	(%)
Squalane	20.0
Cetyl iso-octanoate	8.5
Microcrystalline wax	16.0
Quaternium-18 hectorite	1.3
Polyglyceryl-2-dioleate	5.0
Glycerin	0.2
Preservative, Perfume	9.5
Water	54.0

Procedure: After heating the oil component ingredients together to make a soution, add the clay mineral, surfactant, preservative, antioxidant, and perfume and heat to 70 °C to make a uniform solution which is the oily gel. Add the humectant to the water and heat to 70 °C to make the water phase. Gradually add the water phase to the oil gel, stirring thoroughly. Pass through a Homomixer®, de-aerate, strain and cool to 30 °C.

gel emulsification technique, and emulsification with associative polymers (Chapter 10) produce high stability products, even if the amounts of solid and semisolid oils in the oil phase are low. As a result, it is now possible to prepare emollient creams with appeal to a wide range of needs. Another example is shown in Formula 18.16.

HAND AND BODY PREPARATIONS

Hand and body care preparations represent some of the most widely distributed skin care products. Products falling into this category include creams and lotions for preventing or repairing the dry skin symptoms resulting from exposure to cold and dry air. These preparations are also useful for softening callus tissue and the flaky dry skin on knees, elbows, and heels. These products, which are similar to the over-the-counter (OTC) skin protectants in the United States (Chapter 19), rely to a large extent on moisturization of the affected area. Most product presentations in this genre employ large percentages of moisturizers as, for example, in Formula 18.21. A few additional formulae 18.22–18.25 follow.

MULTIPLE EMULSIONS

Skin treatment products exist now which utilize multiple emulsions of the O/W/O and of the W/O/W types. The objective of such emulsions is to stabilize active agents, to sustain fragrance release, and to produce a sensation on use which is different from that of conventional products. Formula 18.26 describes an O/W/O type. The O/W emulsion is prepared first with a nonionic surfactant.

Formula 18.22 Protective Hand Lotion

	(%)
Mineral oil	2.4
Isopropyl myristate	2.4
Stearic acid	2.9
Lanolin	0.5
Cetyl alcohol	0.4
Glyceryl stearate	1.0
Triethanolamine	0.95
Propylene glycol	4.8
Quaternium-19	0.2
Water	84.45
Color, perfume, preservative	q.s

Procedure: Prepare a homogeneous blend of the first six (lipid) ingredients at 70 °C. Add the remaining water-soluble ingredients to the water at 70 °C. Blend the oil phase into the water phase with stirring. Add the perfume and remaining components. Pass through a Homomixer®, de-aerate, strain and cool.

Formula 18.23 Softening Lotion

		(%)
Humectant:	Sorbitol	4.0
	Dipropylene glycol	6.0
	PEG 1500	5.0
Surfactant:	Oleth-20	0.5
Thickening agent:	Methyl cellulose	0.2
	Quince (*Pyrus Cydonia*) extract	0.1
	Alcohol	10.0
Perfume, Preservative, Chelating agent		q.s
Buffer:		q.s
Water:		74.2

Procedure: Dissolve the chelating agent in some of the purified water and stir the methyl cellulose and the quince extract (thickening agents) into this to form a viscous liquid. Then make a solution of the humectants and buffer in the remaining water at room temperature and add the viscous liquid to this to make a uniform aqueous solution. Dissolve the preservative, surfactant, and perfume in the ethanol; solubilize this in the aqueous solution and strain.

Formula 18.24 Microemulsion Lotion

		(%)
Humectant:	1,3-butylene glycol	6.0
	Glycerin	5.0
	PEG 4000	3.0
Emollient:	Olive oil	0.5
Surfactants:	Polysorbate 60	1.5
	Oleth-5	0.3
	Alcohol	10.0
Perfume, Coloring agent, Preservative		q.s
Buffer:		q.s
Water:		73.7

Procedure: Dissolve the humectants and the buffer in the water at room temperature to make the water phase. Then dissolve the emollient, surfactants, preservative, and perfume in the alcohol, also at room temperature (alcohol phase). Add the alcohol phase to the water phase to form the emulsion.

Though this formula is for a O/W/O emulsion, a W/O/W emulsion can be made through the reverse procedure.

THOUGHTS ON THE FUTURE OF SKIN CARE

For years approaches to skin care were designed to control the water ecology of skin, especially insensible perspiration under dry conditions. Research in this

Formula 18.25 O/W Hand Cream

	(%)
Peg-60 Glyceryl isostearate	2.5%
Glyceryl stearate	1.5
Cetyl alcohol	4.0
Petrolatum	2.0
Mineral oil	10.0
Vitamin E acetate	q.s
Vitamin D	q.s
Glycerin	20.0
Urea	2.0
Water	58.0

Procedure: Follow the method outlined for Formula 18.18.

field is continuing worldwide and may contradict some commonly accepted tenets. For example, Norlén et al. [28] recently suggested that 30-minutes. exposure of isolated stratum corneum (from human breast reduction) to 2% sodium dodecyl sulfate does not alter the water diffusion rate or the water holding capacity. The most recently developed concepts for skin care include enzyme activities, dermal-epidermal interactions and neuroimmunological approaches. What evolves from these novel—and not fully accepted—aspects is that future skin care requires a holistic approach in which skin is not viewed as a single and separate organ but as a part of the body responding to environmental, immunological- and nerve-dominated influences. The future of cosmetic skin care is briefly assessed below on the basis of these principles, which are more fully detailed in a book [24].

THE THEORY OF MOISTURE BALANCE

This idea is based on concepts and principles of skin biology, which in combination can lead to dry skin symptoms. Prevention and control of dry skin requires reestablishment of the humectancy of NMF and the occlusivity of corneal lipids, as visualized in Figure 18.4. It was recently shown that plasminogen activators can contribute to the development of dry skin by enhancing epidermal turnover [29]. Denda et al. not only described the mechanism for this phenomenon but also identified *t*-4-aminomethyl-cyclohexanecarboxylic acid (*t*-AMCHA) as an inhibitor of plasminogen activation [30]. Protease inibition by *t*-AMCHA is reportedly effective against various phenomena caused by dry skin, especially epidermal hyperplasia (Kitamura et al., pages 151–166

Formula 18.26 Multiple Emulsion

O/W Emulsion		(%)
Oil component:	Squalane	5.0
	Glyceryl 2-ethylhexanoate	0.3
	Petrolatum	1.0
Humectant:	Dipropylene glycol	5.0
	Glycerin	5.0
Surfactant:	PEG-60 glyceryl isostearate	2.0
Preservative, Antioxidant		q.s
Water:		79.0
O/W/O emulsification		
Oil component:	Cyclomethicone	15.0
	Dimethicone	10.0
	Pentaerythrityl tetraethylhexanoate	5.0
Clay mineral:	Quaternium hectorite	1.0
Surfactant:	PEG-10 glyceryl tri-isostearate	0.3
Perfume:		q.s
O/W emulsification:		68.7

Procedure: Preparation of O/W emulsion: Make a homogeneous solution of the humectants, preservative, antioxidant, and water at 70 °C. Add the oil component and surfactant, keeping the temperature at 70 °C; then make a uniform mixture using a Homomixer® and cool to 30 °C.

Preparation of the O/W/O emulsion: Heat the oil component to yield a uniform solution and then add the clay, surfactant, and perfume. Create a uniform dispersion/dissolution of an oily gel at 70 °C. Gradually add the previously prepared O/W emulsion to the oily gel, stirring sufficiently. Form a uniform mixture in a Homomixer®, de-aerate, strain and cool to 30 °C.

in Ref. 24). In clinical studies, *t*-AMCHA has proved effective in accelerating barrier repair of the stratum corneum and preventing dry skin.

The fundamentals of skin care have focused on the importance of retaining moisture in the stratum corneum. Moisturizer formulations consisting of water, oil, and humectants were developed that simulated water-lipid compositions controlling the moisture balance of the stratum corneum. As shown in Figure 18.4, the effort was directed to interrupt the dry skin cycle. Scientists now know that moisturizer formulations work by normalizing the keratinization process in dry skin, thereby restoring normal structure and function of the stratum corneum [22]. Skin moisturization therefore involves far more than the simple physicochemical effect of moistening the surface of the skin; instead, it is required for maintaining normal communications with the interior of the skin via the interface of the stratum corneum.

THE THEORY OF ENZYMATIC HOMEOSTASIS

It has recently been shown that the process of desquamation is under enzymatic control and that lipids and adhesion proteins and enzymes participate in the desquamation process. Digestion of desmosomal proteins by two types of serine proteases leads to smooth desquamation and helps to maintain a smooth skin surface [31]. Activities of these proteolytic enzymes decrease with aging or with reduced water content of the stratum corneum. This is believed to be the cause of the thickened stratum corneum of aging skin and the scaling skin surface of dry skin. The maintenance of moisture balance through use of moisturizers affects enzymatic reactions.

In the next stage of skin care, the epidermal control mechanisms by two enzymes were studied; it was found that enzymes that participate in the mechanism of desquamation of the stratum corneum need to maintain their activity continuously. In contrast, activation of plasminogen activators only results in acceleration of keratinocyte turnover and dry skin. For effective desquamation, therefore, some enzymes need to be activated and others need to be suppressed.

Moisturizers and dicarboxylic acids that promote desquamation do not activate plasminogen activators. On the other hand, *t*-AMCHA suppresses plasminogen activators but has no effect on enzymes that regulate desquamation. Utilizing these findings, one can now safely control desquamation for good skin care, as illustrated in Figure 18.5.

DERMAL-EPIDERMAL INTERACTION

As noted in Chapter 1, skin consists of two primary layers, the epidermis and the dermis. Within the epidermis one finds the living cell layers, consisting mostly of keratinocytes, and the nonviable cell layer that forms the external surface of the skin, the stratum corneum. The dermis consists primarily of abundant, collagenous connective tissue, and mesenchymal cells including fibroblasts, separated from the epidermis by a basement membrane. Epidermal proliferation and differentiation in vivo is regulated by the basement membrane and the underlying dermis. Epidermal stem cells within the basal layer generate keratinocytes, which ultimately differentiate to form the corneal cells.

The dermis is physiologically important by producing soluble growth factors required for epidermal cells to proliferate and differentiate. The basement membrane regulates the transmission of these factors to the epidermal cells. The dermis is also important mechanically to the epidermal cells in that it acts as a buffer to protect the epidermis from external pressures. Dermal fibroblasts

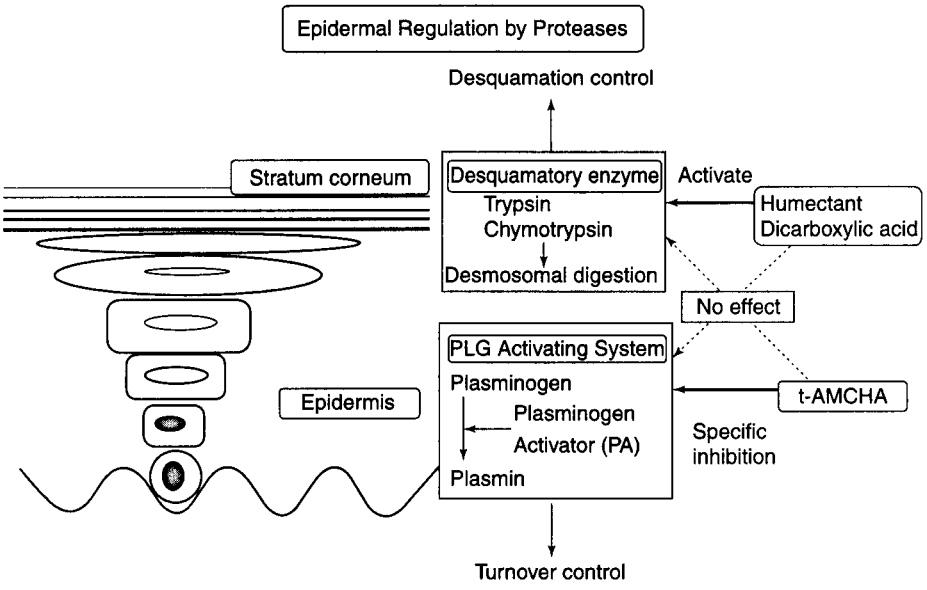

Figure 18.5. Pictorial representation of epidermal regulation by proteases [25]. (Reproduced by permission of Elsevier Science B.V.)

produce collagen fibrils and the proteoglycan complex. These components of the dermis form the extracellular matrix structure, which confers strength and flexibility to skin. In order to maintain skin beauty and health in accordance with this new concept, research in the field of dermal infrastructure must be applied to new concepts in skin care.

Endocrine substances are known to regulate skin structure and function, and hormones from the dermal blood supply elevate production of glycosaminoglycans and proteoglycans. Vitamins also play an important role. Ascorbic acid, for example, is well known to increase production of collagens, including types I and II. Thus dermal care should be a target for the future of skin care studies.

P. Rousselle (working with Burgeson) demonstrated that the basement membrane includes unique structures that maintain attachment of the epidermis to the dermis [32]. Components of the attachment complex provide links to the extracellular intermediate filament network of basal keratinocytes and to the extracellular matrix of the papillary dermis. Laminin 5 is essential for epidermal attachment of the basement membrane. Laminin 5 binds basal keratinocytes to the basement membrane and controls proliferation and

differentiation as these cells differentiate and reach the upper layers of the epidermis. The role played by laminin 5 is likely to be the basis of a future approach to skin care.

Nishiyama and coworkers investigated dermal-epidermal communications utilizing in vitro skin models [33]. Fibroblasts cultured with collagen fibrils form a dense collagen fibril structure. Their skin model of culturing keratinocytes on top of the dermal model also simulates skin in vivo. Interactions of keratinocytes in the epidermis with fibroblasts in the dermis result in the organization of basement membrane structures between the epidermis and the dermis. Dermal-epidermal communications, therefore are of great importance for regulating the structure and function of skin. Future skin care research efforts should include a thorough understanding of dermal-epidermal interactions and their regulation.

THE THEORY OF NEUROCUTANEOUS SKIN BIOLOGY

What should be included in future generations of skin care? Tentatively, this vision incorporates all elements of skin care, including the mechanics of skin and the mental state of the subjects. Care of the mind can impart health and beauty to the body (skin), and conversely care of the body (skin) contributes to good mental health.

The foundation for this important concept is the new belief that the old notion of thinking of the skin as a separate organ from the body must be abandoned. The skin is viewed as part of the whole body, affected by the mind inside the body and by environmental factors outside the body. This concept of the interrelationships of mind and body forms the basis for an entirely new generation of skin care. Attention in today's highly stressed society is directed toward a better understanding of the importance of skin care on relief of stress that can impact skin condition. Skin functions known to be affected by stress include the biosynthesis of sebum, epidermal cell proliferation, recovery of barrier function, and contact hypersensitivity. It is suggested that such changes occur through effects on the neuroendocrine system. Langerhans cells that participate in the cutaneous immune reaction are regulated by the nervous system [34]. Perfumes are known to have an effect on immune functions; fragrances can help relieve psychiatric depression and at the same time influence natural killer (NK) cell activity.

The types of cosmetics that can be produced in the future will be those that deliver skin care both from outside and from inside the body [35,36]. All pathways of regulation of skin function, not only those from the environment but also those involving the nervous, endocrine, and immune systems (including the brain), need more exploration. It is expected that future skin care cosmetics

will rely on interactions between mind and body, or more specifically between mind and skin.

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CHAPTER 19

Miscellaneous Skin Care Products: Skin Bleaches and Others

INTRODUCTION

This chapter includes brief descriptions of a variety of skin care products that by virtue of their claims are classified as over-the-counter (OTC) drugs in the United States. The principle of OTC drugs is not recognized in other countries and needs clarification. An OTC drug is one in which a specific ingredient (or a blend of ingredients) is claimed to benefit the user. The claimed benefit for the (drug or active) ingredient is alleviation or therapy of a medical condition.

An example of such a condition is sunburn caused by incident solar irradiation. This condition is remedied by use of a sunscreen, which commonly includes an ultraviolet (UV)-absorbing compound. This makes the sunscreening agent and the finished product drugs, at least in the United States. The common acceptance of such products as cosmetics does not change their drug status in the United States; this has also been given some recognition in other jurisdictions by requiring identification of UV absorbers and limitations on their concentration in finished products.

In accordance with U.S. regulations, advertising claims are strictly limited to those identified in a so-called OTC monograph. The monographs normally specify the concentration of the actives as well as various combinations. Warnings and directions for use are part of the labeling requirements in the United States. Infraction of these rules can result in action from the U.S. Food and Drug Administration (FDA).

Although the monographs are the basis of the regulations, they include a wealth of scientific documentation that is useful to interested scientists and formulators. For this reason, the cited OTC monographs constitute recommended

reading. In the discussion that follows only the highlights are noted; the pertinent monograph should be consulted before any development program is initiated.

The rigid rules for monographs of OTC drugs in the United States require strict adherence by marketers to certain labeling regulations. These rules apply to all OTC drugs and include the following:

- Definition: Product activity
- Ingredient: Identity of active drug
- Statement of Identity: Acceptable terms for identifying product
- Indication: Intent of product
- Warnings: Potential hazards to user
- Directions: How to use product

For the sake of avoiding repetitive statements, the six U.S. labeling elements are provided only in some of the discussions of OTC drugs.

SKIN BLEACHES

Skin bleaches are products intended to lighten or remove unwanted coloration of the skin. Since they are designed to work by penetrating the skin and interfering with the pigment production by the skin cells and thus have an effect on the normal structure and function of the skin, they are regulated as drugs in the United States.

The drive to reduce the pigmentation of sun-exposed skin is an ethnic or cultural phenomenon. Interference with melanin formation can be achieved by reducing the number of melanocytes in the skin (by applying a melanocytotoxic agent to the skin) or by interfering with the oxidation of tyrosine (by inhibiting the action of tyrosinase).

The exact mechanism by which an agent achieves skin bleaching is not understood. Dermatologists as a group are convinced that melanin in the epidermis can protect skin against UV-induced skin damage.

It comes as no surprise, therefore, that in many jurisdictions, interfering with melanin formation is considered a drug action. Nevertheless, in some cultures light skin is of great importance, and efforts are made to interfere with melanin synthesis. Details of how tyrosine is oxidized in vivo to melanin can be found in most textbooks of dermatology (see also Riley, P.A., The Evolution of Melanin, in *Melanin: Its Role in Human Photoprotection*, Zeisel, L., et al., eds., Valdenmar Publishing Co., Overland Park, Kansas, 1995).

REGULATORY STATUS OF SKIN BLEACHES IN THE UNITED STATES

Recognizing the drug nature of skin bleaches, the Food and Drug Administration (FDA) issued a Tentative Final OTC Drug Monograph, Fed Reg. *47*,

39108, on September 3, 1982. At the time of this writing, the FDA has not yet finalized this regulation. In this monograph the FDA has defined a skin bleaching active ingredient as an agent designed to bleach or otherwise lighten limited areas of hyperpigmented skin through the suppression of melanin pigment formation within skin cells.

Any product that contains an ingredient with this activity and that makes claims asserting the product can bleach or lighten the skin falls under this monograph. This proposed monograph identifies only one active ingredient, hydroquinone at 1.5 to 2%. Even though this monograph has not been finalized, the use of hydroquinone at levels outside the 1.5 to 2% range, or the use of other active ingredients would be considered "non-monograph" and cannot be marketed at this time in the United States without an approved New Drug Application (NDA). In addition to the use of hydroquinone, the proposed monograph also allows some combination drug products, combining hydroquinone with any generally recognized sunscreen active ingredient.

The labeling of the skin bleach must meet the requirements of the proposed monograph; the proposed monograph identifies specific wording for the statement of identity, indications (uses), warnings, and directions for use. These label elements are briefly discussed.

Statement of Identity

The statement of identity identifies the product by one of the following terms.

Skin Bleaching Agent
Skin Lightener
Skin Bleaching (dosage form, e.g., cream, lotion, or ointment)
Skin Lightening (dosage form, e.g., cream, lotion, or ointment)

Indications

After the signal word, "Indications," one of the following statement variations must appear.

"For the gradual fading or lightening of dark (brownish) (select one of the following: discolorations, pigment, spots, blotches, or areas) in the skin such as (select one or more of the following: freckles, age or liver spots, or pigment in the skin that may occur in pregnancy, or from the use of oral contraceptives.)"

In addition, if the product is a combination drug with a sunscreen, the following statement must also appear:

"Contains a sunscreen to help prevent darkening from recurring."

Warnings

The labeling of the product must contain the following under the signal word "Warnings."

"Avoid contact with the eyes. Some users of this product may experience a mild skin irritation. If skin irritation becomes severe, stop use and consult a doctor. Do not use on children under 12 years of age unless directed by a doctor."

In addition, if the product is a combination drug containing a sunscreen, the following statement must also appear.

"This product is not for use in the prevention of sunburn."

Directions

The labeling of the product must contain the following under the signal word "Directions."

"Adults: apply a small amount as a thin layer on the affected area twice daily, or use as directed by a doctor. If no improvement is seen after 3 months of treatment, use of this product should be discontinued. Lightening effect of this product may not be noticeable when used on very dark skin. Children under 12 years of age: do not use unless directed by a doctor." In addition, if the product is not a sunscreen combination, add the following: "Sun exposure should be limited by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin when using and after using this product in order to prevent darkening from recurring."

If the product contains a sunscreen combination, substitute the following statement for the previous direction:

"Sun exposure should be limited by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin after treatment is completed in order to prevent darkening from recurring."

In addition to the labeling requirements these drug products must also meet the general drug requirements. These include full ingredient labeling, compliance with drug current Good Manufacturing Procedures (GMP) and Drug Registration with the FDA. By the time this monograph finalizes, the labeling must also meet all the other requirements of the new OTC drug labeling regulations.

In order to compound a skin bleaching product for the U.S. market, formulators are expected to add hydroquinone to a typical skin care product (cream or lotion), which may then be used in accordance with the directions provided above.

STATUS OF SKIN BLEACHING IN JAPAN

In Western Caucasian societies skin bleaching is not widely practiced, but it plays an important role in Japan and in other ethnic societies. Thus the Japanese legal restrictions on skin bleaching agents are much less restrictive than those in the United States. In addition, research on skin bleaching and the search for potential actives is of great importance to the Japanese cosmetic industry.

Table 19.1 Antimelanogenic Skin Whitening Agents*

Melanocytotoxic agents
Hydroquinones
Hydroquinone monobenzylether
Pyrocatechol
t-Butylcatechol
Carbohydrate synthesis inhibitor
Monensin
Glucosamine
Tunicamycin
Deoxynojirimycin (5-amino-5-deoxyglucose)
Tyrosinase inhibitor
Azelaic acid
Glutathione
Cysteine
Hinokitiol
Kojic acid
Arbutin
Placenta extract
Resorcinol
Ellagic acid
4-*n*-Butyl resorcinol
Magnesium ascorbyl phosphate
Matricaria chamomilla extract

*Approved for use by the Health and Welfare Administration.

The skin bleaching agents of choice are shown in Table 19.1.
The exact mechanism that stimulates melanogensis after UVB exposure is still not fully understood.

UVB-INDUCED PIGMENTATION MECHANISM

Since human melanocyte culture became possible in 1984, various growth factors and chemokines have been reported to stimulate proliferation and melanogenesis of human melanocytes in culture. However, the physiological roles of these factors in epidermal pigmentation have not been clarified because they are cytokines of various origins. To clarify the linkage of cytokines between human melanocytes and human keratinocytes in stimulating epidermal pigmentation, the media derived from UV-exposed keratinocytes on DNA synthesis of human melanocytes were studied, showing that keratinocytes secrete relatively unknown melanogenic stimulatory factors in response to UVB exposure. It seemed reasonable to assume that the unknown factors would be responsible for stimulating melanization in the process of UVB

pigmentation. Based on the studies by Imokawa and coworkers, the unknown factor acted both as a calcium mobilizer and as a stimulator of DNA synthesis, and was associated with endothelins. It became evident that UVB-exposed human skin secretes ET-1, Big ET-1, and IL-10 into the epidermis.

ET-1 receptors on melanocytes respond with enhanced DNA synthesis and melanogenesis. The investigations further established that interference with this endothelin-induced message reduced melanin pigmentation studies. This biochemical analysis forms the rationale for the regulatory acceptance in Japan of various skin bleaching agents (Table 19.1) [1]. In practice one or more of the compounds identified in Table 19.1 is incorporated into a typical skin care product (Chapter 18). The degree of bleaching depends on the frequency and duration of use.

SOAP

Soap, as a personal care item, does not conjure up the image or glamor that many other cosmetic items elicit. However, from a regulatory perspective, soap is one of the most complex and certainly more interesting products. Based on its composition and on the claims made for it, a "soap" can be a drug, or a cosmetic, or a drug and a cosmetic, or a household substance. This unusual situation arises from the "soap exemption" in the Federal Food, Drug, and Cosmetic Act (FDCA) In the Act a cosmetic is defined as follows:

The term "cosmetic" means

(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance and
(2) articles intended for use as a component of any such articles; *except that such term shall not include soap*.

The underlined italics in the earlier definition emphasize and point out the statutory basis for the status of soap. The Act does not define what Congress intended soap to be. In order to fill that void and to create an effective scheme for regulating soap, the FDA issued a regulation defining the composition and criteria that a soap product must meet in order to qualify for the exemption (21 CFR 701.20):

The FDA interprets the term "soap" to apply only to articles that meet the following conditions:

(1) The bulk of the nonvolatile matter in the product consists of an alkali salt of fatty acids and the detergent properties of the article are due to the alkali-fatty acid compounds; and
(2) The product is labeled, sold, and represented only as soap.

Soaps as Household Substances

If a cleansing product meets the criteria as defined by the FDA, the product is not regulated by the FDA and becomes a household substance under the Consumer Product Safety Commission. As long as the soap product meets the safety requirements of the Consumer Product Act and the Hazardous Substance Act, it can be marketed without further effort.

If this product is a consumer item sold to the consumer for use at home, the label must be in compliance with the Fair Packaging and Labeling Act (FPLA) administered by the Federal Trade Commission. This means that the label must contain an identity statement, the net contents, and the name and address of the manufacturer or distributor. The net contents and the name of the manufacturer or distributor are reasonably straightforward. The identity statement can be a word, phrase, or vignette that clearly informs the consumer of the product's use.

Since ingredient labeling was enacted by the FDA under the FPLA for cosmetics, a soap that is a household substance does not require ingredient labeling. Furthermore, since it is not under FDA jurisdiction, this form of soap is not restricted to the use of FDA-approved color additives.

Cosmetic Soaps

A cleansing product that uses detergents as a replacement for or in combination with an alkali fatty acid soap is, by the above definition, a cosmetic. In addition, a soap product otherwise meeting the above definition but making cosmetic claims such as moisturizing or conditioning or some other noncleansing cosmetic claim is also a cosmetic.

As a cosmetic this cleansing product is now under the jurisdiction of the FDA. If it is a consumer product, it must still meet all of the requirements of the FPLA as noted above, in addition to full cosmetic ingredient labeling. Note that the ingredient labeling for these products is in descending order of concentration. If the cleansing product is a professional product to be used only by beauticians, barbers, or some other beauty professional, and is not intended or represented for retail sale to the consumer, then it does not require ingredient labeling or an identity statement. Many professional cosmetics are ingredient labeled voluntarily as a matter of information to the professional beautician or stylist. When these professional products are voluntarily ingredient labeled, the industry practice has been to list the ingredients alphabetically.

The identity statement for a soap bar meeting the FDA composition criteria but making other cosmetic claims should identify the product using appropriate terms. For the above examples, this might include terms such as "moisturizing soap" or "conditioning soap." A cosmetic cleansing product that uses nonsoap surfactants, in part or in total, as the cleansing agent, should not be represented

as "soap." These products can use a wide range of terms for the identity statement including such terms as "moisturizing beauty bar" or "moisturizing cleanser." If the product is in liquid form, the FDA has not taken action against a product identified as "liquid soap" even though these products are detergent-based. The FDA has recognized that the term "liquid" qualifies the "soap" term.

These cleansing products are also restricted to the usage of only approved color additives as identified by the FDA.

Again there are several categories of soaps that are drugs. Any soap bar that is represented to be an antimicrobial or antiseptic soap is a drug. Although a deodorant soap by itself would be a cosmetic, any representation that it is effective because it kills bacteria makes the product a drug. A cleansing product intended for the treatment or mitigation of acne or some other skin condition would also be a drug. A product can be both a drug and a cosmetic, and then must meet the requirements of both categories. These drug products, when intended for sale or resale to consumers, must also meet the requirements of the FPLC.

As a drug these cleansing products are also subject to the provisions of any applicable OTC monographs. Unfortunately, at the time of this writing, the FDA has not finalized the monograph on skin antiseptics or medicated soaps. Therefore the indications, warnings, ingredients, and directions for use are not expressly clear-cut. Manufacturers and distributors of these products should adhere to the relevant tentative final monographs and continually monitor the FDA for new developments. The FDA has not yet identified many antimicrobial ingredients as category 1, safe and effective, for their intended use. Many of the active ingredients in use today may not be category 1 for antimicrobial products when the monograph is finalized.

Any drug product that does not meet the requirements of an applicable OTC monograph is a new drug and must be the subject of an approved NDA. This can be a burdensome task for a consumer cleansing product. However, it should be noted that many antimicrobial soaps that have been on the market for some years do have approved NDAs.

To further complicate this situation, the FDA has recently issued new labeling regulations for OTC drug products (Fed. Reg., page 13254, 3/19/99). As with all drug products, the active ingredients must be listed first using drug nomenclature. This is not always the same as the cosmetic terminology. New legislation now requires listing of the concentrations of all active ingredients for drugs. If the product is not a cosmetic, the inactive ingredients must be listed in alphabetical order. If the drug product is a cosmetic, the inactive ingredients become cosmetic ingredients and must be listed in descending concentration.

Soap Manufacture

The processing of soap starts with alkali catalyzed hydrolysis of all types of naturally available fats and oils. Acidification yields a blend of fatty acids that can be processed to yield soap. Autoclaving of the fat stock yields the fatty acids directly, which can then be processed to generate neutralized soap. The wet base soap can be pumped into a heated agitated blender, a so-called crutcher, and blended with all types of additives. This hot blend is then poured into a mold for forming and cooling. Today, most soap bars are produced by drying, milling, and ultimately plodding, that is, extrusion. The processes require specialized equipment, and most "cosmetic" soap bars are manufactured by commercial soapers upon request by marketers.

SKIN PROTECTANT PRODUCTS

Historically, products for which skin protection claims are made have included protection from dryness, skin aging, chapping, wrinkling, windburn, sunburn, and many other skin conditions. Depending on the claims made, these products were regulated as cosmetics or drugs, or both. Traditionally, moisturizers and general skin treatments that related to the maintenance of normal skin hydration were treated as cosmetics. On the other hand, products that claim a therapeutic effect are considered drugs.

Since the main intention of skin protectants is to protect the skin from some form of damage or other deleterious conditions, they are generally considered to be drug products. This rationale creates a clear distinction between skin protectant and skin treatment preparations; the latter form the basis for Chapter 18. The FDA has published a tentative OTC final monograph on skin protectants in the Federal Register of February 15, 1983 (U.S. Fed. Reg. *48*, 6820, amended U.S. Fed. Reg. *59*, 28767). In this monograph the FDA has defined a skin protectant as a drug that "protects injured, or exposed skin, or mucous membrane surface from harmful or annoying stimuli." The FDA has further subdivided the classification of skin protectants into several categories. These monographs contain the following definitions that relate to these products.

1. *Skin Protectant.* A drug which protects injured, or exposed skin, or mucous membrane surface from harmful or annoying stimuli.
2. *Lip Balm.* A drug product that relieves and prevents dryness, or chapping of the exposed surface of the lips.
3. *Fever Blister or Cold Sore.* Treatment—Therapy for a vesicle that occurs in the junction of the mucous membrane and the skin on the lips or nose, and is caused by the virus *herpes simplex*, type I.

The highlights of this monograph detailing the permitted active ingredients and combinations, identity statement, indications, mandatory warnings, and

directions for use have been included here for reference. However, when preparing packaging or labeling copy, one should consult the latest version of the official monograph.

ACTIVE INGREDIENTS

The list of active (drug) ingredients to a large degree overlaps upon the ingredients used in cosmetic skin care products (Chapter 18).

a. Allantoin—0.5 to 2%
b. Aluminum hydroxide gel—0.15 to 5%
c. Calamine—1 to 25%
d. Cocoa butter—50 to 100%
e. Dimethicone—1 to 30%
f. Glycerin—20 to 45%
g. Kaolin—4 to 20%
h. Petrolatum—30 to 100%
i. Shark liver oil—3%
j. White petrolatum—30 to 100%
k. Zinc acetate—0.1 to 2%
l. Zinc carbonate—0.2 to 2%
m. Zinc oxide—1 to 25%

Combinations

a. Any two or more of the following as long as each ingredient is within the range prescribed earlier in the text.
   Allantoin, cocoa butter, petrolatum, shark liver oil, and white petrolatum.
b. Any two or more of the following as long as each ingredient is within the range prescribed earlier in the text.
   Allantoin, cocoa butter, dimethicone, glycerin, petrolatum, shark liver oil, and white petrolatum.
c. Any two or more of the following as long as each ingredient is within the range prescribed earlier in the text.
   Aluminum hydroxide gel, calamine, kaolin, zinc carbonate, and zinc oxide.

STATEMENT OF IDENTITY

The OTC label must include the statement of identity, "skin protectant," in addition to any established name for the drug.

INDICATIONS

One or more of the following statements must follow the signal word, "Indications."

A. Products containing any of the active ingredients allantoin, cocoa butter, petrolatum, shark liver oil, and white petrolatum:
   "For the temporary protection of minor cuts, scrapes, burns and sunburn."

B. Products containing any of the active ingredients allantoin, cocoa butter, dimethicone, glycerin, petrolatum, shark liver oil, and white petrolatum:
"Helps prevent and temporarily protects chafed, chapped, cracked, or windburned skin and lips."
C. Products containing any of the active ingredients aluminum hydroxide gel, calamine, kaolin, zinc carbonate, and zinc oxide:
"Dries the oozing and weeping of poison ivy, poison oak, and poison sumac."

As is customary with all OTC products, warning statements and directions for use must be shown. For details, the monograph should be consulted.

This OTC monograph for skin protectants has been somewhat controversial since several of the active drug ingredients are materials that have been commonly used in topical cosmetic creams and lotions to moisturize and lubricate the skin surface. Although no attempt has yet been made to convert cosmetic skin moisturizers to drugs, the word "protects" has taken on some new meanings. Cosmetic moisturizers have been used for many years to help hydrate the skin and protect it from dryness.

Until such time as this monograph is published as a final rule, this category will include a certain amount of guesswork. Products that adhere relatively closely to the tentative final monograph or products that have been in the marketplace for many years will undoubtedly continue to be marketed with little or no regulatory guidance. Products that make drug claims outside of the tentative final monograph or new products that use active ingredients not covered by the monograph may well receive FDA action.

It is likely that the FDA will not be concerned with cosmetic products that make simple skin protection claims in their labeling copy as long as that protection is related to a specific cosmetic function. However, the use of the term "Skin Protectant" as the identity statement used in conjunction with the trade name for a skin care product is likely to be restricted to drug products. Cosmetic skin care products will probably require strictly cosmetic terms for their identity statements.

SKIN ANTISEPTICS

At the time of this writing the status of topical antiseptics is not completely resolved. Personal care products that make antimicrobial claims are considered to be drug products by the FDA; they should be in compliance with an OTC monograph or the subject of an approved NDA.

The FDA has published several tentative final monographs that relate to these products in the Federal Register. On July 22, 1991, the FDA issued a tentative final monograph for First Aid Antiseptic Drug Products (U.S. Fed. Reg., *56*, 33644). On June 17, 1994, they published a tentative final

monograph for Health Care Antiseptic Drug Products. Neither of these monographs fully addresses the skin care products on the market today that make antiseptic claims. These monographs identify the category of drugs and the active ingredients that can be used. In addition, they indicate the mandatory identity statements, indications of use, warnings, and directions. Each of these monographs is described in this section. The following summaries are intended to be illustrative and provide general oversight.

Active ingredients	
Ethyl alcohol	48 to 95% by volume
Ethyl alcohol	26.9% (when used in combination as given in this text)
Benzalkonium chloride	0.1 to 0.13 %
Benzethonium chloride	0.1 to 0.2%
Camphorated metacresol	(camphor at 3 to 10.8% and metacresol at 1 to 3.6% in a ratio of 3 parts camphor to 1 part metacresol)
Camphorated phenol	(camphor at 10.8% and phenol 4.7%) in a light mineral oil, U.S.P. vehicle.
Eucalyptol	0.091% (when used in combination as noted in this text)
Hexylresorcinol	0.1%
Hydrogen peroxide	topical solution U.P.S.
Iodine (Tincture U.S.P.)	
Iodine (Topical Solution U.S.P.)	
Isopropyl alcohol	50 to 91.3% by volume
Menthol	0.042% (when used in combination as noted in this text)
Methylbenzethonium chloride	0.13 to 0.5%
Methyl salicylate	0.055 (when used in combination as noted in this text)
Phenol	0.5 to 1.5%
Povidone-Iodine	5 to 10%
Thymol	0.063% (when used in combination as noted in this text)

Tentative Final Monograph for First Aid Antiseptic Drug Products

In accordance with the Federal Food, Drug and Cosmetic Act, a representation of a drug as an antiseptic makes the product a germicide. An antiseptic

containing drug product is applied topically to the skin to help prevent infection in minor cuts, scrapes, and burns.

Combinations

1. Any single first aid ingredient may be combined with any single external analgesic active ingredient.
2. Any single first aid ingredient may be combined with any single skin protectant active ingredient.
3. Ethyl alcohol at 26.9% may be combined with eucalyptol, menthol, methyl salicylate, or thymol at their prescribed concentrations.

Statement of Identity, Indications, Warnings, and Directions for Use. These label or insert statements follow the general pattern established for OTC drug products.

TENTATIVE FINAL MONOGRAPH FOR HEALTH CARE ANTISEPTIC DRUG PRODUCTS

Definitions

This monograph was further subdivided by the FDA to include several distinct end usages. Each of these uses was defined as follows.

Antiseptic Drug. In accordance with the Federal Food, Drug and Cosmetic Act, a representation of a drug as an antiseptic shall be considered to be a germicide. A properly formulated drug product containing an ingredient included in the monograph that possesses in vitro activity against the microorganisms listed in the monograph is included.

Health Care Antiseptic. This is an antiseptic containing drug product applied topically to the skin to help prevent infection or to help prevent cross-contamination. This category includes three different types of products:

Antiseptic Handwash or Health Care Personnel Handwash Drug Product. This is an antiseptic containing preparation designed for frequent use; it reduces the number of transient microorganisms on intact skin to an initial baseline level after adequate washing, rinsing, and drying; it is broad spectrum, fast acting and, if possible, persistent.

Patient Preoperative Skin Preparation Drug Product. This is a fast acting, broad spectrum, and persistent antiseptic containing preparation that significantly reduces the number of microorganisms on intact skin.

Surgical Hand Scrub Drug Product. This is an antiseptic containing preparation that significantly reduces the number of microorganisms on intact skin; it is broad spectrum, fast acting, and persistent.

Active Ingredients

The ingredients shown in this section are the approved actives for antiseptic handwash or health care personnel handwash drug products, patient preoperative skin preparation drug products, and surgical hand scrub drug products.

1. Ethyl alcohol—60 to 95% by volume in an aqueous solution.
2. Povidone-iodine—5 to 10%
   For patient preoperative skin preparation drug products the ingredients include those listed earlier and
3. Iodine (tincture U.S.P.)
4. Iodine (topical solution U.S.P.)
5. Isopropyl alcohol 70 to 91.3% by volume in an aqueous solution.

No combinations of these ingredients were published in this monograph.

Statement of Identity

The statement of identity for products marketed under this monograph and intended for a single use is "antiseptic." In addition, the specific identity of the relevant subcategory must appear either here or be included in the "Indications" (or "Uses") section. The subcategories are:

antiseptic handwash
health care personnel handwash
patient preoperative skin preparation
surgical hand scrub.

For multiple-use products the subcategories listed earlier must also appear in the "Directions" section preceding the specific directions for each use. It is apparent that this OTC drug category is not directly applicable to cosmetic preparations. The remaining label or insert statement (indication, warnings, and directions for use) follow the general pattern established for OTC drug products.

Recent Actions

Products Intended for Preoperative Skin Care Preparation and Surgical Hand Scrubbing are obviously not cosmetic and are, therefore, not discussed here. On the other hand, germicidal claims for cosmetic skin and body washes may not meet the requirements of the tentative monograph. For example, the proposed monographs do not address the antibacterial hand lotions that have become very popular. At the time of this writing the industry is commenting to the FDA about the safety and efficacy of topical antimicrobial creams and lotions. Within recent months, however, there has been some regulatory action against some of these currently marketed products. This is a little unusual since

the FDA generally does not comment on OTC products whose safety is not at issue and that have been marketed with claims or conditions that do not completely match a proposed monograph.

The first of these actions was a "Warning Letter" of May 6, 1998, addressing an antibacterial hand lotion with triclosan. The FDA contended that the product was intended for repeated use on the hands by the general public and health care professionals as an antiseptic moisturizer. The FDA asserted that the claims for the hand lotion were for "prophylatic antimicrobial barrier use."

The second enforcement action was another "Warning Letter" sent on April 22, 1999, for a lotion. Claims for this product include: "long-lasting," "germ protection," and "... helps to reduce everyday germs that can cause infection and illness."

The FDA considered that the claims for the antibacterial antiseptic lotion were for prophylactic antimicrobial barrier use and that the product was not generally recognized among scientific experts as safe and effective. The FDA cited the product as a new drug being marketed without an NDA.

The latest enforcement action is a Federal Trade Commission (FTC) consent order against an antibacterial hand lotion with triclosan, stating that the seller did not have adequate substantiation for claims that were made in television and print advertising, as well as on the product label. The product has been advertised as a hand lotion that stops germs longer than washing alone, that it provides enough germ protection to stop germs for hours, and that it is the skin-caring way to stop germs while you moisturize.

The FTC states that the seller has represented, expressly or by implication, that:

1. The product stops germs on hands longer than washing alone.
2. The product provides continuous protection from germs for hours.
3. The product is effective against disease-causing germs, such as cold and flu viruses.

The FTC argues that although triclosan can reduce the number of germs on a user's hands, the degree and duration of germ protection have not been scientifically established.

Although this order is an FTC action based on the advertising made for a product, it is highly likely that the FTC conferred with the FDA before taking any action. These regulatory actions are interesting at this point in time because they are an indication of the current viewpoint of the regulatory agency. Even though there has been no final action on this category of drug products by the FDA at the time of this writing, these actions may well represent the future direction for this category.

DANDRUFF PRODUCTS

The appearance of visible scalp scales on hair is commonly called dandruff. The precise nature of this phenomenon has not been established. It has been described as a chronic, noninflammatory scaling of the scalp. Many investigators consider dandruff to be a mild form of seborrhoeic dermatitis, while other investigators have considered the two conditions to be separate disorders.

There is considerable evidence that dandruff is associated with *Malassezia furfur*, a dimorphic, lipophilic fungus found as part of the normal resident flora on human skin [2]. The yeast form, which is generally found on the scalp, is termed *Pityrosporum ovale. M. furfur* also appears to be associated with the appearance of seborrheic dematitis, psoriasis vulgaris, pityriasis versicolor, and other skin conditions. Despite these uncertainties, antidandruff agents to treat this condition have been available for a number of years. Products containing these agents, including shampoos, are considered drugs in the United States and are therefore regulated by the FDA.

Table 19.2 lists many of the antidandruff agents commonly used in commercial products. The first five materials in the list have been classified by the FDA, at the concentrations given in the table, as generally safe and effective. These are the only antidandruff agents that can be used over the counter in the United States without the filing of a new drug application. The FDA recently approved a new drug application for the use of ketoconazole in over-the-counter antidandruff shampoos. Finally, the last antidandruff agent in the table, climbazole, is not approved for use in the United States. It can, however, be used in many countries in Europe, Asia, Africa, and Latin America.

Table 19.2 Commercial Antidandruff Agents

Antidandruff agent	Specified concentrations	Type of formulation
Zinc pyrithione	0.3%–2%	Rinse-off
Zinc pyrithione	0.1%–0.25%	Leave-on
Salicylic acid	1.8%–3%	Rinse-off
Sulfur	2%–5%	Rinse-off
Coal tar	0.5%–5%	Rinse-off
Selenium sulfide	1%	Rinse-off
Selenium sulfide (micronized)	0.6%	Rinse-off
Ketoconazole	1%	Rinse-off
Climbazole	0.5%–2%	Rinse-off
Climbazole	0.1%–0.5%	Leave-on

Since the etiology of dandruff is still open to some argument, it is, perhaps, not surprising that there is some question concerning the exact mechanism of action of many of the antidandruff agents in Table 19.2. At least five of these agents, however, exhibit antimycotic activity against *M. furfur*, which strongly supports the assertion that this fungus is involved in the occurrence of dandruff.

Most of the actives listed in Table 19.2 exhibit substantial antimycotic activity. Zinc pyrithione has been shown to exhibit both antibacterial and antifungal activity. The mode of action has been reported to be a disruption of the proton gradients across cell membranes [3].

More than one theory concerning the mechanism of action of selenium sulfide has also been proposed; it possesses antifungal activity. Climbazole and ketoconazole are potent antifungal agents, believed to inhibit synthesis of ergosterol, an essential component of fungal membranes.

The effectiveness of salicylic acid does not appear to be a result of antifungal action but more likely a keratolytic action. This same mechanism may apply to coal tar preparations, although they may act as cytostatics.

Formulating many of these antidandruff agents into shampoos can present problems in terms of stability, odor, and interactions with other raw materials. Selenium sulfide, sulfur, and zinc pyrithione are insoluble solids and require the use of suspending agents to ensure product stability. Zinc pyrithione is unstable outside of a pH range of 4.5 to 9.5. It may slowly degrade in the presence of light and should be packaged in opaque containers. Oxidizing agents, trace ferric ions, and chelating agents such as EDTA are incompatible with zinc pyrithione and must be avoided. It should be apparent that formulation of effective antidandruff products requires careful selection of auxiliary ingredients because they may alter the efficacy of the active. The final monograph allows a wide range of drug concentrations to account for these interactions.

Personal care products intended for the treatment or control of dandruff, psoriasis, or seborrheic dermatitis are considered to be drugs and are subject to the requirements of the OTC final rule published in the Federal Register (*56*, 63554; December 4, 1991) and its amendment (Fed. Reg. 59, 4000, January 28, 1994). Although this section is primarily concerned with antidandruff formulations, OTC products intended for the treatment of psoriasis or seborrheic dermatitis will also be considered. Since these conditions are generally treated in a manner similar to dandruff, their form and formulation are similar and often coincide with those of dandruff preparations.

Most of these products are formulated as shampoos and are thus rinsed from the scalp relatively quickly. Some typical formulations are shown in this section.

Model Antidandruff Shampoo Formula*

Ingredient	Concentration	Function
Primary surfactant	12%–20%	Cleansing agent
Dihydrogenated tallow phthalic acid amide	4–7%	Suspending agent
Zinc pyrithione	2%	Antidandruff agent
Amide	1–5%	Foam, viscosity booster
Miscellaneous	q.s.	pH control, fragrance, preservatives, color, water, etc.

*After Sejic, B., and Shapiro, I., *Cosmet. Toiletries* 1992, **107**(V), 103.

Antidandruff Shampoo with Zinc Pyrithione

A. Water	38.90%
B. Acrylates/C_{10-30} alkyl acrylate cross-polymer	1.00
C. Sodium hydroxide, 18%	0.10
D. Propylene glycol	5.00
Sodium lauryl sulfate, 29%	16.00
Sodium laureth-3 sulfate, 30%	16.00
Cocamidopropyl betaine	4.00
E. Polyquaternium-10	0.25
F. Water	12.00
G. DMDM hydantoin	0.30
Sodium hydroxide (18%)	1.30
H Polyquaternium-30	1.00
Dimethicone copolyol	0.20
Zinc pyrithione 48%	2.50
Fragrance	0.40
FD&C blue #1, 0.1%	1.05

Procedure. Disperse B in warm (45 °C) A using rapid agitation. Reduce mixing speed and mix for 20 minutes. Partially neutralize with C. Add D components in order shown to ABC using slow mixing. Disperse E and F, heat to help hydration. Add G; mix until uniform. Add E, F, and G to batch. Add H components in order shown to batch.

Antidandruff products can also be formulated in nonshampoo forms such as hairdressings or conditioners. Products in this category are formulated into two basic types depending on their form. Some products, such as hair conditioners, are designed to be rinsed from the hair shortly after application. From a regulatory perspective these products are similar to the shampoo products.

Other antidandruff forms have been formulated to be left in the hair and not rinsed after application. These products are distinct from the rinse-off forms and do require slightly different labeling and, in some cases, different levels of active ingredients.

As described, earlier these antidandruff products are drugs and subject to the OTC antidandruff final rule. As with all categories of OTC drugs, the composition and labeling for these products are closely controlled by the FDA. The OTC dandruff monograph requires specific compliance in five general areas: active ingredients, statements of identity, indications of usage, warnings, and directions for use. Since most of these vary slightly depending on the rinse-off/leave-on nature of the products, each of these forms will be tabulated in this section.

ACTIVE INGREDIENTS

The active ingredients for these products vary both with the intended use and with the rinseability of the formulation. Based on these considerations the active ingredients are identified below for their specific approved uses.

Rinse-off products (including shampoos)

The only active ingredients permitted at the present time for rinse-off products are as follows:

For the treatment of dandruff, psoriasis, and/or seborrheic dermatitis: Coal tar 0.5–5%; salicylic acid 1.8–3%

For the treatment of dandruff and/or seborrheic dermatitis: Selenium sulfide 1%.

For the treatment of dandruff only: Zinc pyrithione 0.3–2%; sulfur 2–5%; selenium sulfide (micronized) 0.6%; the combination of sulfur and salicylic acid when both are used within their active level concentration ranges.

For the treatment of seborrheic dermatitis only: Zinc pyrithione 0.95–2%.

Leave-on products

The only active ingredients permitted at the present time for leave-on products are as follows:

For the treatment of dandruff, psoriasis, and seborrheic dermatitis: Coal tar 0.5–5%. When using this ingredient the labeling shall specify the identity and concentration of the coal tar, and its source; the other active is salicylic acid 1.8–3%.

For the treatment of dandruff and seborrheic dermatitis: Zinc pyrithione 0.1–0.25%; selenium sulfide 1%.

For the treatment of dandruff only: Sulfur 2–5%; selenium sulfide (micronized) 0.6%; the combination of sulfur and salicylic acid is sanctioned when both are used within their active level concentration ranges.

In addition to the controlled use of these active ingredients, each product must be labeled with specific statements of identity, indications, warnings,

and directions in compliance with the new OTC drug labeling regulations published in the Federal Register on March 17, 1999. The labeling regulations resemble those for other OTC drugs.

DRUG ASTRINGENTS

Drug astringents are subject to the final rule on astringent drug products (U.S Fed. Reg. *58*, 54458, Oct. 21, 1993) and the amendment of June 3, 1994, Fed. Reg., *59*, 28767). In these OTC monographs the FDA has defined these products narrowly as drug products that are "applied to the skin or mucous membranes for a local and limited protein coagulation effect."

In line with this definition the only active ingredients approved for use as drug astringent products are aluminum acetate (0.13 to 0.5%), aluminum sulfate (46 to 63% based on the anhydrous equivalent) and Hamamelis Virginiana water (U.S.P.). The use of any other active ingredients or of these ingredients at concentrations outside the above ranges would make the product "non-monograph."

The usual labeling requirements, including a statement of identity, indications, warnings, and directions, are required.

CORN/CALLUS REMOVER AND WART REMOVER DRUG PRODUCTS

Products that are intended to treat or remove corns, calluses, or warts are considered to be drugs under the Food and Drug Act. As such, any over-the-counter (OTC) products making claims for these effects must be in compliance with a final monograph for these indications. Although these categories are very similar, the FDA has separated wart removers from the corn and callus remover products and published two separate final monographs in the Federal Register. Both of these monographs were issued on August 14, 1990 (U.S. Fed. Reg. *55*, 33245, 1990; U.S. Fed. Reg. *55*, 33258, 1990); the amended U.S. Fed. Reg. *59*, 60315, 1994.

As with all OTC drugs, products making these claims must meet all of the monograph requirements for composition and labeling. In addition, as drug products, they must also meet the requirements for OTC labeling as published in the Federal Register of March 17, 1999. This includes full ingredient labeling and the identification of the percent of the active ingredients in the product. These monographs include several vehicles, for example, solutions or plasters.

Active Ingredients

The only active ingredients permitted in these products are various concentrations of salicylic acid in a variety of vehicles, which include adhesive plasters.

Indications, directions, and warnings are those intended for topical drugs, not cosmetics. They are therefore not further discussed.

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CHAPTER 20
Sunscreens

INTRODUCTION

The purpose of sunscreen preparations is to prevent or minimize the harmful effects on skin of solar/UV radiation. As such, they are considered to be drug products by the Food and Drug Administration (FDA). In contrast, suntan preparations are cosmetic products because they are intended to enhance skin color. The legal distinction between cosmetic and drug products is not at all trivial and must be well understood by all in the cosmetic industry. Without providing full details, drugs are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and include articles (other than food) intended to affect the structure or any function of the body of humans or animals. In contrast, cosmetics include products designed to provide a topical, short-term, or temporary affect. They can cleanse, perfume, condition, or beautify the skin, nails, or hair.

Many years ago a dark tanned exposed skin was the mark of the working class, people who worked in the fields as it were. The upper class prided itself in presenting a white face free from any signs of the outdoors and sun exposure. As time went by and styles changed, so did the value judgment of a tanned appearance. Not long ago a dark deep tan was equated with health and wealth: "You must have acquired that tan on a glorious vacation on some tropical island," certainly not working in the fields like some hired hand!

Today it is known that a tan is the body's response to having been damaged by exposure to the ravages of sunlight. It has been asserted that the body manufactures melanin in an attempt to prevent/minimize further damage. Chapter 1 provides some limited insight into the argument that tanning minimizes further damage. There is no such thing as a "safe tan."

Sunscreens, which reduce both the tanning response and other (immunological) skin damage, can also alleviate the damaging action of sunlight on hair.

Thus it has become common to include some of the sunscreens discussed in this chapter in a variety of hair products.

SUNSCREEN AGENTS

The FDA defines sunscreen active agents [1] as "An ingredient listed in Sec. 352.10 that absorbs, reflects, or scatters radiation in the ultraviolet range at wavelengths of 290 to 400 nanometers."

Suntanning agents are not defined in the sunscreen monograph since the FDA considers the tanning process to be a cosmetic one and falls outside this drug monograph. However, the FDA recognizes that most consumers erroneously believe that acquiring a tan (either naturally or by application of a "tanning agent" such as dihydroxyacetone) provides some measure of protection from the ravages of sun exposure. Some people apply sunscreen at the beginning of the summer, when their skin is white and untanned, because that is when they need the protection. However, after experiencing several burns, they think they have developed a tan "which protects them from further damage." They then switch to a lower SPF (sun protective factor) sunscreen or none at all! Both scenarios are quite dangerous. It has been estimated that acquiring a rather dark tan gives the same degree of protection as using an SPF 2–4 product. For this reason, the FDA requires that a warning statement be placed on the label of a DHA-containing product without a sunscreen: "Warning: this product does not contain a sunscreen and does not protect from the sun."

The approved sunscreening agents may be divided into two categories:

1. Materials that absorb energy in the UV range—in this category we find the organic sunscreens, sometimes falsely referred to as the "chemical" sunscreens. In fact, of course, all materials are "chemical" in nature.
2. Materials that block, scatter, and may absorb energy in the UV range—titanium dioxide and zinc oxide belong to this group. Titanium dioxide reflects and scatters practically all radiation in the UV and visible range (290–777 nm), thereby preventing or minimizing both sunburn and suntan.

Table 20.1 identifies the sunscreen drug agents currently permitted to be used in the United States and the European Economic Community (EEC).

ULTRAVIOLET RADIATION ABSORPTION

The ultraviolet spectrum influencing man's health on the earth's surface is divided into twosegments:

1. UVB (290–320 nm)
2. UVA (320–400 nm)

Table 20.1 Sunscreens Permitted for use in Final Monograph [1]

Sunscreen active (Drug/FDA Name)	Maximum%(US)	Maximum% EEC
Aminobenzoic acid	15	5
Avobenzone	3	5
Cinoxate	3	10
Dioxybenzone	3	10
Homosalate	15	10
Meradimate*	5	—
Octocrylene**	10	10
Octinoxate***	7.5	10
Octisalate****	5	5
Oxybenzone	6	10
Padimate O	8	8
Ensulizole†	4	8
Sulisobenzone	10	5
Titanium Dioxide	25	—
Trolamine Salicylate‡	12	—
Zinc Oxide	25	—

Current USAN Name	Previous Designation
*Meradimate	Menthyl anthranilate
**Octocrylene	2-ethylhexyl 2-cyano-3,3-diphenylacrylate
***Octinoxate	Octyl methoxycinnamate
****Octisalate	Octyl salicylate
†Ensulizole	Phenylbenzimidazole sulfonic acid
‡Trolamine salicylate	Triethanolamine salicylate

UVAI (340–400 nm)
UVAII (320–340 nm)

Shorter wavelengths (UVC) do not reach the earth's surface because they are absorbed by stratospheric ozone. The energetics of the incident radiation are controlled by the fundamental equations

$$E = h\nu$$
$$\nu = c/\lambda \text{ and}$$
$$E = hc/\lambda,$$

where E = Energy, h = Planck's constant (6.62×10^{-27}erg/s), (ν=Frequency (cycles per second), λ = Wavelength, and c = Speed of light (3.0×10^{10} cm/s)

The radiation energy decreases as the wavelength increases. This means that UVA, recently subdivided into UVAI and UVAII, is the least energetic radiation while, UVC is the most energetic and can used for germicidal

application. However, the opposite is true as regards skin penetration; UVA penetrates the deepest (even down to the dermis), while UVC does not even penetrate the stratum corneum, in spite of its high energy. It is not surprising, therefore, that UVA radiation has been implicated in DNA damage, aging and wrinkling, and other long-term effects. The solar UV energy reaching the earth's surface is 99.5% UVA; UVB accounts for 0.56%, while UVC is absent due to ozone absorption. Nevertheless, UVB accounts for all skin cancers and erythemas resulting from sun exposure.

The chemistry of sunscreens has been studied extensively [2]. While the UV absorbers can differ considerably in their chemical structure, they all share one common property: an ability to absorb energy that corresponds to the wavelengths in the UV range. The molecule starts in a low energy (stable) state, also known as the ground state. It is excited to a higher energy state (less stable). The molecule then disposes of this excess energy and returns to the ground state. The energy can be given off as IR (infrared, fluorescence, phosphorescence, or a change in the conformation of the molecule, that is, (*cis-trans* isomerization when a double bond is present, as with the cinnamates). Sometimes the absorbing molecule is activated to react with neighboring molecules, which results in destruction. As a general rule, sunscreen molecules have an electron-donating group (methoxy and amino being prevalent) and an electron-withdrawing group (carbonyl predominating but a cyano group can also serve this function, e.g., octocrylene). All of the UV-absorbing sunscreens require the presence of a benzene ring. This is not at all surprising since it is quite easy for the benzene ring to absorb energy and then delocalize electrons. The benzene ring can be thought of as having a series of conjugated (alternating) double bonds, which are constantly switching position. It is thus quite easy for the benzene ring to transfer energy from one part of the molecule to another part. The energy needed to do this is approximately 79 kcal/mol, which roughly corresponds to the UV range. Think of the benzene ring as having six positions for groups or atoms to be placed. If an electron-donating group (e.g., a methoxy OCH_3) is in para position to an electron-withdrawing group (carbonyl C=O), an optimal situation for UV absorption is created. The most popular sunscreen in the world (octyl methoxycinnamate) is of this type. If the positioning of the two groups is ortho, then the absorption efficiency is lessened, and the molar extinction coefficient is lowered. The easier it is for a molecule to absorb energy, the more the UV curve is shifted to the right (longer wavelength), and eventually a UVA sunscreen is created. The best of the UVA sunscreens contain more than one benzene ring for this reason. Avobenzone is a good example, with a wavelength of maximum absorption of 358 nm, which is well within the UVA region. Thus chemical structure plays a critical role in the performance of any sunscreen. Another factor to

be considered when using the organic sunscreens is their interaction (from a chemistry standpoint) with solvents [3]. These effects can be considered to be of two types:

1. Effects on UV spectrum
   It is well known that sunscreen absorption curves (maximum absorption, λ_m, and molar absorption, ε) can be influenced by interactions with solvents. Sunscreens, which are nonpolar in their ground state, (e.g., octinoxate) are stabilized when placed into a nonpolar solvent (e.g., mineral oil). Thus it takes more energy for this screen to be elevated to its excited state. This increase in required energy causes λ_m of the curve to shift to shorter wavelengths (higher energy). Additionally, since there are now fewer permitted excitations, the height of the curve (extinction coefficient) is decreased. In the case of octinoxate, for example, ε in aqueous alcohol is 25% higher than in the less polar hexylene glycol. Both of these factors will result in a lowered SPF. If the sunscreen's excited state is stabilized by interaction with a solvent, then the UV absorption curve tends to shift to longer wavelengths (lower energy). These solvent effects are only seen with the para substituted sunscreens. The ortho substituted sunscreens (e.g., salicylates) possess internal stabilization through internal hydrogen bonding and thus do not exhibit these effects.

2. Solubilization effects (solubility parameter)
   Organic sunscreens are commonly placed into the oil phase of emulsions and assumed to be soluble because we observe a clear solution. Unfortunately, this observation is an oversimplification of what may really be happening. One measure of the polarity of a material is its solubility parameter. Generally speaking, as the polarity of the substance increases, the solubility parameter also increases. If the solubility parameter of the solvent is not matched to the solubility parameter of the sunscreen, agglomeration of the sunscreen may occur. This will effectively decrease the concentration of the sunscreen and the SPF will decrease. In fact, when this is seen the formulator will often add additional sunscreen and will be perplexed to see the SPF drop even further.

The final categories of sunscreen materials are the physical sunscreens. Titanium dioxide and zinc oxide are currently approved as sunscreen drugs for use in the United States. Both have been used in the United States and around the world for many years in non-sunscreen applications such as make-up and for zinc oxide as a skin protectant, but it was not until recently that they have gained real popularity in the sunscreen arena. When these two materials were utilized at excessively high levels, unacceptable skin whitening resulted. However, with the availability of micronized titanium dioxide and zinc oxide, they can be incorporated into sunscreen preparations with little skin whitening due to their small particle size. Coatings of these materials facilitate dispersion and minimize agglomeration both in the product and on the skin.

SUNSCREEN UTILITY

AMINOBENZOIC ACID (INCI NAME PABA)

This material has been used for many years and actually predates most of the other sunscreens. It is a para disubstituted material, more widely known as PABA, and has a maximum absorption at 283 nm, which limits its ability to adequately cover the erythemal range (290–320 nm) and thus its effectiveness in achieving high SPFs. Questions about its safety, its poor oil solubility (it is a polar molecule), and inadequate performance as a sunscreen have reduced its usage.

AVOBENZONE (INCI NAME BUTYL METHOXYDIBENZOYLMETHANE)

Approved for use by the FDA in 1997, this off-white powder with limited oil solubility exhibits excellent UVA absorbance (lambda max. 358 nm). Its extinction coefficient (ε) of 34,720 is higher than that of any other sunscreen that is available for use in the United States. Questions have been raised concerning its photostability [4,5]; these investigations are continuing. Due to its limited absorption in the erythemal range, avobenzone does not contribute significantly to the SPF. Avobenzone can be used alone or in combination with the sunscreens included in the following list:

Diethanolamine methoxycinnamate (not currently FDA-approved)

Dioxybenzone
Homosalate
Octocrylene
Octinoxate
Octisalate
Oxybenzone
Sulisobenzone
Trolamine salicylate

CINOXATE

This UVB sunscreen is no longer available for sale in the United States. It is a para disubstituted sunscreen with absorption characteristics similar to those of octinoxate.

DIOXYBENZONE (INCI NAME BENZOPHENONE 8)

One of the benzophenones available as sunscreens, this sunscreen (like the other two benzophenones) has a moderate absorptivity with two peaks: one at

284 nm, extinction coefficient = 13,200 and another in the short UVA range (327 nm extinction coefficient = 10,400). Thus (because of its short wavelength UVA absorption) it is used to boost the SPF.

HOMOSALATE (INCI NAME HOMOSALATE)

An ortho substituted sunscreen (salicylate derivative) that has (like the other salicylate sunscreens) a very low extinction coefficient (4,600) and a lambda maximum of 306 nm, this sunscreen is used as the SPF standard in the United States. While it was used for many years, it was considered to be very inefficient and is thus rarely used.

MERADIMATE (INCI NAME MENTHYL ANTHRANILATE)

The only liquid UVA sunscreen available for use, this ortho disubstituted sunscreen (with an amino group acting as the electron-donating group) has a lambda maximum of 336 nm and a mediocre extinction coefficient (5,600) due to the ortho disubstitution. It can help to boost the SPF when virtually all the UVB energy has been absorbed by other more efficient UVB sunscreens.

OCTOCRYLENE (INCI NAME OCTYLCRYLENE)

Largely unused until the 1980s, this diphenyl acrylate sunscreen has a rather broad curve due in part to the presence of two benzene rings (lambda maximum = 303 nm, extinction coefficient = 12,600), and has been used to boost the SPF and enhance water resistancy.

OCTINOXATE (INCI NAME OCTYL METHOXYCINNAMATE)

A para disubstituted sunscreen with excellent UVB absorbance (lambda maximum = 311 nm, extinction coefficient = 23,300) it is, by far, the most widely used sunscreen in the United States and indeed the world. It has good oil solubility and is most effective when combined with other sunscreens to achieve high SPFs. In addition to having a good electron-donating group (methoxy), it has a conjugated double bond, which further allows for increased opportunity for electron delocalization.

OCTISALATE (INCI NAME OCTYLSALICYLATE)

Another salicylate type of sunscreens (ortho disubstituted) exhibits rather poor absorption in the UV range (lambda maximum = 307 nm, extinction coefficient = 4,900). It is rarely if ever used as the sole sunscreen due to its absorptivity. It is often used in combination with oxybenzone, where it assists in solubilizing it.

OXYBENZONE (INCI NAME BENZOPHENONE 3)

One of the benzophenones available as sunscreens, it is seldom used as the only sunscreen and has a moderate absorptivity with two peaks. One at 288 nm (extinction coefficient = 14,000) and another in the short UVA range 327 nm (extinction coefficient = 9,400). Thus (because of its short wavelength UVA absorption) it is used to boost the SPF and to achieve high SPFs.

PADIMATE O (INCI NAME OCTYL DIMETHYL PABA)

This para disubstituted sunscreen with excellent UVB absorbance (lambda maximum = 311 nm, extinction coefficient = 27,300) was for more than a decade the most widely used sunscreen in the United States and indeed in the world. However, with the onset of the "PABA-free" marketing strategy in the early 1980s, its popularity waned significantly. At the present time its usage is quite limited, in spite of the fact that it is one of the most efficient UVB sunscreens available and is approved as a sunscreen around the world. It has good oil solubility and is most effective when combined with other sunscreens to achieve high SPFs. Its excellent absorptivity is due to the presence of a very good electron-donating group (amino) in the para position (relative to the electron-withdrawing carbonyl group).

ENSULIZOLE (INCI NAME PHENYLBENZIMIDAZOLE SULFONIC ACID)

This sunscreen is sold as a white powder in the acid form and is insoluble in water or oil. It must be neutralized before use with an appropriate material (TEA, NaOH, KOH, etc.) to make it water-soluble (pH range 6.8–8.0). It exhibits excellent UVB absorbance (lambda maximum = 310 nm, extinction coefficient = 28,250) and is actually the most efficient sunscreen available for use in the United States. In addition to its UV absorbance, this is probably due to two factors:

1. It partitions itself into the upper layers of the stratum corneum and thus creates a very uniform and continuous sunscreen film.
2. This sunscreen is more polar in the ground state than in its excited state. Thus, when it "sees" the nonpolar skin lipids the curve shifts to the right (longer wavelengths) since the excited state (less polar) is stabilized. This shift allows for increased sunscreen efficiency.

This sunscreen is rarely used in water-resistant products due to its water solubility. It is widely used in sunscreen gels.

SULISOBENZONE (INCI NAME BENZOPHENONE 4)

One of the benzophenones available as sunscreens, this sunscreen (like the other two benzophenones) is seldom used as the only sunscreen. It has a moderate absorptivity with two peaks: one at 286 nm (extinction coefficient = 13,400) and another in the short UVA range 324 nm (extinction coefficient = 8,400). Thus (because of its short wavelength UVA absorption) it is used to boost the SPF and achieve high SPFs. Unlike the other two benzophenones (dioxybenzone and oxybenzone), this sunscreen is water-soluble due to the presence of a sulfonic acid group.

TITANIUM DIOXIDE (INCI NAME TITANIUM DIOXIDE)

This inorganic sunscreen has been used in makeup products for many years, but only recently has it achieved any measure of popularity in the sunscreen arena. Early sunscreen products used pigment grade material, which resulted in excessive skin whitening. But advances in particle size reduction have allowed the development of titanium dioxide of small particle size (15–75 nm), and narrow distribution of particle sizes has minimized skin whitening during application. Additionally, new surface treatments have all but eliminated agglomeration during the manufacturing process. Cosmetic formulators can also choose to use predispersed materials, which can eliminate the need for high shear mixing. The UV absorption curve for titanium dioxide is principally in the UVB region. When used in sunscreen formulations, care must be taken to ensure good suspension, particularly at elevated temperatures (45–500 °C). While this material (when used as a sunscreen) is regulated in the United States as a drug, it is not regulated as such in the rest of the world.

TROLAMINE SALICYLATE (INCI NAME TEA SALICYLATE)

Another of the salicylate sunscreens (ortho disubstituted), it too exhibits rather poor absorption in the UV range (lambda maximum = 298 nm, extinction coefficient = 3,000). It is rarely if ever used as the sole sunscreen due to its absorptivity. It is made by neutralizing salicylic acid (ortho hydroxy benzoic acid) with triethanolamine. The resulting sunscreen is water-soluble.

ZINC OXIDE (INCI NAME ZINC OXIDE)

This inorganic sunscreen has been used in makeup products for many years and as a skin protectant, but only recently has it achieved any measure of popularity in the sunscreen field. Early sunscreen products used pigment grade material, which resulted in excessive skin whitening. But advances in particle size reduction have allowed the development of zinc oxide of small particle

size (15–75 nm) and narrow distribution of particle sizes, which has minimized skin whitening during application. Additionally, new surface treatments have all but eliminated agglomeration during the manufacturing process. Cosmetic formulators can also choose to use predispersed materials, which can eliminate the need for high shear mixing. The UV curve for zinc oxide, while principally in the UVB region, extends well into the UVA region also. Thus it can be used to provide broad-spectrum protection. When used in sunscreen formulations, care must be taken to ensure good suspension, particularly at elevated temperatures (45–50 °C). While this material (when used as a sunscreen) is regulated in the United States as a drug, it is not regulated as such in the rest of the world. While it is generally thought that zinc oxide is insoluble, this is not quite the case. There is enough solubility that care must be taken in formulating with this material. Since it is a polyvalent material, it cannot be used with electrolyte-sensitive thickeners (e.g., carbomer) or with fatty acids where it will act as a neutralizer and form a polyvalent soap (water-in-oil emulsifier) and cause emulsion instability.

SUNSCREEN REGULATIONS

In the United States sunscreens have been regulated as drugs since the publication of the Proposed Sunscreen monograph on August 25, 1978. A Tentative Final Sunscreen Monograph replaced this document on May 12, 1993, and on May 21, 1999, the FDA issued the Final Sunscreen Monograph, which is expected to become the "law of the land" in the United States on May 21, 2001. This document is more than 60 pages in length and should be studied in detail by anyone who plans to market a product in this category. Before studying these regulations one should understand the concepts of MED and SPF. MED is an acronym for minimum erythemal dose. It is the amount of energy that a person is exposed to before a just perceptible reddening is observed (16–24 hours later). For a person of light skin who burns sometimes and still tans, at the latitude of New Jersey in the summer, considering the noonday sun, it is approximately 20 minutes. The SPF is a dimensionless ratio defined as the MED (PS—protected skin)/MED (US—unprotected skin). Following are a few of the more important points presented in this document:

1. Labeling
   The sunscreens must be listed under the heading "Active(s)" with each sunscreen being listed using its drug approved designation (not the INCI name), the percentage used, and the function (sunscreen) must also be listed. If no cosmetic claims are made (moisturizing, etc.), the other ingredients must be listed in alphabetical order using drug names where applicable. If a cosmetic claim is made (moisturizing, nongreasy, etc.), and this is almost always the case, then the

ingredients must be listed in decreasing order by weight/weight predominance down to one percent or less, below which any sequence is acceptable.

2. SPF Determination
   The SPF is measured using a 20-person test (25 maximum). A sunscreen standard incorporating 8% Homosalate (homomenthyl salicylate) is used which will give an SPF of approximately 4 when the sunscreen is applied at a level of 2 mg/cm^2. At the current time there is no approved high SPF standard in the United States. Details for compounding the standard sunscreen are part of the Final Monograph [1].
3. Water Resistance Measurement
   After the sunscreen is applied and permitted to air dry for 20 minutes, the subject is submerged in water for 20 minutes of moderate activity and then permitted to air dry. This is repeated again, and the SPF is measured. The resulting value is listed as the "water resistant" SPF. If however, two additional 20-minute immersions are performed, then the resulting SPF is listed as "very water resistant." The term "water-proof" is no longer permitted since, in the eyes of the FDA, it implies an absolute (the sunscreen never washes off) that is not the case. Other claims such as "all day protection, rub-proof, and so forth" are also not permitted.
4. Expiration dating is no longer required.
5. Products that make a "claim to accelerate or stimulate the tanning process" are unapproved drugs.
6. The maximum permitted SPF that can be claimed is 30+.
7. Suntanning products or products containing DHA (dihydroxy acetone) that do not contain a sunscreen must carry a warning label: "Warning-This product does not contain a sunscreen and does not protect against sunburn. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn." This is required because, contrary to the public at large, the agency believes that a tan does not provide significant protection.
8. There is no longer a minimum use level for sunscreen actives. However, the SPF must be at least two times the number of sunscreens utilized, and each sunscreen must contribute at least two SPF units to the stated SPF.
9. UVA issues such as claims testing methodology and standards remain unresolved and will be addressed in a "future issue of the Federal Register."
10. Terms such as "natural," "chemical free," and "nonchemical" are "false and misleading" and are thus not permitted.
11. The new Product Category Designations (PCD) are:
    Minimal sun protection SPF 2 to under 12
    Moderate sun protection SPF 12 to under 30
    High sun protection SPF 30 or above
12. The term "PABA Free" is not permitted. However the following claim can be made: "Aminobenzoic Acid (PABA)-free"
13. The term "sunblock" is not permitted since it implies an absolute and complete level of protection.

PHOTOSTABILITY TESTING

As noted earlier, sunscreen agents are chemicals that have the ability to absorb energy and change their state (ground state to excited state transition). In this excited state they are inherently less stable and can undergo further changes or chemical interactions that may or may not be reversible. They dispose of this excess energy in various forms. Unfortunately, this phenomenon has not been studied in depth for more than a few materials. While it can be shown that sunscreens can degrade when exposed to UV radiation [4–7], other factors must be considered in this regard. When the concentration of sunscreen under test decreases to 10 ppm or less, practically all sunscreens will exhibit some degradation; this, however, may not represent a realistic situation. Typically, sunscreens are used at much higher levels in formulations. After the water (in an emulsion) evaporates, the actual concentration on the skin can be as high as 40%. When tested at this concentration, practically all sunscreens are quite stable. Other factors are the intensity and rate of delivery of the radiation used to photodegrade the sunscreen. All sunscreens probably degrade if subjected to a high enough dose of energy. It is not only the total energy that is important; it is also the intensity (rate) that is crucial. The energy used must simulate actual sunlight exposure for the data to be relevant and predictable. Additionally, most formulations contain not just one but several sunscreens, and each sunscreen can exert a protective effect on the other sunscreens. Unfortunately, this is not always the case. Skin topography and skin lipids [8] can also play a most important role in sunscreen degradation. Lastly, and most importantly, one must remember that human (in vivo) testing remains the most meaningful ultimate test.

EVALUATION OF SUNSCREEN PRODUCTS

The evaluation of sunscreen formulas is more complex than that of other (nondrug) products. Many factors must be considered before a product is ready for market.

1. Stability Testing
   The product must be tested in glass and the actual package it will be sold in at accelerated storage conditions. A typical testing protocol follows:
   4 °C (1 year)
   25 °C (1 year)
   37 °C (6 months)
   45 °C (3 months)
   5 freeze/thaw cycles (24 hours at −10 °C/24 hours at 25 °C)
   It has been estimated that three months' storage at 45 °C corresponds to two years' storage at room temperature.

Additional testing to be considered includes:
UV/sunlight exposure
Weight loss testing
Label testing
Drop testing of the filled package
Centrifuge testing (heat the product to 60 °C and centrifuge at 3,000 rpm for 30 minutes)
Things to be monitored include: color, odor, pH, viscosity, analysis of actives, analysis of preservative, and so forth.

2. Efficacy Testing
   As described earlier sunscreens must be evaluated to determine their SPF via a 20-person panel test. In vitro tests [9,10] are available which use "Transpore" tape (3M Corporation), which is a porous tape, or an artificial "skin" called "VitroSkin" (Innovative Measurement Solutions) as the substrate onto which a film of sunscreen has been placed. Animal models have also been used with varying degrees of success. This is then subjected to UV exposure and the resulting "SPF" is calculated. Two popular instruments for performing this test are the SPF-290 (Optimetrics, USA) and UV Transmittance Analyzer (Labsphere Co.).

3. Safety Testing
   Safety testing of cosmetics is not legally required, but any product offered for sale must be "safe." At the present time the RIPT (repeat insult patch test) is most used. This human test is typically performed on 50–200 panelists and is quite predictive of potential irritation. Another test that is commonly performed is the facial sting test. This test predicts the likelihood of the sunscreen to sting the face when applied. There are many other safety tests, both human and alternative to human testing. The reader should consult Chapter 34 for additional information.

FORMULATION OF SUNSCREEN PRODUCTS

Before start of the formulation process a target SPF must be chosen. Depending on the target SPF the sunscreens and their concentrations will be chosen. A variety of claims needs to be selected: "broad-spectrum" (UVA) claim, water-resistant, or target group. All claims and choices are governed by regulatory, efficacy, (PABA-Free?), aesthetics (nonwhitening, etc.), and cost considerations. Some general technical criteria that may help in sunscreen selection and formulation follow:

1. Good absorption in the UVB (and UVA when required) region
2. Photostability
3. Chemical stability
4. Absence of staining on clothes and skin
5. Minimal percutaneous absorption
6. Water solubility (for water-resistant products)

7. Irritation potential
8. Sensitization potential
9. Phototoxicity potential
10. Solubility in cosmetic bases
11. Easy handling in manufacturing
12. Stability in cosmetic bases

CHOOSING THE SUNSCREEN PRESENTATION

The formulator can choose from several presentations, frequently made in collaboration with marketing personnel.

Emulsions (oil-in-water and water-in-oil)
Creams or lotions
Gels (aqueous, hydro-alcoholic, or oleaginous)
Clear, opaque, or translucent
Oils (mineral oil, vegetable oil, silicones, esters, etc.)
Ointments
Sticks
Mousses/Aerosol Sprays
Pump sprays (oils, aqueous, emulsions, alcoholic, hydro-alcoholic, etc.)

Each of these presentations has advantages and disadvantages, but there can be no compromise on sunscreening performance. The product must:

1. Deposit a uniform sunscreen film onto the skin.
2. Provide a thick sunscreen film to maximize the optical path length and thus increase the likelihood of a photon interacting with a sunscreen molecule.

EMULSIONS

The majority (by far) of all sunscreen products sold throughout the world are emulsions. The reason for their popularity is based on their performance with respect to efficacy, skin feel, and cost. Creams and lotions are essentially the same in composition and chemistry, differing only in the apparent viscosity. Creams are categorized by their high viscosity (greater than approximately 50,000 cps), while lotions typically exhibit a viscosity of less than 50,000 cps. Oil-in-water products are easier to manufacture and stabilize, but they are very difficult to make water-resistant due to the presence of hydrophilic emulsifiers. As the emulsion (O/W) is applied to the skin the water evaporates, leaving a film of sunscreen, film formers, and emulsifiers. If the concentration of emulsifier left on the skin is too high, the sunscreen will readily wash off when the person sweats or swims. Careful choice of sunscreen, emulsifier, and film former can minimize this effect. Additionally, the introduction of

hydrophobically modified polymeric emulsifiers (e.g., C10–30 alkyl acrylate crosspolymer) allows development of "emulsifier-free" emulsions, which are inherently water-resistant. There is a formulation strategy that permits development of very water-resistant oil-in-water sunscreen emulsions. A product that contains both hydrophilic and lipophilic emulsifiers and is stabilized by the inclusion of polymeric thickeners (for example, carbomer) that are sensitive to electrolytes, and further includes a film former can accomplish a similar goal. When this sunscreen is applied to skin, the salt on skin salts out the polymer, destabilizing the emulsion. Further rubbing helps to evaporate more water, changing the oil to water ratio, favoring a water-in-oil emulsion. The lipophilic emulsifier now predominates, and the emulsion inverts to a water-in-oil type, which is water-resistant. This approach has indeed been perfected and is currently utilized by several large finished good manufacturers.

The second type of emulsion is the water-in-oil variety. This type of emulsion is inherently water-resistant and will also provide maximum sunscreen efficiency. In this emulsion type, oil and oil phase components (including most sunscreens) form the external phase. When the product is applied to the skin, the continuous phase (containing the sunscreens) creates a uniform film on the skin allowing for a high SPF at low sunscreen use levels. Early emulsions of this type were based on beeswax neutralized with borax (sodium borate). These emulsions were greasy and tacky. Additionally, they were notoriously unstable to both high temperature and freeze/thaw storage conditions. These concerns have been largely overcome with new, more efficient, and easier to use emulsifiers. These new materials can be placed into three categories:

1. Silicone-based materials (alkyl modified dimethicone copolyols)
2. Polyglyceryl esters
3. Ethoxylated di-fatty esters

Each of these materials can function as the sole emulsifier at use levels as low as 2%. Often it is necessary to include electrolytes (sodium chloride and/or magnesium sulfate) as a stabilizer. The addition of polyols (2.5–10.0%) can help to achieve maximum freeze/thaw stability. If thickening is desired to obtain a cream, then the addition of more internal phase (water) will accomplish this end. This may also be achieved through the addition of waxes (hydrogenated castor oil) or silica. Lastly, these water-in-oil emulsions are perfect vehicles for the inclusion of particulate sunscreens (titanium dioxide and/or zinc oxide) either alone or in combination with the organic sunscreens. In these hybrid systems the particulates act synergistically with the organics to boost the SPF to levels higher than would be expected. This is accomplished by increasing the optical path length.

A last category of emulsions that is only now being investigated is based on liquid crystal emulsifiers. Generally, but not always, these emulsifiers are nonionic and occasionally amphoteric in character (sucrose cocoate, cetearyl glucoside, lecithin, etc.), and thus are broadly compatible with all sunscreen types. These oil-in-water emulsions employ emulsifiers that have a low HLB.

GELS

Gels are a visually most elegant product form. They are characterized by their clarity and viscosity. Generally, they are composed of a single phase (oil or water) into which the sunscreen has been solubilized; but this is not always the case. Two examples of clear gels comprised of immiscible materials are microemulsions and the new water/polyol-in-silicone products. To achieve this small particle size in microemulsions it is necessary to use very high levels of solubilizer/emulsifier (sometimes as high as 30–40%). Using levels as high as this elevates the cost and the potential irritation of the finished product. Additionally, sunscreens formulated in this way will readily wash off (due to the high level of hydrophilic emulsifier). The water/polyol-in-silicone gels require high shear to reduce the particle size and precise control of materials with respect to index of refraction matching to ensure clarity. Up to the time of writing only antiperspirant gels based on this technology have been successful. A method used to form an aqueous gel that uses solubilized oil-soluble sunscreens is to incorporate poloxamer types of materials, at use levels of approximately 25%. The gels are known as "ringing" gels. Their ringing is due to the hexagonal liquid crystal structures set up by the high concentration of the poloxamers. It is interesting to note that as these gels are cooled, they lose viscosity and eventually liquefy. This is due to the increased solubility of the ethylene oxide chains (better hydrogen bonding) at lower temperatures. Of course, like microemulsions, these products will readily wash off when exposed to water. Employing a carbomer or acrylic acid polymer, which is neutralized by an appropriate base, can also form aqueous gels. A water-soluble sunscreen (Ensulizole) can be incorporated into these gels, which can achieve an SPF as high as 8–10. Use of other aqueous thickeners based on cellulose can yield translucent thick liquids that approximate gels in consistency but are pituitous (stringy) and quite tacky. Lastly, one can gel various oils by using oil-soluble polymers, metal soaps, polyethylene, fumed silica, or various resins (polyamide being the most popular). A recent development in silicone chemistry now permits the gellation of volatile (cyclomethicone) and fixed (dimethicone) silicone fluids. Oil-soluble sunscreens can be added to these silicone gels with some reduction in viscosity and clarity. These silicone gels possess excellent aesthetic characteristics but have a very high cost of goods, which could put them out of the reach of mass-marketed products.

OILS

Oils present a very old and easy-to-formulate vehicle. Some years ago it was suggested to apply a coating of baby oil (mineral oil) at the beach for moisturization and protection from the sun. Of course, this offered absolutely no protection from the ravages of the sun. Most of the sunscreens permitted for use by the FDA are oil-soluble esters and can readily be incorporated into oily vehicles. Unfortunately, oils are a very poor vehicle for the application of sunscreens. They are nonpolar and will shift the λ_m of most sunscreens to the left (shorter wavelengths), and the SPF will drop. Additionally, oils spread too well on the lipophilic skin, leaving a thin and transparent sunscreen film; this too lowers the SPF performance.

OINTMENTS

Ointments are essentially thickened oils. Like oils, most sunscreens are readily soluble in them. The UV curves are likewise shifted to shorter wavelengths, but ointments can lay down a thick and nontransparent film on the skin. This last factor can result in rather high SPFs. Also like the oil vehicle, they are inherently water-resistant. They are not widely used due to their unpleasant skin feel.

STICKS

For spot application sunscreen sticks are an almost perfect vehicle. Sunscreens are readily incorporated into sticks, which are mostly based on waxes and oils. Particulates (zinc oxide and titanium dioxide) are commonly used in sunscreen sticks.

MOUSSES/AEROSOL SPRAYS

Sunscreen mousses or aerosol sprays have never achieved much popularity. This is due in part to the economics of this packaging, which is quite expensive. Additionally, aerosols are not recommended for use on the beach where temperatures can rise to levels of 45 °C or higher on the sand and can cause leakage, or worse, of the pressurized container.

PUMP SPRAYS

This category can be split into two segments: oil sprays and emulsion sprays. The oil sprays are quite simply low viscosity oils that have been placed into pump spray containers. A more recent development is the emulsion spray. These thin (500–4,000 cps) emulsions can be prepared and stabilized through the use of polymeric stabilizers (C 10–30 alkyl acrylate cross-polymers) that have been neutralized. The resultant product is homogenized to reduce the particle size and to obtain a more stable product.

PROTOTYPE FORMULATIONS

Some sunscreen products illustrating the formulating principles are discussed in Formulae 20.1–20.9:

Formula 20.1 Sprayable Emulsion Sunscreen (Expected SPF 15)

	%
Propylene glycol	2.5
Xanthan gum	0.05
Octinate	7.5
Oxybenzone	3.5
PEG-40 stearate	0.1
Octyl palmitate	7.5
Acrylates/C_{10-30} alkyl acrylates cross-polymer	0.2
Triethanolamine	0.18
DMDH hydantoin	0.2
Trisodium EDTA	0.005
Water	q.s. 100%

Formula 20.2 Very Water-Resistant Lotion (W/O) (Expected SPF 8)

	%
Cyclomethicone and dimethicone copolyol	5.0
Dimethicone	10.0
Octinoxate	6.0
Meradimate	3.0
Sodium chloride	1.0
Quaternium-15	0.1
Water	q.s. 100%

Formula 20.3 Water-Resistant Sunscreen Emulsion (W/O) (Expected SPF 18)

	%
Cetyl dimethicone copolyol	5.0
Octyl palmitate	11.0
Cetyl dimethicone	2.5
Cyclomethicone	7.5
Ceresin wax	1.0
Hydrogenated castor oil	0.5
Titanium dioxide (microfine)	8.0
Zinc oxide (microfine)	4.0
Magnesium sulfate	0.75
Propylene glycol, diazolidinyl urea, methylparaben and propylparaben	1.0
Water	q.s. 100%

Formula 20.4 Sunscreen Mousse (Expected SPF 6)

	%
Propylene glycol	5.0
Quaternium-26	3.0
Octinoxate	6.0
Cetearyl alcohol and ceteareth-20	3.0
Octyldodecanol	5.0
DMDH hydantoin	0.1
Water	q.s. 100%

Formula 20.5 Lip Balm Stick (Expected SPF 15)

	%
Octinate	7.5
Oxybenzone	4.0
Beeswax	15.0
Octyldodecanol	5.0
Ozokerite wax	6.0
Myristyl lactate	4.0
Candelilla wax	6.0
Petrolatum	5.0
Flavor	0.5
Castor oil	q.s. 100%

Formula 20.6 Sunscreen Oil (Expected SPF 10)

	%
Octinoxate	7.5
Meradimate	4.0
Jojoba oil	5.0
Lauryl lactate	5.0
Cyclomethicone	10.0
Tocopheryl acetate	0.25
Bisabolol	0.25
Octyldodecanol	q.s. 100%

Formula 20.7 Water-Resistant Lotion (Expected SPF 30+)

	%
Tetrasodium EDTA	0.1
Glycerin 96%	3.0
Xanthan gum	0.25
Laureth-23	0.25
Sorbitan sequioleate	0.5
Glyceryl stearate	2.0
PEG-100 stearate	1.0
PVP/eicosene copolymer	2.5
Octocrylene	10.0
Zinc oxide (microfine)	6.0
Octinoxate	7.5
Jojoba oil	5.0
Octyl palmitate	5.0
Tocopheryl acetate	0.25
Bisabolol	0.25
Quaternium-15	0.15
Water	q.s. 100%

Formula 20.8 Cationic Lotion (Expected SPF 8)

	%
Disodium EDTA	0.1
Propylene glycol	3.0
Dicetylmonium chloride	1.5
Lapryium chloride	0.5
Steapyrium chloride	1.0
Octinoxate	7.5
Oxybenzone	2.0
C_{12-15} alkyl benzoate	5.0
Tocopheryl acetate	0.25
Bisabolol	0.25
Quaternium-15	0.15
Water	q.s. 100%

Formula 20.9 Very Water-Resistant Sunscreen Lotion (Expected SPF 15)

	%
Propylene glycol	3.0
Acrylates/C_{10-30} alkyl acrylates crosspolymer	0.25
Propylene glycol stearate	2.0
Octinoxate	7.5
Oxybenzone	2.5
Octisalate	5.0
C_{12-15} alkyl benzoate	5.0
Tocopheryl acetate	0.25
Dimethicone	1.0
Bisabolol	0.25
Triethanolamine 99%	0.20
DMDM hydantoin	0.2
Water	q.s. 100%

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CHAPTER 21
Antiperspirants and Deodorants

INTRODUCTION

During the last 100 years, a concerted effort has been made to develop and market products for controlling underarm wetness and odor [1]. Each area of the human body has a characteristic odor. Some cultures accept body odors as natural or even desirable as aphrothrodisiacs. However, in most modern civilizations, in which underarm odor is regarded as unpleasant and socially unacceptable, hygienic and chemical control of both axillary odor and wetness has become a requirement.

Deodorants inhibit or mask odor formation caused by interaction of perspiration and bacteria, while antiperspirants work primarily to retard sweating by reducing the amount of perspiration excreted from the eccrine sweat glands. In the United States, Canada, Australia, and most of the Far East—including Japan—antiperspirants are classified legally as drugs because their action affects a body function, namely, eccrine sweating. Deodorants (except soaps) are designed to reduce axillary odor. Since deodorization is considered a nontherapeutic purpose, and since no function of the body is being altered, deodorants are classified as cosmetics.

On a global scale, the underarm market is represented by a number of product forms: sticks, aerosols, extrudables (gels and soft solids), roll-ons, creams, pump, and squeeze sprays. A consumer's concern when purchasing either an antiperspirant or a deodorant is control of underarm body odor. Thus three basic types of needs must be met: (1) control of underarm wetness, (2) elimination of underarm odor, and, (3) provision of an aesthetically pleasing application that does not whiten axillae or stain garments. Despite the avalanche of topical antiperspirants that has descended upon the consumer, and despite the implications of advertising claims, there is not a single topical

agent available today that completely eliminates axillae sweating in the hidrotic individual.

PERSPIRATION PHYSIOLOGY

As noted in Chapter 1, there are two types of underarm sudoriferous (sweat-producing) glands: apocrine and eccrine. Underarm secretion comes from these sudoriferous glands and assists the body in three important ways: (1) by regulating body temperature (dispelling of heat); (2) by removing lactic acid (formed during muscular exercise); and (3) by moistening and protecting the skin from dryness (even though the moisture is considered offensive) [2].

Human skin odors are produced from the secretions of sebaceous and sweat glands. Sebaceous glands are found with every hair, on the red surface of lips, in the nostrils, in the papillae, on the anus, and on the foreskin and labia minora. Laboratory studies indicate that both eccrine and apocrine sweat are sterile and odorless at the time of discharge. The odor is later produced through the action of bacteria on apocrine secretion, which is rich in organic material and is an ideal substrate for bacterial growth. The far more abundant eccrine sweat secreted by over two million glands is a highly dilute aqueous solution and has been proven to be of lesser importance in the production of axillary odor than that from antiperspirantocrine glands.

Nevertheless, the moisture from eccrine glands promotes odor in two important ways:

(1) Eccrine sweat is thought to enhance the spread over a wider surface of sticky oily material from axillary apocrine glands;
(2) Eccrine sweat, trapped in the warm axilla vault, provides an ideal environment for the proliferation of resident bacteria, acting upon the nonodorous sterile underarm excretion to form the characteristic body odor.

Additionally, axillary hair has also been found to promote the development of odor. It is thought that axillary hair provides a collecting site for apocrine and eccrine sweat, subsequently increasing the surface area available for bacterial proliferation.

Of the sudoriferous glands, the eccrine glands—or small coil glands—are considered the true sweat glands. These simple coiled tubular glands are located in the subcutaneous layer of the skin with an excretory duct projecting up through the dermis and epidermis to a terminal pore at the surface of the epidermis. They excrete a clear dilute hypotonic electrolyte salt solution composed primarily of sodium/potassium chlorides and carbonates. Other components include, but are not limited to, lactates, urea, and ammonia. These

aqueous excretions are transported through the glandular membrane and then to the skin surface, resulting in wetness in the underarm area.

In contrast to the small coiled eccrine glands, there are the apocrine glands—or large coil glands. As these glands begin to function at puberty and are under hormonal control, they have been associated with sexual development; they are found primarily in the axillae, around the nipples, on the abdomen, and in the pubic region. The secretory portion of an apocrine gland is located in the dermal layer of the skin, while the gland's relatively large (approximately 40 micron) excretory duct opens into a hair follicle. The amount of apocrine secretion is increased by emotive stimuli such as fear and fright.

Decomposition of perspiration, both eccrine and apocrine, results from the actions of various organisms residing in the axillae. In most axillae, well over 90% of the organisms present are either aerobic diphtheroids, coagulase-negative staphylococci, or a combination of these two groups [3,4]. Axillary bacteria belong almost exclusively to aerobic coryneform of the species *Corynebacterium xerosis* (71%). Other aerobic coryneforms, such as *Corynebacterium pseudo-diphtheriticum*, *Corynebacterium minutissimum*, or *Brevibacterium epidermidis*, have also been reported present in the axilla.

It has been shown that the action of coccal microorganisms on apocrine secretions produces a "sweaty" odor, which has been identified as resulting from short-chain fatty acids such as isovaleric and butyric acids [5]. In another approach, investigators believe that the pungent/acrid musklike odor generated in the axillae is strongly related to the formation of specific steroidal 16-androstene compounds [2].

MECHANISM OF SWEAT REDUCTION

The actual odor of humans is the sum of natural and acquired odors. Two people of the same sex may smell differently although they are identically dressed, washed, and perfumed. Body odor is apparently a completely individual property just like fingerprints or the characteristic sound of the voice. The intensity of body odor differs from person to person, depending on personal circumstances, environment, and social and psychological conditions. There are several obvious ways to reduce or control axillary odor: (1) reduce apocrine sweating in the axillae; (2) remove the secretions from both types of sweat glands as quickly as practicable; (3) impede bacterial growth; and (4) absorb body odors.

Reducing eccrine secretion will go a long way in reducing the odor. Explanation of the various theories regarding axillary sweat inhibition can be found in several reviews and books [3]. A general overview of some of the more

important theories follows:

(1) Formation of a "*keratin plug*": The antiperspirant salt denatures and binds to keratin protein, disrupting the stratum corneum and causing a functional closure of sweat duct.
(2) Formation of an "*occlusive plug*": An obstructive plug of hydrolyzed metallic cationic salt (through the action of pH change upon entering the eccrine duct) is formed, closing the sweat gland by creation of an occlusive metal hydroxide salt plug.

    (a) "*modified occlusive plug*": The formation of an obstructive plug takes into account the rate of complete hydrolysis of the metallic cationic salt; antiperspirant actives may depend on the thermodynamic stability of hydrolysis by-products.

(3) The "*leaky hose*": The metallic cationic actives alter permeability of the electrolytic fluid across an eccrine duct membrane, causing readsorption rather than transportation of sweat.
(4) The "*electropositive charge*": The antiperspirant salt generates an electropositive charge, which reverses a sweat gland's negative charge potential to a strong positive charge on the skin surface, thus inhibiting sweat production.
(5) "*Anticholinergic activity*": Neurological triggering of sweating is prevented via an anticholinergic mechanism.

Today the "occlusive plug" theory is the most widely accepted theory of inhibition of glandular excretion from the eccrine gland. This concept was first proposed by several authors and is best documented in the antiperspirants by Quatrale et al., who published a series of articles delineating the "occlusive plug" theory with aluminum chlorohydrate (ACH), aluminum zirconium chlorohydrex-GLY (AZG), and aluminum chloride [6]. Quatrale's stripping techniques followed by histological examination of a morin dye stain strip specimen with transmission electron microscopy and optical fluorescence demonstrated that an obstructive material was located near the surface entrance of the eccrine gland ducts shortly after application of an antiperspirant salt. They also noticed that:

(1) after stripping of the occlusive plug, about 50% of treated sweat glands resumed producing sweat after the obstructive plugs were removed,
(2) aluminum chloride plugging was deeper than either ACH or AZG, and ACH was deeper than AZG,
(3) aluminum chloride–treated eccrine glands took longer to resume functioning.

One interesting observation by Quatrale et al. was that even though AZG-caused plugs were not as deep as ACH-caused plugs, the AZG sweat reduction

effectiveness was greater. Consequently, the theory that a deeper plug would result in a greater degree of sweat reduction was weakened.

GOVERNMENTAL REGULATIONS

The United States has led the way in defining and regulating antiperspirants and deodorants during the past 25 years. In 1974 a task force—the Antiperspirant Review Panel—was organized by the Food and Drug Administration (FDA) to develop an antiperspirant monograph that would (1) define the elements to be considered as antiperspirant actives, (2) how to register underarm products with the FDA, (3) what information should be disclosed on antiperspirant and deodorant products (such as labeling and product claims), and (4) inspection protocol.

Almost four years later, the Antiperspirant Review Panel completed its work with a tentative final monograph—known henceforth as the OTC Antiperspirant Drug Products Tentative Final Monograph or Antiperspirant TFM [7]. Since 1978, the Antiperspirant TFM has been amended twice. In its amended form, the Antiperspirant TFM, though not finalized, serves as a reference for all aspects of manufacturing and marketing of underarm products, to include packaging, manufacturing, safety, and effectiveness [8].

The Antiperspirant TFM divides antiperspirant actives into two categories. Products included in Category I are "generally recognized as safe and effective," and those placed in Category II are "not generally recognized as safe and effective." Based on available efficacy and safety data the following actives are included in Category I:

- Aluminum chlorohydrate[a]
- Aluminum sesquichlorohydrate[a]
- Aluminum dichlorohydrate[a]
- Aluminum zirconium octachlorohydrate[b]
- Aluminum zirconium tetrachlorohydrate[b]
- Aluminum zirconium trichlorohydrate[b]
- Aluminum zirconium pentachlorohydrate[b]

15% aluminum chloride (aq. only)

Aluminum sulfate + sodium aluminum lactate (1:1)

(a) Can also be complexes with propylene glycol (PG) or polyethylene glycol (PEG), and then name ending changes to "drex," for example, Aluminum dichlorohydrex PEG; or Aluminum dichlorohydrex PG.

(b) Can also be complexes with glycine (GLY), and then name ending changes to "drex," for example, Aluminum tetrachlorohydrex GLY.

Allowable compositional limits for aluminum, zirconium, chloride, and glycine are defined in the Antiperspirant TFM [8]. Besides the types of actives allowable as antiperspirants, there are regulations defining the maximum amount of an active that can be used in a formulation and still be considered safe and/or effective. Therefore, in all delivery forms (except where noted):

- Aluminum chlorohydrates (ACH) cannot be used above a maximum of 25%, calculated on an anhydrous basis.
- Aluminum zirconium chlorohydrates cannot be used above a maximum of 20%, calculated on an anhydrous basis and only in nonaerosolized products. The FDA banned zirconium-containing antiperspirants for aerosolized use but allowed the use, of zirconium-containing antiperspirants when it is directly applied to the skin (nonaerosol).
- Aluminum chloride can be used up to a maximum of 15% in nonalcoholic, nonaerosolized products.

The OTC Panel has developed a comprehensive and rigorous set of guidelines that are intended to serve as the standard protocol to be employed in chronic animal inhalation studies, designed to bring successfully tested products into Category I classification (safe and effective). The Antiperspirant TFM recommends that all marketed suspension-type aerosol systems in the United States should be formulated so that not less than 90% of emitted particles is greater than 10 (in diameter (less than 10 μ is considered respirable).

CLINICAL EVALUATION OF ANTIPERSPIRANT

In the 1978 edition of the FDA Antiperspirant TFM, average levels of sweat reduction were reported for different dosage forms. For the most part, aqueous systems displayed higher sweat reduction than anhydrous systems. As aluminum becomes more hydrolyzed (less acidic), from ACH at a 2:1 Al/Cl molar ratio (aluminum chlorohydrate) to 1:1 Al/Cl molar ratio (aluminum dichlorohydrate), efficacy increases. There are insufficient data on the tri-, tetra-, penta-, and octa- versions of AZG to determine the effect of total metals to halide and Al:Zr molar ratio on efficacy. Nevertheless, it has been suggested that the "octa region" may possess the optimum efficacy.

Based on population density of sudoriferous glands, age, sex, race, acclimatization to temperature change, and environmental humidity, differences in individual perspiration levels remain. Sweat production basically is triggered as a response to either thermal changes (e.g., physical or environmental) or emotional responses (e.g., mental stress). For example, a person possessing about 20,000 sweat glands in the axillae can produce between 400 to 1,000 milligrams of sweat per hour by

sitting quietly in a warm environment; yet should this same person undergo emotional stress, the volume could be increased four to eight times.

To meet minimum efficacy requirements and to substantiate product label and advertising claims, clinical testing is required for any new formulation or formulation modification. In accordance with the Antiperspirant TFM, to be claimed and marketed as an antiperspirant, a product must effect a minimum reduction in perspiration of at least 20% for 50% of the target population. Both formula ingredients and a product's dispensing characteristics are known to alter active ingredient efficacy. A comparison of some antiperspirant actives is provided in Figure 21.1. The OTC Antiperspirant Review Panel in the United States has proposed a clinical methodology for effectiveness and a statistical protocol for treatment of data that provide reasonable assurance that an antiperspirant product meets the minimum 20% sweat reduction performance requirements. Since a product with a sweat reduction of 20% promises only a barely perceptible antiperspirant effect, antiperspirants that achieve less than 20% effectiveness in hot room tests probably possess minimal wetness control but still possess significant deodorancy (odor control) benefit.

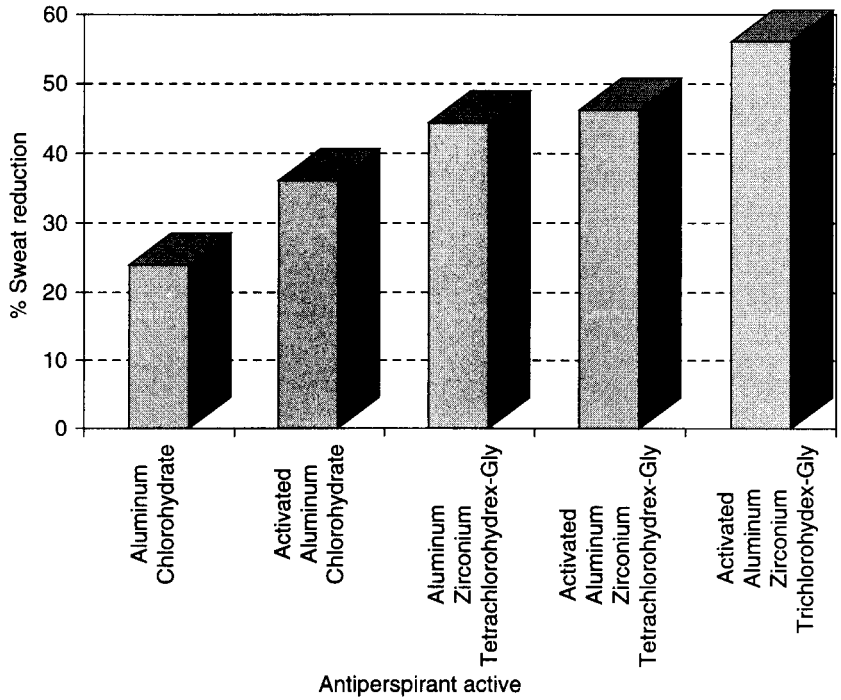

Figure 21.1. Comparative efficacy of antiperspirant actives

AXILLARY SWEAT MEASUREMENT PROTOCOLS

In order to provide an objective measurement of a product's antiperspirancy or deodorancy as expected by consumers during normal daily use, in vivo human clinical measurements have to be performed under specific conditions. These conditions are designed to control a complex combination of factors: climate; level of physical, thermal, and/or emotional stress; bathing habits; tactile sensual aesthetics of a formulation on an underarm; and/or interaction of normal body substances with the formulation's chemical and fragrance ingredients

There are three recognized screening techniques to assist in quantification of product efficacy [3]: (1) visualization (colorimeter), (2) instrumentation (sensor), and (3) gravimetric.

Instrumental, or sensor, methods have been less successful than visualization or gravimetric methods [9]. Despite extensive studies of water loss by infrared gas analyzer, of electrolytic cells containing a water-sensitive mixture of methanol-acetone and oxalic acid, and of electrical types of humidity-sensor elements, these approaches are no longer widely used. In fact, results of these methods have not correlated well with results from in vivo gravimetric methods in demonstrating the effectiveness of diverse antiperspirant actives or formulations.

Visualization methods can help to subjectively determine how many pores are firing (releasing sweat). Usually with this type of test methodology, a staining indicator is painted on a test axilla site (e.g., iodine in a mixture of starch powder and castor oil). Visualization methods have been published detailing modification of staining procedures and use of microscopic techniques [10].

Gravimetric in vivo clinical efficacy testing, as required by the Antiperspirant TFM, is the recognized method throughout the world, even though this type of testing remains difficult to administer and is expensive. The FDA, in 1982, established guidelines [7] setting the basic standards and conditions for evaluating antiperspirant products and for testing the effectiveness of antiperspirant drug products in finished form. One of the more comprehensive publications on gravimetric testing, which also supports current OTC monograph efficacy testing conditions, is that of Wooding and Finkelstein [11].

During in vivo clinical efficacy testing, panelists are required to abstain from using any antiperspirant materials for at least two weeks prior to initiation of the study. Suggested guidelines for effectiveness testing of OTC antiperspirant drug products are summarized in this section:

a) Objective:
To qualify as an effective antiperspirant drug product in finished form

b) Test Subjects:
Subjects are prescreened based on their sweat production. They are then asked to abstain from use of antiperspirants or deodorants for seventeen days

c) Test Conditions:
   1) Controlled temperature hot room:
      - Temperature 100 °F ± 2 °F
      - Humidity 35–40% RH
      - Control air movement, mental or emotional stimuli, and position of trunk and extremities
   2) Ambient:
      - Normal daily routine during collection period

d) Test Procedures:
   1) Treatment versus placebo
   2) Balanced treatment assignment
   3) Normal antiperspirant application amounts
   4) Once a day treatment for 2–4 days
   5) Hot room conditions:
      - Air movement
      - Forty-minute warm-up
      - Two 20-minute weighed sweat collections
   6) Ambient conditions:
      - Three to five sweat collections during normal daily routines
      - Controlled activity of panelists in hot room—they are asked to sit with both feet on the floor, uncrossed (posture can affect sweat output)
      - Right/left axilla—subjects are numbered; equal number of panelists from each group have applied product A or product B to right axilla; the product not applied to right is then applied to left to eliminate the "side-effect" bias

e) Data Analysis:
   1) Nonparametric techniques
      - Projection of results—50% of population will obtain at least 20% sweat reduction

f) Statistical Analysis
   Several statistical protocols that are used in interpreting raw data and reporting results are commonly employed in evaluating test data. Statistical protocols to support antiperspirant efficacy claims include sign test, Wilcoxon signed rank (WSR) test, and student t-test.

There are two evaluation protocols recommended by the FDA in the TFM. In the first protocol, a baseline sweat collection takes place before the axillae are treated. These data are used to calculate a baseline ratio of one axilla divided by the other. This ratio is used to adjust the posttreatment divided by untreated ratio when estimating product efficacy. In the second protocol no baseline data are employed, and efficacy is estimated using only posttreatment data.

In addition to knowing whether a product passes the FDA monograph requirements, most manufacturers wish to estimate the level of sweat reduction. For calculation of estimates of percent reduction, there are a few methods that can be utilized, including the direct method and the adjusted ratio method [12].

DEODORANCY

The desire to control eccrine gland excretions is paralleled by a need to control underarm malodors. Perfumes and antimicrobial actives are the most popular actives in controlling axillary odor. Since axillary odor is largely produced by the action of bacteria on nutrients present in apocrine secretion, any ingredient that inhibits the growth of microorganisms found in the axillae should in theory exhibit deodorant properties.

Three different approaches are used for controlling underarm malodor:

(1) *Odor masking/disguise*: Involves masking unwanted odor by overpowering or disguising it. Strong perfumes are typically used in deodorants to overpower underarm odor. Levels of perfumes in deodorants can vary from fairly low levels (0.5% of total formulation) to levels as high as 10%. Reviews of fragrance components and of combinations of fragrances with deodorant actives have been published [13,14].

(2) *Odor reduction/removal*: Materials can be added to underarm deodorant formulations to adsorb or absorb odors, particularly low molecular weight excretion components. However, these materials usually work on specific chemical types and thus have limited use. Other materials can be added to deodorant formulations to physically absorb glandular excretion, thereby slowing down bacterial growth.

(3) *Odor prevention*: This approach is aimed at inhibiting the growth of bacterial microorganisms in the axilla. Antibacterial agents are by far the most often used materials in deodorant formulations to prevent or slow down odor formation. Other actives are used to provide enzyme inhibition or antioxidation.

In the case of deodorants, the techniques of assessment are relatively straightforward: conventional microbiological methods of analyzing microbial content in properly designed experiments can furnish data on the efficacy of deodorant compounds and products both in vitro and in vivo. The ultimate test, however, for any finished cosmetic deodorant product involves well-designed axillary sniff studies. In the final analysis, it is the well-trained nose capable of relating to consumer perception of odor that will aid the determination of the ultimate success or failure of a deodorant product.

DEODORANCY CLINICAL EVALUATION

In 1987, the American Society for Testing and Materials (ASTM) published a method for the Sensory Evaluation of Axillary Deodorancy [15]. This publication provides a detailed background and explanation of the evaluation of deodorant products, including all important facets required to adequately support deodorant efficacy.

Clinical evaluation of deodorant effectiveness can best be divided into two groups according to subject-odor judge interaction or direct and indirect axillary odor evaluations. Selection of either the direct or indirect method of evaluating axillae is dependent on a judge's training and the ease with which a judge can perform his/her duties most consistently. Other types of evaluations of deodorant effectiveness of antimicrobial actives include removal of body flora with swabs, culturing the flora, and evaluation of cultured antimicrobial activity over time [13].

ANTIPERSPIRANT INGREDIENTS

CHEMISTRY

The most common antiperspirant salts or actives, aluminum chlorohydrate and aluminum-zirconium chlorohydrex-glycine, act by suppressing sweat delivery to the skin surface. As noted earlier in Section III, these actives can decrease sweat production by several mechanisms. In addition, they have been reported to act as good antimicrobials to eliminate the formation of axillary odor.

Aluminum- and zirconium-containing antiperspirant salts (AP actives) are based on distributions of various structures of polycationic, protonated oxohalides. A useful summary of available chemical studies is included in Ref. 3. NMR is now used for unravelling the complexity of the structure–physical property–chemistry relationships of active antiperspirant salts and their hydrolysis chemistry. The antiperspirant industry, at the time of writing this text, depends on size exclusion gel permeation high performance chromatography to determine the basic composition and distribution of the various polymeric species [3].

When aluminum is the only metal present, the AP active is known as aluminum chlorohydrate (ACH). ACH is composed mainly of large octahedral poly-oxo cationic species that are produced under aqueous acidic conditions with an excess of aluminum metal. The pH of the aqueous solution increases with the consumption of hydrogen ions, and poly-oxo-aluminum species are formed with stability constants that are related to the various pH ranges. These species can be detected and characterized by a variety of techniques including ^{27}Al nuclear magnetic resonance spectroscopy [16] and X-ray crystallography [17].

The various synthesis routes to ACH involve the partial hydrolysis of an acidic aluminum salt. ACH is commercially prepared as a concentrated solution by reacting aluminum metal with an acid (aluminum chloride or hydrochloric acid) and subsequent hydrolysis of aluminum metal to hexa-aquo Al^{+3}. This method of synthesis was first described in a patent (U.S.P. #2,196,016) in 1940. A number of years later, aluminum-zirconium chlorohydrate complexes with glycine (AZG or ZAG) were developed and marketed to provide significant improvements in performance in nonaerosolized product forms, such as roll-ons and sticks. When zirconium is present along with aluminum, the antiperspirant active is known as aluminum-zirconium chlorohydrate. As the aluminum-zirconium chlorohydrate is most often buffered with glycine, it is commonly known simply as ZAG or AZG. AZG is a blend of the ACH product with a glycine buffered zirconium-containing complex such as zirconyl chloride or zirconyl hydroxychloride.

In the late 1980s, enhanced efficacy aluminum-containing antiperspirants (ACH) entered the market. Aluminum-zirconium–containing antiperspirants, for example, AZG, followed shortly thereafter. Through heat and dilution processing steps, these species of aluminum and aluminum-zirconium chlorohydrates can be further modified or "activated." An "activated" antiperspirant is based on controlling the polymer distributions (molecular weight and structural morphology) compared to historical "standard" antiperspirant actives. It has been demonstrated that increasing the concentration of certain antiperspirant species significantly improves sweat reduction. Activated ACH differs from unactivated ACH in that there is present a Al_{13}-mer cluster (a small, almost spherical $\{AlO_4Al_{12}\ (OH)_{24}\ (H_2O)_{12}\}^{7+}$ oligomer), which is associated with increased sweat reduction performance. Size exclusion chromatograph/gel permeation chromatograph and/or nuclear magnetic resonance were employed to detect the presence of Al_{13}-mer cluster in the activated ACH [3].

There is less information on structures and compositions of AZG salts than those of ACH salts. What is known is that in addition to the homonuclear oligomeric aluminum clusters and zirconium oxohalides (zirconium tetramer $\{Zr_4\ (OH)_8\ (H_2O)_{16}\}^{8+}$), heteronuclear (aluminum-oxo-zirconyl type) species are present. Also, when glycine is used to buffer aluminum-zirconium chlorohydrate actives, the glycine is coordinated to zirconyl ions via its carboxyl group and is involved in hydrogen bonding through its protonated amino group with the oxo-aluminum part or another zirconyl cation of the AZG.

ANALYTICAL PROCEDURES

Any analytical evaluation of antiperspirant actives should be based on: (1) hydrolysis chemistry and physiology of the metal oxo-halides

antiperspirant active during handling and application; (2) physical state changes that can occur to the active during formulation and application (e.g., liquid to solid state); and (3) interactions of the antiperspirant active with formulation ingredients.

Antiperspirant actives are considered drugs or therapeutics in most parts of the world and are therefore regulated for purity and compliance. The United States has established analytical specifications and test methods that are outlined in the National Formulary/US. Pharmacopoeia (NF/USP). Besides the specifications identified in compendial publications, aluminum, zirconium, chloride, glycine, sulfate, arsenic, heavy metals, iron, and pH, as identified in the NF/USP, other properties can characterize and distinguish one antiperspirant active from another to quantify purity and physical/chemical properties: for example, solubility, specific gravity, bulk density, particle size, size exclusion, and gel chromatography. The manufacturer of the antiperspirant actives should be consulted for the most up-to-date detailed information.

PRODUCT FORMULATION

Consumers' needs can be categorized into three areas: (1) controlling underarm odor to eliminate self-consciousness that others perceive your body odor (need to detect a pleasant odor without competition with other body perfumes); (2) controlling underarm wetness so it is not felt or noted on clothing; and (3) having acceptable aesthetics in delivery, application, and wearability (goes on effortlessly without being wet, sticky, or residual whitening and garment damage) [18,19]. To marketers, these expectations translate into a need for high-performance products that keep underarms dry and odorless, maintain the health of skin, have a "perceived" naturalness and mildness about them, and are easily applied without a perceptible residue.

Whatever form a successfully formulated product takes, it should meet the following criteria:

1. Effectively and uniformly delivers product to the underarm
2. Does not detract from the performance of the active; preferably should enhance
3. Does not harm the body or clothing
4. Remains stable in its package for a reasonable shelf life
5. Is aesthetically appealing
6. Conforms to applicable regulations

On a global scale, underarm products are delivered via a number of product forms: sticks, aerosols, extrudables, roll-ons, creams, pump, and squeeze sprays [1]. Products have been differentiated on the basis of clarity (clear antiperspirant, deodorant sticks, and gels) and applicator delivery systems (gels, soft

solid creams, and concentrated aerosols) [20]. The current trend is focused on aesthetics (e.g., "sheer," "dry," and "invisible") [21] claims associated with wetness control as much as a dry elegant-feeling product that is not perceptible [20].

ANTIPERSPIRANT FORMULATIONS

Antiperspirant actives, being very acidic and water soluble, have distinct formulation limitations, such as: (1) water and glycol solubility that can lead to tackiness on the skin, and (2) high acidity that can cause potential skin irritation and destabilization of pH-sensitive fragrances and gellants.

Antiperspirants are formulated to provide dry-feeling aesthetics upon application and effective delivery of actives. Typically ingredients used in antiperspirant products vary by delivery form and will be identified in various examples that follow. They can include emulsifiers/suspending agents, gellants and viscosity enhancers, propellants and solvents/carriers, silicones (e.g., cyclomethicone and dimethicone), and emollients and feel modifiers. Silicones are useful for antiperspirants as a result of their low surface tension, their good product-spreading characteristics, and formation of a thin, nonoily lubricious film that reduces tackiness of the active during delivery and dry-down.

The following formulas identify the application of antiperspirant actives in various delivery forms.

AEROSOL/PUMP SPRAY

Many combinations of raw materials are available for the formulation of aerosol antiperspirants, and their selection must be carefully considered since the surface chemistry of the system can affect sedimentation and dispersion characteristics of the formula. Further, aerosols are very complex systems because of the need to balance aerosol can construction, valve design, and vapor pressure in order to deliver an antiperspirant effectively.

For antiperspirant aerosol systems, hydrocarbon propellants are recommended. Antiperspirant actives are insoluble in hydrocarbons; thus there is a need to properly suspend an antiperspirant active to prevent (1) uneven discharge of an active throughout the useful life of the aerosol, and/or (2) valve clogging. Proper selection of an antiperspirant active's particle size (micronized or controlled particle size) is required to minimize valve clogging or compaction. Fatty acid esters and silicones help to lubricate the valve, while organofunctional clays are capable of minimizing flocculation by maintaining a fluffy easily redispersible suspension.

Most aerosol formulations start with a concentrate based on incorporation of a suspending agent (e.g., hectorite clays) with an emollient (e.g., cyclomethicone), and a polar activating agent (e.g., ethanol or propylene carbonate) to develop individual clay platelets. Shearing is employed to open the clay platelets, an active powder is added and properly mixed to ensure uniformity; the system is finally screened to remove any agglomerates. This mixture is then placed in an aerosol can, and a propellant is added.

Formula 21.1 demonstrates the use of a typical clay suspending agent (Quaternium-18 hectorite).

Formula 21.2 demonstrates the ability to deliver antiperspirants in a high water content and quick-drying formula with minimal tackiness and reduced residue.

SOLID/STICK

Antiperspirant sticks have evolved significantly over the years. Prior to the late 1970s they held almost no market share. With the emotive issues of

Formula 21.1 Aerosol Antiperspirant

	%
Aluminum chlorohydrate powder (<10 microns)	10.0
Cyclopentasiloxane	15.0
Isopropyl myristate	5.0
C_{12-15} Alkyl benzoate	2.0
Quaternium-18 hectorite	0.8
Propylene carbonate	0.75
Fragrance	q.s
Hydrocarbon propellant	q.s

Formula 21.2 Pump Antiperspirant

	%
Aluminum chlorohydrate powder	49.5
Laureth-2 benzoate	10.0
Alcohol	20.0
Ceteareth-20	5.0
Propylene glycol	3.0
Cyclopentasiloxane	1.35
Water	10.55
Hydrolyzed wheat protein	0.5
Allantoin	0.1

fluorocarbons and their effect on the ozone layer coming to the forefront in the mid 1970s and volatile silicones becoming readily available, sticks reached a predominant role (greater than 55% in the United States in 1998). Sticks are prepared by balancing a solidifying agent (e.g., wax) and volatile cyclomethicone [22]. Other ingredients are added to improve on dry, soft feel and reduce the whitening effect caused by the difference in refractive index of the AP active and skin.

There is an emerging trend toward clear antiperspirant sticks, with dibenzylidene sorbitol as the gellant. Since most gellants are sensitive to low pH, this is a significant hurdle to incorporate traditional gellants. Patents using the dibenzylidene sorbitol acetal have provided at least one approach to overcome this limitation [23]. Stabilization, clarity, and aesthetics continue to be the issues that require improvements for optimum consumer acceptance.

Formula 21.5 is typical of the growing trend toward a "clear" antiperspirant stick

Formula 21.3 Antiperspirant Suspensoid Stick

Represents a typical suspensoid stick	%
Cyclopentasiloxane	55.0
Stearyl alcohol	20.0
PPG-14 butyl ether	2.0
Hydrogenated castor oil	1.0
Talc (325 Mesh)	2.0
Aluminum zirconium tetrachlorohydrex-GLY	20.0

Formula 21.4 Antiperspirant Dry Stick

Typical of the growing trend for "dry" claims	%
Stearyl alcohol	26.0
Octyl palmitate	14.5
Dioctyl adipate	14.25
Cyclotetrasiloxane	20.0
Aluminum zirconium tetrachlorohydrex-GLY	20.0
Arachidyl propionate	5.0
Wheat germ glycerides	0.25
Fragrance	q.s

Formula 21.5 Clear Antiperspirant Stick

Typical clear stick formula	%
Aluminum zirconium tetrachlorohydrex-PG (30% aq.)	50.0
Propylene glycol	33.5
Dipropylene glycol	10.0
Glycine	1.0
Diisopropyl sebacate	2.0
Dimethicone copolyol	1.5
Dibenzylidene sorbitol	2.0

ROLL-ON

Roll-ons can be delivered in four distinctly different ways: solutions (hydro-alcoholic or aqueous), anhydrous cyclomethicone suspensions, oil-in-water emulsions, and water-in-cyclomethicone emulsions. Other than the anhydrous systems, roll-ons employ actives in an aqueous medium that also contains emollients and other aesthetic skin feel enhancers.

Hydro-alcoholic formulations are effective and quick-drying but relatively cold and wet on application. They may cause stinging of freshly shaved underarms. Oil-in-water emulsions (Formula 21.6) are effective but can often exhibit a tacky skin feel during drying. Formula and processing are similar to those of typical cosmetic lotions as long as the emulsifier and stabilizer are acid-compatible. Based on formulation, the viscosity can vary between 500 and 2000 cPs. The formulas typically are opaque.

Water-in-silicone emulsions (Formula 21.7) demonstrate superior aesthetics but are generally poorer in efficacy because of the coating of antiperspirant salt particles by the silicone emulsifiers. These formulas may be either opaque or crystal clear. The best emulsifiers are based on polysiloxane polyether copolymers (represented as less than 1% of active copolymer) with HLBs around 3–5. Viscosity can range from 500 to 2000 cPs, usually controlled by

Formula 21.6 O/W Emulsion Roll-on

	%
Water	26.0
Magnesium aluminum silicate	1.0
Glyceryl stearate, SE	8.0
Glycerin	8.0
Cyclotetrasiloxane (and) Cyclopentasiloxane	7.0
Aluminum tetrachlorohydrex-GLY (50% aq.)	50.0

Formula 21.7 W/Silicone Transparent Roll-on

	%
Dimethicone copolyol	1.0
Cyclotetrasiloxane and cyclopentasiloxane	16.0
C_{12-15} Alcohols benzoate	5.0
Aluminum tetrachlorohydrex-GLY (50% aq.)	50.0
Water	17.0
Propylene glycol	11.0
Fragrance	q.s

Formula 21.8 Anhydrous Suspension Roll-on

	%
Cyclotetrasiloxane	70.0
Dimethicone (0.5 Stokes)	5.0
Quaternium-18 hectorite	3.0
Alcohol	2.0
Aluminum zirconium trichlorohydrex-GLY	20.0
Fragrance	q.s

varying the ratio of aqueous to silicone phase volume (less aqueous phase creates lower viscosity). It is important to keep the aqueous phase above 50% and preferably around 70–75%.

Anhydrous or silicone suspensions (e.g., Formula 21.8) have high consumer acceptance in the United States with dry application, absence of wet feeling, and no sting or stickiness. However, they can leave a white residue or deposit on skin. Like antiperspirant aerosols, anhydrous roll-ons typically use similar suspending agents (organo-clays) to allow for easy redispersion of the suspended antiperspirant active particles upon shaking and after long storage.

EXTRUDABLE GELS AND SOFT SOLIDS

Much activity continues to focus on modifications, improvements, and innovation in this evolving delivery approach. Extrudable clear gels (Formula 21.9) and soft solid anhydrous creams (Formula 21.10) continue to gain in popularity and interest by consumer companies, advancing from nonexistent in 1992 to more than 15% market share in 1998.

Formula 21.9 Clear Antiperspirant Gel

	%
Dimethicone copolyol	1.0
Cyclopentasiloxane	12.1
Dimethicone (0.5 Stokes)	3.9
Isostearyl palmitate	2.4
Water	41.1
Dipropylene glycol	19.5
Aluminum zirconium trichlorohydrate-GLY	20.0
Fragrance	q.s

Formula 21.10 Antiperspirant Soft Solid

	%
Cyclopentasiloxane	43.5
Octyldodecanol	16.0
C_{20-40} Pareth-40 and C_{20-40} Pareth-60 and C_{20-40} Alcohols	2.5
Cetearyl alcohol	2.0
Dihydrogenated tallow phthalic acid amide	10.0
Sodium cocoyl glutamate	2.0
Aluminum zirconium trichlorohydrate-GLY	24.0
Fragrance	q.s

DEODORANT FORMULATIONS AND EXAMPLES

Controlling odor is critical to the success of underarm products. Most technological approaches are focused on fragrance components that either inhibit odor formation or mask already formed odor. Deodorant actives and fragrances tend to have fewer formulation limitations than acidic antiperspirants. Typical deodorants are in the form of sticks/solids, aerosols, and extrudable gels.

Triclosan is the most commonly employed active for antimicrobial activity to inhibit bacterial formation. Fragrances have been the classic approach to masking odor, and a number of disclosures of potentially new inhibitors and masking agents have appeared [20].

The keys to consumer acceptance are minimal tackiness and no visible residue. Typical ingredients found in deodorant aerosol products (Formula 21.11) are volatile hydrocarbons, ethanol, propylene glycol, and functional siloxanes.

Deodorant sticks are based on sodium stearate/propylene glycol systems. The correct grade of sodium stearate and controlled cooling rate significantly

Formula 21.11 Deodorant Aerosol Spray

	%
Dimethicone (0.5 Stokes)	3.0
C_{12-15} Alkyl benzoate	3.5
Triclosan	0.2
Hydrocarbon propellant:	
Isobutane/propane (80/20)	93.3
Alcohol 100%	q.s
Fragrance	q.s

Formula 21.12 Clear Deodorant Stick

	%
PPG-3 myristyl ether	40.0
Sodium stearate	8.0
Propylene glycol	47.75
Water	4.0
Triclosan	0.25
Fragrance	q.s

influence clarity. Over the last few years work has continued on improvements in clarity and stability.

Modern deodorant sticks (Formula 21.12) rely principally on a gelling agent like sodium stearate, diluents like propylene glycol, water, and alkoxylated ethers to improve clarity.

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RECOMMENDED READING

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CHAPTER 22

Antiacne and Oily Skin Products

INTRODUCTION

When one thinks of acne, the vision of an adolescent with facial pimples comes quickly to mind. However, acne is prevalent in the young and in adults. In fact, more than 50% of U.S. population and 80% of all teenagers will develop some form of acne during their lifetime. Recent studies have linked even mild acne with such emotional problems as significant clinical depression and even suicidal ideation. Therefore, the relevance of treating acne and the promotion of healthy skin grows in significance. Acne symptoms occur at the onset of puberty and are a result of changes in metabolic and hormonal systems within the body.

The market for products targeted to the treatment of acne and of oily skin conditions is large. Consumers tend to seek over-the-counter treatments for acne and, unlike many therapies, they expect to see and feel the benefits from their efforts. For development of products to meet the market needs, a basic understanding of acne and its relationship to oily skin is required.

ETIOLOGY AND SYMPTOMS

While there are many clinical classifications of acne, the public generally accepts acne vulgaris as common acne. Consumers primarily recognize acne as blackheads, whiteheads, and surface papules, pustules, and cysts.

Acne vulgaris is characterized by the formation of inflammatory and noninflammatory lesions of the hair follicles and/or sebaceous glands commonly referred to as the pilosebaceous unit. Figure 22.1 shows the pathogenesis of acne from a normal follicle through the comedone stage to the papule and pustule condition [1]. Noninflammatory lesions may be categorized as open comedones (blackheads) and closed comedones (whiteheads). Inflammatory lesions manifest themselves as papules, pustules, cysts, and nodules. Usually if left alone, open comedones will be gradually reabsorbed. More likely, those with acne squeeze the comedones to express the contents and improve appearance.

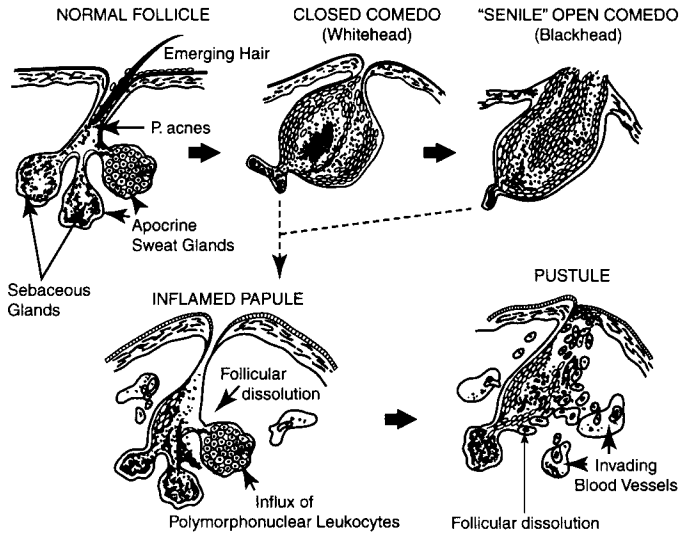

Figure 22.1. Pathogenesis of acne

It is now generally accepted that overproduction of sebum, degradation of the sebaceous follicle epithelium, the opportunistic growth of *Propionibacterium acnes (P. acnes)*, and an inflammatory reaction from an immunologic stimulation occur in acne vulgaris.

Changes in the size of the sebaceous gland and its increased production of sebum may be stimulated by increased levels of androgenic hormones. The most common of these is testosterone. Stimulation of the lipid producing cells within the pilosebaceous unit leads to the generation and accumulation of lipids, the degradation and biotransformation of cells, and the production of a complex mixture known as sebum. Sebum has been shown to be a mixture of triglycerides, sterols and sterol esters, wax esters, and squalene. (Table 22.1) [2]. Eventually the sebum finds its way to the skin's surface traveling alongside the hair follicle. It is the presence and quantity of sebum in and around the pilosebaceous unit that lead to changes in the follicular epithelium. When coupled with the ability of opportunistic *P. acnes* to produce lipases that metabolize sebum into more irritating glycerides and fatty acids, conditions are created to promote comedones, a process referred to as comedogenesis.

Additionally, cyclic hormone levels have been associated with premenstrual flares of acne and breakouts that may occur during pregnancy.

Occupational hazards such as chronic exposure to chemicals and air contaminants aggravate skin diseases including acne. Exposure to high humidity levels for prolonged periods may lead to an increase in the onset of acne by indirectly causing a decrease in the size of the pilosebaceous duct orifice.

Table 22.1 Composition of Skin Surface Lipids

Component lipids	% W/W
Triglycerides—including free fatty acids	57
Wax esters	26
Squalene	12
Sterol esters	3
Free sterols	2

The role of diet in the development or worsening of acne has not been clinically confirmed as a single major cause. Eating chocolate has never been proven to exacerbate acne. However, changes in diet may affect a change in the body's metabolism and could therefore initiate a hormonally induced acne episode. Thus a cause and secondary effect may exist.

Other stimuli and events associated with acne include seasonal effects, excessive sexual activity, emotional or psychological stress, mechanical manipulation of the skin surface, and certain drugs such as corticosteriods. Interestingly, moderate exposure to sunlight may have a beneficial effect. This may account for the reduction in severity of acne symptoms enjoyed by adolescents during the summer months.

In practical terms, acne may be grouped in terms of the severity of the symptoms; that is mild, moderate, and severe. Table 22.2 describes a typical scale of the symptoms used to classify acne vulgaris [3].

Table 22.2 Classification Scale for Acne Vulgaris

Mild

- Noninflammatory lesions confined to a minor facial area
- Few superficial papules and pustules
- No discernible scar formation
- Normal skin surface appearance

Moderate

- Multiple established papules
- Numerous pustules
- Some scar formation
- Few cystic lesions

Severe

- Deep papules and pustules
- Extensive distribution of noninflammatory lesions over face
- Cystic lesions
- Moderate to severe scar formation

COMEDOGENICITY

Since the early 1970s, the comedogenicity of cosmetic ingredients has been a concern to formulators of skin care products. Comedogenicity is defined as the potential of a substance to promote the plugging of the sebaceous gland duct leading to the formation of a comedone. Comedogenicity testing of cosmetic ingredients is completed using the rabbit ear assay or in humans directly. In the rabbit ear assay, the ingredient is applied to a rabbit's ear. A positive response is characterized as a blockage of the sebaceous duct observed as a hyperkeratotic impaction. This hyperplasia of the epithelium is the first response seen and may be followed by secondary responses such as inflammation. A strong positive response in this model suggests that an ingredient may have comedogenic potential, whereas a weak response suggests that the material will be safe on human skin.

Formulators compounding topical products generally try to avoid the use of comedogenic substances. A listing of ingredients reported to be comedogenic is provided in Table 22.3 [4]. When materials with this potential are incorporated, the minimum concentration possible should be used; dilution with other noncomedogenic ingredients is recommended, and substances such as sodium lauryl sulfate that can potentiate the effects of comedogens should be avoided. Not all substances such as sulfur can be diluted to a noncomedogenic level. Decreasing the percutaneous absorption action and reducing the solubility of ingredients are additional means of reducing comedogenic responses.

OILY SKIN AND TREATMENT

Development of oily skin is primarily a naturally occurring event associated with changes in hormone levels that arise during puberty, pregnancy, and menopause. The net result is the accumulation of oily waxes and residues combined with dead cells on the surface of the skin leaving the appearance and feel of an "oily" skin surface. The main oil component is sebum secreted by the sebaceous gland. Sebum production is the greatest during adolescent years, decreases in women after menopause, and remains at relatively constant levels during old age in men [5]. Oily skin is frequently exacerbated by exposures to high humidity or exercise leading to the generation of sweat. The moisture combines with the oils on the skin to form an emulsion and results in an increased "oily" perception of the skin.

There are no approved agents for regulating sebaceous gland secretions and therefore the control of oily skin. The thrust of treatments are products intended to cleanse the skin, to reduce the accumulation of oil on the skin's surface, to reduce the quantity of oil on the skin through the use of absorbents, and the application of products such as liquid foundations that leave the skin with a

Table 22.3 Comedogenic Ingredients

Lanolin derivatives
Acetylated lanolin
PEG-16 lanolin
Fatty acid and derivatives
Lauric acid
Myristic acid
Isopropyl isostearate
Isopropyl myristate
Isopropyl palmitate
Isostearyl isostearate
Myristyl myristate
Alcohol and derivatives
Oleyl alcohol
Sorbitan oleate
Glyceryl-3 diisostearate
Laureth-4
Steareth-10
Natural oils
Cocoa butter
Hydrogenated vegetable oil
Cottonseed oil
Other agents
Sodium lauryl sulfate
D&C Red colorants

dry, matte appearance. Frequent thorough cleansing of the face, neck, chest, and back is the best means of controlling the development of and complications that arise from oily skin.

Skin cleansers are generally detergent- or soap-based and exert their effect by emulsifying oils on the skin and by loosening dead cells, facilitating their removal. The physical actions of washing and scrubbing are important components of the cleansing process.

Numerous approaches to cleansing the skin of unwanted residues have been marketed over the years. These have included soap bars, gels, liquid detergent cleansers, emulsions, creams, pads, and more recently tapes. Emulsion cleansers may mitigate the irritation of surfactants, but may, by their inherent properties, leave behind an oily residue.

Soaps that generally exhibit a high pH are frequently considered irritating. Detergent bars, on the other hand, have a characteristic lower pH closer to the skin's normal pH of 4.5 to 6.5. As a result they are believed to be much milder. Additives such as antimicrobials, oils, vitamins, moisturizers, astringents, and abrasives have been incorporated into products for brand differentiation and adjunctive claims.

Skin cleansers based on detergent systems are a significant part of the market today. These products may be presented for cleansing the face or as a total body wash. Examples of typical cleansing are presented in Formulas 22.1–22.3.

An alternate approach to the problem of oily skin is to incorporate pyrogenic silica into the product. This material has dual properties of absorbing skin oils and leaving the skin with a matte finish [6]. The silica may be incorporated into the oil phase of an emulsion or applied as a suspension from an aqueous or hydro-alcoholic vehicle. This approach leaves a matte layer on the skin surface that reduces the appearance of "shine". Other nonirritating powders used for this purpose include polyethylene, talc, bentonite, and magnesium aluminum silicate.

Regardless of the product used, it is important for the consumer to rinse the skin thoroughly to remove residual detergents, tissue, and skin oils. Consumer

Formula 22.1 Clear Mild Facial Cleanser

Ingredients	%W/W
Water	60.0
Lauramidopropyl betaine	20.0
Ammonium lauryl sulfosuccinate	15.0
Lauramide MEA	2.0
Butylene glycol	2.0
Fragrance, colorant, preservative	q.s.
	q.s. 100.0

Formula 22.2 Antibacterial Cleansing Cream

Ingredients	%W/W
Disodium lauryl sulfosuccinate	25.0
Palm kernelamide MEA	4.0
Polyquaternium-7	0.8
Chloroxylenol	0.5
Fragrance, colorant, preservative	q.s.
Water	q.s.
	q.s. 100.0

Formula 22.3 Facial Astringent Cleanser

Ingredients		%W/W
Water		73.0
Propylene glycol		1.0
PEG-150 Pentaerythrityl tetrastearate		1.5
Dimethicone copolyol		5.0
Disodium cocoamphodiacetate (37%)		10.0
Sodium lauroyl sarcosinate (30%)		10.0
Citric acid	q.s. pH about 6.0	q.s.
Menthol		0.01
Fragrance, colorant, preservative		q.s.
		q.s. 100.0

compliance to a daily regimen of cleansing is by far the most effective means of controlling oily skin.

TREATMENT OF ACNE

Acne cannot be cured with the topical technologies available today. However, the symptoms and appearance caused by this disease can be reduced. A typical course of therapy for acne takes from two to three months to yield a substantial effect. Treatments are currently limited to keratolytics or peeling agents, antimicrobials, and cleansing products.

Active agents and combinations allowed by federal regulation for use in the United States for over-the-counter sale and treatment of acne are shown in Table 22.4 [7]. Only claims provided in this OTC Monograph are permitted in labeling. Benzoyl peroxide currently is classified as Category III—additional data required to confirm this active's safety profile. This action was prompted by a concern for benzoyl peroxide's potential to initiate tumors in mice. Studies to assess this concern were started in 1995. A final action is pending.

In Europe and Japan, OTC monographs do not exist as in the United States. Acne products are generally subjected to product registration activities. Clinical trials against a placebo or a market standard may be required to gain approval to market.

As stated previously, the goal for acne treatment is containment. Use of each of the actives listed in Table 22.4 requires attention to the formulation composition to maximize cosmetic elegance, chemical stability, and efficacy.

Sulfur is usually used in a precipitated or colloidal form. Sulfur's activity is dose-dependent. Its mechanism of action is not known, but it is believed to act both as a keratolytic and as an antimicrobial. Sulfur, however, has been shown

Table 22.4 Active Ingredients and Combinations for Treating Acne

Single actives	
Benzoyl peroxide	2.5 to 10%
Salicylic acid	0.5 to 2%
Sulfur	3 to 10%
Combinations	
Resorcinol 2 or 3% with sulfur 3 to 8%	
Resorcinol monoacetate 2 or 3% with sulfur 3 to 8%	

to be comedogenic both in rabbit ear tests and on human volunteers [8]. For cover-up products sulfur is preferred for its compatibility with alcohol and coloring pigments.

Resorcinol is believed to enhance sulfur's activity in acne, and sulfur combined with resorcinol is commonly seen. This mixture exerts its effect through both keratolytic and mild antimicrobial actions. Formula 22.4 is an example of a typical resorcinol-sulfur lotion.

Salicylic acid exerts a primary activity as a keratolytic agent. To maximize its activity, a low pH (less than 3.0) is necessary. Frequently salicylic acid is formulated in alcohol-containing vehicles because of its solubility in this carrier. Salicylic acid may cause severe irritation. Care should be exercised when this agent is used on the face, especially around the eyes.

Benzoyl peroxide is an antibacterial and an irritant. It has been shown to reduce the population of *P. acnes* on skin [9], to increase the rate of sloughing

Formula 22.4 Resorcinol-Sulfur Lotion

Ingredients	% W/W
Glyceryl stearate	6.0
Isopropyl myristate	3.0
Stearic acid	2.0
Sulfur	3.0
Bentonite	5.0
Ethyl alcohol	10.0
Propylene glycol	3.0
Resorcinol	2.0
Triethanolamine	1.0
Fragrance, colorant, preservative	q.s.
Water	q.s.
	q.s. 100.0

of epithelial cells, and to promote resolution of comedones. Benzoyl peroxide has been shown to be effective in both inflammatory and noninflammatory acne lesions. Consumers may start their therapy with the lower concentration (2.5%) products and then increase the dosage to the maximum strength (10%) until the desired end point is reached. Such a regimen can minimize irritation that is sometimes seen with benzoyl peroxide.

Numerous patents and formulations have been published showing the utility of benzoyl peroxide. The United States Pharmacopoeia (USP) has established monographs for creams, lotions, and gels containing this active [10]. Because of benzoyl peroxide's inherent instability, the USP provides for marketed product concentrations from 90 to 125 percent of label claim. However, this range does not apply worldwide; therefore, local regulations should be consulted. The stability of benzoyl peroxide has been shown to be dependent on the solvents employed in its formulations. Chellquist and Gorman showed the stability of benzoyl peroxide to be better if the vehicle compounded provides a low degree of solubility for the drug [11].

Benzoyl peroxide is an oxidizing agent and can bleach colored fabrics such as shirts, towels, and rugs, with which it may come into contact.

A selection of typical benzoyl peroxide formulations showing the range of product dosage forms is presented in formulas 22.5–22.7:

ADJUNCTIVE THERAPIES

The literature includes many references on the use of antimicrobials (such as triclosan, hexachlorophene, erythromycin, and clindamycin), the role of antimicrobials in reducing the levels of *P. acnes* on the skin, and the positive impact of this remedial treatment on the clinical presentation of acne.

Formula 22.5 Benzoyl Peroxide Lotion

Ingredients		%W/W
Magnesium aluminum silicate		0.90
Xanthan gum		0.40
Water	q s. ca.	75.5
Propylene glycol		6.0
Benzoyl peroxide 70%		7.15
Laureth-4		5.0
Cetyl acetate (and) Acetulated lanolin		5.0
Fragrance, colorant, preservative		q.s.
		q.s. 100.0

Formula 22.6 Benzoyl Peroxide Cream

Ingredients	%W/W
Cetearyl alcohol	1.5
Ceteareth-20	1.0
Diisopropyl adipate	1.5
Cellulose	2.8
Benzoyl peroxide 70%	3.6
PEG-75	5.0
Fragrance, colorant, preservative	q.s.
Water	q.s.
	q.s 100.0

Formula 22.7 Benzoyl Peroxide Hydro-Alcoholic Gel

Ingredients	%W/W
Benzoyl peroxide	5.5
Water	40.7
Ethyl alcohol	44.1
Laureth-12	6.0
Magnesium aluminum silicate	2.5
Hydroxypropylmethylcellulose	1.0
Citric acid	0.05
Fragrance	q.s
	q.s 100.0

Also prevalent are citations to the use of vitamin A acid (tretinoin), vitamin A esters, adapalene, and isotretinoin. These agents are strong, primary irritants that appear to stimulate epithelial growth yielding more rapid turnover of the horny layer of skin. As a result, these agents prevent the closure of the pilosebaceous orifice and the formation of comedones.

Alpha-hydroxy acids such as lactic and glycolic acids have also been reported to promote improvements in the appearance of acne lesions [12], as has N-acetyl-dl-methionine complexed with quaternary ammonium salts [13].

Many of these agents can be used only under the direction of a physician and are mentioned here to provide a complete picture of the current therapies for acne.

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CHAPTER 23

Face, Body, and Hair Masks and Scrubs

INTRODUCTION

The use of facial masks and mud baths dates to antiquity, when muds were credited with almost miraculous healing powers. They were used in skin therapy and to treat internal ailments. The popularity of cosmetic masks and mud scrubs may be attributed to their combined psychological and physiological effect. The mystique and folklore of "wet earth" treatments is incorporated into many currently available skin and hair care products. These preparations are usually considered treatment cosmetics and are applied to the face, body, scalp, or hair in the form of gels, viscous liquids, or pastes. Mask fragrance and drying time are designed to enhance the therapeutic dimension of the mask or mud scrub. Some current preparations combine the therapeutic sensation of the mask formulation with pharmaceutical actives, physical skin and hair modifiers, and cleansing components. These include acne treatments, body mud scrubs with abrasives, gel or clay masks with alpha- or beta-hydroxy acids, and hair modifiers, as well as body boosters or conditioners.

"Wet earth" masks are usually allowed to dry or to set with the intention of improving appearance by cleansing and physically modifying the feel of the epidermis. Changes to the skin are felt as a transient tightening effect produced by the masks drying on the skin. The warmth and tightening that results from their application is the stimulating sensation of a rejuvenated face, while the adsorptive clays present in most contemporary masks adsorb oils and dirt. Epidermal debris and blackheads are removed when the treatment is washed off the face or body. The user interprets this as invigorated skin and the result is usually a noticeably improved complexion.

Masks are also applied to scalp and hair. These masks are usually formulated to remain wet. The scalp masks invigorate, sometimes having an associated cooling or heating effect. Masks that are applied to the hair are intended to

make it feel or appear fuller and thicker. This is usually accomplished by modifying the pH of the hair cuticle, plumping or lifting it by increasing the pH.

Five basic systems will be reviewed in this chapter. The preferred and most common types of masks are based on smectite and kaolin clay combinations with and without gums and polymers supporting the viscosity and feel. The other treatment masks are not as popular as clay masks. These are based on wax, rubber, vinyl resins, and hydrocolloid systems. The wax type mask must be applied heated. The natural rubber latex face mask does not provide pleasant application or feel and may pose a health concern. Facial strips that contain fast-drying resins have replaced the vinyl resin masks. Finally, the hydrocolloid masks do not have the luxurious feel or the following of clay masks. Most significantly, the marketing and promotion of the natural clay-based masks melds with the preference of healthy all natural products.

The marketing story and development of claims is essential for product identity and positioning. The addition of botanicals, fragrance, abrasives, and active ingredients will design the promotional benefits of the mask. Soothing, stimulating, invigorating, and clarifying are usually associated with certain herbs and natural ingredients. Oat flour, lufa, aloe vera, panthenol, and natural oils all carry a certain weight and add value by their mere presence on the label. The lack of pharmacologically active ingredients does not diminish the cleansing effect of the mask or scrub. The application of the mask provides the psychological ritual, be it relaxation or stimulation. The treatment ritual continues for the duration of the suggested drying time. The oil-absorbing properties of the clays and the cleaning ability of the surfactant system provide the real benefit of the mask. With the introduction of acid masks, it is important to remember that even though the application time of a mask is limited, an acid mask with the drying and oil-absorbing properties of kaolin and talc is an effective treatment medium. Excessive levels of acid or lack of pH adjustment may cause skin irritation.

The essential considerations in formulating a contemporary mask are as follows:

- It should be a smooth paste or gel without flocculation or gritty particles.
- It should not have an "earthy" or objectionable odor.
- It should form an adherent coating that can be easily removed by gentle washing.
- It should produce a definite sensation of tightening or a therapeutic tingling or warming.
- It should produce a perceptible modification of skin, hair, or scalp feel.
- It should produce a significant and noticeable cleansing of the skin, scalp, or hair.
- It should enhance volume and impart shine to the hair.
- It must be nontoxic, dermatologically innocuous, and appropriately preserved.

The prototype formulas provided later are simple and offer a starting point. There are many variations possible, and usually the result is a successful product that is stable and aesthetically appealing. The proper order of addition and hydration of the bentonite reduces stability problems such as separation or syneresis. The total formula composition is just as important, and the balance of ingredients must be considered.

CLAY (ARGILLACEOUS EARTH) MASKS

Clay masks are by far the perennial favorite. China clay, colloidal kaolin, Fuller's earth, or smectite clay (i.e., bentonite, magnesium aluminum silicate, and hectorite) may be used as the "argillaceous" material. The naturally occurring smectite clays, commonly referred to as bentonite and kaolin clays, are typically the primary ingredients of a clay mask. Bentonite gels have been described as soothing to the skin. These gels have also been used in a number of dermatological preparations such as acne treatment masks with benzoyl

Formula 23.1 Clay Face Mask Neutral pH

Water	q.s. to 100%
Rheology modifier[a]	1 to 8%
Thickener[b]	0.1 to 1.0%
Oil absorbent[c]	5 to 40%
Humectant[d]	2 to 10%
Surfactant[e]	2 to 20%
Opacifier[f]	up to 1.0%
pH buffer	adjust to between 5 and 8
Preservative, fragrance, and color	q.s.

[a]May include: smectite clays; i.e., bentonite, hectorite, or magnesium aluminum silicate

[b]May include: xanthan gum, methylcellulose, guar gum, or carrageenan

[c]May include: kaolin clay or talc

[d]May include: glycerin, sorbitol, propylene glycol, or butylene glycol

[e]May include: sodium lauryl sulfate, sodium lauryl ether sulfate, ammonium lauryl sulfate, ammonium lauryl ether sulfate, cocamidopropyl betaine, or sodium lauroyl sarcosinate

[f]May include: titanium dioxide or zinc oxide

Procedure and comments: The rheology modifier needs to be hydrated in the water prior to addition of the other ingredients. The thickener (gum) is added into the water vortex either slurried with a humectant or sifted in slowly to avoid formation of aggregates. Mix until uniform, then add the oil absorbent. Follow with the humectant or placticizer and add the surfactant. Addition of the opacifier is optional.

Formula 23.2 Clay Face Mask Acid pH

Water	q.s. to 100%
Rheology modifier[a]	1 to 8%
Thickener[b]	0.1 to 1.0%
Oil absorbent[c]	5 to 40%
Humectant[d]	2 to 10%
Surfactant[e]	2 to 20%
Opacifier[f]	up to 1.0%
Alpha- or beta-hydroxy acids	2 to 10%
pH buffer	to a pH of 3.5 to 4
Preservative, fragrance, and color	q.s.

For the identification of[a] through[f], see Formula 23.1

Procedure and comments: The rheology modifier needs to be hydrated in the water prior to addition of the other ingredients. The thickener (gum) is added into the water vortex either slurried with a humectant or sifted in slowly to avoid formation of aggregates. Add the humectant or placticizer and follow with the oil absorbent and surfactant. Addition of the opacifier is optional. The pH of an acid mask should be adjusted to between 3.5 to 4. This can be accomplished using either TEA or sodium lactate as the buffer. When using sodium lactate to buffer the pH, it is necessary to include the acid generated from the presence of sodium lactate into the final acid concentration and maintain it at the permitted alpha-hydroxy acid level. An acid mask with the drying and oil-absorbing properties of kaolin and talc is an effective treatment medium. Excessive levels of acid or lack of pH adjustment may cause skin irritation.

peroxide. They can also play a significant role in the treatment of eczema, abscesses, sores, and wounds.

Bentonite is characterized by its ability to swell in water and develop desirable rheological properties in aqueous compositions by forming a colloidal dispersion. It will suspend particulates, stabilize formulations, and optimize flow and application characteristics. To employ the benefit of the colloidal structure and improve formula stability, it is important to hydrate the smectite prior to addition of other ingredients. The viscosity of bentonite dispersions varies exponentially with concentration. Blends of bentonite with thickeners are suggested to develop synergies, and they offer a cost-efficient approach to achieving new formula characteristics. Viscosity of the dispersion is influenced by pH and by the addition of electrolytes.

Proper hydration of the bentonite is the most significant step in the formulation of the mask. Failure to properly hydrate the smectite clay may result in formula instability, separation, settling, or syneresis. Syneresis is exhibited as water on the surface of the product. It may also be a result of too much surfactant, salt, cationic material, or a high level of solids in the product. Changing the ratio or increasing the water phase may actually improve stability

Formula 23.3 Clay Face Mask with Emulsion System

Water	q.s. to 100%
Rheology modifier[a]	1 to 5%
Thickener[b]	0.1 to 1.0%
Oil absorbent[c]	5 to 40%
Humectant[d]	2 to 10%
Emulsion system	
Tallow or coconut fatty acids	up to 10%
Cetyl alcohol	up to 2%
Oils[e]	up to 10%
Glyceryl stearate SE	1 to 5%
Opacifier[f]	0.1 to 1.0%
pH buffer	adjust to 6 to 8
Preservative, fragrance, and color	q.s.

[a]May include: smectite clays; i.e., bentonite, hectorite, or magnesium aluminum silicate

[b]May include: xanthan gum, methylcellulose, guar gum, or carrageenan

[c]May include: kaolin clay or talc

[d]May include: glycerin, sorbitol, propylene glycol, or butylene glycol

[e]May include: essential oils, esters, glyceryl esters and derivatives, fats and oils

[f]May include: titanium dioxide or zinc oxide

Procedure and comments: The rheology modifier needs to be hydrated in the water prior to addition of the other ingredients. The thickener (gum) is added into the water vortex either slurried with a humectant or sifted in slowly to avoid formation of aggregates. Add the humectant or placticizer and follow with the oil absorbent. Heat the water phase to ~ 75 °C. Apply good mixing. Blend the oil phase ingredients and heat the oil phase to ~ 75 °C; when both phases are at temperature, add the oil phase to the water phase. Addition of the opacifier is optional. Buffer the pH to between 6 and 8. Mask formulas such as those mentioned earlier can be easily modified to produce mud scrubs by forming soaps using tallow or coconut fatty acids. Detergency can also be achieved by using conventional surfactant systems.

or alleviate the problem. Each bentonite particle is composed of thousands of submicroscopic platelets stacked in sandwich fashion with a monomolecular layer of water between them. The faces of these platelets carry a negative charge, while the edges have a slight positive charge. The hydration process of the smectite clay allows the platelets to delaminate and form the colloidal structure. When the smectite is mixed with water, the latter osmotically penetrates between the platelets, forcing them apart; the shearing force completes the separation. Both mechanical and thermal energy accelerate the hydration process. Increasing shear and water temperature will reduce hydration time.

Formula 23.4 Clay Face Mask/Scrub

Water	q.s. to 100%
Rheology modifier[a]	1 to 8%
Thickener[b]	0.1 to 1.0%
Oil absorbent[c]	5 to 40%
Humectant[d]	2 to 10%
Tallow or coconut fatty acids or a surfactant system[e]	up to 30%
Polyethylene beads	up to 5%
Opacifier[f]	0.1 to 1.0%
pH buffer	adjust to 6 to 8
Preservative, fragrance, and color	q.s.

For identification of[a] through[f], see Formula 23.1.

Procedure and comments: The rheology modifier needs to be hydrated in the water prior to addition of the other ingredients. The thickener (gum) is added into the water vortex either slurried with a humectant or sifted in slowly to avoid formation of aggregates. Add the humectant or placticizer and follow with the oil absorbent. Add the tallow or coconut fatty acids or a blend of surfactants. Addition of the opacifier is optional. Buffer the pH to between 6 and 8.

The actual hydration time will depend on the composition of the particular bentonite, the mixing equipment available, shearing capability, and the water temperature. It is best to consult the raw material supplier. The presence of dissolved substances in the water such as preservatives, emulsifiers, surfactants, cationics, and salts will prolong hydration time by inhibiting the osmotic swelling essential to platelet separation.

Kaolin is used for its ability to impart moisture adsorption, oil absorption, a smooth consistency, and easy spreading to a mask. It is also used to buffer the clay mask. The typical pH of kaolin is about 5, whereas the smectite clays are above pH 9. Increasing the kaolin clay concentration can control the drift in product pH and improve long-term stability. The acid masks such as those that include the alpha- or beta-hydroxy acid and benzoyl peroxide types, use high concentrations of kaolin (as much as 40%) to assist in stabilizing the acidic pH, reducing pH drift, and providing product stability.

As a clay mask dries on the face it hardens and contracts, giving the sensation of mechanical astringency. The presence of absorbent clays such as bentonite and kaolin produces an excellent and instantly noticeable cleaning effect, particularly on oily complexions. Most clays are off-white in color, but white, red, yellow, brown, blue, green, purple, and even black clays are known. If the color of the mask needs to be lightened and brightened, opacifiers or

Formula 23.5 Clay Face Mask/Scrub—Acid pH With Surfactant System

Water	q.s. to 100%
Rheology modifier[a]	1 to 5%
Thickener[b]	up to 1.0%
Oil absorbent[c]	5 to 30%
Humectant[d]	2 to 10%
Surfactant system[e]	up to 30%
Polyethylene beads	up to 5%
Opacifier[f]	0.1 to 1.0%
Alpha- or beta-hydroxy acid	2 to 10%
pH buffer	adjust to 3.5 to 4
Preservative, fragrance, and color	q.s.

For identification of[a] through[f], see Formula 23.1.

Procedure and comments: The rheology modifier needs to be hydrated in the water prior to addition of the other ingredients. The thickener (gum) is added into the water vortex either slurried with a humectant or sifted in slowly to avoid formation of aggregates. Add the humectant or placticizer, then add the oil absorbent and follow with the surfactant. Addition of the opacifier is optional. The pH of an acid mask should be adjusted to between 3.5 to 4. This can be accomplished using either TEA or sodium lactate to buffer the acid mask. When using sodium lactate to buffer the pH, it is necessary to remember to include the acid generated from the presence of sodium lactate into the final acid concentration and maintain it at the permitted alpha-hydroxy acid level. As previously stated, it is important to remember that even though the application time of a mask is limited, an acid mask with the drying and oil-absorbing properties of kaolin and talc is an effective treatment medium. Excessive levels of acid or lack of pH adjustment may cause skin irritation.

whiteners, such as titanium dioxide or zinc oxide, can be added. On the other hand, addition of dark clay and coloring may enable marketing of a black or green sea mud mask.

Other mask components may include surfactants, emulsifiers, and emollients. Gums and polymers such as xanthan, guar, methylcellulose, or carrageenan may be added to stabilize the suspension of solids and to contribute to the mechanical strength of the dried film. Glycerin, propylene glycol, butylene glycol, or sorbitol may be added as plasticizers to improve spreadibility and skin feel and as humectants to control drying rate. They will also improve long-term stability of the product, reducing cracking and separation at cold temperatures or in freeze/thaw cycling. Addition of active ingredients such as sulfur, astringents, bleaching agents, benzoyl peroxide, or other active agents may confer special attributes to the mask. The regulated active agents must be stable and recoverable in the mask over the shelf life of the product.

Because of their consistency and viscosity, clay masks are usually packaged in wide-mouth jars, tubes, or single use sachets. The viscosity can be controlled by the formulation, but heavier consistency masks are commonly preferred.

Addition of cationic raw materials such as conditioning agents, surfactants, or antimicrobials may disrupt the colloidal structure generated by the bentonite. Use levels should be kept below 3%, since higher concentration of cationics may flocculate the anionic bentonite and cause instability. Cationic raw materials should be incorporated at the end of the compounding process, not at the beginning. The addition of a cationic substance prior to hydration of the bentonite will cause improper hydration, that will reduce or even eliminate its desired properties. Cationics may also react with other anionic components, producing flocculation and poor product stability. Correct balance of cationic substances can produce interesting properties of the mask or scrub such as thickening and residual conditioning effects.

Other ingredients commonly added to masks and scrubs are polyethylene beads, lufa, and oat flour. They assist in the marketing story, aid in mask removal, and change the perception of the cleansing of the skin.

Many clay masks also include an emulsion system. Proper equipment is needed to work with these types of products. The viscosity generated and heat requirements may limit lab work capability. Scale-up to production size batches may reveal rheological differences in the formula.

WAX MASKS

Wax-based masks generally consist of paraffin and microcrystalline wax blended to melt a few degrees above body temperature. They may also include petrolatum or mineral oil and polar materials such as cetyl and stearyl alcohols. The more highly formulated wax masks are seen predominantly in professional salons.

Formula 23.6 Wax Mask

Paraffin wax	up to 60%
Microcrystalline wax	10 to 15%
Cetyl or stearyl alcohol	up to 5%
Mineral oil or petrolatum	up to 20%
Quaternium-18 hectorite	up to 3%
Preservatives, fragrance, and color	q.s.

Procedure: Melt all the ingredients together. Apply appropriate mixing to uniformly blend the wax mixture with the oils. Transfer the melted wax into forms while hot. Formulating the wax blend so that the melt is thixotropic will facilitate uniform application. This can be achieved by the incorporation of a small amount of organophilic hectorite clay.

Wax masks are solid at room temperature and are melted prior to use. They are brushed on when warm, just slightly above their melting point. The heat of the preparation opens the pores, and as the wax hardens, it produces a sensation of tightness. The wax film forms a moisture-proof barrier. This induces profuse perspiration that helps to flush impurities from the follicular openings. The occlusive wax coating also softens callused skin by reducing transepidermal water loss.

RUBBER MASKS

Rubber-based face masks are not currently popular because they are not perceived as "natural." There are also other growing concerns. Sensitized individuals are prone to develop contact dermatitis caused by the presence of residual accelerators. The other more serious concern is that of allergic reactions to latex. Natural rubber latex derived from the sap of a rubber tree contains proteins that can cause allergies. These allergic reactions are severe and may include death. There is a deproteinized natural latex available that has been treated with a proteolytic enzyme and should be considered during formulation.

These natural rubber latex masks are applied to the skin as liquids and allowed to set. Once dry, they form a continuous, elastic, and water-impermeable film. Their primary function is to restrict normal skin respiration. The thin film also causes heat retention and increased blood circulation. Rubber masks are removed easily by simply pulling. After removal, slight plumping of the skin is noticeable. This effect, however, is transient and disappears after skin respiration returns to normal. The following formula illustrates a latex-based face mask.

Formula 23.7 Natural Latex Mask

62% Low ammonia natural rubber latex*	72.9%
Potassium hydroxide (10% solution)	2.3%
Ammonium caseinate (10% solution)	2.3%
Zinc oxide (60% dispersion)	1.5%
Sulfur (50% dispersion)	0.9%
Phenolic antioxidant (50% dispersion)*	0.9%
Tetramethylthiuram disulfide (50% dispersion)	0.9%
Zinc dibutyldithiocarbamate (50% slurry)	0.23%
Kaolin clay (50% slurry)	18.1%
Preservative, fragrance, and color	q.s.

*Not listed in the *INCI Dictionary*

Procedure: Prepare the appropriate solution, dispersion, or slurry of the above raw materials. Add in order listed with good mixing after every ingredient addition.

VINYL MASKS

The vinyl-based products are known as peelable face masks. These products enjoyed some popularity in the past but are seldom seen in product lines today because of their "chemical" nature. They are generally based on polyvinyl alcohol or vinyl acetate resin as the film-former. Vinyl masks do not provide the physical and psychological sensations of clay masks. They are therefore considered less luxurious and generally not preferred. Today face strips that pull out impurities and blackheads have effectively replaced them.

Formulas 23.8 and 23.9 use polyvinyl alcohol (PVA). The PVA should be added to cold water. The suggested effective use concentration of PVA is commonly up to a 10% maximum. There are two types of PVAs available: cold water–soluble and those that require that the water be heated to 80 °C after the PVA is wet out. Although the cold water–soluble PVA is dustier than the conventional PVA, it dissolves easily allowing for cold processing. The addition of alcohol is optional, and it is commonly added to the formula to assist in the clarity and to reduce the drying time.

In all the peels, the film is plasticized by the inclusion of humectants such as glycerol, propylene glycol, butylene glycol, or sorbitol. A single component or a combination of humectants can be used. A mild surfactant assists in removing the peel. The pH of the mask should be maintained between 4 and 7. The addition of an opacifier (0.1 to 1.0%) is optional and only suggested for whitening of the opacified masks.

Formula 23.8 Clear Vinyl Mask

Water	q.s. to 100%
Polyvinyl alcohol (PVA)	5 to 10%
Humectant[a]	up to 10%
Surfactant[b]	2 to 5%
Alcohol denat. or SDA	up to 30%
pH buffer	adjust to 4 to 7
Preservatives, fragrance, and color	q.s.

[a]May include: glycerin, sorbitol, propylene glycol, or butylene glycol

[b]May include: sodium lauryl sulfate, sodium lauryl ether sulfate, ammonium lauryl sulfate, ammonium lauryl ether sulfate, cocamidopropyl betaine, or sodium lauroyl sarcosinate

Procedure: Add the PVA to water at room temperature. Then heat to ~ 80 °C until the PVA has dissolved, or use PVA that is cold water–soluble. Organic gum or polymeric thickeners may be added to the PVC mask in order to increase the viscosity. Addition of alcohol will require the use of an alcohol-tolerant thickener. Add the humectant or plasticizer and follow with the surfactant. Mix until uniform. Cool to room temperature before adding the alcohol. The formula is a water-white, clear, slightly viscous liquid.

Formula 23.9 Opaque Vinyl Mask

Water	q.s. to 100%
Rheology modifier[a]	3 to 5%
Thickener[b]	up to 1%
Humectant[c]	up to 10%
Kaolin	up to 10%
Polyvinyl alcohol (PVA)	5 to 10%
Surfactant[d]	2 to 5%
Opacifier[e]	0.1 to 1.0%
Alcohol denat. SDA	up to 20%
pH buffer	adjust to 4 to 7
Preservatives, fragrance, and color	q.s.

[a]May include: smectite clays, bentonite, hectorite, or magnesium aluminum silicate

[b]May include: xanthan gum, methylcellulose, carbomer, guar gum, or carrageenan

[c]May include: glycerin, sorbitol, propylene glycol, or butylene glycol

[d]May include: sodium lauryl sulfate, sodium lauryl ether sulfate, ammonium lauryl sulfate, ammonium lauryl ether sulfate, cocamidopropyl betaine, or sodium lauroyl sarcosinate

[e]May include: titanium dioxide, zinc oxide, or styrene or acrylates copolymer

Procedure and comments: The rheology modifier needs to be hydrated in the water prior to addition of the other ingredients. It is important to remember that improper hydration of bentonite will reduce or even eliminate the desired properties generated by this raw material, causing syneresis, poor suspension, and possible separation or settling. Organic gum or polymeric thickeners may be added to the PVC mask in order to increase the viscosity. Addition of alcohol will require the use of an alcohol-tolerant thickener. Add the PVA at room temperature (heat to ~ 80 °C if necessary) and mix until dissolved. Add the humectants, then follow with kaolin, the opacifier, and surfactant. Cool to room temperature before adding the alcohol. This formula is opaque and uses bentonite to suspend the particulates. It may contain alcohol to improve the drying properties.

HYDROCOLLOID MASKS

Hydrocolloid masks are based on organic gums such as tragacanth gum, xanthan gum, gelatin, casein, carrageenan, sodium carboxymethylcellulose, acacia and guar gum, and polyvinylpyrrolidone, carbomer, and mixtures of the above. Masks are formulated either as high-viscosity sols, which after application lose water and form a flexible gel film, or as solid gels, which are melted before application. The shrinking of the gel upon dehydration produces the sensation of tightness. The film may be plasticized by the addition of common humectants such as glycerol, propylene glycol, butylene glycol, or sorbitol. The viscosity and properties of these masks can be varied considerably depending on the colloid used, its concentration, and by forming synergies with other ingredients.

Formula 23.10 Hydrocolloid Mask

Water	q.s. to 100%
Rheology modifier[a]	up to 2%
Hydrocolloid[b]	1.0 to 20%
Humectants[c]	2 to 10%
Kaolin clay	up to 5%
Opacifier[d]	up to 1.0%
Surfactant[e]	up to 5%
Alcohol denat.	up to 50%
pH buffer	adjust to 4 to 7
Preservatives, fragrance, and color	q.s.

[a]May include: smectite clays, bentonite, hectorite, or magnesium aluminum silicate
[b]May include: tragacanth gum, gelatin, casein, carrageenan, methylcellulose, acacia farnesiana, guar gum, carbomer, PVP K-15, xanthan gum, or a combination of gums and polymers.
[c]May include: glycerin, sorbitol, propylene glycol, or butylene glycol
[d]May include: titanium dioxide, zinc oxide, or styrene / acrylates copolymer
[e]May include: sodium lauryl sulfate, sodium lauryl ether sulfate, ammonium lauryl sulfate, ammonium lauryl ether sulfate, cocamidopropyl betaine, or sodium lauroyl sarcosinate

Procedure: The rheology modifier needs to be hydrated in the water prior to addition of the other ingredients. As the main component of the face mask, choose one or a blend of hydrocolloids. Add the hydrocolloid into the water vortex either slurried with a humectant or sift in slowly to avoid formation of aggregates. The humectants may be used to slurry the hydrocolloids or added independently to promote film properties. Add the kaolin clay, opacifier, and surfactants. Follow with the alcohol and adjust the pH.

Masks based on hydrocolloids are easier to apply and dry more rapidly than clay masks. Their cleansing action, however, is inferior because they do not contain a sufficient amount of solids to effectively adsorb oil and dirt. Drying can be accelerated by the incorporation of alcohol. However, addition of alcohol restricts the choice of hydrocolloid since many are not alcohol-tolerant. Certain grades of methylcellulose, carbomer, and polyvinylpyrrolidone are stable in such systems and can be used in hydro-alcoholic masks.

Face masks based on hydrocolloids may also contain small quantities of fine solids that act as opacifiers and which sometimes facilitate application. Kaolin, bentonite, talc, zinc oxide, or titanium dioxide can be used, but in amounts not exceeding 5%. Too much particulate matter causes formation of a discontinuous film reducing or lacking the mechanical strength and skin-tightening effect. Formula 23.10 demonstrates the composition of a hydrocolloid face mask that permits a number of modifications. To improve stability of the product, the pH of these types of masks should be maintained between pH 4 and 7.

RECOMMENDED READING

United States Pharmacopeia, latest edition, Monograph on Magnesium Aluminum Silicate.

United States Pharmacopeia, latest edition, Monograph on Purified Bentonite.

VEEGUM/VAN GEL Brochure, R.T. Vanderbilt Company, 1999.

Preparation of high solids content VEEGUM/VAN GEL dispersions, Vanderbilt Company Report, 1987.

PVA Mask formulation—Air Products Company.

Ciullo, P.A., Rheological properties of magnesium aluminun silicate/xanthan gum dispersions, *J. Soc. Cosmet. Chem.*, 1981, **32**, 275–285.

Carlson, B.C., *Cosmet. Technol., 2*, 1980, **11**, 26–31,49.

CHAPTER 24
Skin Cleansing Products

INTRODUCTION

Since the beginning of recorded history, cleansing of the body surface has been a hallmark of civilized societies. The preparation of soap from animal or plant lipids with diverse alkalies was an art practiced in the Near East and perpetuated by cultures throughout the Levant. Soap was probably expensive, and its use was restricted to the wealthy; but some level of personal hygiene was widely practiced and was prescribed in the Mosaic scriptures. During the Roman period, soap was readily available, but it became scarce and rarely used after Roman dominance ended until about the eighteenth century. During the Middle Ages, the art of soap making did not advance, and usage of soap for personal cleansing declined. Only when sodium hydroxide became available did soap become a commodity.

Today soap in the form of bars or solutions is widely distributed and used safely—that is, without overt irritation—during daily ablutions by hundreds of millions of people. Regardless of all the adverse comments about the safety of soap and despite the perception of soap as drying, soap is unique as an unpreserved product with no definitive evidence of causing allergic dermatitis. Soap is not universally considered a cosmetic product. In the United States, for example, soaps remain under the control of the Department of Agriculture, unless they include antimicrobials, fragrances, or other additives.

Negative publicity about the use of soaps surfaced first in the German dermatological literature. The perception of soap as an irritant was based on the so-called alkali resistance test, sorption tests, and assessments of erythema, swelling, and scaling.

The cosmetic rinse-off skin cleansers owe their existence to the desire to create replacements for toilet soaps because of their perceived irritation potential. These skin cleansing agents, therefore, must retain the ability to free the

skin of undesirable detritus without causing any harm to the skin. This aspect of skin cleansers is commonly referred to as "mildness."

THE QUEST FOR MILD SKIN CLEANSING

Mildness of skin products is not easily defined; in the context of skin cleansing, it is a relative term. The ultimate answer sought is: Is preparation A as mild or milder than preparation B? Thus product and ingredient testing dominate progress in this field. Mildness of skin cleansers is then simplistically defined as the ability to cleanse without damaging the integument.

THE SOAP DILEMMA

It is proper to begin the discussion of mild skin cleansing agents with an examination of soap, the agent most often accused of causing dryness, scaling, and roughness of skin. The concepts originally verbalized by German investigators were soon confirmed by armies of researchers using all types of closed patch tests [1]. The commercial potential of replacing soap with safer synthetic detergents soon became apparent. Comparative data between soap and detergent bars were brought to the public's attention, and to this day soap is considered drying and irritating, and its use is associated with skin damage. Despite these widely publicized data, a large portion of all living adults massage copious quantities of soap foam into their facial skin before their daily shaving. Is it conceivable that patch test data and information on the protective nature of the acid mantle on the skin surface may not represent the final word on skin safety and mildness? The picture is further obscured by the frequently unreported composition of the soaps tested. Soap manufacturers know, for example, that short-chain fatty acids yield high-foaming and more skin-aggressive soaps than the longer chain acids (C_{16}–C_{18}) that foam less copiously. Nevertheless, soap users still rely on vague descriptions such as coconut fatty acids or hydrogenated soy fatty acids and the like.

The explanation for soap's irritancy was sought in the ability of soap to extract (solubilize) diverse types of skin constituents, soap's water solubility, and the product's pH. The last approach is particularly unfortunate. If alkalinity played any role in irritancy, titrable alkalinity (above a selected pH) would have been a more useful parameter than pH.

Much of the careful work on skin extractables and on the impact of surfactants on this process has been conducted on excised stratum corneum or epidermis. Such studies provide qualitative guidance—at best—since in most cases both the exterior (stratum corneum) and the interior (dermal-epidermal) surfaces are exposed to the action of the surfactant. Questions of solution

access from intact stratum corneum to the interior of the skin are not answered, thus ignoring the well-established effects of corneal protection. In fact, there are no definitive studies supporting the concept that an externally applied soap or aqueous surfactant solution in normal use removes any corneal lipid.

Despite these uncertainties, soap still stands accused of being drying to the skin by armies of investigators using test protocols designed to confirm various adverse effects of soap.

The ubiquitous use with after-rinsing of soap or surfactant skin cleansers by billions of individuals surely demands a rational explanation. The facts clearly show that patch testing with a moderately concentrated (2 to 5%) soap solution elicits a reproducible erythematous response, while washing with a similar soap is performed daily without serious side effects. It is legitimate to ask whether conventional closed patch testing can yield meaningful predictive results with skin cleansing preparations or whether patch testing cannot simulate the short exposure time of typical rinse-off cleansing preparations.

It should not be surprising that the patch test techniques used for assessing soap have also been applied to the evaluation of surfactants used in skin cleansing products. It is also not surprising that formulation approaches and combinations have been found that—for not fully explained reasons—are capable of reducing the adverse effects attributed to one or another surfactant.

Reduced irritation from blends of typical soaps with other components clearly demonstrates that manipulation of a soap formula can provide less damaging skin cleaners. Among these efforts are observations that high levels of glycerin (10%) in soap, combinations of soaps with isethionates or hydrophobically modified celluloses, or with nonionic surfactants appear to modify the undesirable side effects of soaps. Even the simple addition of free fatty acids (which results in the formation of superfatted soaps) has been shown to be useful. Reasons for the enhanced mildness of these and similarly modified soaps have been provided, but these reasons must be viewed with caution. Ease and completeness of rinsing, dye uptake by washed skin, and absorption of alkanoic acid by skin proteins may play a subtle role in skin mildness, but these phenomena are less persuasive than the clinical assessment of scaling or dryness or the more parametric analyses via TEWL or conductance.

MILDNESS OF CLEANSING PRODUCTS BASED ON SYNTHETIC SURFACTANTS

The first suspicions about the safety of soap-based skin cleansing products were raised in Europe during the years preceding Word War II. The dislocations produced by the war delayed serious efforts at resolving these questions

until the war's end. Bars based on nonalkaline synthetic surfactants were introduced in 1948 in the United States. Over the years, some of these surfactants were suspected of eliciting adverse reactions; this led to the development of carefully designed mild cleansing bars.

However, the synthetics used in cleansing preparations during the 1950s were soon also suspected of eliciting irritation. Investigators began to report on the adverse effects of patch testing with alkyl sulfates. As a result, cosmetic formulators have to this day avoided the use of alkyl sulfates in products intended to remain on the skin. Even under conditions of use with rinsing, clinicians reported on skin dryness from exposure to alkyl sulfate–containing products. However, efforts to explain these results have not been successful. Neither skin water content nor elution of the natural moisturizing factor seemed to provide unequivocal answers, although an increase in transepidermal water loss generally followed alkyl sulfate exposure. Extraction of skin lipids by detergent exposure also failed as a potential definitive explanation. Other explanations were invoked involving direct damage to keratinocytes and denaturation of hydrolytic enzymes in the skin. Today many investigators believe that the protein sorption of some surfactant is predictive of dermatitic responses. There can be little doubt that sorption of surfactants by skin proteins does occur. This does not establish a direct causal relationship, but such sorption may in turn alter the skin's water-swelling response, as explained by several investigators (see, for example Ref. 2).

It is by no means clear how surfactant skin permeation and protein sorption occur during the short exposure of skin to cleansing preparations. Imokawa [3] proposed an explanation some 20 years age in which the initial step was removal of the skin's hydrophoblic (sebaceous) coating. This facilitates imbibition of water and surface adsorption of the surfactant. Drying of the skin then leaves the sorbed surfactant film (on the surface), and the water loss causes disorganization of the stratum corneum.

Formulators of mild wash-off skin cleansers are urged to keep Imokawa's concepts in mind until alternate and perhaps more plausible explanations are provided. Particularly significant to formulators is the principle that multiple exposures have effects on skin. Thus compounding with "safe" surfactant mixtures (as assessed by patch tests) does not ensure that the product is innocuous during repeated use. The acute test protocol [4] as described on many occasions cannot stand on its own. Instead it must always be supported by in-use data derived from relevant patterns of exposure [5]. Reliance on in vitro tests as documented in Ananthapadmanabhan and coworker's paper and its many references is only a first step in ensuring creation of a mild product [6]. Currently some complex in vivo skin washing tests are used to confirm the mildness of dish washing preparations and cosmetic cleansers. Details of

these protocols are available from laboratories specializing in these procedures. Formulators must also consider seasonal effects that can modify the results of any test.

Patch test data and diverse in vitro procedures should be used by formulators primarily to identify ingredients that are likely to be safe and to segregate them from ingredients that should be used with caution. Even this approach can be misleading. For example, quaternary substances can be used successfully (and without skin irritation) in leave-on skin care products despite numerous eye and skin testing protocols showing that quaternaries can elicit adverse skin effects. More disturbing is the fact that the results of combining two presumably safe ingredients are unpredictable.

This discussion is properly brought to a close with a brief comment concerning subjectively reported skin phenomena unaccompanied by any overt dermatological signal. Instead users complain about a low level of discomfort referred to as skin tightness. It is unlikely that the tightness or discomfort sensation originates in the dermis or even lower lying tissues. It is more probably related to some unexplained stiffening of the stratum corneum that is perceived as tightness. A mechanism based on Imokawa's concept [3] is probably operative. Readers should also keep in mind that perceived or label-implied safety ideas should be accepted with caution. Thus it was recently reported that a detergent-based children's hand cleanser was more damaging to skin than two industrial hand cleaners [8].

FORMULATION OF SKIN CLEANSING PRODUCTS

The marketed forms of rinse-off, surfactant-based skin cleansers include liquids, gels, and solid products. Primarily they contain substances intended to remove soil and adhering sebum from the skin surface by detersive processes. Some include substances that modify this basic function by providing emolliency, moisturization, or antimicrobial activity. Table 24.1 shows that the

Table 24.1 Functionality of Skin Cleansing Products

Foaming bubble baths
Skin cleansers (shower and tub)
Facial cleansers
Hand cleansers
Abrasive cleansers
Towelette-based cleansers
Antibacterial cleansers

skin cleansing cosmetics that are discussed in this chapter can serve diverse functions in a number of differing products. Most of them are water-based and rarely contain more than about 10% of active detergent(s). The product forms are created by judicious use of viscosity builders or by reducing the water content. Perfumes, sequestrants, colorants, and preservatives are essential for presenting a safe, attractive, and stable product to customers.

The creation and formulation of any skin cleansing product requires identification of the attributes of the finished products, as suggested in Chapter 6. Only after establishment of these criteria can the formulator select the detersive constituents for the product and the best-suited modifiers. Some typical desired product attributes are listed to help ingredient selection:

Mildness and safety
Flash foam
Dense and copious foam
Cleansing efficacy
Rinsability
Skin conditioning
Biodegradability

This listing could probably include many additional characteristics, but this enumeration is sufficient for help in selecting major components. Formulators should under no circumstances rely on the use of components with questionable mildness and safety without further testing. Foaming characteristics and ease of rinsing are subject to modification. Skin condition at the end of the rinsing step must meet high standards. By contrast, cleansing efficacy of body skin is not a primary criterion for the marketability of a cleansing product.

Primary surfactants for cleansing products include many representatives of all major groups of surfactants.

ANIONIC SURFACTANTS

The most frequently used detersive substances are the anionic surfactants (Table 24.2). In this table, the surfactants are listed alphabetically; the irritation or mildness ratings are based on documentation that in many cases is not very substantial. It includes the extensively studied alkyl sulfates, isethionates, and soaps. The comments in the right-hand column of Table 24.2 are provided only as a general guide. Safety assessment is based on historical data on substances not always well identified chemically. Users of these ingredients should be aware of the fact that impurities and changes in synthetic processes may alter the safety profile of these ingredients. As noted already in passing, skin irritancy by anionics can be reduced or modified by all types of additives. Many

Table 24.2 Anionic Skin Cleansing Agents

Chemical type	Irritation/Mildness rating
Acyl phosphates	Probably nonirritating
Acyl polypeptides	Probably nonirritating
Acyl sarcosinates	Fairly innocuous
Acyl taurates	Probably nonirritating
Alkylaryl sulfonates	Reportedly harsh on skin
Alkylether sulfates	Less irritating than alkyl sulfates
Alkyl phosphates	Probably nonirritating
Alkyl sulfates	Irritating in patch test
Isethionates	Mild, nonirritating
Olefin sulfonates	Mildly irritating
Soaps	Irritating in patch test
Sulfoacetates	Fairly innocuous

nonionic, amphoteric, and cationic surfactants have the potential of enhancing skin mildness of anionics. Proteins, gums, and polymeric substances can also reduce adverse responses to anionic surfactants. Thus formulators can pick and choose from many sources. Particularly noteworthy is the combination of isethionates and soaps that can reportedly eliminate many of the adverse effects attributed to the use of soap alone. Other combinations with alkyl-glyceryl-ether sulfonates offer additional possibilities for modifying the classic soap systems.

With a few exceptions, most anionics have been identified as irritants in a variety of patch test protocols [3,4]. Nevertheless, the use of these substances in skin cleansers has persisted, presumably because anionics—as a group—seem to provide useful characteristics to products.

One of the key attributes expected by the consumer is rapid flash foam that should persist during the actual washing cycle. Consumers expect the cushioning dense foam commonly created by soaps and other anionics in combination with foam boosters. Frequently the foam produced by anionics may be too lacy or may not persist during the normal application period. This defect was remedied in the past with the aid of foam boosters. The list of useful and effective foam boosters has been severely limited by the elimination of diethanolamides because of their participation in nitrosamine formation. If alkanolamides are excluded, formulators are limited to the use of fatty alcohols, alkyl betaines, alkylamine oxides, and alkylamido amines to assist in foaming. Additional agents and combinations will reach the market in the future and gain acceptance.

Some anionics and their combination products are briefly described in this section, in a sequence roughly based on frequency of use.

Soaps

The field of surfactants useful for skin cleansing is dominated by soaps. Skin bar cleansers based on soaps have become a commodity in modern life. The manufacture of soap requires formation and neutralization of a mixture of fatty acids from various plant and animal triglycerides. The alkali alkanoates are further processed and then formed into compressed bars. In this form, they require no preservative. Soap bars—essentially in the presentations currently available—were introduced into the market in about 1830. The important attributes of soap bars include the ability to lather copiously and to deliver a rich creamy foam. The skin-aggressive nature of soap is in part related to the alkalinity of the product and the fatty acid chain length (palmitates, e.g., are milder than laurates).

A great deal of effort has been made to create low pH soaps and especially to add lipids to reduce the potential for irritation and create an image of conditioning (superfatted soaps). The range of emollients and other additives included in various soap bars is endless and expands continuously. Today's promotion includes "cleansing cream," while in earlier years promotion has centered around antimicrobials.

Attempts to lower soap's pH have clearly failed. The only carboxylates in Table 24.2 are derivatives of amino acids, especially the sarcosinates. These have sometimes been called interrupted soaps and form lathering solutions at pHs close to 7. Aside from their attraction as nature-derived substances acylated amino acids should all be viewed as soaplike.

Sulfates

Alkyl sulfates are generally identified as particularly irritant. As in the case of soaps, the C-12 derived sulfates are most likely to induce adverse skin reaction. The ether sulfates are adjudged as milder, but precise data are missing. The potential of irritancy from alcohol sulfates is reduced by the presence of water-soluble nonionic surfactants, betaines, and other surfactants. The commonly accepted mechanism involves micellization with a reduction in free monomeric species in solution [2]. This might lower skin permeation, skin binding, or related phenomena induced by the surfactant.

Sulfonates

This group includes the sulfosuccinates, isethionates, taurates, and diverse aliphatic and aromatic sulfonated hydrocarbons. Mildness of these substances appears to depend on the size of the hydrophilic head and its accessibility to water. Evidence for such a relationship is tenuous but is in accord with studies on sulfates in which skin permeation is size-dependent.

The isethionates, which are characterized by a large hydrophilic head, are particularly mild. The other sulfonates with large hydrophiles, the sulfosuccinates and the taurates, are widely viewed as mild and suitable for use in skin cleansers. The aliphatic and cyclic sulfonates produce a less acceptable after-feel on the skin and are not widely used for this application.

Phosphates

The number of alkyl phosphates on the market is small. In contrast to alkyl sulfates, they are more tolerant of low pHs and are reported to be relatively mild. The related alkoxylated phosphates are currently reaching the market. If mildness is indeed related to the size of the hydrophilic head, these substances should find application as skin cleansing agents.

AMPHOTERIC SURFACTANTS

Amphoteric surfactants have gained wide acceptance by cosmetic formulators because they are believed to be substantive to the skin and to act as skin conditioning agents. They are generally compatible with anionics and can provide some foam boosting. Only two types of amphoterics have been included in skin cleansing preparations: alkylated amino acids and alkylamido alkylamines.

Alkylamido Alkylamines

Alkylamido alkylamines as a group are identified as "ampho" compounds. These substances are mild to skin and eye. They foam sufficiently well to be used alone. Their foams are stable, and they act as foam boosters for anionics. They are compatible with quaternaries, anionics, and nonionics. They reportedly reduce eye sting from anionics.

Alkylated Amino Acids

Alkylated amino acids form the second group of useful amphoterics. They are obtained by N-alkylation of various amino acids, creating structures such as sodium lauriminodipropionate. These compounds foam adequately well to be useful in skin cleansers.

QUATERNARIES

Most quaternaries produce a lacy foam that is insufficient to allow their use as primary surfactants in skin cleansers. They are commonly viewed as irritating or toxic because many of them exhibit germicidal activity. The only exceptions are the widely used alkyl betaines.

Betaines

Betaines are exceptionally useful ingredients in skin cleansers. They tend to foam well, producing foam in hard or soft water. They cause minimal eye irritation, and they are reported to lower the irritation potential of alkyl sulfates in patch testing. The reasons for this unusual behavior have not been fully explained. Despite their obvious merits, they should be used with caution in light of sensitization reports in the European literature, which attribute allergic phenomena to the presence of unquaternized amines.

NONIONIC SURFACTANTS

As a general rule, nonionic surfactants derived from ethylene oxide are poor foaming agents. Many of them are useful solubilizers for diverse lipids, a feature that helps skin cleansing. It was noted earlier that nonionics modify the irritation potential of anionic surfactants. This feature provided an entree for nonionics into the hair and skin cleansing field. Only three types of nonionics require consideration as potential ingredients in skin cleansing preparations: the poloxamers, the amine oxides, and the alkylglucosides.

Poloxamers

Poloxamers are generally described as block copolymers derived from a central polypropylene oxide polymer in which the terminal OH groups are further reacted with ethylene oxide. A wide variety of these and related polymers (meroxapols and poloxamines) are available to the formulator. These block copolymers can be tailor-made to act as solubilizers, foaming agents, or detergents. Like all nonionic ethers, these substances can be combined ad lib with other types of surfactants. The safety of many of these polymers is well documented.

Amine Oxides

Amine oxides form the second group of nonionics that has achieved acceptance in skin cleansing compositions. Their ability to foam is decreased, and their tendency to form salts with anionics increases as the pH is lowered.

Alkyl Glucosides

Alkyl glucosides, the third and final nonionic surfactant type found in skin cleansers, are particularly attractive. They are fully biodegradable, foam well, exhibit good detergency, and can be combined with nonionics and amphoterics. The alkyl glucosides are acetals of glucose. They are notoriously unstable under acid conditions but evidently possess sufficient stability in systems used for skin cleansing.

THE CREATION OF AN EFFECTIVE SKIN CLEANSING PRODUCT

Many of the surfactants, especially those briefly described earlier, have attributes that may make them attractive constituents of skin cleansers. For this purpose the selected primary surfactant must be combined with other ingredients to create the final product. These added ingredients should not interfere with the surfactant's detersive or cleansing ability. They should be selected to perform tasks that are critical to the marketability of the product. A short list of the desired properties was provided in Table 24.1 (which was presented with little or no explanation). The production of foam during the application step requires that foam suppressants such as solvents and lipidic substances be reduced to a minimum. The desired copious and dense foam requires judicious adjustment of the product's viscosity. If the product is dispensed as a high viscosity product, it may not readily spread on the skin surface. If it is too thin, it may run off too rapidly. Good foam development will probably require the presence of some polymeric viscosity builder. The removal of the product after lathering is facilitated by low viscosity, and the selection of the optimal viscosity for the product may require much manipulation. Product viscosity plays a critical role if insoluble or abrasive substances are included. Scrubbing agents, for example, such as insoluble abrasives, will not remain uniformly suspended unless the base exhibits a fairly high viscosity.

Cleansing efficacy is probably not very critical as long as the major surface soil is flushed away during the rinsing step. As a matter of fact, it seems wise to lower the cleansing ability to reduce the need for a skin conditioner. Exhaustive surface cleansing, lipid removal, and potential "extraction" of the stratum corneum are not desirable attributes for a cosmetic skin cleanser. A truly squeaky clean skin is a skin that needs conditioning with an emollient. It probably makes little sense to add a modest level of a water-soluble moisturizing humectant to a skin cleansing product. Such products do not remain on the skin sufficiently long for any penetration and are flushed away during the rinsing step. Polymeric humectants with demonstrated corneal substantivity may have some merit.

The addition of antimicrobial substances requires a more complete discussion. Medicated soaps became the rage shortly after their introduction about 100 years ago. At that time, dermatologists were easily convinced that degerming of skin was desirable for hygienic purposes, and mercurials and salicylic acid–containing soaps were widely used. Phenol became the agent of choice for the preparation of deodorant washing products. Hexachlorophene and several other antibacterials then began to dominate the market. Some of these agents were subsequently identified as powerful photosensitizers.

In the United States, the FDA asserted its control over the active antimicrobials present in bar and liquid cleansers. The regulatory status of antimicrobial drugs in skin cleansing agents has not been resolved worldwide. The *INCI Dictionary* carefully created two functional categories: a short list of antimicrobial agents that meet the conditions for degerming set by the FDA, and a much longer list of "cosmetic biocides."

The primary antimicrobial agents in use today in the United States include chloroxylenol (intended chiefly for food handlers), triclosan, and triclocarban. Formulators must review the pertinent regulations in each country before adopting any antimicrobial for topical use. It is also essential that the developed product(s) meet the commonly used antimicrobial efficacy tests. Details of some well established procedures were provided in the review by Morrison et al. [9].

PROTOTYPE FORMULATIONS

A few skin cleansing compositions follow; they are taken from the patent and suppliers' literature. Some of them are complex, while others are simplistic. Most of the cleansers seem to rely on the presence of alkyl or alkylether sulfates, although these substances have been indicted as potential skin irritants. The ingredient compositions are given in percentages; the ingredients listed represent commercially available substances (Formulae 24.1–24.12).

Formula 24.1 Foam or Bubble Bath

Sodium laureth sulfate	50.0
Bisabolol	0.1
PEG-40 hydrogenated castor oil	5.0
Polyquaternium-16	10.0
Sodium chloride	1.0
Fragrance, perservative	q.s.
Water	q.s. 100.0

Formula 24.2 Bubble Bath for Children

Disodium laureth sulfosuccinate	10.0
Disodium cocamido MIPA sulfosuccinate	10.0
Sodium laureth sulfate (30%)	9.0
Hydroxyethylcellulose	1.0
Preservative, fragrance	q.s.
Water	q.s. 100.0

Formula 24.3 Body Shampoo

Sodium C_{14-16} olefin sulfonate	20.0
TEA lauryl sulfate	15.0
DEA lauryl sulfate	14.0
Cocamidopropyl amineoxide	10.0
Cocamide DEA	4.0
Cocamidopropyl betaine	6.0
Sodium chloride	1.0
TEA oleate	1.0
Oleth-20	0.2
Glycol stearate	0.5
Polyquaternium-7	0.15
Butoxyethyl stearate	0.2
Tetrasodium EDTA	0.15
Preservative	q.s.
Water	q.s. 100.0

Formula 24.4 Shower Gel

Tetrasodium EDTA	0.10
Ammonium laureth sulfate	30.0
Cocamidopropyl betaine	7.0
Lauramidopropyl betaine	10.0
PEG-55 propylene glycol oleate	2.0
Dimethicone copolyol	0.5
Sodium lactate, sodium PCA, hydrolyzed animal protein, fructose, urea, niacinamide, inositol, sodium benzoate, lactic acid, and citric acid to pH 6.0	0.5
Ammonium chloride	1.5
Fragrance, color, and preservative	q.s.
Water	q.s. 100.0

Formula 24.5 Skin Conditioning Cleansing Bar

Sodium stearate	24.0
TEA lauryl sulfate	18.0
Acetamide MEA and lactamide MEA	5.0
PEG-45 palm kernel glycerides	10.0
Cocamide DEA and Cocoyl sarcosine	20.0
Propylene glycol	10.0
Glycerin	1.0
Urea	2.0

Formula 24.6 Scrubbing Cleanser

Carbomer	0.2
Cetyl esters	1.0
Glyceryl stearate, SE	1.0
Isostearyl isostearate	3.0
Octodecyl stearate	3.0
Triethanolamine	0.3
Pumice	2.0
Preservative, color	q.s.
Water	q.s 100.0

Formula 24.7 Body Wash

Disodium EDTA	0.2
Glycerin	3.0
Polyquaternium-10	0.4
Sodium laureth sulfate	12.0
Cocamide MEA	2.8
Sodium lauramphoacetate	6.0
Myristic acid	1.6
Magnesium sulfate	0.3
Trihydroxystearin	0.5
PEG-6 caprylic/capric triglycerides	3.0
Sucrose cocoate	3.0
Sucrose behenate	3.0
Citric acid	1.4
Preservative, etc.	q.s.
Water	q.s. 100.0

Formula 24.8 Moisturizing Cleansing Gel

Sodium laureth sulfate	16.0
Cocamidopropyl betaine	2.0
Lanolin alcohol	2.5
Stearic acid	1.25
Polyquaternium-10	0.25
Glycerin	5.00
Preservative, fragrance	q.s
Water	q.s. 100.0

Formula 24.9 Mild Shower Gel

Cocamidopropyl betaine	5.15
Sodium laureth sulfate	5.80
Sodium lauryl sarcosinate	0.50
Polyquaternium-10	0.10
Cocyl alcohol	0.40
Sodium sulfate	2.10
Citric acid	0.10
Preservative, sequestrant, etc.	q.s.
Water	q.s 100.0

Formula 24.10 Skin Cleansing Composition

Polyethylene (beads)	4.0
Glycerin	3.0
Sodium lauryl sulfate	3.0
Sodium cocoyl isethionate	2.0
Cocamidopropyl betaine	2.0
Polyquaternium-10	0.5
Sodium laureth sulfate	0.4
Preservative, sequestrant	q.s
Water	q.s. 100.0

Formula 24.11 Cleansing and Moisturizing Liquid [10]

Sodium laureth sulfate	5.5
Sodium cocoglycerylether sulfonate	5.5
Sodium lauroyl sarcosinate	2.0
Cocoamidopropyl betaine	2.0
Sodium carbomer	1.5
Polyquaternium-10	0.8
Tallow alcohol	2.0
Oleyl alcohol	1.0
Petrolatum	11.6
Hydrogenated polybutene	2.9
PEG-9 M	0.5
Glycerin	7.8
Tetrasodium EDTA	0.1
Preservatives, fragrance	q.s.
Water	q.s. 100.0

Formula 24.12 Liquid for Skin Cleansing Towelette

PEG-30 laurate	10.0
Sorbitol (70%)	4.0
Alcohol	5.0
Fragrance, preservative	q.s.
Water	q.s. 100.0

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CHAPTER 25
Shaving Preparations

Over the years men have incorporated the task of shaving into their daily routine. Frequent shaving has been a burdensome chore for men until recently when plastic coating of blades and special designs help to make shaving less onerous. Each routine is as unique as the individual himself depending on the implements used, the beard preparation, the type of beard, the time between shaves, the time of day, the time constraints, and so forth. Regardless of the process, the common goal is to obtain as close a shave as possible with the least amount of trauma during and after the process.

In today's hectic world, which puts time at a premium, the ritual and the art of shaving have been replaced by a scientific technology that addresses the needs of the shaver.

WET SHAVING PREPARATIONS

INTRODUCTION

Cosmetic preparations for shaving serve several functions. The most significant of these is softening the hair to facilitate cutting. The observation that softening of hair is best achieved by hydration gave rise many years ago to the concept of wet shaving. The hallmarks of a good wet shaving preparation are twofold:

- to soften the hair
- to act as a lubricant between the shaving hardware and the face

Both of these attributes contribute to a trauma-free shave. For assessing the merits of various preparations, one should evaluate foam stability during the life of the shave; easy spreading on the skin; rapid wetting of the beard; ready adherence to the skin; and easy rinsability from both the shaving hardware and the face.

A number of factors promote beard softening. Absorption of water by the beard effects changes in the mechanical properties of hair, which translates into beard softening (see Chapter 2). Studies have been conducted to measure

the softening of the beard in water by various means—hair swelling, weight increase in water, and lengthening. All studies showed that water softened the hair and that soap hastened the process. This concept was confirmed by the conclusions of the subjective results of a shaving study conducted in 1937 [1].

Deem and Rieger subsequently showed that the presence of skin lipids did not inhibit hydration. The cutting force of surfactant-treated wet hair vs. nontreated wet hair was similar. In addition, solution pH had only meager effects on cutting force or hydration rate [2]. Thus the alkalinity of aqueous soap solutions does not seem to assist in painless shaving by a mechanism involving hair softening or hair swelling. The cutting of a beard is more likely to cause some painful pulling on the papilla, which is minimized by lubrication between the blade and the fiber that is about to be cut. The moderately viscous soap coating on the blade is evidently well suited for this purpose. Modern shaving technology with coated blades materially reduces the need for this type of lubrication.

Another benefit attributed to the soap lather on the face is its function as a water reservoir for imbibition of water by the hair. The shaving soap has also been identified as a lubricant between the razor and the skin.

For most shavers, prepping the beard with soap and warm water (120 °F) for 15 to 30 seconds appears to be the most commonly used technique.

FOAMING SHAVE PRODUCTS

The physical presentation of a foaming shave product makes it ideal to supply moisture to the beard. The foam also serves as a "marker" on the face.

Lather Shaving Creams

Customarily these types of formulations are based on $Na^+/K^+/TEA^+$ soap systems. The level of soap can range from 10% to as high as 55%. These types of systems can pose problems during scale-up from laboratory to manufacture. Attention to details such as mixing times, rates of addition, cooling rates, and time of mixing after neutralization are crucial. Stability and product texture can be adversely affected.

Typically blends of fatty acids are employed. Trials with stearic acid alone appear to yield harder and inferior foams. Blends of stearic acid with isostearic acid, palmitic acid, coconut fatty acids, lauric acid, and myristic acid can be used in varying ratios. From this list, a wide range of textures can be obtained. As a good starting point approximately 60% to 90% of the total fatty acid content of the formula should be stearic acid. The shorter the chain length, the softer the resultant cream. Careful attention must be given to high temperature stability, especially with higher percentages of shorter chain acids. Fatty acids

with a high degree of unsaturation should be avoided because of the possibility of peroxidation.

The selection of alkali is of major significance to the final product texture and foaming properties. The alkali should not be a single agent but instead a carefully chosen mixture of NaOH, KOH, and perhaps TEA. Soaps made solely with NaOH tend to be hard and pituitous and thus do not produce a satisfactory foam. Systems using only KOH may lead to stability issues at elevated temperatures. TEA soaps, while milder and softer, do not provide adequate foaming properties and tend to discolor on aging. Thus a blend of KOH:NaOH:TEA in a ratio from 4:1:0.5 to 6:1:0 may prove a good starting point. The total quantity of alkali should be calculated to yield the presence of 2% to 10% free fatty acid. This level of free fatty acid gives the final product some firmness. This ratio is a key factor in determining the temperature at which the cream retains its structure and, therefore, is crucial to the high temperature stability profile. Agents such as xanthan and cationic guar gums can be added to impart structure to the water phase to prevent phase separation. In addition, these agents have a slippery tactile effect, thus possibly further lowering the coefficient of friction between the razor and the beard or skin.

Controlling the percent free fatty acid (FFA%) is a common quality control parameter. Since these systems are essentially viscous soap systems, FFA% can be an effective means to determine the efficiency of the top-to-bottom mixing of the manufacturing vessel as well. The ratio of alkali relative to fatty acid also affects the characteristic pearly appearance of the cream.

Other Ingredients

Other ingredients are needed to transform the basic soap system into an elegant product. To prevent drying out of the cream, various humectants should be added. Typical humectants such as glycerin, propylene glycol, dipropylene glycol, sorbitol, and butylene glycol have been used. In general, these humectants will make the cream softer; concentration ranges can be as high as 12% to 18%.

Various emollients are also recommended to lubricate the skin surface and thus lower the coefficient of friction between razor and skin. Mineral oil is most common, probably because of its low cost and efficiency. Lanolin, lanolin fractions, and lanolin derivatives are also of value both as emollients and to improve spreadability of the cream. Fatty alcohols and emollient esters can be of merit as well. In general, these materials tend to suppress foam, so there is a limit to their utility. Levels of up to 5% to 7% may be used before loss of foam becomes an issue.

A wide range of surfactants has been incorporated into these systems to aid in the rinsability of the shaving debris from the shaving hardware, to enhance

the foaming properties, and to stabilize the foam. Sodium laureth sulfate and various betaines are typically used at 0.5% to 1.5%.

Sensorial agents such as menthol and menthoxypropanediol have often been added to give a cooling effect. The pH of the cream should weigh heavily in the selection of preservatives.

Additional pearlizing agents (glycol distearate) can be added; however, typically they are not needed owing to the effect from the free fatty acids and stearate soaps. Generally, the amount of pearliness can be affected by processing parameters such as the rate of cooling during the temperature interval of the melting points of the various soaps and the amount of mixing during this temperature interval. Often the pearly appearance can take up to 24 hours to fully develop.

Various skin-soothing ingredients are often incorporated to enhance the marketing story. Typical ingredients such as bisabolol, aloe, and chamomile are often included. Because of the extreme pHs of these systems (pH 10 to 12), base labile ingredient such as allantoin should be avoided.

A typical shave cream [3] is illustrated by the following:

Formula 25.1 Shaving Cream

Oil phase	%w/w
Mineral oil and lanolin alcohol	5.0
Cetyl acetate and acetylated lanolin alcohol	2.0
Polysorbate 80 and cetyl acetate and acetylated lanolin alcohol	0.5
Stearic acid	10.0
Water phase	
TEA	1.2
Glycerin	4.0
Water	77.3
Fragrance/preservative	q.s.

Lather Shaving Sticks

These systems are essentially modifications of a standard deodorant stick formulation—alkali metal soap with a glycol and water. In this case, however, the level of soap is higher—in the range of 70% to 85% —with the remainder being approximately equal parts glycerin and water. Other ingredients such as perfume, surfactants, and talc can be milled into the formulation prior to molding. These forms offered little more than novelty but currently do not enjoy market success.

AEROSOL SHAVE FOAMS

Aerosol shave foams by far dominate the market because of their economy, ease of use, and ability to efficiently soften the beard and to act as a lubricant between the shaving hardware and the skin. Aerosol shave foams differ from the previous systems described in that these systems are oil in water (o/w) emulsions. The hydrocarbon propellant liquid under pressure is part of the internal phase of the emulsion. When pressurized, the emulsion is in a constant state of flux owing to the varying external can temperature.

Some of the earliest patents on aerosol shave foams described systems containing TEA stearate and TEA cocoate soaps; others contained potassium soaps with minor levels of the sodium salt [4]. In the patents, the lower soap levels produced thin unstable forms, which led to the use of synthetic thickeners. Polyacrylic acid and derivatives were cited for both their thickening properties and lubricating effects, much the same way as xanthan and guar gums previously described for shave creams.

Later patents suggested the use of a novel combination of oily emollients that do not suppress foam. The emollients, mineral oil, cod-liver oil, vegetable oils, and select esters in combination with an alkanolamide in a sodium or potassium stearate system, lubricated the skin while still yielding an adequate foam [5].

Since then, great strides have been made in shave technology. For example, patents granted to Grollier and Caudet claimed compositions containing polyorganosiloxane with either a hydroxyalkyl or acyloxyalkyl group. The inclusion of these silicones produced foams that provided increased lubricity and less trauma to the skin and offered a superior skin feel, yet did not exhibit the typical defoaming properties of silicones [6].

General Formulating Tips

As stated previously, these systems are pressurized o/w emulsions. They generally contain stearic acid; shorter chain fatty acids are often used in combination with stearic acid to modify foam texture and dispensing qualities. Total fatty acid content should be about 6% to 10%. Foams based solely on stearic acid are stiffest; to soften the foam, approximately 10% of the stearic acid is replaced with shorter chain fatty acids. The shorter the fatty chain, the softer the foam. Coconut oil and palm oil are often used to soften foams. To prevent gelation of the pressurized formula, isostearic acid can be incorporated at a rate of 10% of the total fatty acid content of the formula.

The selection of bases is also crucial for the texture of the foam. TEA and potassium hydroxide are used either alone or in combination. Sodium hydroxide should be avoided; sodium stearate has a tendency to gel.

The quantity of base is selected by calculating amount needed to stoichiometrically neutralize all but 2% to 8% of the total fatty acid content. Some

free fatty acid is needed to aid in foam stability, but at the upper extreme the foams can be stiff, dry, and difficult to dispense. In this case, more base or more shorter chain fatty acids are added, or the amount of humectant (see below) can be increased.

Other Ingredients

Surfactants. Nonionic and anionic surfactants are also included for several purposes. They help stabilize the emulsion, aid in the rinsability of the debris from the shaving hardware, and improve the spreadability of the foam over the skin and stabilize the foam. Inclusion of 1% to 2% of a high HLB nonionic emulsifier will tend to improve spreadability and to stabilize the emulsion. It can be added as a subphase with the fragrance to solubilize the fragrance as well. Sodium laureth sulfate at 1% will also suffice to improve rinsability and the spreadability of the foam. Acetylated lanolin derivatives can be used in a dual role of emolliency and of imparting lubricity during shaving [3].

Humectants. Humectants are required to prevent the foam from dry-out during the shaving process. They also tend to soften the foam texture. Typical humectants can be incorporated at levels from 3% to 5%. Glycerin, sorbitol, and propylene glycol are almost exclusively used, usually as single agents.

Conditioning Agents and Lubricants. The list of agents that can be incorporated to ultimately lessen the trauma of shaving is quite lengthy. Suffice it to say that many oils, silicone derivatives [6], lanolin and its derivatives, quaternary ammonium compounds, water-soluble polymers, and gums can be used. There are limitations to their use. For instance, oils and oil-soluble materials will tend to suppress foam; usually levels of 2% to 3% depending on the material should be considered an extreme.

Quaternary ammonium compounds and cationic guar gums are excellent choices for inclusion. They leave the post-shaven skin feeling conditioned, not taut, and create creamy luxurious foams. The mechanism by which quaternary ammonium compounds work is electrostatic attraction. The positively charged ammonium group reacts with the negatively charged sites on the skin. The hydrophobic portion of such agents acts to reduce the friction between the shaving hardware and the skin.

Among this list, the following can be selected: polyquaternium-7, polyquaternium-39, polyquaternium-24, polyquaternium-10 plus polyquaternium-39. Again, these have a limitation in that some may thicken the concentrate so that dispensing becomes an issue. Reducing the level should suffice.

Additionally, it has been reported that polyquaternium-10 at 2% in shave preparations can lessen the trauma of shaving associated with pseudofolliculitis

barbae (PFB) [7]. PFB is a painful skin condition predominant among African Americans. Features of this condition are inflammatory lesions called "razor bumps," which are due to the hairs curling back under the skin surface [8].

Propellants. After the ban of fluorocarbon propellants in the United States in the mid-1970s, the common propellant is a blend of *n*-butane, isobutane, and propane. Since then, shave foams have become a regulated product class under the California Clean Air Act of 1988 in which the concentration of volatile organic compounds (VOCs) is legislated [9]. The concentration of VOCs (propellants) is limited to 5% maximum. It is prudent to check the current regulations regarding VOCs as this is an evolving standard. The usual range of propellant in shave foams is between 3.0% and 4.5%. In general, the higher the percent propellant, the drier the foam. Foams with higher propellant levels are also difficult to spread and wet the beard poorly. Instead of adding a high HLB nonionic surfactant as earlier described, it would be best in this case to add less propellant.

When initially formulating, it is best to try a range of propellant:concentrate ratios in order to optimize the desired texture and properties. A quality control specification of foam density is crucial to ensure consistent batch-to-batch foam texture or richness.

Since the propellant comprises a fair proportion of the internal phase of the emulsion, it is a common practice to agitate the pressurized units for one to two minutes to hasten emulsification of the liquefied propellant. An obvious point to do this is after removal of the cans from the hot water bath (leakage check) while the cans are still warm (see Chapter 7). In the laboratory, manual shaking suffices; in production scale, modified commercial paint shakers can be used.

Fragrance. Fragrance oils are added in the range of 0.25% up to 2%, depending on the fragrance and the intended purpose. However, as the fragrances are notorious defoamers, there may be a practical upper limit on their use. At the upper extreme, a solubilizer may be required. This can serve multiple roles:

- solubilizing the fragrance
- wetting the beard
- improving the spreadability of the foam
- aiding in the clean up process of the shaving hardware

An antioxidant, such as BHT at 700 ppm, can be added to the fragrance phase with the solubilizer, if needed to protect the fragrance and any unsaturates in the formulation from oxidation.

Preservatives. Many shave foams on the market do not contain preservatives. However, if the concentrate will be held before filling for a period of time or if the concentrate must be shipped to an alternate site for filling, one may want to

consider preserving the concentrate. The idea is to prevent contamination until the concentrate is filled. Once pressurized, contamination is no longer an issue. Phenoxyethanol, EDTA, triclosan, and sodium methylparaben can be used. The pH of the concentrate will be a consideration when selecting preservatives.

Corrosion Inhibitors. As a result of advances in can technology based on various coatings, corrosion inhibitors are generally not required.

Evaluation of Aerosol Shave Foams. At the preliminary formulation stage, it is a good idea to evaluate the foams initially (as would be done during manufacture) and 24 hours after pressurization. One may need to set different specifications depending on the results.

Another important aspect in assessing shaving foams is the need to evaluate the whole can from beginning to end. Essentially, when formulating, one tends to depend heavily on the initial texture. However, as more and more foam is expelled from the can, the ratio between concentrate and propellant becomes leaner in propellant. Thus the foam is wetter and thinner toward the end of the can; eventually the actuation may not even be usable, as the product will not adequately foam because of the little remaining propellant.

Other parameters typically measured as a quality control means are spray rates, pressure, and foam density.

Spray rates are typically in the range of greater than 2.5 g/sec at 21 °C. Lower spray rates may indicate a clogged valve. This could be because of incomplete dissolution or melting of solids during manufacture, material precipitating in the concentrate, or foreign matter contamination of the can or valve assembly.

Internal can pressure is an assurance that the proper propellant was used in the filling operation. Generally, it is measured at 21 °C. It will also indicate if the proper amount of vacuum was pulled on the units before crimping. If not properly vacuum-crimped, the pressurized units will display a wide range of pressures and will lose airy foams.

Foam densities control the foam quality as well. Foam densities should be in the range of 0.07 g/cc at 21 °C. If the densities are low, this indicates that the concentrate may have been excessively aerated before filling. This parameter also will indicate if the fill weights of the concentrate and propellant (i.e., the ration) are correct. As described earlier, the foam density will increase as more of the can is evacuated. Thus the foam density calculations should be made on virgin cans.

Evaluation of the Concentrate. Generally, after the concentrate is made, it too should be subject to a variety of quality control parameters. Specifications for pH, specific gravity, viscosity and, perhaps, water content are typically measured as a control of the integrity of the manufacture of the concentrate.

POST-FOAMING SHAVE GELS

There are many patents protecting these forms, which claim to offer superior beard-wetting properties [10,11]. Primarily these systems are gelled soaps containing 3% to 7% of a "blooming" gas packaged in a two-compartment can. The gel with the "blooming" gas is contained in the inner compartment with the valve assembly. The outer compartment is filled with a hydrocarbon mixture (isobutane, *n*-butane, and propane) to create the pressure, which is the driving force to expel the contents of the inner compartment. When the gel is expelled, the heat from the skin vaporizes the "blooming" gas and thus causes the foam. The "blooming" gas is generally *n*-pentane or isopentane but also can be an isopentane or isobutane mixture. Two typical examples are shown below, Formulas 25.2 and 25.3 [11,12].

Formula 25.2 Post-Foaming Shaving Gel [11]

	%w/w
Palmitic acid	7.50
Stearic acid	2.50
Sorbitol	2.00
Propylene glycol	2.00
Hydroxyethylcellulose	0.25
TEA laureth sulfate	2.50
Dimethicone	1.00
Stearyl heptanoate	2.00
Stearyl octanoate	1.00
TEA	7.50
Water	q.s. 100

Formula 25.3 Post-Foaming Shaving Gel [12]

	%w/w
Water	77.65
Hydroxyethylcellulose	1.25
PEG-14M	0.10
Palmitic acid	6.00
TEA	5.00
Oleth-20	2.00
Glycerin	2.00
Isopentane	6.00
Fragrance or preservative or dye	q.s. 100

From formula 25.2, 97 g is added to 3 g of the "blooming" gas, which is comprised of a mixture of 75% isopentane and 25% isobutane. Pressurization is achieved by introducing 4 g to 10 g of a hydrocarbon mixture of isobutane, butane, and propane in the outer compartment of the can.

The introduction of the "blooming" gas does present issues in handling. Because of the volatility, these gases must be chilled to 4 °C prior to addition. They can be phased into the gel with chilled glycol. Care must be taken to avoid aeration of the gel.

In 1999, the California Air Resources Board (CARB) proposed that shave gels become a regulated product class vis à vis volatile organic compounds (VOCs). CARB has proposed a VOC limit of 3% maximum to become effective sometime from 2002 to 2004. It is prudent to check the current regulations, as this is an evolving standard [13]. This proposal will present a major problem to the formulator because foaming qualities will be affected.

BRUSHLESS SHAVE CREAMS

Like shave foams, brushless shave creams are o/w emulsions. However, unlike shave foams, brushless shave creams are nonlathering. Owing to the popularity in the aerosol market of foams and gels, these forms are disappearing from the market. They enjoy some benefits and have some disadvantages in use. First, brushless shave creams can be formulated at pH 7.5 to 8.0 and thus might be milder than lathering creams (pH 9.5 to 10.5). On the other hand, the beard-softening efficiency of brushless shave creams is meager when compared with that of foams and gels. The poor rinsability of the shaving debris from the shaving hardware is another drawback.

Essentially, brushless shave creams are a variation of cold creams. They contain a soap system and a nonionic emulsifier with a huge excess of fatty acid (20% to 30%), which gives the pearlacious effect. Since foam suppression is not of consequence here, the list for selection of internal phases is endless. Typically, mineral oil, various esters, silicones, and petrolatum can be used. Percentages can be as high as 12% to 15%. Suitable soap systems can be selected from choices described for foams, gels, and shave creams—potassium and/or TEA salts of stearic, palmitic, and coconut fatty acids. To further increase emulsion stability, a nonionic emulsifier is required, usually at 1% to 3%. Typical examples include glyceryl stearate, propylene glycol stearate, glyceryl stearate/PEG-100 stearate blends, and ethoxylated fatty alcohols.

Much the same thought process for additional ingredients could be taken from the previous discussion of shave creams. Low levels of an anionic surfactant such as sodium laureth sulfate can be added to improve beard-wetting and cleanup. Various water-soluble gums may be required to structure the water

phase to prevent creaming. Humectants are necessary to aid in freeze and thaw stability and to prevent dry-out of the cream. Various secondary emulsifiers such as fatty alcohols, cholesterol, and lanolin derivatives will further stabilize the emulsion and add slip and lubricity to the formula.

Quaternary ammonium compounds previously discussed impart a conditioned feel to the skin and can lessen the trauma of shaving.

DRY SHAVING PREPARATIONS

INTRODUCTION

It is generally recognized that electric shavers do not cut the beard as close to the skin surface as a razor blade. This was confirmed in a study by Bhaktaviziam et al. [14], which also demonstrated that the ends of hair observed 24 hours after shaving with an electric razor showed ragged edges and some vertical splitting of the hair shaft. Both electric and blade shaving result in the removal of skin, the amount removed for an individual being dependent on the pressure applied to the face. Generally, the closer the shave, the greater the amount of skin damage. It has been suggested that preelectric shave preparations may not increase the quality of the shave but may assist in reducing skin damage.

In contrast to blade shaving in which it is preferable to soften the beard, the beard should be dry when using an electric razor, with individual hairs raised and stiffened so that they can be caught between the razor's combs and removed. The removal of the film of perspiration from the face reduces the friction between the razor and skin and prevents the beard from being slippery and elusive to the cutting edge of the electric razor. This is achieved in different ways by the two most popular forms of preelectric shave preparations: the lotion based on an alcoholic solution and the talc stick. It should be noted that a completely contrary view of the function of a preelectric shave preparation has been expressed in a patent granted to the Sunbeam Corporation [15].

In this patent, it is claimed that the removal of moisture from the skin and beard prior to electric shaving is not desirable; in fact, water softens the beard and by causing hairs to swell and to become elongated ensures a smoother, more efficient, and closer shave. Furthermore, alcoholic lotions are claimed to cause shrinking of the hair into the follicle, making it more difficult to obtain a close, clean shave. The preparations claimed in the patent are o/w emulsions containing 5% to 20% of fatty acid esters such as isopropyl myristate and an emulsifying agent that is mixed alkali metal or amine salt of polyacrylic acid.

PREELECTRIC SHAVE LOTION

In formulating a preelectric shave lotion the following attributes are considered desirable:

- adequate astringency to stiffen the beard and possibly to stimulate the hair follicle muscles
- quick drying to allow rapid evaporation of any moisture present on the face
- a pH below the iso-electric point of keratin to prevent swelling of the hair (pH 4.5 to 4.8)
- provision of a coating on the skin on which the razor will glide, thereby preventing irritation of the skin and providing lubrication for the cutting edge of the electric razor
- freedom from any substances likely to corrode the cutting head
- absence of any lubricants likely to have an adverse effect on plastic components of the electric shaver

The alcoholic preelectric shave lotions may be either astringent or oily. The astringent lotions are intended primarily to dry and stiffen the hairs and, theoretically at least, to assist in raising them. The astringent effect of the alcohol can be further enhanced by the inclusion in the preparation of mildly astringent substances, such as aluminum chlorhydrate, zinc phenolsulfonate, or lactic acid. Menthol or camphor may be included to give a cooling effect together with a suitable antiseptic. Compounds having pilomotor activity may also be added to preelectric shave preparations. Examples are shown in Formulas 25.4 to 25.6.

Lotions of the oily type aim to deposit on the face a film of lubricant, which reduces the drag of the cutting head against the skin. It has been shown that a film of silicone oil substantially reduces the frictional force between skin and a smooth steel probe. The mechanism involved is hydrodynamic lubrication—that is, the frictional force is dependent on the viscosity of the lubricant. Perhaps the most frequently used lubricants for this type of product are the esters of higher fatty acids such as isopropyl myristate. By suitable choice of lubricant type and concentration, it should be possible to provide for a comfortable shave even in warm humid conditions without leaving the skin feeling oily. It is claimed by some that the oily type of preparation lengthens the life of the cutting edge of the electric razor because of its lubricating action. A typical formula is provided in Formula 25.7.

A roll-on type of applicator may be used to apply preelectric shave lotions directly to the face. In such circumstances it may be necessary to adjust the viscosity and wetting properties of the lotion to prevent seepage around the ball when the applicator is inverted.

Formula 25.4 Preelectric Shave Lotion

	%w/w
Alcohol	45.0
Sorbitol	5.0
Lactic acid	1.0
Water	49.0

Formula 25.5 Preelectric Shave Lotion

	%w/w
Zinc phenolsulfonate	1.0
Distilled extract of witch hazel	40.0
Alcohol	40.0
Water	18.8
Menthol	0.1
Camphor	0.1

Formula 25.6 Preelectric Shave Lotion

	%w/w
Aluminium chlorhydrate (50%)	5.0
Isopropyl myristate	5.0
Alcohol	80.0
Water	10.0
Perfume	q.s.
Antiseptic	q.s.

Formula 25.7 Lubricant Preelectric Shave Lotion

	%w/w
Alcohol	77.0
Isopropyl myristate	13.0
Oleyl alcohol	4.0
Perfume	1.0
Water	5.0
Color	q.s.

PRE- AND POST-SHAVING PREPARATIONS

Preelectric Shave Gel Stick

Solid preelectric shave sticks of the cologne type can be formed by gelling ethanol with sodium stearate in the presence of glycerol and a suitable lubricant.

Preelectric Shave Talc Stick or Powder

Talc is used as the main component in some preelectric shave preparations to absorb perspiration and sebaceous secretions from the skin and to confer its characteristic slip so that the head of the shaver will glide smoothly over the face. A reduction of 50% in the frictional force between skin and polished steel was observed after treating the skin with talc. Colloidal kaolin is usually present in the preparation to improve the moisture-absorbing capacity and adhesion to the skin. Zinc or magnesium stearate is included to enhance both adhesion and slip. Magnesium carbonate or precipitated chalk serves as the carrier for the perfume and increases the absorbent properties. An important stipulation is that powders for preelectric shave purposes should be free from grit to avoid abrading the cutting edge of the electric razor. This can be achieved by grinding the powders before use.

The most convenient way to apply the talc preparation to the face is to form it into sticks. The sticks can be molded from an aqueous dispersion of the powders using colloidal magnesium aluminum silicate as the binder.

A method and formula for the manufacture of talc sticks without the use of a binder was disclosed in a U.S. patent [16]:

Formula 25.8 Preelectric Shave Stick

	%w/w
Talc	50
Zinc oxide	10
Chalk	10
Kaolin	10
Colloidal silica	20

The sticks are formed by compression molding the powder mixture at pressures ranging between 450 and 600 psi (3–4 MPa), then coating (except on the end) with a suitable film-forming polymer to protect them against cracking or crumbling.

Preelectric Shave Powder

The composition of a loose powder is shown in Formula 25.9.

Formula 25.9 Preelectric Shave Powder

	%w/w
Talc	50.0
Kaolin	14.0
Magnesium carbonate	12.0
ANM powder (etherified starch)	10.0
Cetyl alcohol	3.0
Glyceryl stearate	1.0
Zinc stearate	4.0
Zinc oxide	5.5
Perfume	0.5

AFTER-SHAVE PREPARATIONS

After-shave preparations are intended to alleviate the trauma of shaving because of irritation and possibly from the irritating effects of the shaving preparations themselves. This irritation can be mitigated in several ways. The forms range from simple after-shaves (hydro-alcoholic solutions of fragrance), after-shave gels (hydro-alcoholic gels), or after-shave balms (o/w emulsions) either with or without alcohol. Regardless of form, the function is to calm the skin by providing either a cooling effect, an anesthetic effect, an astringent effect, or any combination of these.

After-Shave Lotions

Generally, this is the most basic type of after-shave preparation. They typically contain 50% to a maximum of 75% alcohol, the remainder being water, fragrance, coolants, and so forth. It is prudent to check the current volatile organic compounds (VOC) regulations, as this is an evolving standard. According to the regulations [9], after-shaves, after-shave gels, balms, and so forth are regulated as to the concentration of a VOC (i.e., ethanol) they can contain. In this instance, the level is dependent on the fragrance concentration. At the time of this writing, the maximum % VOC for this class is 75% if the fragrance level is 20% or less; 65% maximum if the fragrance level is greater than 20%.

Depending on the alcohol content and the fragrance, a fragrance solubilizer may be required to yield a clear system. Typically, high HLB nonionic surfactants suffice. If a nonionic solubilizer is used, the system may become cloudy at either elevated or low temperature but clears upon returning to room temperature. This can be explained by the fact that the efficiency of nonionic surfactants to solubilize oils results in part from the hydrogen bonding of the hydrophilic portion of the molecule. Hydrogen bonds are relatively weak—about 5 kcal/mole—and thus can be broken by temperatures of 40 °C to 45 °C, resulting in reduced efficacy of the solubilizer. At extremely low

temperatures, the ability of alcohol to dissolve the fragrance may be impaired. Thus the balance between solubilization and solubility should be considered in the formulation process. Upon cooling to room temperature, the hydrogen bonds re-form, and clarity should be restored. Slight agitation may be required to obtain clarity.

The soothing effect can be attributed to the evaporation of the alcohol even though high levels of alcohol can sting a freshly shaven face with even the slightest of razor nicks.

Other ingredients can be incorporated to enhance the soothing effect. Typically, allantoin (to promote healing), bisabolol (antiinflammatory), witch hazel extract (astringent), or menthol (cooling effect) can be incorporated to enhance overall efficacy.

Novel two-phase systems have also been patented [17]. These systems are comprised of an oil phase containing a volatile silicone and a hydro-alcoholic phase containing the fragrance. The resultant product is clear, contains no emulsifier, and must be shaken prior to use. The phases separate upon standing into two discrete phases. Coloring the phases permits a vivid visual effect to be showcased in a clear component. An example protected by European patent follows [17]:

Formula 25.10 After-Shave

	%w/w
Aqueous Phase:	
Alcohol (95%)	40.0
PEG-8	5.0
Glycerin	5.0
Sodium chloride	0.1
Water	4.9
Fragrance	5.0
Color	q.s.
Oil Phase:	
Cyclomethicone	29.0
Sunflower seed oil	1.0
Isopropyl myristate	10.0
Color	q.s.
	100.0%

Each phase is manufactured separately and filled separately into the container. The product must be well shaken before each use.

After-Shave Gels

Carbomers and some cellulosics can tolerate varying amounts of alcohol and thus are good choices to include in the after-shaves previously described to create an after-shave gel. Other film-formers, of course, can be used as well to provide a skin protective effect. These systems can tend to remain tacky on drying. A water-soluble silicone, dimethicone copolyol for example, at 2% to 3%, can mitigate this effect. Typically, the alcohol can range from about 50% to a maximum of 75%, depending on fragrance. Requirements of any current VOC regulations [9] must be met At the upper alcohol levels, incorporation of the fragrance should not be a problem. At lower levels, a fragrance solubilizer may be needed, as discussed earlier.

Various astringents can be added for a desired effect. Zinc or aluminum salts and witch hazel extract perform adequately in this regard. Low levels (1% to 2%) of the metal salts are used to reduce the potential for irritation.

Typical after-shave gel formulae could be detailed as follows:

Formula 25.11 After-Shave Gel

	%w/w
Alcohol (95%)	65.00
Hydroxypropylcellulose	1.50
Menthol	0.10
Fragrance/solubilizer	q.s.
Witch hazel *(Hamamelis Virginiana)* extract	5.00
Water	q.s.
	100.00

Formula 25.12 After-Shave Gel

	%w/w
Alcohol (95%)	75.00
Carbomer	0.40
Water	22.20
TEA	0.40
Dimethicone copolyol	2.00
Fragrance	q.s.
	100.00%

After-Shave Balms

After-shave balms are o/w emulsions with sufficient "play time" to permit adequate massaging into the freshly shaven face. They may or may not contain

alcohol. The selection of the internal phase of the emulsion is limitless. This can range from oils, esters, silicone derivatives, waxes, and so forth. A unique marketing story can be created by selecting exotic natural oils.

The application of after-shave balms tends to give a wet, cool feeling on the face. First, the phase volume ratio should be heavily skewed toward the water phase—typically 86:14 to 90:10. Second, the minimum level of emulsifier that will give the required stability can yield emulsions that will feel cool and wet upon application and yield sufficient "play time" for massaging into the skin. Another method to achieve the wet or cool feeling and the increased "play time" is by the addition of alcohol. A word of caution should be noted: alcohol can destabilize an emulsion. Also, as stated earlier, high alcohol levels can sting with even the slightest of razor cuts. Levels of 5% to 15% alcohol represent a good balance between the desired attributes and adequate stability.

Formula 25.13 Alcohol-Free After-Shave Balm

		% w/w
A	Glyceryl stearate	0.25
	PEG-100 stearate	0.25
	Jojoba oil	1.50
	Sesame oil	1.50
	Borage oil	0.50
	Stearic acid	0.25
	Stearyl alcohol	0.25
B	Water	90.15
	Glycerin	4.00
	Xanthan gum	0.05
	Allantoin	0.15
	Carbomer	0.15
C	Polyquaternium-10	0.50
D	TEA	0.25
E	Bisabolol	0.25
	Fragrance/solubilizer	q.s.
F	Preservative, color	q.s.

Procedure: In the manufacturing vessel, heat water of Phase B to 80 °C; add glycerin, xanthan gum, and allantoin. Mix until uniform. Start homogenizer. Add carbomer. Mix until uniform. Add phase C. Heat the ingredients of Phase A to 80 °C. Add Phase A to Phases B and C in the manufacturing vessel. Continue homogenization until emulsion is adequate. Cool bath to 60 °C. Add Phase D. Continue cooling to 30 °C. Add the remaining Phases stepwise. Cool to 25 °C.

Quaternary ammonium compounds often are added to impart a conditioned feeling to the skin by virtue of their substantivity. Healing agents and natural extracts can further enhance the efficacy and provide a marketing story. Ingredients such as bisabolol, chamomile extract, or aloe are often included. Allantoin is sometimes added as a healing agent at 0.25%; solubility is a limiting factor.

Since the level of alcohol is lower than that in other after-shave products, it may be possible to support moisturization claims. Humectants such as glycerin, propylene glycol, or sorbitol at levels of 3% to 6% could prove beneficial.

Xanthan or guar gum can provide a dual role, that of stabilizing or structuring the water phase and that of adding slip to formulas 25.13 and 25.14.

A gel lotion represents another variation on the theme of after-shave balm textures. In essence, the oil phase is dispersed and finely divided in a gel matrix in the absence of an emulsifier. The viscosity must be sufficient to prevent the oil phase from separating. Second, the amount of oil phase must be limited so as not to violate the laws of physics and separate. These types of systems can be a challenge to the formulator since they are inherently unstable and are process-dependent. Enough shear must be applied to disperse the oil phase.

Formula 25.14 Alcoholic After-Shave Balm

		%w/w
A	Water	78.45
	Carbomer	0.30
	Sorbitol	5.00
B	Hydroxypropyltrimonium guar	0.10
	Glycerin	3.00
C	Cetyl alcohol	0.30
	PEG-25 propylene glycol stearate	0.45
	Apricot kernel oil	2.00
D	TEA	0.30
E	Fragrance/solubilizer	q.s.
F	Alcohol (100%)	10.00
	Bisabolol	0.10
G	Color/preservative	q.s.

Procedure: In the manufacturing vessel, heat water to 80 °C. Start homogenizer. Add carbomer and sorbitol. Continue mixing until carbomer is adequately dispersed. Disperse hydroxypropyltrimonium guar in glycerin, then add to Phase A. Heat contents of Phase C to 80 °C. Add to manufacturing vessel. Continue homogenization until emulsion is adequate. Cool to 60 °C. Add Phase D. Cool to 30 °C. Add Phase E. Cool to 25 °C. Add remainder of ingredients. Further homogenization may be needed to ensure uniformity and to improve the emulsion.

The matrix can typically be formed with acrylic acid copolymers. The oil phase should be limited in quantity with 10% to 12% as an upper limit. Typical among oil phase components are cyclomethicones and other silicone derivatives and oils and liquid esters. It is advisable to use a fragrance solubilizer, which may alter the presentation. The product appearance may become less translucent, depending on the fragrance and solubilizer and their respective levels.

Should separation occur during the stability trials, obvious remedies are to increase the concentration of the matrix-forming agent; to add xanthan gum; to decrease the content of the oil phase; to increase the fragrance solubilizer; to add a secondary emulsifier; or to modify the process to include higher shear mixing. Because of the viscosity, limitations may be placed on the package.

After-Shave Powders

These systems are mainly talc, kaolin, ZnO, TiO_2, and magnesium carbonate. The benefit of after-shave talcs is a reduction of the shine associated with the use of brushless shave creams. Other ingredients can be added to enhance additional attributes such as cooling or astringency. A more thorough discussion of powder manufacture and formulation can be obtained from the chapter on "Face Powders and Makeup."

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CHAPTER 26
Color Cosmetics

INTRODUCTION

Color cosmetics have been used since ancient times to impart color to the human body. The purpose of these products is to improve appearance either by hiding skin imperfections or by intensifying and highlighting eyes, lips, and nails. Categories of makeup include foundation, blusher, mascara, eyeliner, eye shadow, lip color, and nail color. Color cosmetics are supplied in many product forms: pressed and loose powders, suspensions, oil in water and water in oil emulsions, and anhydrous sticks, compacts, and pencils. To create a functional makeup product, the formulator must develop a stable base formula and also achieve adequate pigment dispersion within the vehicle in a form that can be delivered uniformly during application.

Much of the technology utilized in the production of color cosmetics is similar to that found in the paint or ink industry, with the requirement that the "coatings" achieved be nontoxic and nonirritating under conditions of use. In addition, the consumer requires that color cosmetics have an appealing look, feel, smell, and, in the case of lip products, taste.

Cosmetic colorants are subject to specific government regulation throughout the world. In most countries, regulations are patterned after those followed by the United States (Food and Drug Administration), the European Union (European Commission), or Japan (Ministry of Health and Welfare). U.S. regulations for food, drug, and cosmetic colors are found in the *Code of Federal Regulations (21CFR), Title 21, Parts 73* and *74* available from the U.S. Government Printing Office, Washington, D.C. For the worldwide regulatory status of colorants, the CTFA *International Color Handbook* is an excellent reference. Some details of regulations concerning cosmetic colorants are included in Chapter 7. The United States, European Union, and Japan also have specific chemical purity requirements, often dealing with permitted levels of heavy metal content with which the formulator must also become familiar. Suppliers of cosmetic grade pigments are a good source of information on regulations

governing cosmetic colorants and physical and chemical characteristics of the various pigments that can affect performance in actual cosmetic products.

Because formulators try to utilize the pigments permitted worldwide that also have the best chemical and physical stability and the best tinting strength, the actual number of compounds utilized is quite small, approximately 15 organic pigments and 12 inorganic or natural colorants. From these chemical entities, pigment suppliers create variations in shade and tinting strength to aid the formulator in creating a full range of shades. Filler pigments are chosen for their impact on coverage and skin feel, varying from low-priced talcs to high-priced specialties, including boron nitride, spherical polymers, spherical silicas, and lauroyl lysine.

FOUNDATION/SKIN COLORANTS

The function of foundation is to impart a smooth finish to the skin, masking minor imperfections and evening out skin tones, in other words, to make the skin look and feel pleasant to the touch. Degree of opacity can vary from highly opaque and covering to sheer and transparent. The finish provided can be moist and dewy, natural, semimatte, or matte, depending on the pigment and emollient content of the formulation. Many foundations include skin treatment functions: either for moisturizing dry skin or for absorbing the excess sebum produced by oily skin. In either case, the goal is to maintain an even, flawless appearance throughout the day.

Vehicles for foundations include suspensions, oil in water emulsions, water in oil emulsions, pressed and loose powders, anhydrous cakes, and anhydrous sticks. Preferred foundation forms vary throughout the world according to fashion and climate. Examples are the popularity of emulsion liquid foundations in the United States, cream foundations in Europe, and powder or powder-cream foundations in Japan.

COVERAGE

Coverage in color cosmetics is provided primarily by the white pigments such as titanium and zinc oxide, kaolin, certain talcs, and, in some cases, the colored pigments. Other materials that contribute to coverage, particularly in powder products, are bismuth oxychloride, metallic soaps, carbonates of alkaline earths, fine particle size pearlacious pigments, and boron nitride.

The ability of a material to scatter light determines the amount of coverage. The greater the difference in refractive index between a pigment and the vehicle in which it is dispersed, the greater the degree of light scattering observed, thus the greater the coverage. For this reason fillers such as talc and

mica, which have refractive indices in the range of 1.5–1.6 will lend opacity in powder formulations in which the vehicle is the surrounding air, with a refractive index close to 1. When totally wetted out in oils or polymers, which generally have refractive indices in the range of 1.4–1.6, these filler pigments become transparent.

Other properties that affect light-scattering power are particle size and particle surface roughness. Finer particle size pigments give more coverage due to the greater volume and surface area of a given weight of material. However, below 350 nanometers in diameter, pigments become more transparent as size decreases, as light is no longer totally reflected by particles having dimensions less that one half their wavelength.

Titanium Dioxide

Titanium dioxide is the white pigment most commonly used to provide coverage to color cosmetic formulations. Titanium dioxide occurs in two crystal forms, anatase and rutile, having respective refractive indices of 2.55 and 2.75. The high refractive index of the rutile form is due to the closer atom packing in the crystal structure, resulting in higher coverage. Both are dense white materials, with anatase being bluish-white and rutile having a yellower tone. As specified in *21 CFR*, for food, drug, and cosmetic use, the colorant titanium dioxide must be 99% pure, based on analysis of dried material. Paint-grade titanium dioxide, coated with additional stabilizers, wetting agents or dispersants, is not permitted.

Titanium dioxide is also a Category I sunscreen active ingredient, permitted at levels from 2% to 25% of the formulation. Ultrafine grades, having particle size ranges below 100 micrometers, which are relatively transparent to visible light yet opaque to ultraviolet radiation, are used to provide sun protection without a whitening effect. Although the larger particle size pigmentary titanium dioxide is sufficiently light-stable in most cosmetic application, the ultrafine grades require additional inorganic and organic coatings to prevent darkening on exposure to light and chemical reactivity with the vehicle. The USP monograph for titanium dioxide was modified in 1999 to reflect the need for coatings and the higher water content of UV light–attenuating grades of titanium dioxide. However, the 99% purity specification for titanium dioxide as a color additive remained unchanged.

Zinc Oxide

Zinc oxide has a lower refractive index than titanium dioxide, 2.1, and thus has lower covering power. Compared to titanium dioxide, zinc oxide is a yellowish-white pigment. These properties are used to advantage in providing coverage in shades for darker skin tones, in which the higher hiding power of titanium dioxide results in an "ashy" appearance. Zinc oxide is difficult to use

in the aqueous phase of water-based formulations because formula instability can result from the solubility of the Zn^{+2} ion, particularly below pH 6. Zinc oxide is also a Category I sunscreen active that provides protection from UVA radiation. In the OTC Skin Protectant monograph, zinc oxide is listed as an active ingredient due to its astringent and soothing properties.

Kaolin

Kaolin, generally considered a "filler" pigment, is a hydrous aluminum silicate, which does provide coverage and gives a smooth feel to powders and dispersed systems. In aqueous emulsions, kaolin acts as a pigment dispersant and helps to stabilize the suspension by acting as a spacer between the pigment particles. The platy structure of kaolin, which gives good skin adhesion in combination with absorbency for water and oil, makes kaolin a useful ingredient for improving the wear of color cosmetics. Slip of dry kaolin is less than that of talc or mica, which sometimes limits the percentage that can be used in powder formulations.

FINISH

The finish of a foundation is determined by the relationship between the pigments/filler content and the amount of the vehicle remaining after the product has set or dried on the skin. Consumer requirements vary, based on skin type, fashion, and climate. Oily skinned individuals prefer a matte or semimatte appearance, while moisturizing, emollient formulations are preferred by those with dry skin. Since they contain close to 100% dry ingredients, powder foundations will give a matte appearance that can be softened by the use of translucent reflective materials such as mica and low levels of fine pearlaceous pigments. The finish of emulsified foundations can be varied from dry and matte to moist and dewy. A formula having 12–14% pigment and 5–10% nonvolatile oil will be relatively matte, probably suited to younger, more oily skin types. In contrast, a product having 14–16% pigment in a base containing 25–35% nonvolatile oil would be positioned for older, drier skin. Usually, anhydrous formulations are matte to semimatte to natural in finish and are not moist, because a dewy anhydrous formulation has an extremely greasy feel on application and poor wear characteristics.

APPLICATION

Foundation is applied with the fingers or a wet or dry sponge. If an applicator is to be used, during product development the formulator must examine the proposed applicator to ensure acceptable performance. Criteria for application are spreadability, blendability, and play time. The product should remain

sufficiently mobile for a period of time to cover the face evenly, without streaking or unevenness. If additional material is needed to be applied to achieve coverage, the newly applied product should blend smoothly with no lines due to overlap.

WEAR

Users of foundation makeup want their appearance to remain fresh throughout the day, with possibly only light touchup with a complementary pressed powder. Consumers with oily or combination skin are particularly concerned about wear due to the change in appearance over time caused by oil breakthrough. Ingredients used to prolong wear include oil-absorbing fillers to soak up excreted sebum and film-formers to prevent shifting of the deposited film. A semimatte or natural looking foundation has a better chance than does a matte product of remaining unchanged over the period of wear, because once a part of a matte finish becomes saturated with oil, the contrast with the still dry portion is very noticeable.

PIGMENTS AND FILLERS

Filler pigments are materials whose main function is not to contribute color or coverage but to act as "extenders" for the pigments, improving dispersion to lessen the amount of true pigment actually needed. A filler is generally chosen as the material to vary as color content changes within a shade line of a product to maintain a constant pigment percentage. Because of their occasional high percentage within a formulation, filler pigments often have a strong impact on the functional and aesthetic properties of a product. Platy fillers are known for their smooth skin feel and their ability to adhere to the skin.

Talc

Talc, a hydrated magnesium aluminum silicate, is the most common filler pigment used in foundations. The standard for the softest known mineral (1 MOH scale) is talc, which in combination with its platy structure, results in excellent skin feel. Cosmetic grade talc must be clean and bright white in color, free of asbestiform minerals, and low in heavy metals (<20 ppm lead, <3 ppm arsenic). Talc is a natural mineral. Cosmetic talcs are mined in Italy, France, the United States, India, and China. Talc ore is crushed, dry ground, sometimes washed, and classified to obtain specific particle size ranges. Morphological forms are macrocrystalline and semimacrocrystalline. Examples of platy macrocrystalline ores are Italian, French, and Vermont talc. Macrocrystalline talcs are characterized by translucency, smooth skin feel, excellent slip, and moderate compressibility. Of these, Italian talc has long

had the reputation of being the finest talc with the highest translucency and smoothest feel, due to the predominance of large, thin platelets relatively free from surface defects. Another property of Italian talc, of importance in dusting powders, is good fragrance retention. Although fragrance levels are much lower in foundation, talcs, low in iron content are preferred for lack of reactivity with fragrance compounds. Alabama talc and Chinese talc are semi-macrocrystalline talcs, which are more compressible than the macrocrystalline varieties, thus especially suited for use in pressed powders. Many Chinese talcs are of high quality with clean color, good skin feel, and good compressibility. Although higher in cost, jet-milled grades of talc are available, which are characterized by fine (<5 m) particle size, exceptionally soft, smooth skin feel, and good compressibility.

In spite of periodic concerns regarding safety, talc remains the most common filler pigment used in color cosmetics, probably due to low cost, ease of handling, and ready availability. To date, there is no evidence that cosmetic-grade talc is hazardous to health under normal use conditions.

Mica

Mica is a platy potassium aluminum silicate that is somewhat harder (MOH scale 3) and more translucent than talc. Cosmetic-grade muscovite mica is mined in the United States, China, and India and is finished by wet or dry grinding. Wet ground mica has a higher bulk density, smoother skin feel, lower vehicle absorption, and lower opacity than the less expensive dry ground material. Following the grinding step, the mica is dried and classified according to particle size range. Fractions used as fillers in foundation are usually under 44 μm. Supplied as smooth, translucent flakes, mica is used in powder and dispersed foundations to impart a smooth, silky feel without additional opacity. In powder systems, mica's refractive index of 1.58 results in a slight luster, which may or may not be desirable.

Sericite

Sericite is a type of mica having properties intermediate between those of talc and other micas. Compared with most mica, sericite is more opaque, has a higher bulk density, better compressibility, lower oil absorption, and less luster. Due to a generally higher level of water of crystallization than most mica, sericite has an almost moist skin feel. Sericite is particularly useful in pressed powder foundation to impart a smooth, emollient skin feel, good slip, and good pick-up without dusting.

Specialty Fillers

Specialty fillers are used as texture modifiers to lend superior performance properties to color cosmetics. Platy materials with smooth surfaces such as

bismuth oxychloride, boron nitride, lauroyl lysine, starch derivatives, and mica composites have excellent skin feel due to the tendency of the platelets to slide over one another when rubbed. Spherical compounds, both organic and inorganic, act like ball bearings, allowing other particles in a formulation to slide easily over the skin. Materials available in spherical form include nylon, polymethylmethacrylate, polyurethane, polyethylene, polyethylene/polyacrylates copolymer, polyvinylidene copolymer, talc, ceramic composites, and silica. Levels of spherical compounds in a formulation are limited by their tendency to reduce adhesion of product to the skin. Fillers capable of absorbing water or oil are utilized to provide resistance to perspiration and oil breakthrough to prolong the wear of foundations. Examples are kaolin, porous silica, calcium silicate, and acrylate copolymer particles. Properties of the specialty fillers vary widely according to chemical composition and structure: from low to high oil absorption, low to high opacity, low to high bulk density, and low to high compressibility. The formulator chooses materials for use based on formula requirements and cost.

COLORED PIGMENTS

Red, yellow, and black iron oxides are the principal coloring oxides used in foundation makeup. In combination with titanium dioxide, which functions as a white pigment and provides coverage, almost all skin tones can be matched using the iron oxides. Ultramarine blue is sometimes used, but shade matching is easier and better reproducibility is obtained from blue shades of iron oxide. The commercially available brown iron oxides are blends of red, yellow, and black iron oxides. Better shade control and reproducibility in foundation is achieved by restricting one's choice of pigment to a yellow, a medium shade red, and a black iron oxide and learning the effect of each on the shade. It is advisable to keep color combinations as simple as possible so that matching with fresh batches of raw material is made easier.

The color effect produced on the skin is dependent on the opacity of both white and colored pigments, degree of dispersion, thickness of the applied film, and skin color. During formulation the chemist should strive to obtain a close relationship between product mass tone and skin tone through adequate pigment dispersion and good wetting. When shade matching under production conditions, skin tone should take precedence, although the cause of any significant deviation in mass tone should be identified and corrected.

Surface-Treated Pigments

The concept of the incorporation of surface-treated pigments into color cosmetics was introduced into the United States from Japan by Ryota Myoshi of Myoshi Kasei and Shoji Murata of Koken Chemical in 1981.

Surface-modified pigments revolutionized the formulation of foundations, particularly pressed powder forms and anhydrous systems. Pigment particles that are uniformly coated with a hydrophobic substance compress better, have a markedly smoother skin feel, and wet more easily into oil. The wide variety of surface treatments available can be classified according to the method of preparation.

Mechanical Blend. Examples are silica sphere, boron nitride, and nylon coatings. Under high intensity mixing, the small particles of the treating agent are attracted to the generally larger pigment or filler particles via electrostatic attraction. Materials coated in this fashion are characterized by enhanced slip and skin feel of greater magnitude than would be obtained by incorporating the same amount of the treating agent into the formulation.

Mechanical/Heat. Wax coatings are deposited onto pigments or fillers as a hot melt with or without the use of solvent under intense agitation. Wax treatments improve feel, improve compressibility in pressed powders, and impart moisturizing and emollient properties. When formulating dispersed systems, the formulator should be aware that the coating may dissolve off the surface during processing or aging and change the properties of the final cosmetic product.

Precipitation. A water-soluble version of the treatment compound is precipitated from aqueous solution in the presence of the pigment or filler by conversion into an insoluble form. Examples are lecithin[2], amino acid[3], lauroyl lysine[4], and metal soap, which not only improve skin feel but also coat the surface with a naturally derived material for which treatment claims may be possible. Precipitated coatings are utilized in powders and dispersed systems. Again, a careful evaluation should be performed to ensure that product performance will not change due to softening or dissolution of the coating under prolonged processing conditions in manufacture or filling.

Chemical Reaction. Reacted coatings are chemically bonded to the pigment/filler surfaces formed during the treatment process. Such coatings are used in powder products and are most suitable for use in dispersed systems, including anhydrous products and water in oil emulsions. Chemically modified surfaces will not solubilize under conditions occurring during normal cosmetic manufacture and so are much more durable than those coated by other means. Methicone, alkyl trithoxysilane, and phosphated perfluoro treatments are examples that chemically react with pigment and filler surfaces to modify wetting and dispersion characteristics.

Further mention of specific surface treatments will be made during the discussion of the formulation of the various color cosmetics.

Fragrance

The odor of a cosmetic strongly affects consumer acceptance. Because color cosmetics are "leave-on" products, worn in continuous contact with the skin, excess fragrance levels are to be avoided due to the potential for skin irritation and sensitization. By utilizing ingredients with the lowest potential for the development of unpleasant odors, the need for fragrance is reduced or avoided. In fact, many marketers of color cosmetics in the United States prefer unfragranced products in order to be able to make the claim "fragrance-free." Where fragrance is used, the fashion in the United States is for a light, pleasant scent.

The compatibility of the fragrance with the other constituents of the product must be carefully evaluated at room temperature and elevated temperatures. Many ingredients of color cosmetics, including talcs, kaolins, and metallic stearates, are known to be capable of degrading fragrance. The fragrance in a color cosmetic will be affected not only by product composition but also by heat when required in processing. Purchase of fragrance from a well-known fragrance manufacturer is recommended to help ensure suitability of the fragrance for the application and a composition having the least potential for adverse skin reactions.

FORMULATIONS

Emulsified Foundation

Liquid and cream emulsion foundations are sold throughout the world, with liquid makeup being the most popular form in the United States. The emulsion bases can be oil in water or water in oil systems with pigment, dispersants, and suspension aids added to the external phase. A wide variety of natural and synthetic emollients are used in the oil phases to provide slip and adequate play time during application and, upon evaporation of the volatile constituents, to act as the vehicle for the formula pigments and fillers.

The pigment phase of emulsion foundations varies from 10% to 16%, with the titanium dioxide content determining the degree of coverage. The titanium dioxide content remains constant through light to medium shades, then is reduced for darker shades to avoid an "ashy" appearance. Talc or another filler is used to maintain a constant percentage of dry ingredients as color content is adjusted for the range of shades. Talc or another filler is used as the substrate when dry extenders are milled in advance to provide better

dispersion. Specialty fillers are added to improve feel or give a light-diffusing effect, as do spherical silicas and some titanium dioxide–coated polymers. Small amounts of absorbent compounds such as nylon or fumed silica in the water phase or hydrophobic fumed silica in the oil phase can significantly improve wear by absorbing sebum.

Manufacture. Several different processing systems are frequently used to manufacture emulsion foundations. The formulator should utilize equipment in the lab that duplicates that which is used in actual production. In order to increase shear, pigment can be dispersed by a high-speed agitator, a homogenizer, a high-speed impeller, or a colloid mill. If a homogenizer is used, better pigment wet out is achieved if the pigments are added to the water phase prior to the gums, whereas a colloid mill is capable of dispersing pigment added after the gum phase. With foundations, the emulsion is usually formed by the addition of the internal phase to the external phase, due to the greater difficulty in pumping the pigment-containing external phase. Agitation used at emulsification varies from counterrotation to homogenization or even colloid milling. Sample manufacturing instructions are included with the formulas given below.

Oil in Water Foundations

Anionic oil in water makeup emulsions, those in which the surface active molecule carries a negative charge, are easier to formulate than those formed with nonionic or cationic emulsifiers. Most pigments and fillers carry a negative charge at approximately pH 7, so that, in an anionic system, the mutual repulsion between the like-charged oil droplets, pigment particles, and the stabilizing gums acts as a strong stabilizing mechanism. Cationic emulsion foundations can be formed by first dispersing the pigments in water and gradually adjusting the pH to a point below the isoelectric point of all the pigments. As the pigments pass through their point of zero charge, some agglomeration occurs due to the lack of stabilizing electrical forces. At a still lower pH, usually below pH 5, the pigments and fillers acquire a positive charge and will again disperse. Once a dispersion is achieved at a low pH, cationic emulsifiers can be added to the system without causing agglomeration and an emulsion is formed. Nonionic systems that have no stabilizing forces due to charge are not recommended.

Because foundation is a "leave-on" cosmetic, used every day, the emulsifiers used must be mild and their percentage kept at a minimum to avoid skin irritation and sensitization. The emulsifiers (and all ingredients) should have as little odor as possible to minimize or eliminate the need for fragrance.

Often a combination of anionic and nonionic surfactants will provide the best stability at the lowest emulsifier level. In addition, waxy materials that form liquid crystalline matrices such as fatty alcohols, glyceryl esters, and excess fatty acid act as secondary emulsifiers, stabilizing the system and controlling viscosity. For many years, "soap" systems, having triethanolamine-stearate (TEA), isostearate, or oleate as the primary emulsifier were the basis for over 90% of the emulsion foundations on the market (Formula 26.1). Due to

Formula 26.1 A Medium Coverage Foundation, Suitable for Normal Skin

Ingredients	%
Deionized water	54.58
Lecithin	0.05
Polysorbate 80	1.00
Triethanolamine 99%	1.00
80% Titanium dioxide and 20% talc extender	10.00
80% Iron oxide extenders and 20% talc extender	2.50
Talc	1.50
Propylene glycol	4.00
Magnesium aluminum silicate	1.00
Propylene glycol	2.00
Cellulose gum	0.12
Methylparaben	0.20
Propylene glycol dicaprylate/dicaprate	10.00
Isocetyl stearate	6.00
Stearic acid	1.50
Isostearic acid	0.50
Glyceryl stearate	1.50
Sorbitan oleate	1.25
Propylparaben	0.10
Diazolidinyl urea	0.20
Water, deionized	1.00

Manufacturing Procedure: Combine water, lecithin, and polysorbate 80. Begin heating to 70 °C while mixing. Add pigment phase while homogenizing. Combine glycol and Mg Al silicate. Add to batch. Heat to 85–90 °C for 15 minutes while homogenizing. Cool to 75–80 °C. Combine glycol and cellulose gum. Add to batch. Add methylparaben.

Combine oil phase. Heat to 77–82 °C while stirring. When both phases are homogeneous, add oil phase to water phase while homogenizing. Maintain temperature and agitation for 15 minutes. Cool to 45 °C with counter rotation agitation. Combine water and diazolidinyl urea and add to batch. Cool to 30 °C. Drop batch.

concerns over possible carcinogenicity of some amines, some formulators use no amines, switching instead to the less soluble and less effective potassium soap or using potassium hydroxide neutralized phosphate esters as the primary emulsifier (Formula 26.2). Examples of a pair of nonionic emulsifiers are polysorbate 80 and sorbitan monooleate, used in conjunction with TEA-stearate/isostearate in Formula 26.1 or sucrose cocoate/sorbitan monolaurate in Formula 26.2.

Formula 26.2 A Light Feeling, Natural Coverage Makeup, Suitable for Normal to Oily Skin

Ingredients	%
Water, deionized	54.46
Dimethicone copolyol	0.10
80% Titanium dioxide and 20% talc extender	9.00
80% Iron oxide, yellow, and 20% talc extender	0.75
80% Iron oxide, red, and 20% talc extender	0.42
80% Iron oxide, black, and 20% talc extender	0.07
Talc, jet milled	1.76
Potassium cetyl phosphate	1.50
Butylene glycol	4.00
Magnesium aluminum silicate	1.00
Butylene glycol	2.00
Cellulose gum	0.14
Sucrose cocoate	1.50
Methylparaben	0.20
Disodium EDTA	0.05
Propylene glycol dicaprylate/dicaprate	6.00
Cetyl alcohol	1.25
Sorbitan laurate	2.50
Propylparaben	0.10
Cyclomethicone (D_5)	12.00
Water, deionized	1.00
Diazolidinyl urea	0.20
	100.00

Manufacturing Procedure: Combine water and dimethicone copolyol. Add pigment while homogenizing and heating to 70 °C. Add potassium cetyl phosphate. Mix for 15 minutes, avoiding aeration. Combine and add glycol and Mg Al silicate. Heat to 85–90 °C for 15 minutes while homogenizing. Cool to 75 °C. Combine and add cellulose gum and glycol. When homogeneous, add remaining water phase ingredients.

Combine oil phase, except for cyclomethicone. Heat to 75–80 °C. When homogeneous, add cyclomethicone. Adjust temperature back to 75–80 °C. Add oil phase to water phase while homogenizing. Maintain temperature and agitation for 15 minutes. Cool to 45 °C with counterrotation agitation. Dissolve diazolidinyl urea in water. Add to batch. Cool to 30 °C. Drop batch.

In general, for pourable products that stay fluid over time, a majority of the surfactants should be liquid at room temperature, while solid surfactants should be used for cream makeups.

The number of emollient oils available to the formulator is almost infinite. Oils chosen for use in emulsion foundations should be noncomedogenic (non–pore-clogging) and stable to hydrolysis in the presence of water. Low viscosity esters such as neopentyl glycol dicaprylate/dicaprate, isostearyl neopentanoate, or propylene glycol dicaprylate/dicaprate are used to provide slip and emolliency in formulations for normal to oily skin. Cyclomethicone, a volatile silicone, can contribute to slip and play time but evaporates slowly after application to avoid an excessively oily finish. Higher levels of oil and higher molecular weight esters, for example, isostearyl stearoyl stearate, diisopropyl dimer dilinoleate, or pentaerythrityl tetraisostearate, are added to formulations intended for drier skin types to leave a moisturizing, protective film on the surface of the skin.

The most common stabilizer used in the aqueous phase is magnesium aluminum silicate in combination with protective colloids such as cellulose gum or xanthan gum. The clay mineral and the gum together form a colloidal matrix to maintain pigment suspension and prevent creaming (rising to the top) of oil phase droplets.

Other ingredients employed in the water phase are humectants, particularly glycols, to aid spreadability, lengthen play time, and augment the preservative system. Wetting agents are included to wet out the pigment phase. Preservatives used are those recommended for all "leave-on" applications: parabens, phenoxyethanol, formaldehyde releasers (not permitted in Japan), benzyl alcohol, and so forth.

Water in Oil Foundations

Several polymeric emulsifiers are available that form stable water in oil foundations. Dimethicone copolyol, cetyl dimethicone copolyol, and PEG-30 dipolyhydroxystearate are examples. Formula 26.3 is an example of a water in volatile silicone formulation designed for normal to oily skin.

Formula 26.3 has a light skin feel characterized by the excellent slip and spreading ability of the cyclomethicone. To ensure compatibility of the pigments with the external silicone phase, all pigments and fillers are coated with a chemically bound hydrophobic treatment; methicone is cited in the patent. In addition to the dimethicone copolyol, oil-soluble coemulsifiers, laureth-9, are needed to form a stable emulsion. Inorganic salts are added to the water phase to favor the migration of the polymeric emulsifier at the water/silicone interface to maintain stability.

Formula 26.3 Water in Silicone Foundation (U.S. Patent 5, 143,772, Revlon, 1992)

Ingredients	%
Cyclomethicone (D_4)	12.00
Dimethicone/10cs	5.00
Cyclomethicone and dimethicone copoloyol	20.00
Laureth-9	0.50
Propylparaben	0.10
Iron oxide, red	0.70
Iron oxide, yellow	1.50
Iron oxide, black	0.20
Talc	3.30
Titanium dioxide	8.50
Water, deionized	38.00
Sodium chloride	2.00
Propylene glycol	8.00
Methylparaben	0.20
	100.00

Manufacturing Procedure: Silicone phase ingredients are stirred together until homogeneous. Pigment phase is added and milled with a high-shear mixer until a fine grind is obtained. Water phase ingredients are combined and stirred until homogeneous. The water phase is added to the silicone phase while homogenizing. Homogenization is maintained for 15 minutes.

Alkyl dimethicone copolyols are used to formulate water in oil systems that contain significant amounts of organic oils for greater emolliency (see Formula 26.4). Formulation techniques are similar to those above: salts are added, coemulsifiers are included, and surface-modified pigments, preferably treated with alkyl silane coatings, are employed.

Unlike some water in oil systems, the pigmented emulsions are not particularly easy to preserve. Combinations of parabens with water-soluble preservatives such as benzoic acid, salicylic acid, dehydroacetic acid, or sorbic acid are effective. The heat-sensitive formaldehyde-releasers can only be added to cold process water in oil emulsions, because they will not disperse in the external (oil) phase during the cooling cycle. As in oil in water emulsions, glycols are added to increase formula resistance to microbial attack.

Water in oil emulsions are more difficult to stabilize than oil in water emulsions. There are no stabilizing forces due to charge because the external oil phase is nonconductive. Additives to control of the oil phase must be carefully evaluated to avoid incompatibility with the polymeric emulsifiers. Cyclomethicone-soluble dimethicone crosspolymer silicone elastomers are

Formula 26.4

Ingredients	%
Phase A	
Cetyl dimethicone copolyol	0.50
Polyglyceryl-4 isostearate and cetyl dimethicone copolyol and hexyl laurate	2.00
Cetyl dimethicone	2.00
White beeswax	0.80
Hydrogenated castor oil	0.40
Propylparaben	0.10
Phase B	
Titanium dioxide, caprylyl silane coated	8.50
Iron oxide, yellow, caprylyl silane coated	0.80
Iron oxide, red, caprylyl silane coated	0.40
Iron oxide, black, caprylyl silane coated	0.04
Talc, caprylyl silane coated	4.26
Cyclomethicone	9.00
Phenyl trimethicone	2.50
Octyl palmitate	7.90
Phase C	
Dimethicone/100cs	1.50
Cyclomethicone (D_5)	9.00
Phase D	
Butylene glycol	6.00
Methylparaben	0.20
Water, deionized	43.50
Sodium chloride	0.60
	100.00

Manufacturing Procedure: Combine Phase A with stirring. Heat to 85–90 °C. Cool to 70 °C with stirring. Combine Phase B. Mill with a high-speed impeller mixer in a sealed kettle until a fine grind <25 (m) is obtained. (Check using a Hegman gauge.) Combine and add Phase C to Phase A. When homogeneous, add Phase B to combined Phases A & C while homogenizing. Adjust temperature to 50 °C.

In a separate kettle, add Phase D salt to water with stirring. Predissolve methylparaben in butylene glycol and add to remainder of Phase D. Adjust temperature to 50 °C. Add Phase D to combined Phases A & C while homogenizing. Maintain homogenization for 15 minutes. Cool to 30 °C with counterrotation agitation. Drop batch.

useful in thickening external phases that are primarily silicone. Viscosity of oil phases composed of primarily organic esters and hydrocarbons can be controlled with waxes that form a gel structure (Formula 26.4), alkyl galactomannan, hydrophobic starch derivatives, or organically modified clays.

Powder Foundation

Pressed powder is the form of choice for powder foundation, while loose powder is used as a final step to provide a flawless finish following the use of other types of foundation.

A basic pressed powder consists of pigment, fillers, dry binders, wet binders, and preservatives. As in all foundations, titanium dioxide and zinc oxide at use levels of 3–20% provide coverage. One filler, usually talc, sericite, or a starch, is chosen to vary with the pigment content to maintain formula texture throughout the shade line. Even if cost of goods is a concern, the use of at least one surface-treated filler is recommended to give the tactile benefits of the treated pigments, to improve compressibility with a lower binder level, and possibly to improve wear.

Dry binders are materials that compact well by themselves and have adhesive qualities either dry or wet, to aid compaction of other formula ingredients. Metallic soaps of fatty acids, such as zinc stearate, magnesium myristate, and lithium stearate, used at percentages from 3% to 8%, are the best-known dry binders. Other materials that aid compaction are powdered polyethylene, other powdered waxes, calcium carbonate, magnesium carbonate, kaolin, acrylate copolymers in powder form, bismuth oxychloride, and calcium silicate.

Wet binders are cosmetically acceptable oils that partially wet the pigment phase. From among the many synthetic hydrocarbons, esters, and silicones, the formulator chooses one or more oils to provide good pressing characteristics. Wet binders also affect product texture, skin feel, and color development. Oil-soluble wetting agents or waxes may also be added to the binder phase. Waxes present the added need to heat the oil phase and maintain temperature prior to addition and may crystallize during aging. Water has been used to aid compaction but can lead to color changes during processing and additional risk of microbial contamination.

A properly formulated pressed powder will pass a drop test (e.g., three drops from a height of 20 cm), exhibit good pickup without glazing or dusting, and apply evenly to cover the skin. By experimenting with different binder combinations and different pressing conditions during product development, performance can be optimized.

Manufacture. As in the case of emulsions, to avoid problems during scale-up, lab procedures for pressed powders should be developed that will produce

results similar to those on the equipment used to manufacture the final product. Small lab scale trial batches are often prepared in a kitchen blender such as an Osterizer. Larger batches still need to be made in the lab in equipment more closely duplicating that found in production.

The sequence of steps in production is blending, milling, then wet binder addition. Blending is a low-energy operation that can be carried out in ribbon blenders, twin shell blenders, V-blenders, or "plow" blade mixers. Some blenders also are equipped with a high-speed agitator capable of breaking up soft agglomerates. The high energy input of a hammer mill, pin mill, or jet mill is almost always required to adequately disperse pigments and the more cohesive dry ingredients.

Wet binder addition must be carried out carefully to ensure good distribution throughout the dry ingredients. A spray assembly through which the wet binder can be pumped as the powder is strongly agitated is the best option. In V-blenders and twin shell blenders equipped with high-speed "intensifier" bar assemblies that run along the axis of rotation, the binder can be added through the bar and dispersed through orifices in the bar by centrifugal force as the bar spins at high speed.

Formula 26.5 is a basic pressed powder foundation, containing methicone-treated mica to improve feel and texture. Zinc stearate is the sole dry binder, with coco caprylate/caprate as the wet binder.

Texture modifiers play a significant role in pressed powder formulation due to their considerable effect on the feel and performance of the product.

Formula 26.5

Ingredients	%
Talc, semimacrocrystalline	43.40
Mica (< 50 μm) and methicone	30.00
Titanium dioxide	15.00
Iron oxide, yellow	2.80
Iron oxide, red	1.30
Iron oxide, black	1.20
Zinc stearate	3.00
Methylparaben	0.20
Propylparaben	0.10
Coco caprylate/caprate	4.00
	100.00

Manufacturing Procedure: Blend the powder phase in a twin shell blender. Pulverize once, using a hammer mill, through an 0.027″ screen. Spray on oil with agitation. Pulverize again through the 0.027″ screen. Press at 1500 psi.

Formula 26.6

Ingredients	%
Talc, lecithin-coated	38.22
Titanium dioxide, lecithin-coated	14.00
Iron oxide, yellow, lecithin-coated	1.50
Iron oxide, red, lecithin-coated	0.90
Iron oxide, black, lecithin-coated	0.08
Sericite, lecithin-coated	30.00
Boron nitride	5.00
Magnesium myristate	2.00
Polyethylene	2.00
Silica, spherical	0.50
Methylparaben	0.20
Propylparaben	0.10
Dimethicone/20cs	2.50
Octyl palmitate	2.50
Polyglyceryl-3 diisostearate	0.50
	100.00

Manufacturing procedure is the same as that for Formula 26.5.

Formula 26.7

Ingredients	%
Talc, Italian	48.69
Mica (< 15 μm)	25.00
Titanium dioxide	10.00
Iron oxide, yellow	0.60
Iron oxide, red	0.35
Iron oxide, black	0.06
Nylon	7.00
Zinc stearate	2.00
Methylparaben	0.20
Propylparaben	0.10
Mica and Iron oxide (Bronze Pearl)	3.00
Isocetyl stearate	3.00
	100.00

Manufacturing Procedure: Mix the pigments and fillers in a twin shell blender equipped with intensifier bar for 15 minutes at high speed. Add the pearl. Blend for 5 minutes at low speed. Spray in the oil. Blend for an additional 5 minutes at low speed.

Formula 26.8 is pleasant to the touch, both in the cake and when applied to the skin. The combination of lecithin-treated pigments and fillers, boron nitride, and dimethicone in the wet binder gives the formulation a soft, emollient feel with excellent slip.

Loose powder is formulated similarly to pressed powder, only with lower levels of binders. Two percent of a metallic stearate is sufficient to provide skin adhesion, and just enough oil is added to wet the pigments and develop their color. If the blender used to process a loose powder has a high-intensity agitator, pulverization may be avoided, because small agglomerates will not be observed as they are in a pressed cake. Pearlaceous pigments can be also be added to brighten the appearance of the skin. When pearlaceous pigments are added, only low-energy agitation can be utilized due to their fragile nature.

Anhydrous Foundation

Most anhydrous foundations are high coverage formulas that apply with the slip of a cream, yet have the dry feel on the skin of a powder and set to a powdery finish. The names "cream-powder" and "liquid-powder" are used to describe these products. Although sold worldwide, compact cream powder foundation is particularly popular in the Far East in countries where high coverage makeup is in fashion.

Light dry-feeling oils are used in the formulation of powder cream systems, especially those that act as co-solvents for silicones, allowing the incorporation of low molecular weight dimethicone or organically modified silicones. Silicones are especially useful in cream powder formulation because of their slippery but dry feel, which enhances spreading and blending properties without an increase in emolliency. Examples of light dry esters are octyl palmitate, isostearyl neopentanoate, octyldodecyl neopentanoate, coco caprylate/caprate, neopentyl glycoldicaprylate/dicaprate, and propylene glycol dicaprylate/dicaprate.

To obtain a powder-like feel and finish from a cream, the pigment load must be maximized while still maintaining fluidity in the melt so that the product can be poured into pans or compacts. To achieve the degree of wetting needed, surface-treated pigments are used, which are not hydrophobic but lipophilic. Reacted coatings having alkyl functional groups, including alkyl silanes and alkyl titanate esters, are the most effective surface modifiers in improving the wetting properties of the inorganic pigments and fillers in wax/oil-based systems.

As in all foundations, titanium dioxide and zinc oxide are used for coverage. Color is obtained from the iron oxides, and a dense talc or sericite is the filler of choice to vary. Platy minerals, either sericite or mica, are incorporated for their slip and adhesion to the skin. Spherical materials such as

nylon, polymethylmethacrylate, polyurethane, and polyvinylidene copolymer, preferably having low to medium oil absorption, provide slip and give the sensation of dryness. Oil-soluble wetting agents are employed to further improve the wetting of the pigments and fillers.

The level of waxes in powder cream foundations should be as low as possible but allow the formula to withstand 50 °C conditions without syneresis (oil exudation) or melting. The waxes utilized should be nontacky and completely soluble in the formula oils. Extra care must be taken when formulating cream powder systems because of their tendency to exhibit surface crystallization. The high pigment load reduces the amount of oil available to solubilize the waxes, and any silicones in the formula will be poor solvents, possibly leading to incompatibility manifested by the development on the surface of micro or even macro wax crystals. Because accelerated aging tests involve heating, room temperature is usually the condition in which crystal growth occurs. Samples should be checked regularly for hardening of the disturbed or undisturbed surface, often the first sign of wax crystallization.

Formula 26.8 is an example of a powder cream foundation.

Formula 26.8

Ingredients	%
Octyl palmitate	42.20
Glyceryl tribehenate	7.00
C_{30-45} Alkyl methicone	7.00
Polyglyceryl-3 diisostearate	0.50
Methylparaben	0.20
Propylparaben	0.10
Titanium dioxide, caprylyl silane coated	15.00
Iron oxide, yellow, caprylyl silane coated	1.80
Iron oxide, red, caprylyl silane coated	1.40
Iron oxide, black, caprylyl silane coated	0.12
Talc, caprylyl silane coated	4.68
Mica (< 10 μm), caprylyl silane coated	8.00
Polymethylmethacrylate, caprylyl silane coated	12.00
	100.00

Manufacturing Procedure: Waxes and oils are combined and heated to 70 °C with stirring until clear. Pigments and preservatives are added and milled with a high-intensity impeller mixer until no undispersed particles are observed. Bulk is filled into pans at 70 °C. If no high intensity mixer is available, a three roll mill may be used to disperse the pigments in a portion of the oil; this is combined with the batch using counterrotation agitation.

Stick foundations are formulated similarly to those packaged in compacts. Due to the need for three-dimensional stability, some harder high melting point wax is used. Carnauba wax and C_{20-40} alcohols are suited for this purpose due to their 85 °C melt points and relative lack of tack.

LIPSTICK

CHARACTERISTICS

Lipsticks, the lip cosmetics molded into sticks, are essentially dispersions of coloring matter in a base consisting of a suitable blend of oils, fats, and waxes.

Lipstick is used to impart an attractive color and appearance to the lips, accentuating their good points and disguising any bad ones. Narrow lips may be widened and broad lips' made to appear narrower by its use. In addition, emollient lipsticks have a treatment function, providing an oily protective film to prevent chapping and drying out of the lips' sensitive mucous membranes.

A good lipstick should have the following characteristics:

(1) An attractive appearance, a smooth surface of uniform color free from defects such as pinholes or grittiness due to color or crystal aggregates. Stability should be maintained during shelf life and usage life; the stick should not exude oil, develop a bloom, flake, cake, harden, soften, crumble, or become brittle over the range of temperatures likely to be experienced.
(2) Pharmacologically inert when topically applied and when ingested.
(3) Easy to apply, giving a film on the lips that is neither excessively greasy nor too dry, that is reasonably permanent but capable of deliberate removal, and which has a stable color.

LIPSTICK INGREDIENTS

Coloring Materials

The color of a lipstick is one of the major selling points, but it is one that can be dealt with only in general terms, since the precise shades are dictated by fashion. It is usual for the color to contain some measure of red, which allows shades ranging from orange-yellow to true red to purple-blue and red-brown, although even greens and blues are not unknown. Depth of color, degree of gloss, and opacity are also variable. During periods when the fashion trend is to a "no makeup" look, uncolored or lightly tinted lipstick bases of high gloss are marketed under the name "lip gloss." Highly lustrous shades are also created through the use of pearlaceous pigments, particularly titanium dioxide–and iron oxide, coated mica pigments. However, the main accent in this discussion will be on the predominantly red conventional shades, which utilize the basic principles of lipstick formulation.

The color is imparted to the lips in two ways: (1) by staining the skin, which requires a dye in solution, capable of penetrating the outer surface of the lips; (2) by covering the lips with a colored layer that serves to hide any surface roughness and give a smooth appearance. This second requirement is met by insoluble dyes and pigments that make the film more or less opaque.

Formulators should check very carefully with their color suppliers to determine the use of the various colors in the individual countries in which the lip products are to be sold. A useful reference is the CTFA *International Color Handbook*. A brief summary of the status of the most popular organic colors, as used in the United States, the European Union, and Japan is given in Table 26.1. Typical proportions for the colors in a lipstick are as follows:

Ingredients	%
Staining dye (bromoacids)	0–0.2
Insoluble pigment	8–10
Titanium dioxide	0–4
Pearlaceous pigment	0–20

Table 26.1 Current Status of Organic Lipstick Colorants

Color	US status	EU Status; CI#	Japan status; name
D&C Red #6	permitted	permitted; 15850	permitted; Red 201
D&C Red #6 Ba Lake	permitted	permitted; 15850	not permitted
D&C Red #7 Ca Lake	permitted	permitted; 15850	permitted; Red 202 mixture
D&C Red #21	permitted	permitted; 45380	permitted; Red #223
D&C Red #21 Al Lake	permitted	permitted; 45380	not permitted
D&C Red #22 Al Lake	permitted	permitted; 45380	permitted; Red 230(1) Lake
D&C Red #27	permitted	permitted; 45410	permitted; Red 218
D&C Red #27 Al Lake	permitted	permitted; 45410	not permitted
D&C Red #28 Al Lake	permitted	permitted; 45410	permitted; Red 104(1) Lake
D&C Red #30 Lake	permitted	permitted; 73360	permitted; Red 226 mixture
D&C Red #33 Al Lake	permitted	permitted; 17200	permitted; Red 227 Lake
D&C Red #33 Zr Lake	max. 3%	not permitted	not permitted
D&C Red #36	max. 3%	max. 3%; 12085	permitted; Red 228
D&C Orange #5	max. 5%	permitted; 45370	permitted; Orange 201
D&C Orange #5 Al Lake	max. 5%	permitted; 45370	not permitted
FD&C Blue #1 Al Lake	permitted	permitted; 42090	permitted; Blue 1 Lake
FD&C Yellow #5 Al Lake	permitted	permitted; 19140	permitted; Yellow 4 Lake
FD&C Yellow #6 Al Lake	permitted	permitted; 15985	permitted; Yellow 5 Lake
D&C Yellow #10 Al Lake	permitted	permitted; 47005	permitted; Yellow 203 Lake

Staining Dyes

The formerly widely used staining dyes are halogenated derivatives of fluorescein, which are generally referred to collectively as "bromoacids," a term originally applied to acid eosin, tetrabromofluorescein.

Eosin

Eosin, also known as D&C Red No. 21, is an insoluble orange compound that changes to an intense red salt when the pH value is above 2. When applied to the lips in the acid form, it produces a relatively indelible purple-red stain on neutralization by the lip tissue.

Other halogenated fluoresceins can be used alone or in combination to give different staining colors and varying degrees of indelibility. Thus D&C Red No. 27 tetrachlorotetrabromofluorescein produces a brilliant bluish red stain, and D&C Orange No. 5 (dibromofluorescein), an orange that changes to the red salt form above pH 4, often used in conjunction with D&C Red No. 21.

Unfortunately, eosin and some of its derivatives can give rise to sensitization or photosensitization, leading to cheilitis (inflammation of the red portion of the lips) or more general allergic reactions. The exact cause was never determined, but the fact was that it did occur in a small proportion of lipstick users. At lower use levels adverse reactions are less frequent. Another disadvantage of the staining dyes was that a variety of shades could not be achieved. Currently, the staining dyes are used chiefly in "mood" lipsticks, which are popular from time to time. The mood lipsticks are unpigmented or pigmented with an extremely low level of contrasting color, for example, FD&C Blue #1 Lake, and develop the red coloration when applied to the lips. Some long-wearing lipsticks contain low levels of one or more of the staining dyes.

Much attention was given in the past to the difficulties encountered when the use of bromoacid dyes failed to yield homogeneous dispersions of these dyes in the lipstick mass, which resulted in shade variations in lipsticks. Alternatively, the low amounts currently in use are active when incorporated as part of the pigment grind in formulations in which they are insoluble. To prevent the bromoacid dyes from converting to the highly colored salt form prematurely in the lipstick mass, 0.1% citric acid may be added to the pigment grind.

Pigments

Both organic and inorganic pigments are used to create a full range of shades.

Titanium dioxide, used at levels up to 4%, is an effective white pigment for obtaining pink shades and giving opacity to the film on the lips. However, the use of titanium dioxide requires great care in the grade of material selected (anatase or rutile), the presence of any surface treatment to enhance lipophilicity, and also in the method of incorporation, if unexpected problems

such as oily exudation, streaking, dullness, and coarse texture are to be avoided.

Bismuth Oxychloride

This dense, white, generally lustrous pigment is an alternative opacifier in pearlaceous shades. It has fewer negative effects on stick integrity than titanium dioxide. Bismuth oxychloride is a dense pigment, having a low oil absorption and a smooth feel on the skin and lips. Matte versions are available for incorporation into "cream" or nonpearlaceous shades.

Iron Oxides

Iron oxides are used for matching the russet and brown shades. Surface-treated versions may be used to improve wetting.

It should be noted that *ultramarine blue* (ferric ferrocyanide) and the *chromium pigments* are classified in the United States as "for external use only," and, therefore cannot be used in contact with mucous membranes, including the lips.

Organic Pigments

Organic pigments, which are primarily organic lakes, provide the bright clean red, orange, and violet tones that are the mainstay of modern lipstick shade lines. The classic definition of a lake is an insoluble pigment prepared by the precipitation of a water-soluble dye with a metal ion onto a substrate. An example is the precipitation of FD&C Blue #1 with aluminum ion onto alumina to form FD&C Blue #1 Aluminum Lake. D&C Red No. 36, is so insoluble in both water and oil that it may be considered as a pigment. Lakes of many of the D&C colors with metals such as aluminum, barium, calcium, and strontium are suitable pigments for lipsticks. When selecting lakes, the possibility of reaction with the base, for example, metal soap formation with free fatty acid, must be borne in mind, particularly with the aluminum lakes. Aluminum lakes are not usually favored because of their lack of opacity but are often the only available option for a given colorant.

The following lakes are considered to be the most useful lipstick colorants:

Calcium lakes of D&C Red No 7, strong red to blue-red
Barium lakes or sodium salt (for use in Japan) of D&C Red # 6, a strong red-orange
Aluminum lake of FD&C Yellows #s 5, a true yellow
Aluminum lake of FD&C Blue #1
Aluminum lakes of D&C Reds #22, red, and #28, a bright magenta

When the parent D&C color is subject to restriction, the lakes are also restricted in the same way. As noted above, pigments and lakes are used at levels between 4% and 10%.

Pearlaceous Pigments

Pearlaceous pigments as mentioned, previously, provide opacity in pearlaceous shades. Mica coated with titanium dioxide or with iron oxide, as well as bismuth oxychloride, are utilized at levels of up to 20% to provide a range of pearly effects. Care must be taken not to incorporate too high a level of mica pigment to avoid dryness or brittleness of the lipstick.

Filler Pigments

Filler pigments in lipsticks function to modify texture, to reduce tendency to syneresis, and to improve wear. When the color content does not vary significantly between shades, it is not necessary to use a filler to maintain the percentage of solids at one value, but if an effect on texture is noted some adjustment should be made. Fillers such as talc or filler levels that excessively soften, destabilize, or cause the sticks to become brittle should be avoided.

Fine particle size mica is often incorporated into cream (nonpearly) shades to reduce oiliness and improve wear. The spherical fillers discussed in the section on foundation are used to improve feel during application.

Lipid Base Materials

Apart from the color, the quality of the lipstick during manufacture, storage, and use will be determined for the most part by the composition of the fatty base. This quality is largely concerned with the rheology of the mixture at various temperatures. For instance, during manufacture (usually while warm) it must be possible to mill and grind the mass and to pour and mold it while holding the insoluble colors evenly dispersed without settling. In the molds it must set quickly with good surface and good release properties. During shelf life and usage life the stick must remain rigid and stable, and generally in good condition. In use the stick must soften sufficiently in contact with the lips and be sufficiently thixotropic to spread on the lips to form an adherent film that will not smear or transfer to cups or glasses.

Bromoacid Solvents

Many of the normal fatty materials that are used in the base are too non-polar to dissolve the dyes, so it is convenient to consider first those ingredients that do have solvent properties for eosin, if they are to form some part of the base. To solubilize the low amounts of bromoacid dyes currently in use, liquid fatty alcohols, dipropylene glycol, highly polar esters, or, to an extent, castor oil can be used.

Table 26.2 details the solubility of eosin in a number of fatty or lipophilic materials. In general terms, polar vegetable oils have the greater solvent power for eosin but may be unstable to oxidation. Mineral oils are more stable but are poor solvents.

Table 26.2 Solubility of Eosin

Solvent	% Solubility @20 °C
Castor oil	0.20
Cocoa butter	0.35
Diisopropyl adipate	1.40
Dipropylene glycol	2.00
Isopropyl myristate	0.20
Oleyl alcohol	1.00

Castor Oil

Castor oil is a traditional material for lipstick bases due to many useful properties. It acts as a solvent for bromoacid; its high viscosity, even at elevated temperatures, and its tack make it an excellent vehicle for pigment suspension and milling. Other properties include the oiliness that contributes to gloss and emolliency, although excessive amounts cause drag during application and could create an unpleasant heavy, greasy feel. Castor oil is also an excellent solvent for the waxes that give structure to lipsticks and yielding sticks that have a fine crystalline structure, good stability, and resistance to breakage. As much as 60% has been used, despite its unpleasant taste and potential for rancidity. Use of a high quality grade of castor oil will minimize odors, allowing the formulator to take advantage of the low cost of the material.

Liquid Fatty Alcohols

Liquid fatty alcohols are good solvents for the polar waxes often incorporated in lipsticks and are also solvents for bromoacids. Branched chain alcohols, such as isocetyl, isostearyl, and octyldodecyl, are preferred to oleyl alcohol for their lower odor and lack of tendency to rancidity. Liquid fatty alcohols contribute to slip during application and act as co-solvents between polar and nonpolar materials in formulations.

Esters

Esters of many structures and molecular weights are components of lipstick bases, including linear and branched alkyl esters of mono-, di-, and tribasic fatty acids, short and long chain-length acid esters of fatty alcohols, mono-, di- and triesters of glycol or glycerol, and dimer or trimer esters. The higher molecular weight esters, such as triisostearyl trilinoleate, triisocetyl citrate, polymerized vegetable oil, tridecyl trimellitate, isostearyl stearoyl stearate, glyceryl triacetyl hydroxy stearate, polyglyceryl isostearates, and so forth, act as partial or complete replacements for castor oil. The lighter esters, including isopropyl isostearate, caprylic/capric triglyceride, octyl palmitate, octyl hydroxystearate, acetylated lanolin alcohols, and coco caprylate/caprate, provide a lighter feel and increased slip. Lactate esters impart a slippery yet nongreasy feel.

A major criterion for the acceptability of any mixture of emollient oils is solvency for the formula waxes in both the molten and the solid state. Crystal structure of the mass should be fine and homogeneous, exhibiting no "sweating" as temperature varies up to 50 °C.

Mineral Oil

Mineral oil has been used to provide a glossy surface to the sticks and to the material deposited on the lips. Highly purified hydrocarbons are available for formulators who wish to avoid the negative connotations the name "mineral oil" carries of greasiness and "petroleum-based." When adding hydrocarbons to generally polar lipstick formulations, the proper choice of co-solvents must be made to ensure stability.

Waxes

Waxes are included in lipstick bases to provide the high melting points or the hardness that are required to give satisfactory molding properties, that is, quick setting and good release with a glossy surface and a rigid stick. This function is generally fulfilled by the inclusion of waxes or waxlike materials at levels between 8% and 15% of the formulation.

Carnauba Wax

Carnauba wax is a very hard vegetable wax used for raising the melting point, imparting rigidity, hardness, and gloss, and providing contraction properties in the molding process.

Candelilla

Candelilla is another hard vegetable wax serving the same functions as carnauba wax, but it has a lower melting point and is less brittle.

Amorphous Hydrocarbon Waxes

Amorphous hydrocarbon waxes in mineral oil, for example ozokerite or ceresin, give a short-fibered texture to the product and improve three-dimensional stability.

Microcrystalline Waxes

Microcrystalline waxes are used to modify the rheology of the product, increasing mass release without lowering melt point. Microcrystalline waxes also promote a more stable structure with lower shrinkage, which has no transition point below the solidification temperature, thus tendency to syneresis is less. Excessively high levels can cause tackiness and poor mold release properties.

Beeswax

Beeswax is the traditional stiffening agent for castor oil; it can produce a grainy and dull effect or contribute to oil exudation, if used in large quantities.

Cocoa Butter

Cocoa butter might be thought of as an ideal material owing to its sharp melting point just below the human body temperature, which makes it so useful in other products. However, there is a definite tendency to cause a "bloom" of waxy material on the stick surface as with chocolate.

Hydrogenated Vegetable Oils

Hydrogenated Vegetable Oils are waxlike materials that are more solid and less prone to rancidity than the unhardened oils. Of particular interest is hydrogenated castor oil, a hard high melting wax with good solvency in polar oils. Some other softer materials will be found to be of use in lipstick manufacture.

Lanolin, Lanolin Oil, and Lanolin Absorption

These bases are very useful ingredients up to about 10% by virtue of their emollient properties. They have good solvent properties and act as binding agents for the other ingredients, tending to minimize sweating and cracking of the stick, acting as plasticizers, and wetting out the pigments. Lanolin oil acts as a high viscosity carrier with good wetting properties for the pigments and provides the tack needed for adhesion to the lips. Due to reports of sensitization, a scare over pesticide residues, strong odor, and bitter taste, the use of lanolin has declined. Highly purified esters derived from lanolin sterols offer many of the advantages in a "cleaner" product.

Petroleum Jelly

Petroleum jelly and the more viscous *paraffin oils* may be used to adjust consistency, to act as lubricants, and to improve spreading properties. Large amounts tend to impair the adhesion properties and can be difficult to solubilize in a polar base.

Polyethylene

Polyethylene is used to raise the melt point and to improve high temperature stability. Polyethylene can only be incorporated into formulations having a significant level of nonpolar oils to act as solvents. Bulk must be heated above 90 °C to dissolve the polyethylene; this may contribute to degradation of other formula raw materials. Synthetic high molecular weight fatty acids and alcohols ($> C_{22}$) also improve high temperature stability and are easier to solubilize in polar oils than polyethylene.

Organically Modified Silicones

Organically modified silicones, either waxes or fluids, are used in lipstick formulation for their slip, light feel, and detackifying properties. Polar low molecular weight esters are used as co-solvents between the silicones and organic waxes to achieve compatibility.

From the foregoing description of the properties of the various materials it will be seen that no one or two materials are able to provide all the properties and qualities required in a lipstick; this serves to explain the almost invariable complexity of lipstick formulations, which is evident in the examples given below.

ADDITIONAL BASE INGREDIENTS

Wetting Agents

Wetting agents, generally low HLB surfactants, are used to improve pigment wetting and dispersion, particularly that of the inorganic pigments. Lecithin is another possible component that acts as a dispersing agent for pigments, in addition to facilitating the application of the lipstick and improving the adhesion to the lips.

Antioxidants

Antioxidants are incorporated into lipstick formulations to slow the development of rancidity of the waxes and oils. BHA, BHT, propyl gallate, rosemary extract, and citric acid are examples that are available from suppliers in pure form or as ready-made combinations. Tocopheryl acetate and ascorbyl palmitate are also used; however, stability at the prolonged high processing temperatures found in lipstick manufacture is questionable.

Antimicrobials

Antimicrobials are not routinely required. The anhydrous nature of most lipstick formulations is not a hospitable environment for microbial growth; the parabens often will be found to adequately preserve lipstick formulations.

Perfumes

Perfumes require special attention because they are frequently used in relatively high amounts to ensure consumer acceptance and freedom from irritation. Perfumes selected should mask the fatty odor note of the base and should be nonirritating to the lips. Since the consumer is likely to taste the perfume in the mouth as well as perceive the aroma, the flavor must be considered as well as the odor. Perfumes should be stable and compatible with the other constituents of the lipstick base. The preferred perfumes are of the light floral or light sophisticated type, with no single essential oil predominating.

FORMULATIONS

The following examples illustrate some of the many lipstick formulations in existence. The preparative procedures follow the pattern described on p. 556 for the Manufacture of Lipsticks.

Formula 26.9 is a low-cost frosted lipstick made with a high level of castor oil:

Formula 26.9

Ingredients	%
Candelilla wax	6.00
Carnauba wax	3.00
Ozokerite	4.00
Paraffin (mp 140)	2.00
Beeswax	6.00
Lanolin oil	6.00
Octyldodecanol	10.00
BHT	0.05
Mica and titanium dioxide	7.00
Castor oil	39.50
D&C Red No.7 Calcium lake	1.50
D&C Red No.6 Barium lake	1.50
Iron oxide, red	0.75
Castor oil	12.50
Fragrance	0.20

Formula 26.10 is a "mood lipstick," containing only a low amount of pigment to create a blue-green stick tone in combination with a bromoacid dye to stain the lips a red tone upon application.

Formula 26.10

Ingredients	%
Castor oil	
Candelilla wax	7.70
Carnauba wax	2.30
Ozokerite	2.00
Microcrystalline wax	4.00
Caprylic/capric triglyceride	25.00
Octyldodecanol	6.00
Methylparaben	0.20
Propylparaben	0.10
BHT	0.05
Castor oil	3.00
D&C Red No. 21	0.30
FD&C Yellow No. 5 Aluminum lake	0.10
FD&C Blue No. 1 Aluminum lake	0.05

Formula 26.11 is a glossy formulation, cream shade, that illustrates the use of light oils to lessen tack and provide better slip during application. Isostearyl stearoyl stearate is a viscous oil with good wetting and wax solvency properties but is more stable than castor oil.

Formula 26.11

Ingredients	%
Castor oil	35.00
Carnauba wax	2.10
Candelilla wax	7.00
Ozokerite (m.p.75–77 °C)	1.80
Microcrystalline wax	3.50
Caprylic/capric triglyceride	18.50
Octyldodecanol	6.00
Isostearyl stearoyl stearate	10.00
Hydroxylated lanolin	1.00
Methylparaben	0.20
Propylparaben	0.10
D&C Red No. 7 Calcium lake	1.25
D&C Red No. 6 Barium lake	1.25
Castor oil	8.30
Mica (<15 m)	4.00

Formula 26.12. Matte lipsticks, which although still somewhat emollient, have a high pigment/filler load and remain in fashion. The high solids level results in a film that scatters light in all directions, creating the matte effect. Fillers, such as spherical silica, nylon, polymethylmethacrylate, bismuth oxychloride, hydrophobically modified starch, and so forth, contribute to the solids content, yet as in pressed powders contribute to slip during application.

Formula 26.12

Ingredients	%
Carnauba wax	1.80
Candelilla wax	7.00
Ozokerite, (m.p. 75–77 °C)	2.00
Microcrystalline wax	2.50
Isostearyl stearoyl stearate	15.00
Castor oil	8.60
Triisostearyl trilineolate	1.00
Isononyl isononanoate	10.00
Octyldodecanol	7.00
Hydroxylated lanolin	1.00
Methylparaben	0.20
Propylparaben	0.10
D&C Red No. 7 Calcium lake	3.80
D&C Red No. 6 Barium lake	2.40
FD&C Blue No. 1 Aluminum lake	0.60
Castor oil	22.00
Silica, spherical 2–5m	1.00
Nylon-12	5.00

Formulas 26.13 and 26.14

Ingredients	26.13 %	26.14 %
Synthetic wax	6.00	6.60
Ceresin	4.00	4.00
Paraffin	3.00	3.00
Isododecane	10.00	10.00
Cetyl acetate and acetylated lanolin alcohol	5.00	5.00
Methylparaben	0.30	0.30
Propylparaben	0.10	0.10
BHA	0.10	0.10
D&C Red No. 7 Calcium Lake	4.00	3.00
FD&C Yellow No. 5 Aluminum Lake	3.00	—
Titanium dioxide and mica	5.00	—
Titanium dioxide, mica, and iron oxide	3.00	—
Bismuth oxychloride	10.00	15.00
Cyclomethicone	41.50	40.40
Isostearyl trimethylolpropane siloxy silicate	5.00	5.00

Formula 26.15

Ingredients	%
Castor oil	6.20
Octyl palmitate	10.00
Carnauba wax	4.00
Ceresin, (m.p. 80 °(C)	10.00
Microcrystalline wax	6.00
Cyclomethicone (D_5)	42.00
Dimethiconol beeswax	4.00
Methylparaben	0.20
Propylparaben	0.10
D&C Red No. 7 Calcium lake	3.50
D&C Red No. 6 Barium lake	0.50
Mica and methicone	7.50
Bismuth oxychloride	6.00

Manufacturing Procedure: Predissolve the dimethiconol beeswax in the cyclomethicone in a closed container by stirring at 50–55°C. In a sealed kettle, combine the dimethiconol beeswax solution and the remaining waxes and oils. Heat to 85°C with stirring. Add the pigments. Mill with a high-speed agitator until a fine grind is obtained. (Alternatively, the lakes and any inorganic colors can be milled into the octyl palmitate using a three-roll mill before addition to the batch. Some type of homogenizer will still be required to disperse the mica and BiOCl.) When pigment is dispersed, cool to 70°C and fill into hermetically sealed packaging.

Formulas 26.13 and 26.14 (from Ref. 1). Transfer-resistant lipsticks are formulated similarly to stick eyeshadows, having 40–50% volatile oils, which evaporate following application. The oils used are the volatile cyclomethicones and hydrocarbons, generally in combination with lighter esters. Silicone-based film-formers have been added to increase the film's removal resistance, while offering the desirable characteristics of flexibility and softness. Care must be taken that packaging utilized be hermetically sealed and be compatible with the formulation, since hydrocarbons and light esters will attack many plastics. Surface-treated pigments may be added to increase the amount of solids that can be wet into the systems. The deposited pigment/wax film is somewhat dry but does not smear, feather, or bleed, and will remain on the lips far longer than conventional formulations. While no formula may be totally "transfer-proof", many will not transfer to a cup or saucer and leave little trace when skin is kissed. The disadvantage of these formulations is that they offer no emolliency and, under low humidity conditions, dry out the lips.

Formulas 26.16 and 26.17 are conventional anhydrous formulations that moisturize the lips by providing an occlusive barrier, preventing water vapor loss. A more active approach to lip treatment is the incorporation of water-soluble humectants [2] to bind water or the formation of a water in oil emulsion stick [3] to actually add moisture to the lip surface.

Formula 26.16 (Ref. 2)

Ingredients	%
Castor oil	3.10
Polybutene	0.64
Isopropyl palmitate	9.28
Caprylic/capric/adipic triglycerides	2.02
Candelilla wax	7.59
Medium-chain triglyceride oil	1.65
Cetyl ricinoleate	10.50
Polyglyceryl-3 beeswax	3.26
Ozokerite	2.88
Lanolin oil	2.00
Carnauba wax	0.46
Glyceryl monostearate	2.77
Propylene glycol and glyceryl oleate 1:1	4.70
Lecithin	1.03
Ascorbyl palmitate	0.50
Propylparaben	0.10
Colorants	30.00

Formula 26.17 (Ref. 3)

Ingredients	%
Castor oil	19.50
Isopropyl palmitate	11.60
Caprylic/capric/isostearic/adipic triglyceride	7.00
Lanolin	7.00
D&C Red No. 21 Aluminum lake	7.00
Candelilla wax	6.60
Propylene glycol myristyl ether acetate	6.00
Caprylic/capric triglyceride	5.80
Glycerol	5.00
Water	5.00
Titanium dioxide	4.70
Beeswax	4.10
Monoglyceride	3.50
Lanolin oil	2.50
Ozokerite	2.50
Lecithin	1.00
Polybutene	0.80
Carnauba wax	0.40

MANUFACTURE OF LIPSTICKS

Lipstick manufacture is by no means a simple operation. The method employed will depend to some extent on the formulation and the plant available.

In general, the manufacture of lipsticks consists of three stages: (1) the preparation of component blends, that is the wax/oil blend and the color grind; (2) the blending of these intermediates to form the lipstick mass; (3) the molding of the lipstick mass into sticks.

Preparation and Blending

The colors, that is, the pigments and lakes, are blended separately using a high-speed mixer such as a Cowles dissolver with one or more of the viscous oils in the base and then milled to a fine grind (<10 m) using a three-roll mill or media mill.

The object of the operation is to produce a completely homogeneous dispersion of colorants conducive to the preparation of a smooth stick that will not be perceived as gritty when applied to the lips. As received, the dry colors are somewhat agglomerated and tend to be difficult to wet into the oils, so it is necessary to employ some type of milling or grinding process. A variety of mills—ball mills, sand mills, roller mills, colloid mills, edge or end runner mills, and so forth—have been used. It is desirable that the portion of the base used should be a viscous liquid having some tack during the milling to

provide sufficient shear during the process. Any soluble dyes are first blended with the dye-solvent materials, using heat if necessary to achieve solution.

The remainder of the base materials, for example, the high melting waxes that may not have been used in the dye or pigment blends, are melted and blended together while stirring with a propeller mixer, often at 85–100 °C to ensure complete dissolution of the waxes. Temperature is then lowered to 75–85 °C to add the color grind and, finally, any pigments not requiring milling. In order to secure an intimate mix a final milling or homogenization operation may be performed. If at all possible, the bulk should be transferred to a jacketed closed vessel in which it can be kept fluid and stirred gently while sufficient vacuum is applied to remove all occluded air. When the air has been removed, vacuum is shut off, the mass is stirred and the perfume and any other heat-sensitive materials are added and mixed thoroughly. Otherwise, prolonged gentle agitation of the melt is necessary to remove entrapped air, which can result in degradation of the waxes and oils.

Vacuum processing of the lipstick melt facilitates dispersion of pigments by removing the film of adsorbed gas on the pigment particles, which otherwise acts as a barrier and causes incomplete wetting. It has been established elsewhere that petroleum jelly, for instance, will dissolve 10% air by volume at 90 °C but only 5% at 20 °C. If, therefore, the mix has been held at high temperature and allowed to absorb its full quota of air and then cools, the air is not released until the viscosity of the mass is too great to allow it to escape completely, and it may collect around the pigment particles, displacing the oil and giving the effect of incomplete wetting.

Therefore the manufacture of lipsticks should be conducted at the lowest temperature convenient for the process, and it is very desirable that when mixing is complete, the mixture should be transferred to a jacketed closed kettle in which it can be kept fluid and stirred gently while sufficient vacuum is applied to remove all occluded air. When the air has been removed, the vaccum is shut off, perfume is added (if present in the formulation), and the mass is mixed thoroughly.

The mass is then ready for molding immediately or can be set into blocks that are stored and molded as required.

Molding

When required, the lipstick mass is gently remelted in a small jacketed pan and agitated slowly for about 30 minutes, in order to allow any entrapped air to rise to the top and thus prevent pinholing of the finished product. The molten mass is then run into molds for casting.

Molds are usually filled to excess to prevent the formation of a depression in the center of the stick. After they have been allowed to stand, to allow

this excess to congeal, the latter is scraped off and the mold is then carefully cooled to allow the mass to set, without overcooling, which would delay the removal of the stick from the molds.

The molds are made of brass or aluminum. They may be of the vertical split type (with a split down the center to allow for the easy removal of the sticks) or the automatic ejection type. A cooling table or cabinet is required with the split molds. With formulations having a set point of 70 °C or above, a preheating device may be useful, which can then raise the temperature of the molds to about 40 °C before filling with the lipstick mass, thus avoiding "flow marks," which would otherwise be visible on the molded stick. With the water-jacketed automatic ejection mold, a cooling cabinet is unnecessary. The jacket is filled with warm water prior to pouring the lipstick mass, and then the cold water is introduced and kept running to chill the lipstick mass. When cooled, the molds are opened and the sticks are pushed out automatically or with a rubber-covered finger.

It has been stated that no type of automatic ejection mold (whether air-cooled or water-cooled) will produce a good "bullet"-shaped stick because a small ring or ridge is left near the tip of the stick caused by the thickness of the metal edge of the ejection plunger. It is considered that such molds are best for the wedge-shaped stick. After molding, the sticks can be stored for up to a week before being filled into the lipstick holders, after which they are subjected to a procedure known as "flaming," in which the lipstick is passed rapidly through a small gas flame to melt the surface layer in order to remove any surface spots and to produce a bright, smooth, and glossy surface.

In large plants the procedure is fully mechanized. An example of a totally automated lipstick filler is a rotating table with stations that perform the successive steps involved in producing a finished lipstick: filling in the inverted position, chilling, remelting the bottom or double pouring to fill the shrinkage hole, chilling, placing the cup of the case onto the stick, adjusting to the upright position, flaming, swiveling the stick down, and capping.

LIP BALMS AND GLOSSES

The lip balm is used not for decoration but for protection against exposure to cold, in winter or subarctic conditions. The requirement is simply for a fairly substantial, flexible, adherent, moisture-resistant film on the lips; there is no need for staining dyes and hence none for dye-solvent materials. The base can be made largely from mineral oils, jelly, and waxes, but it is necessary to include a proportion of a more hydrophilic material to promote adherence, perfume blending, and general properties. In some cases a small amount of

antiseptic can be added, and occasionally some users will prefer a colored balm, in which case the color is provided by a small amount of inorganic or organic pigment

A suitable base is given in Formula 26.18.

Formula 26.18

Ingredients	%
Paraffin wax	30.0
Petrolatum	35.0
Mineral oil	20.0
Beeswax	15.0

A lip balm that is used as a decorative item has been identified in recent years as a lip gloss. This periodically popular item can be applied to the lips without other makeup or over the normal lipstick. Lip gloss preparations are softer than conventional lipsticks or are fluid, so packaged in swivel-up cases, vials with sponge applicators or roll-on applicators, or pots. These compositions may also contain a pearl pigment to confer a transparent sheen in addition to the normal gloss.

Formula 26.19

Ingredient	%
Glyceryl tribehenate	5.0
C18–36 Acid triglyceride	5.0
Mica and titanium dioxide and iron oxide (80–150 m)	8.0
Lanolin oil	8.0
Triisostearyl citrate	74.0
Perfume, antioxidant, preservative	q.s.

Procedure: Melt waxes with the oils. Disperse the pearlizing agent with low shear and de-aerate at 65 °C. Fill off at 50 °C into pots.

Formula 26.20

Ingredient	%
Polybutene	30.0
Lanolin oil	70.0
Perfume, antioxidant, preservative, flavor	q.s.

BLUSHERS

INTRODUCTION

Rouge is one of the oldest types of makeup preparation used to apply color to the cheeks. The Hittites used cinnabar for this purpose, the ancient Greeks colored their cheeks with a root, and the Romans were known to use a seaweed to impart a rosy tint to pale cheeks.

In Elizabethan days, red ochre, vermilion, and cochineal were used as rouge, as well as extracts of sandalwood and brazilwood. Cochineal was still the standard material for rouge in the eighteenth century. In the late nineteenth and early twentieth centuries liquid rouge made from ammonia and carmine was popular, while in theatrical rouges the red pigment carthamine and the aluminum lake of the dye obtained from brazilwood were extensively used to enhance the facial coloring of actors under the glare of footlights on the stage.

In the early 1920s liquid rouges still consisted of carmine and ammonia, whereas grease rouges were composed of carmine dispersed in a tallow and ceresin base. Also available was dry rouge, prepared by mixing carmine solution and eosin with pumice, chalk, and gum arabic. Another preparation employed alloxan in a wax base. The precursor of the modern compact rouge at the beginning of the twentieth century was a small book of thin paper leaves coated with various shades of red and white powder, which were detached and rubbed on the cheeks.

The modern description is "blusher." If a distinction had to be made between the two terms, it could be said that a rouge produces a bright red color, whereas a blusher produces a more subtle effect. The preparations are available in anhydrous creams and pressed powders, of which the pressed powder blush is the most popular. Emulsion blushers are sometimes made but offer no special benefit for the extra efforts required to formulate a stable product that can be manufactured consistently. Pigments used in blushers are the inorganic pigments and the organic lakes.

Pressed Powder Blush

Compact rouge differs from an ordinary compact powder in being more highly tinted. The desirable properties of powder blush are therefore virtually identical with those of compact powder foundations. The finished product must be smooth and free from grittiness and should be easy to apply; it should have good adhesion to the skin and provide good covering power. These products can be highly tinted and the undispersed pigment or filler is conspicuous if not adequately blended, so it is essential that component colors are distributed evenly throughout the product. Blushers should have some opacity so as not

to show settling into pores or other skin imperfections, yet not be so opaque as to look artificial.

Powder blushers may thus be manufactured broadly along the lines discussed for compact powders. The component raw materials must be very finely divided to facilitate their intimate blending as a prerequisite to a uniform distribution of component colors. The constituents are, therefore, intimately mixed and simultaneously ground in hammer mills or attritor mills after being blended in ribbon mixers. This operation is carried out in the absence of large quantities of liquids, though the presence of a little water or oil can be used to achieve better color development. The liquid binders at levels from 3% to 10%, frequently containing a wetting agent to enhance color development, are sprayed into the powders while they are being mixed at high intensity. Any pearlaceous pigments are added after the high-energy milling step.

The raw materials used in the manufacture of powder blush are the same as for powder foundation: talc, mica, sericite, kaolin, calcium carbonate, magnesium carbonate, titanium dioxide, bismuth oxychloride, inorganic oxides, specialty fillers, certified colorants, and perfumes.

Metallic stearates are also essential components of powder blushers and improve the adhesion of the products to the skin. They are used alone and in combination with other dry binders extensively for powder blushers in amounts ranging between 3% and 10%.

Powder Blush Formulation

Typical powder blusher formulations are given in Formulas 26.21 and 26.22.

Formula 26.21 A Matte Shade

Ingredient	%
Talc (4–6 m)	48.00
Sericite, methicone	20.00
Magnesium myristate	3.00
Calcium silicate	0.20
Bismuth oxychloride	6.00
D&C Red No. 30 Lake	1.00
Iron oxide, yellow	0.50
Iron oxide, red	0.25
Methylparaben	0.20
Propylparaben	0.10
Imidazolidinyl urea	0.25
Dicapryl malate	3.00
Dimethicone (10 cs)	2.00
Polyglyceryl-3 diisostearate	0.50

Formula 26.22 A Frost Shade

Ingredient	%
Talc (4–6 m) and methicone	37.75
Sericite and methicone	20.00
Magnesium myristate	5.00
Polyethylene (6 m)	2.00
Calcium silicate	0.20
Bismuth oxychloride	10.00
D&C Red No. 30 Lake	1.00
Iron oxide, red	1.00
Methylparaben	0.20
Propylparaben	0.10
Imidazolidinyl urea	0.25
Dicapryl malate	5.00
Dimethicone	3.00
Polyglyceryl-3 diisostearate	0.50
Mica and iron oxides	15.00

The proportion of coloring matter may vary from 1.5% in the case of the lighter shade to approximately 6% with the deeper shades.

Anhydrous Blush

Wax-based blushers are in many respects similar to cream powder foundations, being formulated to have a nongreasy, dry feel, yet apply with adequate slip and spreadability.

Formula 26.23

Ingredient	%
C18–36 Acid glycol ester	12.10
Glyceryl tribehenate	1.90
Octyl palmitate	37.40
Caprylic/capric triglyceride	3.00
Polyglyceryl-3 diisostearate	0.50
Methylparaben	0.20
Propylparaben	0.10
Talc (Italian)	18.00
Bismuth oxychloride	15.00
Mica (< 15 μm) caprylyl silane coated	12.00
Color grind: 50% D&C Red No. 6 Barium lake in caprylic/capric triglyceride	2.00

Manufacturing Procedure: Color grind is prepared in advance using a three-roll mill. Combine waxes, color grind, and oils. Heat to 80–85 °C, stirring until homogeneous. Add the talc, mica, and bismuth oxychloride. Agitate with a high-speed mixer until no agglomerates remain. Fill into pans at 70 °C.

EYE MAKEUP

INTRODUCTION

Eye makeup too has been used for thousands of years. The accepted eye makeup used by the women of many ancient civilizations was a black coloring, kohl, based on antimony trisulfide. In addition to kohl, Egyptians used malachite to confer a green tint, while Indian women tinted their eyelids with an antimony-based material. Chinese and Japanese women used Peruvian bark for eye makeup, and Phoenician women lengthened their eyebrows with a black paste composed of gum arabic, musk, ebony, and powdered black insects.

Big eyes were also considered a mark of beauty, and it was the practice of women of these ancient civilizations to make their eyes appear larger and shinier.

Modern eye preparations include mascara, eyeshadow, and eyebrow pencils. These preparations will now be discussed under their respective headings.

In the Code of Federal Regulations, [Title 21, part 74] the use of coal tar (certified organic) colors in preparations to be applied in the area of the eyes is restricted to those colors for which approval for eye area use is specifically mentioned. The area of the eyes is defined as "the area bounded by the supra-orbital ridge and the infra-orbital ridge, including the eyebrow, the skin below the eyebrow, the eyelids, the eyelashes, the conjunctival sac of the eye, the eyeball and the soft areolar tissue that lies within the perimeter of the infra-orbital ridge." Thus defined, the "prohibited area" extends from the top of the eye socket to the top of the cheekbone.

Thus, in the United States, inorganic pigments and three certified organic lakes, FD&C Blue #1, FD&C Yellow #5, and FD&C Red #40, may be employed in eye makeup compositions. D&C Green #5 dye is also permitted, but, being soluble, is not useful in pigmented products.

Black pigments used in eye makeup preparations are now restricted to black iron oxide (Fe_3O_4). This is sometimes used in conjunction with ultramarine blue to impart blue-black shades. Red iron oxide (Fe_2O_3) and yellow iron oxide (FeOOH) are combined with black iron oxide to produce brown shades. For bluish shades ultramarine blue is employed, while for green shades chromium oxides and for red shades, carmine, the aluminum lake of cochineal, are used. White pigments such as titanium dioxide and bismuth oxychloride may also be sometimes included to lighten shades. Titanium dioxide and iron oxide coated mica pigments are used in pearly shades.

A wider range of pigments, including carbon black, D&C Red No. 6, and D&C Red No. 7 Calcium lake, are permitted for eye area use in the European Union and Japan. Efforts to reinstate approval for carbon black are to date (1999) unsuccessful.

MASCARA (EYELASH COSMETIC)

Mascara is a pigmented preparation for application to the eyelashes to lengthen, thicken, and curl the lashes. Mascara is marketed almost exclusively in vials and must possess the following characteristics:

(1) It must be capable of easy and even application with an adequate deposit.
(2) It must be long-wearing, resistant to flaking or smudging.
(3) It must not cake or clump, causing the eyelashes to stick together.
(4) It must not dry too rapidly to interfere with the evenness of the application, but it should nevertheless dry fairly rapidly and be reasonably permanent once applied.
(5) It must be neither toxic nor irritating.
(6) It must be resistant to repeated microbial insult.
(7) It must be easily removed.

Mascaras and eyeliners consist of one or more film-formers, pigment, and the vehicle that mostly evaporates to allow the film to set. Packaging is critical to the performance of mascaras, because the interaction of the rod, the brush, and the wiper help determine the amount of deposit and the degree of separation of the lashes. Narrow rods with small brushes give a light, natural deposit, while thick rods and big brushes will deposit greater amounts of product on the lashes.

Cake (Block) Mascara

Cake mascara was a very common form of product but is no longer in use due to the inability to maintain a microbiologically pure product during repeated use with water.

Formula 26.24

Ingredients	%
Stearic acid	27.0
Triethanolamine	12.0
Beeswax	30.0
Carnauba wax	50.0
Iron oxide	15.0

Procedure: The various components are melted, mixed, and then cast or extruded to the proper form, or after mixing they may be milled and passed through a warm plodder, after which the mascara strip is cut to the desired lengths.

Three types of formulations are currently in use:

- anhydrous, solvent-based suspension: waterproof, but not smudgeproof; difficult to remove
- water in oil emulsion: also waterproof, not smudgeproof; some formulations can be removed with soap and water
- oil in water emulsion: "water-based"; if the film is sufficiently flexible, can be "flake-proof" and smudgeproof. Water resistance can be achieved with the addition of emulsion polymers, that is, acrylics, polyvinyl acetates, or polyurethanes.

Anhydrous Mascara

These formulations are composed of pigment suspended in hydrocarbon solvent gelled by organomodified clay and waxes. Upon evaporation of the solvent, the waxes act as the film-formers. Rosin derivatives can be added to strengthen the film.

Formula 26.25 (Anhydrous Mascara)

Ingredients	%
Petroleum distillates and quaternium-18 hectorite (gellant) and propylene carbonate	35.00
C_{10-13} isoparaffin	30.95
Polyethylene	11.50
Candelilla wax	5.00
Hydroxylated lanolin (plasticizer)	0.25
Pentaerythrityl rosinate	2.00
C_{10-13} Isoparaffin	2.00
Methylparaben	0.20
Propylparaben	0.10
Zinc stearate (gellant, tackifier)	1.00
Iron oxide, black	12.00

Manufacturing Procedure: Waxes and solvents are heated in a jacketed sealed kettle until homogeneous. Gellants are added and milled with high-speed agitation until homogeneous. Pigments are added and milled with high-speed agitation until dispersed. Batch is stirred slowly with counterrotation agitation or planetary agitation while cooling to 35 °C.

Water in Oil Mascara

The oil phase consists of hard, high melting waxes such as carnauba and candelilla, modified by flexible waxes with high melting points, including beeswax and ozokerite, dissolved in petroleum solvent and possible volatile

Formula 26.26 (W/O Emulsion Mascara)

Ingredients	%
Oil Phase	
Petroleum distillates, quaternium-18 hectorite and propylene carbonate	20.00
C_{10-13} isoparaffin	13.30
Lanolin acid	6.00
Iron oxide, black	8.00
Carnauba wax	4.00
Ozokerite	5.00
Candelilla wax	3.50
Beeswax	3.20
Propylparaben	0.10
Water Phase	
Water, deionized	10.00
Propylene glycol	6.00
Methylparaben	0.20
Ammonia (28%)	0.60
Acrylates copolymer (emulsion)	20.00
DMDM Hydantoin	0.10

Manufacturing Procedure: Premill pigment in dry form using a hammer mill once through an 0.027″ screen. In a sealed kettle, combine isoparaffin and lanolin acids. Heat to 60 °C until clear. Add gellant, milling until dispersed. Add pigment, milling until dispersed. Add remaining wax phase ingredients. Heat to 85 °C until homogeneous. Predissolve methylparaben in propylene glycol. Combine with water and ammonia in a sealed kettle, heating to 85 °C. Add water to oil while homogenizing. Maintain temperature and agitation for 5 minutes. Cool to 45 °C. Slowly add acrylate and preservative with counterrotation agitation. Cool to 30 °C. Drop batch.

silicone. Fatty acids are the oil-soluble portion of the soap to be formed in situ. The alkali used to neutralize the soap is often ammonia, which evaporates following application to leave behind a water proof film. Addition of an emulsion acrylate will strengthen the film and increase deposit.

Oil in Water Mascaras

Oil in water mascaras are generally anionic emulsions, often soap systems, with the pigment, suspending agents, and dispersants in the water phase. The waxes in the oil phase are the same as those used in the water in oil systems. Emulsion or solution polymers are often added to provide a strong film. The larger the wax phase, the higher the viscosity, and the greater the deposit achieved. Faster drying formulations will produce the curling effect as the lashes are held in a bent position while drying.

Formula 26.27 (O/W Emulsion Mascara)

Ingredients	%
Water Phase	
Water, deionized	45.32
PVP (dispersant)	2.00
Hydroxyethylcellulose (low viscosity)	1.00
Triethanolamine 99%	2.00
Methylparaben	0.30
Disodium EDTA	0.10
Iron oxide, black	10.00
Oil Phase	
Stearic acid, triple pressed	4.50
Glyceryl stearate	2.00
White beeswax	7.00
Carnauba wax	4.50
Hydroxylated lanolin	1.00
Propylparaben	0.10
Acrylates copolymer (solution)	20.00
DMDM Hydantoin 55%	0.18

Manufacturing Procedure: Charge water into a stainless steel jacketed kettle equipped with homogenizer and counterrotation agitation. Add ingredients in order, homogenizing at low speed until each is dissolved while heating to 75 °C. Following pigment addition, homogenize at high speed until dispersed. Combine ingredients of oil phase, heating to 85–87 °C. Adjust water phase temperature to 85 °C. Add oil phase to water phase while homogenizing. Maintain temperature and agitation for 5 minutes. Cool to 50 °C. Add acrylate slowly with counterrotation agitation. At 45 °C, add preservative. Cool to 30 °C. Drop batch.

EYELINER AND EYEBROW MAKEUP

Pencils are the most popular form of eyeliner. Suspensions or emulsions are also available, packaged in vials with the applicator brush attached to the cap.

Pencils

Pencils are manufactured by specialty contract manufacturers. In addition to eyeliners, eyeshadows, eyebrow makeups, lipliners, blushers, and concealers are offered in pencil form. Cosmetic pencils are produced by two techniques: molding and extrusion. Molded products are anhydrous combinations that are processed in the melted state and poured into premolded pencil shells. Principles of formulation are the same as those for any anhydrous system; waxes and oils must be compatible to avoid syneresis or waxy exudation during storage.

Formula 26.28 (molded poured eyeshadow/eyeliner pencil). Eyeliner should be slightly harder than eye shadow, by using higher percentages of waxes. Due to the volatility of cyclomethicone content, the cap for such a pencil must fit sufficiently tightly to achieve a seal.

Formula 26.28

Ingredients	%
Octyldodecyl stearoyl stearate	20–30
Candelilla wax	1–3
Beeswax	1–3
Carnauba wax	1–3
Ozokerite	1–3
Silica silylate	0.2–2.0
Lanolin acid	0.5–1.0
Propylene carbonate	0.3–1.2
Quaternium-18 bentonite	1–4
Iron oxide	5–30
Titanium dioxide	1–3
Mica	6–23
Bismuth oxychloride	0–25
Cyclomethicone (D_5)	15–25

Manufacturing Procedure: Eyeliner and eyebrow pencils are generally extruded. Waxes are melted, pigments are added, and the entire bulk is passed through a three-roll mill to disperse the pigments. In the melted state, the bulk is subjected to a high vacuum to dispel entrapped air, then passed through one or more high-pressure extrusion steps before being extruded through a single orifice to form the pencil lead. Both elevated temperature and pressure are used to soften the bulk to the point where it can be extruded; thus the wax content of these systems is much higher than that of poured products—up to 60% for hard eyebrow pencils.

Formula 26.29 (Extruded Eyeshadow/Eyeliner Pencil)

Ingredients	%
Japan wax	25.0
Beeswax	20.0
Ceresin	4.0
Carnauba wax	6.0
Glyceryl triisostearate	3.0
Hydrogenated palm oil	10.0
Hydrogenated vegetable oil	5.0
Pigment	17.0

The cosmetic chemist's responsibility for eye makeup pencils is limited to the evaluation of shade, texture, sharpenability, application, wear, and stability

of samples received from a contract manufacturer. When evaluating extruded systems, one must be aware that setup takes several weeks before the final hardness is reached. Only by experience can one develop the judgment to predict final performance in the short time often available.

Emulsion Eyeliners

Emulsion eyeliners are similar to mascara formulations, only lower in viscosity.

Formula 26.30 (O/W Emulsion Eyeliner)

Ingredients	%
Water Phase	
Water, deionized	55.10
PVP	1.00
Iron oxide, black	8.00
Butylene glycol	6.00
Hydroxyethylcellulose (medium viscosity)	2.00
Methylparaben	0.20
Potassium cetyl phosphate	1.50
Oil Phase	
Beeswax	5.50
Carnauba wax	3.50
Cetyl alcohol	1.00
Propylparaben	0.10
Polyurethane	14.80
Water, deionized	1.00
Diazolidinyl urea	0.20

Manufacturing procedure is identical to that of Formula 26.27, the oil in water mascara.

Eyeshadow

Pressed powder eyeshadow is the predominant form; the remainder are either cream or stick anhydrous systems containing significant amounts of volatile solvent to achieve long, creaseproof wear. Eyeshadows are chosen by their color, but their quality is judged by their application and wear. Application should be smooth, the feel on the delicate eyelid area should be light, and the deposit should be even. Assessment of wear is based on the amount of product remaining on the eyelid and lack of shifting; neither bald spots on the lid nor settling into the crease of the lid should be observed, ideally over an eight-hour day. The only true creaseproof eyeshadows are the anhydrous formulations having high levels of volatile solvent, which evaporates, leaving a tenacious wax/pigment film. Through the use of pigments treated

with compounds impervious to oil and the use of oil-absorbing materials, powder eyeshadows do wear well for 6–8 hours if the climate is not too hot and humid.

The ingredients used in powder eyeshadows are discussed in the section on pressed powder foundation. Eyeshadows have a higher variation in pigment content, up to 30%, to meet the wide range of shades needed. In addition, depending on fashion, the pearlaceous pigment level can be as high as 60%, a difficult composition to compress satisfactorily. Texture enhancers, which contribute to a soft feel, such as nylon, bismuth oxychloride, and boron nitride, are particularly useful in eyeshadow formulation due to the sensitivity of the eyelid.

Formula 26.31(a): (Compressed matte eyeshadow powder) The pigments are treated with a reactive perfluoro compound to make them impervious to water and oil; sericite is treated with magnesium myristate to promote adhesion.

Formula 26.31(a)

Ingredients	%
Talc and perfluoropolymethylisopropeth phosphate	37.0
Mica and magnesium myristate	30.00
Bismuth oxychloride	5.00
Zinc stearate	3.00
Boron nitride	5.00
Methylparaben	0.20
Propylparaben	0.10
Iron oxide, red, and perfluoropolymethylisopropeth phosphate	3.00
Iron oxide, yellow, and perfluoropolymethylisopropeth phosphate	4.70
Iron oxide, black, and perfluoropolymethylisopropeth phosphate	4.50
Dimethicone/10 cs	3.00
Octyl palmitate	3.00
Polyglyceryl-3 disostearate (wetting agent)	0.50

Manufacturing Procedure: The dry ingredients are combined with agitation in a twin shell, plough blade, or ribbon blender. The phase is pulverized once with a hammer mill (0.027″ screen). The oil phase is blended, then sprayed onto the powder while under high intensity agitation. Pulverization is repeated.

Formula 26.31(b): (Compressed high gloss eyeshadow powder) There is less need for specialty fillers to improve feel, because the platy pearl pigments have excellent slip and also adhere well to the skin, increasing duration of wear.

Other forms of anhydrous eyeshadows include sticks or creams, packaged in swivel-up cases, sealed jars, pencils, or vials. To achieve long wear, all contain a volatile solvent; thus dry out is a concern during storage and use. Even if

Formula 26.31(b)

Ingredients	%
Talc and magnesium myristate	21.05
Magnesium myristate	5.00
Polyethylene	2.00
Bismuth oxychloride	5.00
Iron oxide, red	1.00
Iron oxide, yellow	1.50
Iron oxide, black	1.50
Calcium silicate	0.15
Methylparaben	0.20
Propylparaben	0.10
Dicapryl maleate	12.00
Polyglyceryl-3 diisostearate	0.50
Mica and titanium dioxide and iron oxide	50.00

Manufacturing Procedure: The dry ingredients plus 20% of the mica-based pearl are blended and pulverized once through an 0.027″ screen. The oil phase is combined and is sprayed on while the bulk is being agitated. Pulverization is repeated. The remaining pearl is added with gentle agitation, and the batch passed through the hammer mill equipped with a "jump gap" (a "screen" having 0.25″ openings) to ensure homogeneity without breaking the pearl particles. Part of the pearl must be added to the pigment phase because there is not enough dry material in which to disperse the oil.

Formula 26.32 Creaseproof Stick Eyeshadow

Ingredients	%
Carnauba wax	4.50
Ceresin, (m.p. 75–77 °C)	12.00
Octyl palmitate	7.50
Manganese violet	7.50
Ultramarine blue	7.50
Bismuth oxychloride (matte)	20.00
Silica silylate	0.50
Polyglyceryl-3 diisostearate	0.50
Cyclomethicone	38.70
Methylparaben	0.20
Propylparaben	0.10

Manufacturing Procedure: The waxes and oils are combined in a sealed, jacketed kettle, equipped with a high-speed, high-shear mixer and heated to 85–87 °C. Pigments are added and the batch mixed at high speed until a good dispersion is achieved. Store in sealed containers until ready to fill. Remelt in a sealed kettle with agitation. Fill at 70 to 72 °C.

the component is adequately sealed, the product may dry out after opening by the consumer. The volatile solvent acts as a vehicle for the formula waxes and pigments, allowing smooth, even application, and then evaporates to leave behind a film that resists removal. As in transfer-resistant lipsticks, waxes and oils are chosen for their compatibility with the volatile solvent, usually cyclomethicone. Generally, light, low molecular weight polar esters act as good co-solvents for the silicones and waxes.

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3. Dunphy, P., Colored cosmetic stick, U.S. Patent 5,108,737, et al., assigned to Elizabeth Arden, div. of Conoco, April, 28, 1992.
4. Goldner, T., Cosmetic composition, U.S. Patent 4,431,673, et al., assigned to Revlon, February 14, 1984.

RECOMMENDED READING

Information on cosmetic pigments and dyes and their use in colored makeup preparations is scattered in the brochures of pigment suppliers, which should be consulted. The colorants are listed in the *INCI Dictionary* (CFTA, Washington, D.C.) as Color Additives (under Chemical Classes).

CHAPTER 27
Nail Polishes

INTRODUCTION

Nail polishes, like so many other cosmetic products, have been used since the very early ages. Egyptian mummies have been found with golden nails. Later on women polished their nails, to enhance their gloss, using a cloth and some fine abrasive powders such as pumice. They also used preparations consisting of a styrax benzoin gum/ether solution, shellac, beeswax, and other natural products derived from animals or plants.

As early as 1885, a solution of nitrocellulose in a mixture of alcohol and ether (nitrocellulose collodion) was reportedly used in the United States [1]. This new technology was further developed in the 1920s, as very large stocks of nitrocellulose (used in explosives during World War I) were left over. The film-forming properties of the nitrocellulose were first used in the automotive industry, where the production was delayed by the drying time of the paints used at that time. The fast-drying, glossy nitrocellulose lacquers became an answer to this problem.

At that point the first "nail lacquer" was formulated using the same principle. It was a clear, thin product, but it was an improvement over the slow-drying, sticky products the consumers used to apply. Later on rhodamines were added to give some color or tint to the clear products, but the lacquer obtained was still transparent and stained the nail. To resolve the transparency and staining problems, pigments (dyes precipitated on a mineral base) came into wider use.

From these early beginnings, changes were made slowly to reach the nail polish products we know today and which are reviewed in this chapter.

NAIL POLISH FORMATION

To understand better the formation of nail polishes, it is important to identify the qualities required for an acceptable nail polish and the defects that one has to avoid. As in any formulation, raw materials can then be selected to fulfill these requirements.

a) Innocuousness:
The raw materials used have to be harmless and should be part of a positive list of accepted raw materials (or exclude substances on the negative list) in the country in which it is marketed.

b) Wear:
Application of a nail polish takes a long time, and working women are unwilling to apply the product repeatedly. Thus the longer the nail polish will stay on the nail with an acceptable appearance, the better its acceptance. The parameters that will play a primary role in the wear properties are film-formation and adhesion on the nails. These objectives are met by using two main families of raw materials: film-formers to create the film and resins to promote the adhesion.

The nails are alive; they grow every day; they are in contact with many objects and surfaces; and they transpire water. To ensure good wear, the film formed on the nail has to be flexible enough to follow the growth of the nail but tough enough to resist the various destructive effects to which it is subject.

For this purpose a third family of ingredients identified as plasticizers is included to balance the properties of film-formers and resins.

c) Glossy Color and Appearance:
Colors and shades are obtained by using coloring agents that provide opacity but keep the nail polish glossy. For this purpose very finely dispersed powders that do not dissolve in the nail polish are used. They provide opacity but, because they are so well dispersed, will not adversely affect gloss. These powders are part of a fourth family, the color and nacreous pigments.

d) Application:
Nail polish has to be applied on the nails. After various attempts to find ways of applying nail polish (stickers, sprays, etc.), the choice of the formulators has been for decades to use a liquid nail polish and apply it with a brush. For this we have to introduce a fifth family of compounds that will be the vehicle of the former compound, that is, the solvents.

e) Dry-time:
Drying has to be as quick as possible but not too fast to avoid affecting the other properties (gloss, wear, etc.). These properties are affected by poor film-formation that will occur if the dry-time is too short, because the time allowed for molecules to rearrange themselves is too short. For these reasons the formulators must study both solvents and resins, and their interactions.

f) Stability:
Stability here refers to the physical and chemical stability of marketed nail polishes in their bottles. For marketing convenience, nail polishes are sold in glass bottles. Any defects of the liquid product will be immediately noticed.

Two major problems may affect the appearance of the liquid polish in the bottle. One is the settling of the heavy particles to the bottom of the bottle, where they will form

a layer of a different color than the nail polish. The other is called syneresis, in which an upper translucent layer of tinted solvents is formed on top of the nail polish. To prevent these undesirable phenomena, it is necessary to control the viscosity of the product by using a sixth family, the additives, especially viscosity modifiers.

g) Others:
Other qualities and properties of a nail polish are resistance to abrasivity, resistance to water, ease of removal, homogeneity of the film, trendy colors, marketing claims, and so forth. All these other properties may be obtained using the ingredient families described earlier, that is film-formers, plasticizers, resins, solvents, pigments and nacreous pigments, and additives (viscosity modifiers and suspending agents).

All these characteristics apply to colored nail enamels and related clear nail products, such as base coats and top coats. A base coat is a transparent, sometimes slightly tinted product applied to the nails before the colored nail polish. It must dry fast and not be diluted by the nail polish that will be applied on top of it, and it must be formulated to adhere to the nails. Its gloss is not the primary objective. A top coat is also transparent and sometimes tinted; it must also dry fast to avoid any dilution with the nail polish beneath it, but it must be formulated to be as glossy as possible. Here the adhesion to the nail is not a key priority.

RAW MATERIALS

FILM-FORMERS

A film-former is defined as the agent that forms the nonsticky, flexible, and glossy coat adhering to the surface of the nail after the solvents have evaporated. During the years many products have been used (styrax benzoin gum, shellac, waxes, etc.), but polymers rapidly became the first choice for this family of ingredients as they have shown properties, such as film toughness, gloss, and so forth without the defects of stickiness or dullness.

For film-forming, acrylic polymers or copolymers and cellulose esters are the best candidates, with a preference for cellulose esters such as cellulose acetate isobutyrate and, of course, the nitrate, which provide the best results. The last product, cellulose nitrate, better known as nitrocellulose, is indeed the most widely used polymer in nail polish formulations, as it gives an excellent film transparency. It has a very low solvent retention and a quick dry-time. The film obtained is hard and exhibits good water and abrasion resistance.

Nitrocellulose (NC) is an ester and is obtained by reaction of an acid with an alcohol. The acid is a mixture of nitric and sulfuric acid; the alcohol is one of the several hydroxy groups on the cellulose heterocycles. The simplified reaction is:

$$ROH + HNO_3 \rightarrow RONO_2 + H_2O$$

The cellulose used in this reaction is a natural product derived from wood or from cotton. It is a polymer formed by a chain of heterocycles, each of which had three free hydroxy groups (OH).

The nitration of this chain may affect one, two, or three of these available groups per glucopyranose unit. An important characteristic of the NC is its nitration level [2], also known as the degree of substitution. The degree of substitution is linked to the solubility of the NC: a low level of nitration (nitrogen content 11.5% to 12%) leads to solubility only in ketones and esters.

A second important characteristic of the NC is its chain length. This will play a very important role in the viscosity of the NC solutions and in the performance of the film after solvent evaporation. The shorter the chain, the lower the viscosity and the more brittle the film, while a long chain will give higher viscosities and softer films.

The NC manufacturers provide tables and references that will help the formulator in finding the right grade of NC. Generally, the most commonly used NC for nail polishes is soluble in esters (ethyl and butyl acetate) and is of a medium chain length (identified as E27 and E32 in Europe and RS 1/4s and 1/2s in the United States). In this nomenclature, E stands for soluble in esters and ketones (as opposed to the A grade, partially soluble in alcohol and soluble in esters and ketones) and 27 refers to the molecular weight (MW). A higher number leads to greater MW and chain length and higher viscosity. This nomenclature system is mainly used in Europe (France).

In the United States, 1/4s gives an indication of the viscosity, as it is the time that a given steel ball will take to fall in a given NC solution for a given distance. Everything being equal, longer time leads to higher viscosity (and thus greater MW or chain length). As an example, a 1/2s NC has a longer chain and a greater MW, and gives a higher viscosity and a softer film than a 1/4s NC.

PLASTICIZERS

Nitrocellulose forms a very bright and transparent film, but it is very tough and can be brittle. The nail plate is flexible and grows, and the film must adapt to this flexible, moving, and changing surface. The nail polish formulator has to include components that will make the film more flexible: the plasticizers. They must remain in the film; hence they have a very high boiling point. They must be compatible with the solvents and other components. Their migration within the film must be essentially absent, and finally they must be harmless.

As usual, the early formulators used natural products such as castor oil; but of these early products, only camphor is still used in the modern nail polishes. The most commonly used plasticizers today are synthetic and include: phthalates such as dibutyl phthalate, adipates such as dioctyl adipate [3,4], and citrates such as acetyl triethyl citrate [5].

RESINS

Polymeric resins remain as major components of the film after evaporation of the solvents. Depending on their chemistry, polymeric resins can be considered as plasticizing or softening agents, dry-time enhancers, secondary film-formers, gloss promoters, and nail adhesion improvers. Any polymer that remains in the dry film and improves film properties (film formation, evaporation of solvents, hardness, flexibility, resistance to abrasion, gloss, etc.) is commonly identified as a resin. The natural resins such as benzoin, dewaxed dammar gum, and so forth are no longer used. Instead the most commonly used families of resins are aryl sulfonamide resins, acrylic copolymers, vinyl esters, vinyl acetates/vinyl chloride copolymers, and polyesters.

The aryl sulfonamide resins are among the earliest and currently the most widely used ingredients, specifically the tosylamide/formaldehyde resin (TSFR.) Since its early use in the 1930s it has been very difficult to replace this resin as a result of the good characteristics that it imparts to the nail polish films (gloss, water, and wear resistance). However, TSFR is synthesized from a sulfonamide and formaldehyde. The low levels of unreacted formaldehyde, together with the free formaldehyde formed due to the degradation of the polymer, have caused sensitization in some individuals; and TSFR therefore may be a candidate for replacement, although it is generally considered as safe [6]. Many attempts have been made to replace this resin. The more successful replacements for TSFR include the polyester resins such as the phthalic anhydride/trimellitic anhydride/glycol copolymer, in combination eventually with sucrose derivatives such as sucrose acetate isobutyrate [7,8].

The choice of resins is critical. The formulator must consider various legal aspects (is the product accepted in all countries, or might any of its by-products be undesirable?) and the customers' requirements such as transparency, non-yellowing, brittleness/softness, and adhesion to the nails.

SOLVENTS

Solvents are liquids that allow a nail polish to flow and make it applicable. They also play a primary role in the dry-time of the film and in the characteristics of the dry film, as very small quantities of these solvents remain in the film [4].

The first criteria that these products must meet is innocuousness. All the solvents used in modern nail polishes belong to one of the categories of esters (ethyl acetate, butyl acetate, etc.), aromatics (toluene, xylene, etc.), alcohols (ethyl alcohol, butyl alcohol, etc.), or silicones.

Of this list, the most discussed as far as toxicity is concerned are the aromatics. Aromatics were banned in the United States after California issued its Proposition 65, California's Safe Drinking Water and Toxic Enforcement Standard. Toluene has been widely discussed since the 1987 meeting of the International Federation Societies of Cosmetic Chemists in Munich, where a Japanese team published a study on the damage that toluene can cause to the nail. They claimed that toluene causes splitting of the nails in layers but documented it only on dead nails. However, although aromatics are known to be very toxic by inhalation or skin penetration, the evidence that they may cause severe damage to the nail is sufficient to exclude aromatics from the majority of U.S. formulations. They are still present (with restrictions) in the beauty salon industries in the United States and in the retail industry in many other countries.

To conclude this discussion of aromatics, it should also be mentioned that they are not real solvents but act as diluents that can be blended, to a certain level, with a previously made solution of polymers in true solvents. Aromatics are not good solvents for the majority of the polymers used in nail polish, such as nitrocellulose, polyester, TSFR, and so forth.

Besides the aromatics, the esters are the most commonly used solvents in modern formulations. Alcohols are very often included with other raw material, such as nitrocellulose (dampened with isopropanol), organic waxes (in suspension in butyl alcohol), resins, or dyes.

The real solvents play a critical role in two major characteristics of the nail polish: its dry-time and its viscosity. It is clear that the more diluted the solution (i.e., the higher the ratio of sovent to solids), the lower the viscosity (with a constant solid composition).

The dry-time is very important, as the time necessary to apply the nail polish is the most often mentioned hurdle that prevents consumers from using nail polish. Hence formulators have tried to reduce the dry-time as much as they could. However, one must be careful not to go too far. An excessively fast drying nail polish will dry on the brush or during the transfer from the brush to the nail, making the application very difficult or impossible.

If the solvents are released too rapidly when the polish is applied, a coating on top of the film may be formed, trapping the remaining solvents in the film and giving a very soft nail polish film that transfers to clothes and is very mar-sensitive. On the other hand, if the drying time is considered as too long, consumers will lose patience and use their fingers before completion of the film, leading to the nail polish having the same problems mentioned earlier. A

compromise has to be found, and the balance between each solvent together with the ratio of solvents to solids are two of the keys for the formulation's success.

Table 27.1 gives a list of evaporation rates of often used solvents:

Table 27.1 Physical Properties of Common Nail Polish Solvents

	Boiling point (°C)	Evaporation rate (ethylether = 1)	Flash point
Acetone	56.2	2.1	0
Amyl acetate	139	13	108
n-Butyl acetate	126	11.8	74
i-Butyl acetate	116	7.7	65
Sec Butyl acetate	118	80	77
n-Butyl alcohol	118	33	95
i-Butyl alcohol	108	24	82
Sec Butyl alcohol	100	—	75
Ethyl acetate	77	2.9	23
Ethyl alcohol	78	8.3	57
n-Propyl acetate	102	4.4	57
i-Propyl acetate	89	4.2	45
Toluene	111	6.1	40
Dibutyl phthalate	340	—	329

Dibutyl phthalate is not a true solvent (although it dissolves the nitrocellulose), but it is included in Table 27.1 to demonstrate what was stated earlier on the nonvolatility of a plasticizer.

Solvents also play a role in the viscosity of the liquid nail polish not only with the ratio of solvents to solids but also with the choice of the solvents, as demonstrated in Table 27.2; this lists the viscosities of an RS 1/2s nitrocellulose solution at 10 g/100 ml in various solvents:

Table 27.2 Viscosity of a Nitrocellulose Solution in Different Solvents

Solvent	Viscosity (mPa.s) at 25 °C
Methyl acetate	26
Methyl ethyl ketone	33
Ethyl acetate	43
Methylisobutyl ketone	76
n-Butyl acetate	79
Ethylhexyl acetate	281
Ethyl lactate	287
Butyl lactate	328

PIGMENTS AND NACREOUS PIGMENTS

The first nail polishes were clear. Then came the tinted nail polishes using erythrosine (acid red 51, CI 45430), carmine (aluminum lake of cochineal, CI 75470), or basic violet 10 (rhodamine B, CI 45170). Although these colorants, gave some color to the liquid nail enamel, they retained the film's translucency and stained the nails. In the 1930s Charles Revlon revolutionized the nail enamel industry by using pigments instead of dyestuffs.

The DCMA (Dry Color Manufacturers Association) defines a pigment as a colored particulate organic or inorganic solid that is usually insoluble in, and essentially physically and chemically unaffected by, the vehicle or substance into which it is incorporated. In the nail polish industry and more widely in the cosmetic industry, pigments are divided into three categories: mineral pigments or inorganic pigments, organic pigments, and nacreous pigments.

The inorganic pigments were the first means found by humans to color their paintings and their bodies. The colored earths found in their environment were mainly iron oxides. They are still used today, together with titanium dioxide, as pigments in the cosmetic industry. The most commonly used inorganic pigments include titanium dioxide (TiO_2), an amphoteric polymorphous crystal existing in two commercially available forms, tetragonal rutile and tetragonal prisms of anatase yellow iron oxide ($Fe_2O_3 \times H_2O$), also known as ocher, sienna, yellow limonite; red iron oxide (Fe_2O_3), found in nature or derived from calcining limonite; brown and black iron oxide, which contains limonite, carbon, and manganese oxide; and ferric ferrocyanate or Pigment Blue 27.

The density of inorganic pigments is higher than that of nail polish. This causes undesirable settling of the pigments to the bottom of the bottle, a problem that will be examined later in this section.

The most commonly used organic pigments are included in Table 27.3. They have been classified as either toners or lakes in the United States. A toner is an organic pigment that is free of inorganic pigment or extender; a lake is an

Table 3 Organic Pigments Used in Nail Polishes and Their Lakes

Dye	Lakes
D&C Red No. 6	Ba, Ba/Sr
D&C Red No. 7	Ca
D&C Red No. 30	—
D&C Red No. 34	Ca
FD&C Yellow No. 5	Al, Zn
FD&C Yellow No. 6	Al

organic pigment that has been combined with an inorganic or organic extender substance (aluminum hydroxide, barium sulfate, etc.). In Europe, however, a toner is an acid or basic dyestuff converted to an organic pigment through precipitation as insoluble salts. When this precipitation occurs in the presence of inorganic substances or carriers, it is a lake. Despite the confusing definition, both pure organic colorants and lakes are used in nail polishes.

The use of colorants in nail polish is limited to those allowed by the regulations promulgated by the Food and Drug Administration in the United States or similar government offices in other countries.

The preceding list is not limited, and other pigments or dyestuffs may be used in nail polish to provide more opacity or help to yield the desired shade. A complete listing can be found in the CTFA *International Color Handbook* [9].

Nacreous pigments used in nail enamels include a variety of different chemical entities. Nacreous pigments create a frosted appearance or iridescent light effects. They are large particles (up to 50 microns) with a very high refractive index. Three types of pigments are used in nail polishes:

Natural Pearl Essence. Known as guanine (2-amino-6-hydroxypurine); it is derived from fish scales (as Atlantic herring) and gives a soft luster. It was the first to be used and is very convenient, as its density is the lowest among the nacreous pigments. Its use has decreased because of its high cost.

Bismuth Oxychloride. To reduce the price and keep a luster, bismuth oxychloride is widely used. The dimension of its crystals is controlled by the manufacturer, giving different levels of lusters. It has very high density and is very difficult to suspend, and may also show some darkening upon light exposure. Both natural pearl essence and bismuth oxychloride are most commonly available in suspension paste or dispersions made out of nitrocellulose.

Coated Mica. Mica is a mineral product that exists in large flat particles with high refractive index. When coated with various substances, such as titanium dioxide, iron oxides, and so forth, the particles give very interesting interference effects. The micas are lighter than the bismuth oxychlorides and are widely used in the industry. They are available in powder form and also in nitrocellulose-based slurries.

As noted above, the density of many of the colorants used in nail polish is very high and tends to settle during storage. The resulting unattractive appearance of the nail polish must be controlled. One approach will be reviewed later in this chapter (under additives) and is based on the enhancement of viscosity.

The second approach is based on modification of the surface of the pigment to make it more "friendly" with the vehicle and lessen the apparent density differences that exist. These surface treatments (identified below) impart better

dispersibility, which in time offers several advantages: (1) the resulting dispersions contain fewer agglomerates, and the apparent density is lower; (2) the color strength is at its maximum development, with all particles dispersed; (3) higher concentrations of pigments are obtained with a workable viscosity because the dispersion is better and the surface is modified; (4) the pigments have better stability and resist flocculation; and (5) any hydrophobic treatment imparts water resistance to pigments or micas.

The mechanism most widely accepted for the performance of these treatments is that long-chain molecules are linked to the surface of the pigment. These long chains act as "tails" that are compatible with the solvent vehicle and also tend to sterically separate the particles and keep them separated. Some of the treatments used in the nail polish industry are silicone-treated pigments [10], metal soap/fatty acid/amines acid-treated pigments [11], fluorochemical treated pigments [12], and polyethylene-treated pigments [13].

Again, this list is not exhaustive, and other treatments may be or will be used in the nail polish industry.

ADDITIVES

Additives are used in nail polish formulations for various purposes: (1) for marketing claims acrylics, polyesters, polymers, or nylon are included to improve nail strength; (2) water or quaternaries that may improve wetting of the nail may be added; and (3) vitamins, proteins, and even diamond dust can be incorporated. Other additions include color stabilizers, primarily to the UV absorbers such as benzophenones, fragrances, and—most importantly—viscosity modifiers. Of all the additives mentioned, the last category is of primary importance.

As a rule, nail polishes are sold in glass bottles, and pigment settling is a serious detriment. The formulator faces a dilemma: to avoid the settling of the heavy particles the viscosity of the nail polish must be raised as high as possible, but the nail polish has to be fluid enough for application. The only way to meet these two opposing requirements is to create a product exhibiting varying, that is, non-Newtonian viscosity (Chapter 11). Shear thinning characteristics should provide the highest possible viscosity at rest, which should be rapidly followed by a change to the lowest possible viscosity during polish application, and rapid restoration of the highest possible viscosity after brushing has been completed. Ideally, such a fluid should be pseudoplastic, and time should not be an issue. However, a truly pseudoplastic nail polish has not yet been found. Instead another property known as thixotropy is used, in which the viscosity of the polish decreases under shear but builds up, in time, when the shear stops.

This desirable characteristic is obtained in nail polishes through use of special additives, the organoclays and more specifically modified smectite clays. Of these, stearalkonium hectorite is currently the most widely used. The performance is commonly explained by clays being very thin (= 10 A°) and wide (= 10, 000 A°) particles that can pile up. Between the particles one can find positive ions (Ca^{++}, Na^{+}) that are linked to the surface. The organic treatment of the clay replaces these positive ions by long-chain quaternary ammonium compounds. During dispersion of the organic modified clay, these chains tend to separate the particles and then rearrange them in a network. The particles now are linked by their edges (electrical forces) and occupy the entire volume of the product, giving high viscosity to the polish.

When a force is applied to this system (agitation, shear), the weak electrical forces between the particles will break, and these very thin particles orient themselves in the same direction as the shear, that is, parallel to each other. The viscosity is now lower and the liquid flows, as the network that hampered the flow is destroyed. When shear stops, the edges will be attracted to each other again by the electrical forces and the particles will rearrange themselves to create a new network, building up viscosity in time. Such a thixotropic nail polish with quaternized clay additives enhances several nail polish properties but still is not a perfect system. If the thixotropy index (ratio high/low viscosity) is too small, gravitational settling will occur. By contrast, if the thixotrophy index is too high, syneresis may occur in which a thin layer of tinted solvent appears on top of the bottle. This is caused by an excessively dense network, which allows the particles to approach too closely, squeezing out the solvents. Therefore, the amount of thixotropic agent used must be carefully controlled and studied by the formulator.

PRODUCTION AND CONTROLS

Production of flammable nail products is hazardous and has been left to specialists in this field. What is required is explosion-proof mixing equipment to dissolve the various raw materials (nitrocellulose, resins, plasticizer, additives) in the solvents and high-shear dispersers to disperse the solids in the vehicle (pigments, clays).

Of course, color and shades have to match standards or the customers' requirements. As many of the ingredients used in the production may vary within specifications, the final controls on the finished products must be strict and include assessment of viscosity, using viscometers or rheometers, hardness of the dry film using a rocker apparatus (such as Sward), dry-time, color (visual or colorimetric), and oven stability (40/50 °C).

FORMULAS

Some protoype formulas, shown below, may be used as guides (all percentages are by weight):

Nail polish base [15]	%
Nitrocellulose (30% IPA)	13.0
Tosylamide/formaldehyde resin	11.0
Dibutyl phthalate	5.0
Ethyl acetate	22.0
Butyl acetate	41.0
Isopropyl alcohol (IPA)	6.0
Stearalkonium hectorite	2.0
	100.0

Clear nail base coat (with toluene)	%
Nitrocellulose (30% IPA)	14.0
Tosylamide/formaldehyde resin	7.0
Camphor	2.0
Dibutyl phthalate	5.0
Isopropyl alcohol	10.0
Butyl acetate	25.0
Ethyl acetate	7.0
Toluene	30.0
	100.0

Clear nail base coat (toluene-free)	%
Nitrocellulose (30% IPA)	18.0
Phthalic anhydride/trimellitic anhydride/glycols copolymers	9.5
Camphor	1.0
Dibutyl phthalate	6.5
Isopropyl alcohol	5.0
Ethyl acetate	40.0
Butyl acetate	20.0
	100.0

Clear nail top coat (toluene-free)	%
Nitrocellulose (30% IPA)	13.5
Phthalic anhydride/trimellitic anhydride/glycols copolymer	7.0
Acrylates copolymer	3.7
Camphor	0.7
Dibutyl phthalate	3.7
Benzophenone 2	0.4
Butyl acetate	31.0
Ethyl acetate	40.0
	100.0

Moisturizing base coat	%
Nitrocellulose (30% IPA)	15.0
Phthalic anhydride/trimellitic anhydride/glycols copolymer	9.0
Acrylates copolymer	2.0
Camphor	0.7
Dibutyl phthalate	3.0
Isopropyl alcohol	8.0
Butyl alcohol	1.0
Benzophenone 2	0.4
Distilled water	3.1
PPG 20 methyl glucose ether distearate	1.0
Ethyl acetate	38.5
Butyl acetate	18.3
	100.0

Nonnitrocellulose base coat	%
Butyl ester of PVM/MA copolymer	20.0
Ethyl alcohol	20.0
Castor oil	3.0
Alcohol, SDA 40	57.0
	100.0

Red nail lacquer	%
Titanium dioxide	0.5
D&C Red No. 7, Ca lake	0.5
D&C Red No. 34, Ca lake	0.2
Nitrocellulose (30% IPA)	13.0
Isopropyl alcohol	8.0
Tosylamide/formaldehyde resin	8.0
Camphor	2.0
Dibutyl phthalate	4.0
Stearalkonium hectorite	1.3
Butyl acetate	40.3
Ethyl acetate	22.0
	100.0

Pink nail lacquer	%
Iron oxide (red)	0.2
Titanium dioxide	0.7
D&C Yellow No. 5, Al lake	0.1
D&C Red No. 7, Ca lake	0.1
D&C Red No. 34, Ca lake	0.1
Nitrocellulose (30% IPA)	15.0
Isopropanol	8.0
Tosylamide/formaldehyde resin	7.0
Camphor	2.5
Dibutyl phthalate	5.0
Stearalkonium hectorite	1.2
Butyl acetate	42.0
Ethyl acetate	18.1
	100.0

Nail polish drier	%
Olive oil	90.0
Castor oil	3.5
Ethyl alcohol	6.5
	100.0

Oily nail lacquer remover	%
Ethyl acetate	98.0
Castor oil	2.0
Color	q.s
Perfume	q.s
	100.0

Nonsmear nail lacquer remover	%
Water	10
Acetone	90
Color	q.s.
Perfume	q.s.
	100.0

Nail hardener	%
Hydrolyzed collagen	0.1
Nitrocellulose (30% IPA)	15.0
Butyl alcohol	6.0
Tosylamide/formaldehyde resin	7.0
Dibutyl phthalate	5.0
Camphor	3.0
Isopropyl alcohol	8.0
Butyl acetate	35.0
Ethyl acetate	20.9
	100.0

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CHAPTER 28
Specialty Nail Products

A complete manicure treatment can involve a number of different cosmetic preparations required for cleansing and preparation of the nail and for its decoration. In addition, there are a number of cosmetic products designed to address specific nail problems. These will be dealt with in subsequent sections, approximately in frequency of use.

CUTICLE REMOVER

After the free edge of the nail has been shaped by mechanical means such as cutting or filing, the next problem is to shape the base of the nail. Where the skin adjoins the nail it becomes cornified, and the dead cells, together with sebum, form an irregular appendage that grows thick and ragged and partially obscures the "half-moon" or lunula. Some improvement can be effected by mechanically loosening and pushing back the cuticle, and when the removal of excess cuticle by cutting is unsatisfactory, cuticle removers are used.

Cuticle removers are based principally on alkaline materials in liquid or cream form [1]. One of the most effective and relatively inexpensive materials is potassium hydroxide, and about 1–5% of this material in aqueous or hydro-alcoholic solution forms the basis for many preparations. The incorporation of humectants such as glycerin or propylene glycol, at a level of 10–20%, helps to counteract the irritation potential of alkali hydroxides, to retard evaporation, and to increase viscosity. The latter effects can also be achieved by the use of suitable water-soluble gums or hydrocolloids.

Milder but correspondingly less effective preparations can be obtained by using polybasic alkaline salts such as trisodium phosphate or tetrasodium pyrophosphate, with the possible addition of 2–3% sodium or TEA lauryl sulfate. An example of a basic formula is:

Formula 28.1 Cuticle Remover (in%)

Trisodium phosphate	8.0
Glycerin	12.0
Water	80.0
Perfume	q.s.

Still milder products are based exclusively on alkanolamines such as monoethanolamine or isopropanolamine at 8–10% or triethanolamine at about 10–12%.

To improve the convenience in use of cuticle removers, attempts have been made to present them in cream form, which also reduces the potential risk of damage to furniture and carpets from accidental spillage. Formula 28.2 represents a starting composition for such a preparation:

Formula 28.2 Cuticle Remover (in%)

Sorbitan monopalmitate	2.0
Polysorbate 40	2.0
Mineral oil	15.0
Cuticle, removing alkanolamine	81.0
Water	q.s.

Special emulsions—not subject to hydrolysis—have to be prepared to allow the incorporation of highly alkaline materials, as shown in Formula 28.3.

Formula 28.3 Cream Cuticle Remover (in%)

Cetyl alcohol	2.5
Myristyl alcohol	3.5
Laureth-5	1.0
Glycerin	4.0
Potassium hydroxide	1.6
Water	87.4

A combination of phosphate and caustic alkali can also be used with this type of cream emulsion, although the presence of phosphate can drastically affect the viscosity of the final product. This can be controlled, however, by careful homogenization of the cooled emulsion.

A more recent and effective approach is to formulate cuticle removers with a lower level of potassium hydroxide in a creamy gel vehicle that does not interfere with the softening effect of the alkaline on the cuticle, in accordance with Formula 28.4.

Formula 28.4 Cuticle Remover (Reduced Alkali, in%)

Water	84.75
Carbomer 940	0.50
Glycerin (96%)	12.00
Stearic acid (triple pressed)	0.50
Potassium hydroxide (85%)	1.25
Lytron 614*	1.00

*An opacifier manufactured by Morton Chemical Co. and composed of a mixture of styrene/acrylates copolymer, octoxynol-9 and sodium dodecylbenzene sulfonate.

A variety of additives has been incorporated into cuticle removers of this type. Color, fragrance, "medicating" components, and other promotional materials such as aloe vera are often seen. A so-called "oily" cuticle remover contains 6% sulfated castor oil, 12% glycerin, and 3% potassium hydroxide in a water base, with a trace of EDTA.

Care must be taken in packing all such alkaline preparations in glass containers, which should be fitted with alkali-resistant stoppers such as rubber or plastic. Even so, the alkaline preparations are liable to give rise to glass etching and silicate precipitates. The latter can be masked by the use of opaque containers or prevented, as has been claimed, by the inclusion of about 1% of potassium oleate or about 1% of the tetrasodium EDTA. Today plastic packaging has largely replaced glass for these products.

CUTICLE SOFTENERS

Another type of widely used preparation is the cuticle softener in cream form, which by its action and emolliency facilitates subsequent mechanical removal of the cuticle.

Quaternary ammonium compounds are prominent in one class of this preparation. Their softening action is the result of their affinity for protein and increases with increasing molecular weight. Cetyl pyridinium chloride and stearyl dimethyl benzyl ammonium chloride are typically used at levels of 3–5%. They also exert some bactericidal action. Urea may be added to promote the swelling of keratin and enhance cuticle softening, and lanolin or isopropyl myristate will confer improved emolliency. Nonionic thickening agents such as methylcellulose or hydroxyethylcellulose are used to increase the viscosity.

NAIL BLEACH

Nail bleaches are solutions or creams used for the removal of ink, tobacco stains, vegetable stains, and so forth from the nails. Such stains may yield

either to oxidation or to reduction, depending on the type of stain. Oxidation may be achieved by the use of hydrogen peroxide, either at 20 vols or diluted to about 1:4, by chlorine compounds such as hypochlorites and chloroisocyanurates, and by sodium perborate and zinc peroxide (the latter two substances decompose in aqueous solution). Use of sulfites with dilute acid is a relatively easy method for achieving pigment reduction in such preparations. These can be packed in two-solution form, one the stabilized oxidizing or reducing agent and the second containing enough acid or alkali to shift the pH sufficiently (when the two solutions are mixed) to render the agent to be employed unstable and hence active.

A number of stain-removing preparations are based on aqueous solutions of organic acids such as citric or tartaric acids, and even a 4% solution of concentrated hydrochloric acid in water and glycerin was recommended for such purposes some time ago.

Abrasive nicotine stain remover formulas may be based on the composition as shown in Formula 28.5:

Formula 28.5 Stain Remover (in%)

Beeswax	10.0
Paraffin	5.0
Mineral oil	46.0
Pumice (powder)	8.0
Sodium borate	0.5
Water	30.0
Perfume	0.5

NAIL CREAM

Nails are not porous, although they permit the penetration of externally applied materials through the nail plate, including moisture that helps maintain flexibility [2]. The moisture content of nails is less than half that of the stratum corneum, and total lipid content is less than 1%. Truly occlusive coatings that prevent moisture transpiration can promote conditions that favor fungal infections. Nails can become brittle from various causes; a common response is to apply some preparation to counteract this brittleness, which is probably due to dehydration.

One early recommendation for the relief of brittle nails was to massage them with olive oil after bathing them in warm water. It was stated, however, that nail plates will regain their normal consistency and elasticity only after several weeks of treatment [3].

A more practical preparation is the use of an emollient cream containing a suitable humectant. Emollient creams for use as nail creams have been formulated from lanolin absorption bases or from beeswax-borax emulsions. These creams should be applied after soaking the hands in warm (soapy) water and thoroughly drying them, just before retiring for the night. This treatment should be carried out at least once and preferably two to three times per week (that is, on alternate nights), depending/on the condition of the nails. Wearing fingerstalls or gloves may assist the treatment.

Claims have been made that certain fatty substances, in particular cholesterol, appear to assist in maintaining the natural elasticity of the nail. In this connection the water-in-oil emulsifying properties of cholesterol should be borne in mind, since it may assist in maintaining the requisite degree of moisture in the keratin. Although much remains to be discovered, it would appear that the use of a nail cream containing oils in an emulsified form with water (and possibly incorporating a mild antiseptic) should be of value.

Any of the cold, vanishing, foundation, or all-purpose cream formulas cited in various chapters of this book may be modified slightly—if necessary—for use as a cream for brittle nails by the inclusion of some lanolin or other emollient and an adequate amount of humectant.

Another example is the cuticle massage cream shown in Formula 28.6, which consists of an oil-rich emulsion that is massaged into the nail plate and cuticle.

Formula 28.6 Cuticle Massage Cream (in%)

	%
Water	45.35
Tetrasodium EDTA	0.15
Aloe barbadensis gel	0.10
Propylene glycol	2.00
Carbomer 940 (2% Soln)	25.00
Glyceryl stearate	4.00
Cetearyl alcohol and ceteareth-20	3.00
Cetearyl alcohol	1.50
Stearic acid	4.00
Lanolin	5.00
Tocopheryl acetate	0.40
Safflower oil	2.00
Macadamia ternifolia nut oil	2.00
Beeswax	4.00
Triethanolamine (99%)	1.50
Preservative	q.s.

NAIL STRENGTHENER

The fact that dry fingernails tend to split and break off easily is bound to spoil their appearance and make manicuring difficult and often painful. This has led to the development of various products for strengthening brittle nails and for eliminating brittleness and dryness [4,5].

A liquid composition consisting of an aqueous solution of 3% steartrimonium chloride, 1.5% nonoxynol-10, and 0.5% TEA stearate was claimed in several patents [6] for eliminating brittleness and dryness of nails, counteracting the effect of solvents present in nail polish removers, and improving the adhesion of nail lacquer applied subsequently.

Other nail-hardening preparations for increasing the resistance of nails to cracking, splitting, and laminating were based on solutions of water-soluble metallic astringent salts such as aluminum sulfate, potassium, sodium and ammonium alums, zinc acetate, and zirconium chloride. Treatment consists of wetting the nails by dipping them into or painting them with a 1–5% aqueous solution of metallic salt and keeping the nails in contact with the solution for five to ten minutes at an ambient temperature. If the recommended concentration is exceeded, drying and wrinkling of the skin of the fingertips may occur. These nail-hardening compositions preferably also contain 5–20% of a humectant such as glycerin or propylene glycol to retard evaporation of the aqueous solvent and to provide an even coating and a "slightly enhanced penetration."

A slight bactericidal effect has also been claimed for these salts, which may be further enhanced by the inclusion of other bactericidal substances such as formaldehyde. Formula 28.7 contains the nail-hardening composition contained:

Formula 28.7 Nail Hardener (in%)

Potassium alum	3.00
Glycerin	10.00
Formaldehyde	0.01
Menthol	0.001
Water	to 100.000

Even the low level of formaldehyde used in this formulation might be considered unacceptable in modern cosmetics. Other formulations that used higher concentrations of formaldehyde or formaldehyde releasers as a nail hardening agent [7] have disappeared from the market in the face of the numerous questions about the safety of formaldehyde in cosmetics.

Partially polymerized formaldehyde resins have also been used as the cross-linking agent in nail-hardening compositions. However, attention must be drawn to the reaction of the formaldehyde component of a nail-hardener reported by Lazer [8], which resulted in nail damage including subungual

hemorrhage, discoloration, subungual hyperkeratosis, and dryness of the skin, and also necessitated oral administration of a steroid to relieve the accompanying pain and edema. The use of the preparation had to be discontinued to allow the nails and the skin to return to a normal condition. In recent years the use of formaldehyde, formaldehyde resins, and formaldehyde donors have come under increasing attack, and commercial use of these materials has almost disappeared. Additional information on adverse reactions to—now essentially discontinued—cosmetic nail treatments can be found in Chapter 3.

Solutions of dimethylol- or diethylol-thiourea have been recommended for nail-strengthening compositions, and a nail-strengthening product was described containing a nontoxic cysteine derivative. An example of a more conventional liquid nail-strengthening preparation that can be applied to the nail with a brush or applicator or can be used as a nail soak as shown in Formula 28.8:

Formula 28.8 Nail Soak

	%
Water	90.50
Polyquaternium-11	5.00
Ethoxylated lanolin	2.00
Hydrolyzed keratin	1.50
Tetrasodium EDTA	0.10
Benzalkonium chloride	0.10
Quaternium-15	0.30
Octoxynol-9	0.25
Tocopheryl acetate	0.03
Retinol	0.02
FD&C Yellow #5 (0.1% soln)	0.20

Despite their long history of popularity, the use of nail hardeners is decreasing. The major types still in demand include protein (collagen) hydrolysates in emollient bases in compositions similar to Formula 28.8.

NAIL WHITE

Nail whites are preparations used to produce an even white edge to the nails. They are based on an inert white pigment such as zinc oxide, titanium dioxide, kaolin, talc, or colloidal silica, of which the first two are the best. The pigment forms 20–30% by weight of the preparation, which is generally presented as a stiff paste.

For general purposes a fatty base is preferable. Titanium dioxide is incorporated in the following simple example (Formula 28.9). Milling the titanium

Formula 28.9 Nail Whitener (in%)

Titanium dioxide	38.0
Petrolatum	62.0

dioxide into the melted petroleum jelly readily produces this simple preparation. Various mixtures of suitable fats and waxes may replace the petrolatum as desired.

Nail white pencils generally obtained from pencil manufacturers have largely replaced nail white creams, since they are easier and less messy to use and simply require moistening with water before application to the undersurface of the nail's free edge before the pencil is recapped.

A wax may be used as a base if desired, as shown in Formula 28.10:

Formula 28.10 Nail Whitening Wax (in%)

Beeswax	55.0
Hydrogenated cottonseed oil	9.0
Cocoa butter	9.0
Castor oil	8.0
Lanolin base	9.0
Titanium dioxide	10.0

Such a base is ready for use and is not wetted before application. The usual type, which requires preliminary dampening, is prepared by mixing casein or gum arabic with the inert pigment, or by suspending it in a sodium stearate-containing base.

The making of white pencils is a job for firms specializing in the manufacture of ordinary pencils and not for the ordinary cosmetic manufacturer. Consistency of the base will have to be adjusted according to plant operating conditions, and hence any formulations given here probably bear little resemblance to those actually used by the pencil manufacturers.

DRY NAIL POLISH

A distinction is drawn between those polishes that by abrasive action bestow a gloss on the nail surface and a nail varnish, which is addressed in Chapter 27. The former, by reason of the friction set up in the buffing process, draws the blood to the numerous capillaries of the nailbed and, by increasing the blood supply, may exert some slight stimulating effect on the growth of the nail. The latter, which depends on the deposition of a thin film of highly lustrous cellulose nitrate lacquer on the nail plate, is becoming increasingly popular. They have largely

replaced the abrasive type, although abrasive polish may also be used between two successive coats of varnish to enhance the luster. Abrasive polishes are still the preferred form for men who choose to get professional manicures.

Abrasive polishes consist of a suitable finely powdered abrasive, which is applied to the nail and then polished with a shaped chamois leather pad. The principal constituents of such powders are stannic oxide, talc, silica, kaolin, precipitated chalk, and so forth, the first being an excellent abrasive but rather more expensive than the others listed (Formula 28.11).

Formula 28.11 Dry Nail Polish (in%)

Stannic oxide	90.0
Hydrated silica	8.0
Butyl stearate	2.0
Pigment, perfume	q.s.

Butyl stearate is included to render the product less gritty and may be replaced, if desired, by oleic acid. The method of preparation is by simple trituration in a mortar or revolving mill. By the addition of a suspending agent, such as methylcellulose or tragacanth gum together with glycerin or one of the glycol ethers, they may be prepared in liquid form or compressed into a paste or pencil.

Historically, wax polishing pencils containing a large proportion of abrasive powder replaced the older powder and block type (Formula 28.12). They were effective and could be carried and used without the danger of spilled contents:

Formula 28.12 Wax Polishing Pencil (in%)

Hydrogenated palm kernel oil	22.0
Synthetic wax (high melting point)	7.0
Stannic oxide	71.0

A softer stick may be obtained by omitting the synthetic wax and making a simple mixture of abrasive powder with the hardened oil. Alternatively, a base of rosin, beeswax, ceresin, and petrolatum, or other suitable combination of waxes may be employed.

NAIL DRYER

Nail dryers are aerosol formulations that make use of the rapid evaporation of a propellant to speed up the drying of freshly enameled nails by drawing off the solvent present in the nail varnish. Sometimes drying is combined with

the deposition of a transparent film of oil over the freshly applied enamel, to reduce its tackiness and to prevent it from smearing if touched.

PLASTIC FINGERNAILS AND ELONGATORS

Plastic fingernails and elongators are used to improve the cosmetic appearance of damaged or short, stubby nails. The polymerization or copolymerization of monomers in the presence of a polymer, a catalyst, and a polymerization promoter produces them. A plasticizer, an opacifier, a pigment, and a filler may also be included.

Due to the high incidence of allergic reactions to methyl methacrylate monomer and serious deep fungal infections believed to be caused by the occlusivity of the resulting polymer, the sale and use of these products has almost disappeared.

Another form of artificial nails is made of preformed acrylic plastic, which is cemented to the nail using an appropriate glue. Care should be exercised when using cyanoacrylate glues since a significant population exhibits allergic reaction to the cyanoacrylate, not to mention the danger of gluing the skin to itself.

NAIL-MENDING COMPOSITIONS

Mending compositions are basically mixtures of an adhesive, a fiber reinforcing material, and a solvent. The first two components produce a film that forms a strong bond between the broken parts of the damaged fingernail, improving its appearance and preventing further damage, while the solvent, which permits easy application of the composition to the fingernail, will quickly evaporate and allow the reinforced adhesive film to set and to mend the damaged fingernail. These preparations are preferably applied in four coats, each coat being applied in a direction perpendicular to the previous one and allowed to become surface-dry before application of the next coat. The nail polish is applied about one hour after the application of the final coat of the mending preparation, to allow all the coats to dry thoroughly.

The preferred organic film-forming material of the mending composition is nitrocellulose. A resin, for example, tosylamide formaldehyde, is also included to make the film produced by the composition more adherent, flexible, and tough, and a plasticizer may be added to make the film flexible. Short rayon fibers (1.5 mm long) and of small diameter (1.5–5 denier) are used as reinforcing agents. Other fibers may also be used if they are not soluble in the mending composition. A viscosity-increasing agent (preferably silica) is also present to ensure that the fibers used remain suspended within the adhesive. Useful solvents include ethyl acetate, butyl acetate, and toluene used in a

combination of 30–50%, 5–20%, and 20–30%, respectively. Pigments or dyes may also be included to confer the desired color. The compositions just described are illustrated in the Formula 28.13. It has been claimed that nail polish can be applied to and removed from such mended nails without difficulty and without disturbing the "repair."

Formula 28.13 Nail-Mending Composition (in%)

Nitrocellulose	10.3
Tosylamide formaldehyde resin	4.1
Silica	2.0
Dibutyl phthalate	0.5
Rayon fibers	0.5
Ethyl acetate	46.2
Butyl acetate	5.1
Toluene	31.3

Also patented have been keratin, containing compositions, which may be used either as nail varnishes or for the repair of chipped or cracked nails and for producing artificial nails. They are intended to provide coatings that are compatible with natural nails. The keratin, which is resistant to various solvents including dilute acids and alkalis, is combined with a suitable water-insoluble bodying agent, for example, cellulose nitrate, and suspended in a suitable solvent, preferably methyl ethyl ketone or a mixture of ethyl and butyl acetates. Synthetic resins may be included to increase adhesion, solid content, and water resistance, and to enhance gloss. Plasticizers may also be incorporated to avoid excessive brittleness of coatings.

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CHAPTER 29
Shampoos

INTRODUCTION

The primary function of a shampoo is to clean the hair and scalp. In this respect the action of a shampoo has much in common with other types of cleansers, such as dishwashing liquids, laundry detergents, and hard surface cleaners, all of which rely on similar types of surfactants to effect soil removal from a particular surface. As a result, much information concerning shampoo action can be found in existing general reviews on detergency.

However, there are many requirements for shampoos that differentiate them from other types of cleansers. In particular, a shampoo must clean at relatively low temperatures and quickly—in minutes. The product must develop a rich, stable foam that can be easily rinsed, while the viscosity of the shampoo should be at least 2,000 cps so that it does not easily run off the hand. In part to satisfy the last two specifications, surfactant levels in shampoos must be relatively high, generally ranging between 10% and 20%. Finally, safety is an important issue: shampoo ingredients must exhibit low skin and eye irritation.

The above requirements, to a large extent, determine, and also restrict, the types of surfactants and additives that can be used in shampoos. They also influence cleaning efficacy and the particular mechanisms by which soil removal is effected.

Further restrictions apply to the active ingredients in those shampoos, such as two-in-one's, that provide benefits in addition to cleaning. The actives in these formulations must deposit on the hair without significantly interfering with soil removal or negatively impacting a variety of important hair attributes, including feel, shine, body, and manageability.

Recent years have also seen an increase in complexity in the advertising of shampoos. This has been especially evidenced by a marked increase in therapeutic types of positionings for products. Much of this type of positioning is based on health-related additives such as vitamins, pro-vitamins, herbal

extracts, and marine extracts. Claims have ranged from general assertions related to making hair look healthy and shiny to specific assertions concerning outright repair and restructuring of damaged hair. The increased frequency of shampoo usage has led to a greater interest in developing milder shampoos and in understanding the damaging effects of frequent shampooing and grooming.

The technology of complex shampoo emulsions has also become more important as a result of the development of effective two-in-one shampoos, which clean and condition hair at the same time. This has created an increased effort to develop new stabilizers, especially for silicone emulsions, combined with work directed toward more efficient deposition of emulsified or solubilized actives.

Much confusion has been generated by the aggressive, therapeutic claims employed in recent years for shampoos. Many of the health-related additives associated with these claims are added to support a product image and have no real effect. Other additives provide benefits only under contrived conditions or at concentrations too high to be utilized in a commercial formula. In view of the current proliferation of health-related advertising, it has become increasingly important to distinguish between real and unrealistic claims and to understand what benefits different raw materials can and cannot provide.

In the following sections covering shampoo ingredients, specific examples of how meeting the above requirements affect shampoo form and content are considered. The subsequent sections on hair cleaning then discuss how these requirements affect cleaning efficacy and mechanism.

PRIMARY AND SECONDARY SURFACTANTS IN SHAMPOOS

The role of the primary surfactant in a shampoo formulation is to provide the principal detergency and foaming benefits, whereas the secondary surfactant delivers improved detergency and foaming, according to hair condition.

ANIONICS

Soaps

Soaps, typically the potassium and ammonium salts of oleic and coconut fatty acids, were the primary detergents in early shampoos. They lather poorly in hard water due to the formation of insoluble Ca^{2+} and Mg^{2+} salts, which may precipitate on the hair, resulting in a dull appearance [1]. Synthetic detergents have replaced soaps as the primary surfactant in shampoos because of their superior performance in hard water.

Alkyl and Alkyl Ether Sulfates

The alkyl and alkyl ether sulfates represent the two most widely used classes of surfactants for the formulation of shampoos. They form separate chemical classes in the *INCI Dictionary*. Lauryl (ammonium, sodium, triethanolamine,

and diethanolamine) and laureth (sodium and ammonium) sulfates have dominated the market. These surfactants, whether formulated alone or in combination with other surfactants, are the primary detergents currently used in the majority of shampoos. Sodium lauryl sulfate (SLS) is not very soluble at low temperatures, but its solubility increases substantially with temperature. Water solubility is increased by the addition of ethylene oxide groups to the alkyl sulfates. Thus the performance of laureth sulfates is frequently preferred by formulators. Formulating with laureth sulfates can be particularly advantageous in regions with hard water.

The alkyl and alkyl ether sulfates are highly stable against hydrolysis at alkaline pHs. However, hydrolysis of these esters can readily occur at pHs below 4.0, forming free fatty alcohols.

Alkyl sulfates have been found to elicit skin irritation when allowed to remain on the skin or when repeatedly applied to the same skin site. Such reactions are infrequent and not severe during short shampoo use followed by rinsing. The safety of shampoos is discussed below in more detail. The ethoxylation of the fatty alcohol with varying amounts of ethylene oxide prior to sulfation reduces irritation.

A shampoo's ability to produce a rich, luxurious, and abundant lather is one of the most important performance attributes to consumers. As a result, shampoos are formulated with high surfactant levels (12–20%) even though many soils, such as sebum, are adequately cleaned at lower surfactant concentrations. Both lauryl and laureth sulfate detergents produce abundant lathers, but the foam produced is light and airy and collapses readily. For this reason, lauryl and laureth sulfate–based shampoos are formulated with a secondary surfactant to improve the foam quality. The addition of foam boosters turns a lacy foam into a thicker, creamier lather that imparts a feeling of richness. Therefore cocamidopropyl betaine or alkanolamides are employed as secondary surfactants. The ability of alkanolamides to stabilize foam results from complexation with the surfactant molecules via van der Waals forces and hydrogen bonding. This increase in micellar interactions also leads to an increase in film viscosity [2]. Foam stability of the alkyl and alkyl ether sulfates can also be explained by the electrostatic repulsion between the two sides of the foam film due to the surfactants' negative charges. Most foam evaluations are conducted below and up to the critical micelle concentration (CMC), while actual use concentrations are well above the CMC. Alkanolamides and inorganic salts are the most common additives used to increase the viscosity of shampoos formulated with alkyl and alkyl ether sulfates. Most commercial shampoos typically exhibit viscosities between 2,000 and 5,000 cps.

The structures of the primary surfactant and additive species determine a shampoo's viscosity at a given concentration. This is a result of formation of

ordered structures among the various ingredients of a shampoo. This effect is aided by long linear alkyl chains. For these reasons, the viscosity of linear alkyl sulfates is greater than that of the corresponding branched species. Similarly, fatty acid–derived alkanolamides provide viscosity increases. Monoethanolamides are more effective in enhancing viscosity than the corresponding diethanolamides. Alkanolamides are discussed in further detail in the section on nonionic surfactants. The ability of inorganic salts to increase viscosity can be explained by the reduction in opposing intermicellar forces caused by the decreased charge effect as the electrical double layer is compressed. This permits formation of larger micelles and more ordered structures, leading to a reduction in translational motion and increased viscosity.

α-Olefin Sulfonates

Alpha olefin sulfonates (AOS) rank second in usage behind the alkyl and alkyl ether sulfates but currently find only limited use in nonpremium shampoos.

AOS is a mixture of the following four surfactants: $R-CH_2-CH=CH-CH_2-SO_3-Na$; $R-CH=CH-CH_2CH_2SO_3-Na$; $R-CH_2-CHOH-CH_2-CH_2-SO_3-Na$; and $R-CHOH-CH_2-CH_2-CH_2-SO_3-Na$. R in the above formulas is a hydrocarbon between C10 and C12. This range in the hydrocarbon chain lengths provides optimum detergency, solubility, and foaming attributes. The compounds are chemically classified as Sulfonic Acids in the *INCI Dictionary*. AOS is prepared by continuous sulfonation of a mixture of C14 to C16 olefins and subsequent alkaline hydrolysis under pressure.

Because of the lower costs of the raw materials and of sulfonation, AOS is less expensive than sodium lauryl sulfate and sodium lauryl-2 sulfate (SLS and SLES). Additionally, AOS is more soluble than SLS and can therefore be sold as a 40% active low-viscosity liquid. Unlike the alkyl and alkyl ether sulfates, the SO_3 group in the AOS compounds is not bonded via a C–O–S bond but via a C–S bond. AOS therefore exhibits excellent stability over a wide pH range, including those low pHs at which the alkyl and alkyl ether sulfates would be rapidly hydrolyzed.

The foaming properties of AOS have been reported to be comparable to those of SLS and SLES in the presence of sebum. As with the alkyl and alkyl ether sulfates, viscosity buildup and foam quality improvements can be accomplished using various additives, including monoalkanolamides and salt. However, it should be noted that viscosity building of AOS is more difficult than for alkyl sulfates.

Miscellaneous Anionic Surfactants

There are many more anionic surfactants that are available to shampoo formulators. They are not widely used as the primary surfactant in shampoos,

but they have been incorporated as secondary surfactants or used in specialty products.

Sulfosuccinates. Sulfosuccinates, which contain both a carboxylate and a sulfonate group, are prepared by reacting maleic anhydride with a suitable moiety followed by sulfonation of the resultant half-ester or amide. The alkyl group may be derived from a fatty alcohol, ethoxylated alkyl phenol or a fatty acid ethanolamide. These compounds form the Sulfosuccinate chemical class in the *INCI Dictionary.*

The foaming properties of the sulfosuccinates are inferior to those of the alkyl and alkyl ether sulfates and the olefin sulfonates, but they can be used in combination with these surfactants to produce shampoos that exhibit reduced eye and skin irritation, light conditioning, and improved lathering. Because of their mildness, sulfosuccinates are often used in baby and "frequent use" shampoos.

Linear Alkylbenzene Sulfonates. Linear alkylbenzene sulfonates (LAS) classified as Alkylaryl sulfonates in the *INCI Dictionary*, are low-cost surfactants that have been formulated into shampoos. Although they are widely used in laundry detergents, they find limited usage in shampoos.

N-Acyl Methyltaurates. N-acyl methyltaurates (AMT), listed under Sulfonic Acids in the *INCI Dictionary*, are the fatty amides of methyltaurines. They are noted for their low irritancy and claimed to protect hair against cuticle damage. This class of surfactants finds limited use in shampoos because of poor solubility and foaming performance, especially in hard water.

N-Acyl Sarcosinates. N-Acyl sarcosinates are produced via condensation of fatty acids with N-methyl glycine (sarcosine). They form the chemical class of Sarcosinates in the *INCI Dictionary*. The acyl moiety is most often a cocoyl, lauroyl, or oleoyl group, and Na^+ is the counter ion. These surfactants are less irritating than alkyl sulfates. Detergency and foaming performance is good in soft to moderately hard water, but decreases in hard water and at low pHs. They are reported to be compatible with a wide range of cationics.

Acyl Isethionates. These surfactants, listed as Isethionates in the *INCI Dictionary*, are condensation products of fatty acid chlorides and the sodium salt of 2-hydroxyethanesulfonic acid. They are very mild to the scalp and hair and produce a creamy, soap-like lather in both soft and hard water. They hydrolyze easily at low and high pHs. Their limited solubility at room temperature precludes their use in clear shampoo formulations.

N-Acyl Polypeptide Condensates. This class of surfactants is produced by the condensation of fatty acid chlorides and low molecular weight protein hydrolysates. They are included in the class of Protein Derivatives in the *INCI Dictionary*. Most often the cation is either potassium or triethanolamine (TEA), and the acyl group is a cocoyl moiety.

These detergents are mild and leave the hair feeling soft and manageable. Although their foaming properties are inferior to those of alkyl sulfates, they produce a creamy lather that is easily rinsed. They have been used in combination with alkyl or alkyl ether sulfates to reduce irritation and improve foaming and conditioning performance. Care should be taken to ensure the preservation of shampoo formulations containing these protein derivatives.

Polyalkoxylated Ether Glycolates. This group of surfactants includes acids derived from polyalkoxylated fatty alcohols. They are listed as Organic Salts or Carboxylic Acids in the *INCI Dictionary*. The salts yield a creamy lather and are reported to impart some conditioning to the hair.

Monoglyceride Sulfates. These detergents are sulfation products of monoglycerides and are classified as Sulfuric Acid Esters in the *INCI Dictionary*. Aside from improved solubility of the sodium salt, their properties are similar to those of lauryl sulfates.

Fatty Glyceryl Ether Sulfonates. These surfactants have the benefit of hydrolytic stability at all pHs; additional properties include mildness and a superior flash foam. They are included in the chemical class of Sulfonic Acids in the *INCI Dictionary*.

NONIONIC SURFACTANTS

Fatty Alkanolamides

Identified as Alkanolamides in the *INCI Dictionary*, fatty alkanolamides were discussed as foam and viscosity enhancers in the preceding section on alkyl and alkyl ether sulfates. Although most alkanolamides contain free anionic amine soaps, the main component is the uncharged nonionic amide. Because the alkanolamides and the amine oxides have very different properties from other nonionics, they are considered separately.

Fatty alkanolamides are produced by the condensation of a mixture of a primary or secondary alkanolamine with a fatty acid or a derivative. The ratio of the amine to fatty acid yields differing products. The 1:1 condensates, referred to as "superamides," are much more prevalent in shampoo formulations. The amide is the major chemical component (over 90%) with a small amount of soap, ester amide, and ester amine impurities. The product is a

waxy solid that is water-insoluble. The other type consists of a 2:1 ratio of amine to acid and was used originally in commercial alkanolamides. These 2:1 condensates typically contain a much lower level of pure alkanolamide in addition to soap and other impurities. This product is a liquid and is more water-soluble than the corresponding superamide. There is no distinction in INCI nomenclature between the two amides. Products derived from different fatty derivatives and different condensation ratios carry the same name, and wide variations in the chemical composition and performance of alkanolamides from different manufacturers is not unexpected.

A major concern in formulating with alkanolamides is the potential for free amine, particularly diethanolamine (DEA), to form carcinogenic N-nitrosamines. Because of this, DEA derivatives are typically monitored for the presence of nitrosamines. With growing concern over nitrosamines, particularly in the European Union countries, there is an emphasis in reformulating shampoos with alternatives to DEA amides.

Amine Oxides

This class of chemicals, identified as such in the *INCI Dictionary*, is prepared by the oxidation of tertiary amines with hydrogen peroxide. The N–O bond is highly polarized, and at low pHs amine oxides exist in a protonated form and may provide conditioning and antistatic benefits. Amine oxides are best known for their ability to enhance foam characteristics as secondary surfactants. They provide a thick, creamy, more stable lather at moderately acidic pHs; they are reportedly comparable in performance to the alkanolamides; they are also mild surfactants.

Improvements in product specifications have been made to address concerns that some amine oxides, particularly lauramine oxide and stearamine oxide, are precursors of N-nitrosamine.

Other Nonionics

Although the detergency of nonionic detergents is equal to, and in many instances superior to, that of anionic surfactants, nonionics are generally not used as primary surfactants in shampoos. This is due to inferior foaming characteristics, which result from their large surface area per molecule and the lack of charge on the surface films in nonionic foams [2]. However, nonionics are used extensively in a secondary capacity as foam modifiers, viscosity builders, emulsifiers, solubilizing aids, lime soap dispersants, and in some cases, conditioning agents.

Many nonionics have been used as cosurfactants due to their ability to reduce eye irritation and sting without adversely affecting shampoo foam. One such nonionic surfactant is polysorbate 20, the monoester of lauric acid and anhydrosorbitol condensed with an average of 20 moles of ethylene oxide. In

combination with anionic and amphoteric surfactants, polysorbate 20 reduces eye irritation and is therefore widely used in baby shampoos.

Another nonionic surfactant used in baby shampoos is PEG-80 sorbitan laurate, an ethoxylated sorbitan monoester of lauric acid with an average number of 80 moles of ethylene oxide.

The poloxamers are block polymers classified as polymeric ethers in the *INCI Dictionary*. They are polycondensates of ethylene oxide and propylene oxide. Although they are not good foamers, the poloxamers are very mild surfactants that are nonirritating to the skin and eyes. They can be used to control viscosity and have good rinsability.

The nonoxynols, listed in the Alkoxylated Alcohols class the *INCI Dictionary*, are produced by condensation of nonyl phenol with ethylene oxide. These nonionic surfactants function as lime soap dispersants and as solubilizers for fragrances.

AMPHOTERICS

The amphoterics derived from imidazoline, classified as Alkylamido Alkylamines in the *INCI Dictionary*, have a very low irritation potential and are almost completely nonstinging to the eyes. These surfactants are compatible with a wide range of other surfactants and can be formulated into many different types of shampoos. For instance, they are often found in conditioning shampoos due to their compatibility with quaternary compounds.

The amphoteric glycinates and propionates exhibit characteristic mildness to the skin and eyes. Formulators should avoid low pHs at which the amphoterics become positively charged since this can result in increased irritation. Commonly used members of this group include cocoamphocarboxyglycinate, cocoamphocarboxypropionate, cocoamphoglycinate and cocoamphopropionate.

Betaines

These quaternary carboxylates are derived from trimethylglycine where one methyl group is replaced with either a C12–18 fatty alkyl or a fatty amido alkyl radical. They can exist only in their zwitterionic and cationic forms. They function as foam and viscosity enhancers when utilized as secondary surfactants, having good water solubility over a wide pH range. As discussed previously in the section on alkyl and alkyl ether sulfates, cocamidopropyl betaine is often employed as a secondary surfactant in these systems to enhance foam characteristics and viscosity.

The free amine content is generally regarded as the major contributor to skin and eye irritation of betaines and other amphoterics. Combinations of betaines and other amphoterics, formulated to optimize performance and mildness, have been reported. Other betaines include sultaines, where the carboxylic group

is replaced with a sulfonic analogue. This modification results in improved mildness to the skin and eyes.

Alkyl-Substituted Amino Acids

The amino and imino propionates are amphoterics that can impart a light conditioning effect to the hair. This class of amphoterics provides increased conditioning in acidic systems, although foam characteristics are best at alkaline pHs. The pH of such systems should be adjusted to optimize these properties. Members of this group of surfactants include sodium lauraminopropionate and sodium lauriminopropionate.

CATIONICS

For several reasons, the use of cationic surfactants in shampoo formulations is more limited than that of surfactant classes discussed in the previous sections. They are generally not as effective detergents due to their ability to strongly bind to the hair's negatively charged surface. Their foaming properties are inferior to those of anionics. Furthermore, because they are not efficiently removed during rinsing, the hair is left more hydrophobic with the cationic's hydrophobic tails extending from the surface. This results in increased attraction of oily, hydrophobic soils to the hair and the potential for resoiling.

Therefore their use (at low levels) has been limited to their hair conditioning, lubricating, and antistatic benefits.

MECHANISM OF HAIR CLEANING

An understanding of how surfactants carry out the hair-cleansing function is necessary in order to assess the relative cleaning efficiencies of different surfactants and surfactant combinations. It is also important for determining how best to balance, in a formulation, the often conflicting aims of optimum cleaning, foam, viscosity, actives deposition, mildness, and so forth.

The structure of hair, from which soil must be removed, was described in Chapter 2 and is discussed in detail in Robbins's book [3]. As noted previously, the epicuticle of hair is substituted and coated with material responsible, in large part, for the observed hydrophobicity of untreated hair surfaces. Because of their protein composition, however, these surfaces can also contain charged, hydrophilic sites. For virgin hair, the observed isoelectric point is near 3.67, which ensures that the hydrophilic sites on this hair will carry a negative charge at the ordinary pH levels of shampoos. This combination of negative charge and hydrophobicity affects not only the type of soils and actives that bind to the hair but also the ease with which different soils are removed from the fiber surface.

Also affecting cleaning is the fact that the distribution of negatively charged sites on untreated hair is uneven, increasing from root to tip. This is a result of exposure to sunlight, which oxidizes cystine in the hair to cystine S-sulfonate and cysteic acid. In addition to oxidation by sunlight, hair can also be chemically oxidized as a result of perming, bleaching, or permanent dyeing. These treatments, all of which include oxidative steps, convert cystine to cysteic acid. The degree of resultant negative charge is generally greater than that from sunlight oxidation. In many cases after sufficient treatment, the entire hair surface can be converted from a hydrophobic to a hydrophilic character. This, of course, also affects deposition and removal of materials on the hair surface.

CLEANING OF SOLID PARTICULATES

For studies of hair surface cleaning, it is convenient to divide possible soils into two types: solid particulates and oily or liquid deposits. Particulate soils can come from the environment or from hair care products. Examples of the latter include many antidandruff agents, while the former includes carbon particles in the form of soot, clays, or rubber abraded from automobile tires.

In general, solid soils adhere to the hair surface through ionic or van der Waals forces. The ease of removing these soils from a surface in water depends on the relative affinities for each other of the water, soil, and substrate. A hydrophobic particle, for example, would be much easier to remove from a hydrophilic substrate than from a hydrophobic surface. This can be seen in the equation for the work of adhesion, Wa, which is defined as the free-energy change per unit area involved in removing a solid particle from a surface to which it is adhered:

$$\mathrm{Wa} = \gamma_{\mathrm{PW}} + \gamma_{\mathrm{HW}} - \gamma_{\mathrm{PH}}.$$

In the above equation, γ is the interfacial tension between any two surfaces, P represents the particle, H represents the hair surface, while W represents water. For hydrophobic particles, γ_{HW} would be larger and γ_{PH} would be smaller for hydrophobic surfaces than for hydrophilic substrates. The resultant larger work of adhesion indicates again that hydrophobic particles are more difficult to remove from hydrophobic than from hydrophilic surfaces.

Anionic and nonionic detergents can effect removal of particles from hair surfaces by adsorbing to these substrates with their hydrophobic portions in contact with the surface and their hydrophilic heads oriented toward the water. This reduces γ_{HW} and, therefore, Wa. Similarly, binding of surfactant to a hydrophobic soil reduces γ_{PW}, effecting an additional decrease in the work of adhesion.

A more effective cleaning mechanism than the preceding results when anionic surfactants adsorb to solid particles and the surfaces to which they are adhered. Such adsorption effectively deposits negative charge on both soil and substrate, facilitating soil removal as a result of mutual charge repulsion. Since nonionics cannot impart a charge potential on surfaces, they are not, in general, as effective as anionic surfactants in cleaning solid soils [2].

CLEANING OF OILY SOIL

The second major class of soils found on hair is hydrophobic, or oily, soil that is liquid, at least at cleaning temperatures. Examples include sebum from the scalp, which is mostly liquid at body temperature; silicones, oils and waxes from hair care products; and lipids from skin cells. There are a number of possible detergency mechanisms for these types of soils, including roll-back, emulsification, solubilization, and mesophase formation. These are discussed in the following sections.

Roll-Back Mechanism

The expression for work of adhesion in the previous section applies to oily soils as well as particulates. As with particulates, the more hydrophobic the liquid soil, the more difficult it is to remove from a hydrophobic substrate [4,5]. Also as with particulates, detergents can effect soil removal of oils by adsorbing to the hair surface. In this case, the increased affinity of the surface for water permits the water to displace the oil droplet and simply roll it up. This process is termed the roll-back mechanism This mechanism is described quantitatively by Young's equation (Chapter 9), which for aqueous systems is written as:

$$\gamma_{HW} = \gamma_{HO} + \gamma_{OW} \cos \Theta,$$

where γ is the interfacial tension between two phases, H represents hair, O represents the oil phase, and W represents water. Θ in the above equation is the contact angle between the soil and the hair surface; the lower this angle, the greater is the contact between the two phases.

It is implicit in Young's equation that adsorption of a surfactant to the hair surface, which lowers γ_{HW}, will increase the contact angle of the oil droplet. For sufficiently large increases in γ_{HW}, Θ will increase to 180°, and the oil droplet will spontaneously separate from the hair surface (Fig. 29.1). In practice, application of mechanical work during shampooing, for example, flexing and rubbing of hair, will help to completely remove those soils having contact angles increased to less than 180° but greater than 90°. Increased temperature also aids in soil removal, facilitating droplet roll-up by reducing soil viscosity and also by increasing rates of surfactant adsorption. These

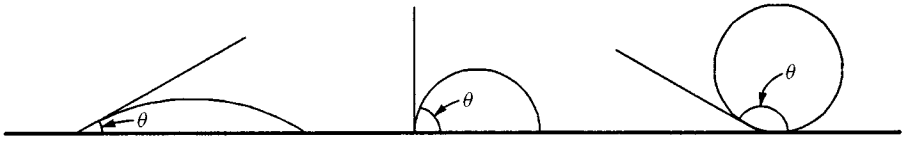

Figure 29.1. Different stages in cleaning by the roll-back mechanism. Note increase in the contact angle as the oil droplet is rolled back from the substrate

temperature effects are particularly important in view of the short cleaning times involved in the shampooing process.

Solubilization of Soils

The roll-back process is the most important soil removal mechanism for laundry detergents and other products that are highly diluted during cleaning so that surfactants are present primarily in the form of monomers.

If surfactant concentration is sufficiently high during use, then soil removal can also proceed via solubilization. This is accomplished by surfactant aggregates called micelles, which form above a certain concentration termed the critical micelle concentration, or CMC. The surfactants in micelles are arranged so that the surfactant heads form a hydrophilic surface in contact with the water, while the tails are lined up in the micelle interior, forming a hydrophobic core (Chapter 9).

Micelles solubilize soils by incorporation into the micellar structure. More polar soils are incorporated near the hydrophilic heads, while hydrophobic soils end up deep in the micelle interior. Kinetic investigations on fatty acid solubilization indicate that solubilization begins by diffusion of micelles to the soil surface, followed by surfactant adsorption onto the soil and incorporation of soil into the surfactant aggregate. The process ends by desorption of the soil-containing micelle and diffusion away from the surface. The latter two steps were found to control the rate of the solubilization process. The critical micelle concentrations for most anionic shampoo is about 5×10^{-3} M surfactants. It can be seen that in a shampoo containing 10–20% sodium lauryl sulfate most of the detergent (98–99%) is present in the form of micelles. Even if the shampoo is diluted 10-fold upon application to wet hair, as much as 88% of the surfactant is still in the form of micellar aggregates. The possibility exists, therefore, that solubilization is a major factor in shampoo cleaning.

Information concerning the relative importance of solubilization in soil removal comes from studies reporting that maximum detergency for several surfactants in cleaning fats and oils occurred at six to ten times the surfactant CMC. In these studies nonionic surfactants were found to have a greater solubilization capacity than anionics. This is presumably true because, as a result

of charge repulsion between adjacent surfactant heads, anionic surfactants generally have higher CMC values than nonionics [2]. At the low concentrations employed in these studies, there were simply fewer anionic micelles present and available for solubilizing soils. In addition, nonionic micelles tend to have larger aggregation numbers than anionics and, therefore, more room in the micelle interior to solubilize oily soils.

Under actual shampooing conditions, it is expected that anionics can solubilize significantly more oily soil than under the studied experimental conditions. One reason for this is the high surfactant concentration in shampoos, which results in a greater number of micelles available for solubilization. This number is increased by the fact that the effective CMC of anionic surfactants in commercial shampoos can be significantly reduced by the presence of common additives.

Inorganic salts, for example, decrease the CMC of anionic surfactants by compressing the electrical double layer around the hydrophilic heads, thereby decreasing charge repulsion. The CMC of sodium lauryl sulfate, for instance, is decreased by a factor of 10 in the presence of 0.1 M NaCl, a not uncommon amount of added salt. This effect, however, is decreased during rinsing as a result of shampoo dilution. A more important effect, since it is not reduced by rinsing, is that of viscosity and foam builders such as betaines and alkanol amides, which decrease CMC by forming mixed micelles with anionic surfactants, thereby shielding negative charge. The decrease in CMC engendered by these additives also causes an increase in micelle aggregation number, promoting solubilization as a result of increased room for hydrophobic materials in the micelle core. As with roll-back, soil removal by solubilization is greatly increased through rubbing and flexing of hair (mechanical work) and increasing temperature. More work needs to be done to precisely determine the contribution of solubilization in the hair-cleaning process. The work performed to date, however, clearly indicates a major role for this mechanism in the hair-cleaning process.

Emulsification, Penetration, and Mesophase Formation

Emulsification and mesophase, or liquid crystal, formation are two important mechanisms that can be involved in removal of soil from hair. Emulsification involves breaking down of an oily soil into smaller particles that can form a stable suspension. It requires a low interfacial tension between the oily soil and the bath medium which may be accomplished by adsorption of shampoo surfactant onto the soil surface. Mechanical work also helps in breaking up of the soil.

Amphiphilic compounds in soils, such as fatty alcohols or fatty acids, can greatly aid the emulsification process by interacting with the shampoo detergent to spontaneously emulsify the soil. Since the shampooing process is short, emulsified soils need be suspended for only a few moments.

Phase diagrams of detergents, water, and certain polar salts such as fatty acids and alcohols can contain large regions that flow easily and are composed of a liquid crystalline phase. Such mesophase formation with amphiphiles, or oily soils containing amphiphiles, constitutes another important mechanism for soil removal from hair.

EFFICACY OF SOIL REMOVAL BY SHAMPOOS

The soils most commonly found on hair originate from three sources: secretions from the body, residues from hair care products, and deposits from the environment. The first type of soil is composed mostly of sebum from the sebaceous glands. Residues from hair care products include hair spray resins and various conditioning materials, while environmental soils include particulate matter from soot, clays, rubber from automobile tires, and so forth.

The efficiency of shampoos in removing these soils and the types of mechanisms by which such removal is carried out depend on a number of factors, including the nature of the soil, the state and condition of the hair surface, and the particular surfactant or combination of surfactants employed in the shampoo. In the following sections the principles of cleaning of different soils by shampoos will be discussed.

CLEANING OF SEBUM

Sebum is probably the single most important soil found on human hair. It is composed of a mixture of lipid materials, briefly decribed in Chapter 1, that are secreted into the follicular duct by the sebaceous glands [5]. The emerging terminal scalp hair is coated with sebum, and mechanical actions such as combing and rubbing against pillows ensure that the sebum becomes distributed more or less evenly over the entire hair surface.

Sebum, which is almost completely molten at body temperature, lubricates the hair, giving it (when not present in excess) a smooth, moisturized feel. Hair with too much sebum on the surface, however, becomes limp and clumped together and is perceived by consumers as dull, dirty, and greasy. Moreover, because it is sticky, the presence of sebum leads to further soiling as a result of adhesion of airborne particulates and other material with which it comes in contact [5]. In addition, sebum can act as a binder, cementing many soil particles together.

Detergents do not penetrate hair appreciably during the relatively short times involved in shampooing. As a result, cleaning of soils such as sebum by shampoos is confined primarily to the hair surface. Internal lipids, however, do not appear to contribute to consumer-perceivable soiling effects. Thus Robbins [3] found that the same quantity of internal lipid (as much as 9% of the total hair

weight) could be extracted from both oily and dry hair, indicating that the oily feel of the hair was entirely due to surface sebum. Because of its composition and physical state, sebum can potentially be cleaned from hair by any of the cleaning mechanisms presented in the previous sections. Sebum can be removed from hair by a roll-back mechanism. Sebum is also subject to removal by emulsification and mesophase formation. Finally, since the concentrations of surfactants during cleaning are generally well above the surfactant CMCs, sebum can also be cleaned from hair by solubilization.

The relative importance of these mechanisms in cleaning sebum from hair is not identical and more than one cleaning mechanism can certainly operate simultaneously. In any case, the multiplicity of possible cleaning mechanisms for sebum might lead one to expect that shampoos would be very effective in removing sebum from hair. This expectation is supported by much of the literature: a number of studies have demonstrated that anionic surfactants at normal shampoo concentrations can clean surface lipids effectively [6]. Effective cleaning of lipids by anionic surfactants was also reported by Thompson [7], who used gas chromatographic techniques to measure percent removal from hair of the various components of an artificial sebum. Table 29.1 lists some of the results from Thompson's work. It can be seen that the more polar fractions of the sebum, such as free fatty acids, were removed from hair to a greater extent than the less polar fractions, such as paraffin. In other words, hydrophobic soils, like paraffin, have a greater affinity for the hydrophobic hair surface than do more polar deposits and are therefore more difficult to remove.

Sodium laureth-2 sulfate (SLES-2) is seen in Table 29.1 to remove sebum fractions from hair more effectively than ammonium lauryl sulfate, a result also found in other studies [6]. One reason for this may be related to higher adsorption of SLES-2 than of SLS, which would favor increased removal of sebum by the roll-back mechanism. This could explain the superior cleansing by SLES-2 observed by Clarke at concentrations below the CMC [6].

Table 29.1* Sebum Cleaning by Surfactants

Sebum Component	% Removal by SLES-2	% Removal by ALS
Triglycerides	94.7	94.6
Free fatty acids	96.2	97.1
Spermaceti wax	96.2	84.6
Squalene	98.4	87.6
Paraffin	95.2	80.8
Average % removal	95.9	85.9

*After Ref. 7

The results may also reflect differences in the CMC and the aggregation numbers of the surfactants [2,8]. In addition, the reported studies were conducted on untreated (hydrophobic) hair; the effects of diverse treatments that make the hair more hydrophilic must always be considered when surface sebum removal is examined.

CLEANING OF QUATERNARY AMMONIUM COMPOUNDS

Conditioners are used to increase ease of hair combing, reduce flyaway, and improve the feel of the hair [3]. The most widely used conditioning agents in commercial products are quaternary ammonium compounds. These compounds are generally used in combination with lipid conditioners such as long-chain alcohols [8].

Two of the most widely used quaternary conditioners are stearalkonium chloride (SAC) and cetrimonium chloride (CTAC). Other important quats include steartrimonium chloride, dicetydimonium chloride, and tricetylmonium chloride. The most important lipid conditioners include cetyl and stearyl alcohols. Concentrations of cationic surfactants in commercial conditioners are generally on the order of 1–2%, while lipid concentrations are equal to or greater than those of the quats.

Conditioners are generally used at pH levels above the isoelectric point of hair, that is, on negatively charged fiber surfaces. Quaternary ammonium compounds, by virtue of their positive charge, are therefore substantive to the hair surface. Treating hair with these compounds results in a hydrophobic coating that is soft and easy to comb. The binding to hair of quaternary compounds has been found to increase with increases in the hydrophobic chain length and number of chains [9]. This hydrophobic dependence indicates that van der Waals forces play an important role in the deposition of quats on hair. Deposition of quaternary conditioners on hair is also a function of the degree of negative charge on the hair surface. Compared to virgin hair, bleached hair, which has a more negatively charged surface, retains more than twice the amount of stearalkonium chloride.

Table 29.2* Detergent Cleaning of Stearalkonium Chloride

Treatment	SAC (mg)/g Wool	Detergent (mg)/g Wool
1% SAC	6.68	—
5% ALS	—	1.94
1% SAC/5% ALS	4.58	4.09
5% SDES-2	—	1.94
1% SAC/5% SDES-2	2.52	2.12

*After Ref. 9

Many quats deposited from conditioning products have been reported to build up over time, indicating that removal of these materials from hair may be more difficult than is the case for sebum. One reason for this is simply the strong electrostatic attraction between the positively charged quats and the negatively charged hair surface. Another reason is that, since quaternary ammonium conditioners are solids, they are not subject to removal by the roll-back mechanism. In addition, the positive charge on quats interferes with the mechanism for particulate soil removal, that is, the introduction of negative potentials on soil and substrate as a result of adsorption of anionic surfactant.

Solubilization is a possible mechanism for cleaning of quaternary conditioners. Reich and coworkers have shown [9], however, that, at least for SAC and CTAC, solubilization by lauryl and laureth sulfates is ineffective. Instead, cleaning with these surfactants results in the formation of insoluble surfactant:quat complexes that are dulling and difficult to remove from hair. Reducing the hydrophobic chain length of the cleaning surfactant to 10 carbon atoms results in formation of more soluble surfactant:quat complexes, which can be more readily cleaned from the hair. Thus washing deposited SAC with 5% sodium deceth-2 sulfate (SDES-2) resulted in higher removal of the deposited conditioner.

The above findings apply to cleaning of the pure quaternary conditioners; cleaning of deposits from fully formulated conditioners lead to improved removal by ALS.

Despite increased quat removal from a fully formulated conditioner, insoluble complex formation between SAC and ALS still occurs. This is evidenced by the increase in deposited ALS measured after cleaning the residue with this surfactant [9].

CLEANING OF POLYMERIC RESIDUE

Several types of polymers can be found on hair as a result of use of hair care products, including hair spray resins, silicone conditioners, and cationic conditioning polymers. The ease of removal of these polymers from hair depends/on several factors, including charge, molecular weight, structure, nature of side chains, and so forth. In the following sections, the ease of cleaning of several important examples of hair care polymers will be discussed.

Cationic Conditioning Polymers

Several cationic polymers are available commercially that provide conditioning benefits, especially increased ease of wet combing. Important examples include polyquaternium-10, a quaternized hydroxyethylcellulose polymer; polyquaternium-11, a copolymer of vinylpyrrolidone and dimethylaminoethyl

methacrylate quaternized with dimethyl sulfate; polyquaternium-16, a copolymer of vinylpyrrolidone and quaternized vinylimidazole; polyquaternium-7, a copolymer of diallyldimethylammonium chloride and acrylamide; and polyquaternium-6, a homopolymer of diallyldimethylammonium chloride. As a result of their cationic nature, these conditioning polymers are substantive to hair. Deposition on hair fibers has been claimed to be an inverse function of charge density, an effect that has been explained by noting that the greater the charge density, the lower the weight of polymer needed to neutralize the total negative charge on the hair.

Polyquaternium-10 is quite substantive to hair, resisting complete removal by SLS even after exposure to detergent for as long as 30 minutes. Similar results were obtained in cleaning experiments with radiotagged polyquaternium-10 [10]. First, as with monofunctional quats, deposition of polyquaternium-10 was found to increase with increasing negative charge on the hair. Thus bleached hair was found to bind more than 2.3 times the amount of polyquat as did untreated hair. In addition, bound polyquaternium-10 was found to be difficult to remove: only 43% of the polyquat could be removed from wool swatches in a single washing with SLS.

Reducing the charge density on the polyquaternium-10 led to more complete cleaning. Thus in a single SLS wash, 75% of this polyquaternium could be removed from wool swatches [10]. Results similar to the above were obtained with polyquaternium-7, which was found to be about as resistant as polyquaternium-10 to removal from wool substrates. The difficulty in cleaning these polymers does not appear to be related to formation of insoluble conditioner:detergent complexes, as was the case with SAC and CTAC. This is evidenced by the fact that cleaning polymer-treated wool with SLS was not observed to result in detergent buildup, even after several cycles of polymer/detergent treatment. It is concluded, therefore, that the difficulty in cleaning polyquats is most likely related to the multiple points of attachment between the polymer and the keratin surface. In order to clean these polymers, it is necessary to break all the points of attachment at the same time, a more difficult proposition than the elimination of the single point of attachment between a small molecule and the hair surface.

Fixative Residue

The holding properties of styling products such as hair sprays, mousses, gels, and setting lotions are provided by various polymeric resins. These materials are generally neutral or negatively charged in order to facilitate removal from hair. Typical examples include the copolymer of vinyl acetate and crotonic acid, the ethyl ester of the copolymer of polyvinyl methyl ether and maleic anhydride (PVM/MA), the copolymer of polyvinyl pyrrolidone and vinyl

acetate (PVP/VA), and the copolymer of octylacrylamide/acrylates/butylaminoethyl methacrylate.

The ease of cleaning of hair spray resins was measured using the radiotagged ethyl ester of PVM/MA [10]. A single washing with 10% SLS resulted in removal of 89% of the deposited resin. This is also consistent with the expectation that non-cationic fixatives would be easier to remove from hair than positively charged polymers.

Dimethicone Residue

As was stated in the introduction, the active ingredient in most two-in-one shampoos is dimethicone, a hydrophobic polymer (polydimethylsiloxane), which is commonly found in many conditioners.

As was the case with fixative resins, little has been published in the literature on the ease of removal of dimethicone. One quantitative study, however, was performed by Rushton and coworkers [11], who used electronic spectrum for chemical analysis (ESCA) and atomic absorption measurements to study buildup and cleaning of dimethicone. ESCA measurements by Rushton indicated a dimethicone buildup of roughly 35% after five washings of virgin hair with a commercial two-in-one shampoo. After five washings, however, no further buildup was observed. In addition, Rushton found that more than 90% of deposited dimethicone could be removed by a single wash with a commercial shampoo.

CLEANING OF MIXED SOILS

The previous sections have dealt with cleaning of isolated soils from the hair surface. The situation closest to this condition is that of a person washing frequently, whose only hair care product is a simple cleaning shampoo. In this instance, sebum is the primary soil on the hair. Other soils are likely to be present, however, even in this case, since sebum will retain airborne particulates and other matter with which it comes into contact. Even in the absence of this additional matter, the nature of the sebum residue can change over time, as a result of lipolysis and other environmental processes that reduce the fluidity of the sebum. Depending on the nature and configuration of mixed deposits, the presence of other soils may make cleaning of a particular soil easier or more difficult.

EFFECT OF SHAMPOOS ON HAIR

The immediately preceding sections dealt with cleaning of soils by shampoos. Shampoos are also involved in damage of hair, either directly, through removal of structural components of the hair fiber, or indirectly, through removal of

protective deposits on the hair. These processes are discussed in the following sections.

DIRECT DAMAGE BY SHAMPOOS

Studies in the literature have indicated that the nonkeratinous regions of the hair, which include the endocuticle, or inner portion of the cuticle, and the cell membrane complex are susceptible to damage by surfactant molecules (Chapter 2).

These and additional experiments indicate that exposure to shampoos can have a deleterious effect on hair structure over time. The extent and consequences of these effects are unclear, especially since preexisting damage may render the hair more susceptible to surfactant damage.

INDIRECT DAMAGE BY SHAMPOOS

The use of shampoos can damage hair indirectly as a result of fiber abrasion occurring when hairs are rubbed against each other during cleaning. More important to the damage process, however, is the removal of sebum from the fiber surface during shampooing. This is because sebum acts as a natural lubricant for hair; removal of this material increases damage from grooming, due to chipping, fragmenting, and tearing away of cuticle cells, and it should be attributed to combing and brushing.

Figure 29.2 shows an example of the damage than can occur from grooming. This rather extreme example was induced by washing a tress of virgin hair with a cleaning shampoo and then combing it 700 times while wet. It can be seen that cuticle damage is widespread, with noticeable loss of some cuticle cells and extensive lifting of others from the hair surface. Repeated grooming of the hair gradually erodes the cuticle cells, with the greatest loss occurring at the tips of the hair. Eventually all of the cuticle cells can be lost, exposing the cortex and resulting in a split end. An example of such splitting is shown in Figure 29.3.

DAMAGE TO CHEMICALLY TREATED HAIR

Permanent waving, bleaching, and oxidative dyeing can result in significant damage to the hair. In addition to causing tensile damage, all of these treatments oxidize the surface of the hair, resulting in a considerable increase in surface friction. This subjects the hair to increased grooming damage because sebum is easier to clean from an oxidized hair surface, while combing forces are increased as a result of increased friction.

Chemically treated hair is also subject to increased water swelling and penetration by different materials as a result of reduced disulfide cross-linking and

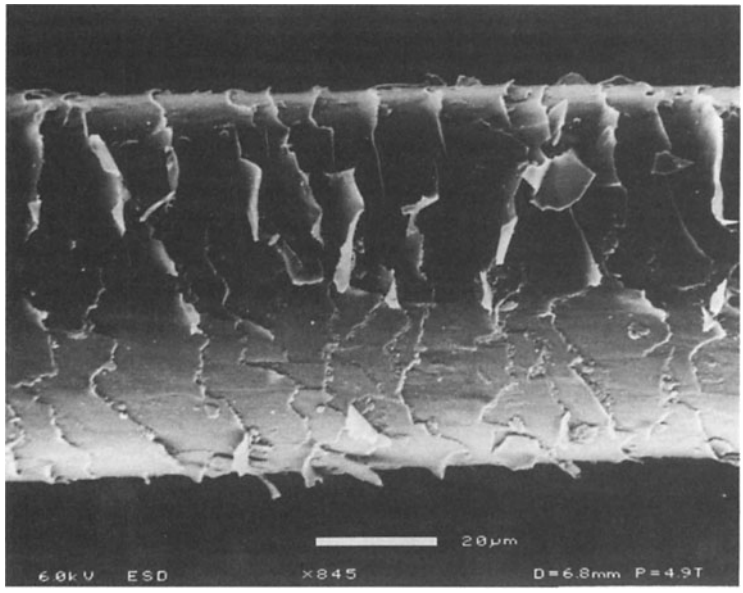

Figure 29.2. Combing damage resulting from washing a hair tress with a cleaning shampoo and then combing 700 times while wet. The scanning electron micrograph (SEM) is typical of hair taken from the combed tress. Note raised and chipped cuticle cells, and areas where cells have been completely torn away

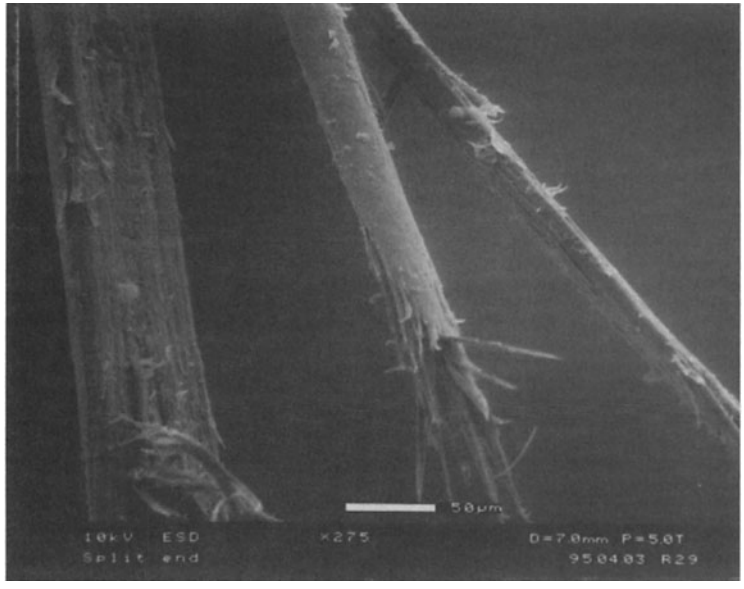

Figure 29.3. SEM photograph of a split end. Note the structure in the exposed cortex

damage to nonkeratinous regions of the hair, including the cell membrane complex [12,13]. Increased uptake of surfactants can, of course, lead to direct damage as a result of increased extraction of structural components of the hair fiber.

A shampoo formula intended for reduced hair damage follows below. This patented formula (Japan Patent 10,139,640) resembles the composition of a typical silicone-free two-in-one shampoo.

Shampoo for reduced hair damage*

Ingredient	%
Sodium laureth sulfate	7.00
Sodium lauroylalaninate	3.00
Lauramidopropyl betaine	3.00
Cocamide DEA	5.00
Ethoxylated hydrogenated castor oil	3.00
Acylated collagen	0.20
Hydrolyzed keratin	0.10
Cationic cellulose	0.20
Dimethyldiallylammonium chloride/acrylamide copolymer	0.20
Fatty acid ethylene glycol diesters	1.00
Sodium sulfate	2.00
Sodium benzoate	1.00
Fragrance	0.50
Color	q.s
Water	q.s. to 100

*Some of the ingredients listed have no INCI designation.

ADDITIONAL SHAMPOO INGREDIENTS

The shampoo ingredients discussed below provide various additional benefits or aesthetics to the formula; some are critical to delivering a product that is acceptable to consumers, and others are completely optional.

Viscosity Modifiers

A variety of raw materials can provide a thickening effect to a shampoo formula. As discussed previously, many of these components, including fatty alkanolamides, betaines, amine oxides, quaternary polymers, and fatty materials, can also enhance foaming and conditioning.

As discussed previously, inorganic and organic salts are effective thickeners for anionic systems. The two most commonly used salts are sodium and ammonium chlorides. Ammonium chloride is reported to be more effective [14] but must be formulationed at pHs well below 7 to avoid liberation of ammonia. A broader pH range is possible with the addition of sodium chloride, but viscosity effects are more sensitive to variations in temperature and salt concentration. The salt concentration vs. viscosity curve is bell-shaped, and care should be taken during salt addition to avoid the downside of the curve.

Cellulose derivatives are water-soluble polymers that are easy to incorporate and are compatible with most shampoo formulations. These materials disperse easily in water at the levels used (0.5–1.5%). The most frequently used cellulose polymers are hydroxyethycellulose, methylcellulose, and hydroxypropyl methycellulose. Synthetic polymers, such as carbomers, can enhance a shampoo's viscosity and stability. A modified acrylate derivative (acrylates/steareth-20/methacrylate copolymer) and PEG-120 methyl glucose dioleate are also reported to be effective thickeners. Formulators should note that the addition of different thickening agents can result in variable rheology profiles.

Opacifying and Clarifying Agents

Opacity or pearlescence can be imparted to a shampoo by several different types of raw materials. Ethylene glycol stearate, glyceryl stearate, and cetyl or stearyl alcohols are frequently used with alkyl sulfates. These materials are incorporated into the surfactant solution at temperatures above their melting points and then crystallize upon cooling, producing a pearlaceous appearance. The opacifying effect is dependent on the crystal size, distribution and reflectance.

Solubilizing agents can be utilized to improve and stabilize the clarity of a shampoo. These include alcohols, such as ethanol, isopropanol, propylene glycol, butylene glycol, hexylene glycol, glycerin and sorbitol; phosphates and nonionic solubilizers, such as polyethoxylated alcohols and esters, have also been used.

Antioxidants/Sequestrants/UV Absorbers

Antioxidants are included in shampoo formulations to avoid oxidation of unsaturated components, such as vegetable oils and oleic acid derivatives. Typical antioxidants used are BHT, BHA, and tocopherol (Chapter 12).

Sequestering agents are included in shampoos to prevent discoloration and to improve the performance of the antimicrobial agents by forming soluble complexes with metal ions. Typically, EDTA and its salts, citric acid, or

polyphosphates are used. Additionally, shampoo formulations in clear packaging should contain a UV absorber, such as benzophenone, to protect against color fading or discoloration upon prolonged exposure to light.

Fragrance

Fragrance has become an increasingly important aspect of a shampoo formulation. The ability of a fragrance to influence consumers' perception of a shampoo should not be underestimated. The fragrance also serves the purpose of covering any base odor in the formula, particularly as the product ages. The level of fragrance incorporated into a shampoo formula above that necessary to cover base odor depends primarily on the intended shampoo market. Particular geographical regions, such as Asia and Latin America, prefer higher impact fragrances than other parts of the world, The fragrance must be compatible with the shampoo formula. It should not adversely affect viscosity or stability, nor should it induce irritation. Factors affecting fragrance selection include evaluations of the residual fragrance left on the hair following shampooing in addition to assessments of the fragrance in the package and during use.

Preservatives

Preservatives are essential components of a shampoo formulation to protect against microbial growth. Among the potential sources of microbial contamination are water supplies, improperly cleaned manufacturing equipment, and raw materials.

Frequently used preservatives include parabens, such as methylparaben and propylparaben, formaldehyde, imidazolidinyl ure, DMDM hydantoin, quaternium-15, and a mixture of chloromethyl isothiazolinone and methyl isothiazolinone (Chapter 14). DMDM hydantoin used at a level of 0.5% is an effective preservative. As discussed previously, the addition of a sequestering agent can enhance antimicrobial activity. Formaldehyde-releasing preservatives should not be used with protein derivatives as they are inactivated during condensation with the free amino groups. Care should be taken to ensure that manufacturing procedures and product specifications do not inactivate their antimicrobial activity.

SHAMPOO BENEFITS

There are many types of shampoo formulations available in the market. Formula differences arise from differences in consumer usage and preferences, water hardness, and regulatory requirements, to name a few. In order to deliver

the diverse benefits expected by consumers, compounders need to include agents other than cleansing or conditioning surfactants. In the abbreviated discussion that follows, shampoo formulations are classified into four basic functions: cleaning, mild (or baby), conditioning, and antidandruff. Variables such as the type and concentration of surfactants in the shampoo, the nature and concentration of any suspending agents, and the particle size of any solid actives employed, will all have an important impact on deposition and activity. Clinical studies correlating performance with deposition on hair and scalp can provide useful information on the true clinical efficacy of different antidandruff agents.

CLEANING SHAMPOOS

Basic cleaning shampoos may contain a variety of primary and secondary surfactants in order to obtain the desired aesthetics. These include whether the formula is to be clear or opaque, lathering properties and viscosity, and surfactant concentration. A typical cleaning shampoo formula follows:

Cleaning Shampoo

Ingredient	%
Ammonium lauryl sulfate	15
Cocamide DEA	2
Cocamidopropyl betaine	2
Fragrance	0.7
Preservative	0.5
Citric acid	0.3
Ammonium chloride	0.2
Color	0.001
Water	q.s.

MILD OR BABY SHAMPOOS

The primary requirement of a mild or baby shampoo is to allow only minimal eye, scalp, and skin irritation. Lather and detergency attributes are often compromised to deliver adequate mildness. They often contain mild surfactant systems, such as nonionics and amphoterics, as discussed previously. An example of a typical baby shampoo formula follows:

Baby Shampoo

Ingredient	%
PEG-80 sorbitan laurate	12
Sodium trideceth sulfate	5
Sodium lauroamphoacetate	5
PEG-120 methyl glucose dioleate	2
Cocamidopropyl hydroxysultaine	1
Fragrance	0.7
Preservative	0.5
Color	0.001
Water	q.s.

CONDITIONING SHAMPOOS

Conditioning shampoos are formulated to impart conditioning to hair, for example, improved combing, softness, and manageability, in addition to the usual cleaning benefits. In the past, the conditioning agents used in shampoos included fatty amides, fatty esters, quaternary compounds, protein derivatives, sterols, and polyols. For a variety of reasons, such as insufficient deposition and incompatibilities with anionic surfactants, shampoos using these conditioning agents were found to be deficient in performance, providing only a low level of conditioning, a coated heavy feel, or both. This state of affairs changed with the introduction of two-in-one conditioning shampoos in the latter part of the 1980s. These shampoos, based on dimethicone or related silicone conditioning agents, provide a much higher level of conditioning than was previously possible from a shampoo, together with a smooth, soft feel that is generally well liked by consumers.

Silicone Conditioners for Two-in-One Shampoos

Silicone conditioners for two-in-one shampoos include dimethicone, dimethiconol, amodimethicone, and dimethicone copolyol.

With the exception of most commercial dimethicone copolyols, the above silicone polymers are quite hydrophobic. They have very low surface free energies, spreading easily on hair to form uniform films that provice excellent conditioning, including reduced combing forces and a smooth, lubricious feel.

Because silicones like dimethicone are quite insoluble, they are formulated into shampoos in the form of emulsions and therefore require use of a suit-

able stabilizer or emulsifying agent. Delivery of dimethicone from two-in-one shampooos to hair is expected to occur at the rinsing stage, during which time the emulsion breaks, releasing the silicone for deposition. This separation of cleaning and conditioning permits the shampoo to perform each function without interference from the other.

In general, the level of conditioning from two-in-one shampoos is lower than that from stand-alone conditioners. Nevertheless, conditioning can be sufficiently high to protect hair from grooming damage. This is demonstrated by combing experiments similar to those described in the section on hair damage. In these experiments, the hair exposed to two-in-one shampoo is characterized by only minor chippping and fragmenting of cuticle cells. The lubrication provided by the dimethicone in the shampoo was sufficient to protect the hair from any major damage.

One reason for the improved efficacy of two-in-one shampoos is the relatively low amounts of dimethicone necessary to achieve significant conditioning [15]. Typical results were reported by Nanavati and Hami, who measured conditioning on slightly bleached European hair treated with dimethicone fluids or dimethiconol gums [16].

Formulation of shampoos containing one of the silicones exhibit as a rule reduced foaming, although amodimethicone and dimethicone copolyol did not interfere with foam development [15].

Silicone gums and high viscosity fluids can be difficult to emulsify mechanically without specialized plant equipment. As a result, many suppliers provide silicones as preformed emulsions or microemulsions that can be easily dispersed in a formulation [17]. A generic two-in-one conditioning shampoo is described below.

Conditioning Shampoo

Ingredient	Concentration	Function
Primary surfactant	12–20%	Cleansing agent
Dihydrogenated tallow phthalic acid amide	4–7%	Stabilizer
Dimethicone	0.5–3%	Conditioning agent
Cocamide DEA1%–5%		Foam, viscosity booster
Miscellaneous	q.s.	pH control, fragrance, preservatives, color, water, etc.

Pearlescent Conditioning Shampoo

Ingredient	%
A. Guar hydroxypropyltrimonium chloride	0.5
B. Water	q.s.
C. Citric acid	to adjust pH
D. Hydroxypropyl methylcellulose	0.6
E. TEA-lauryl sulfate (40%)	15.0
Glycol stearate	1.20
F. Sodium lauroamphoacetate (and) sodium trideceth sulfate (34.5%)	10.0
Cocamide DEA	2.50
G. Fragrance	0.75

Procedure: Disperse A in a vortex of well-agitated B. Reduce pH to 7.0 with C to promote dissolution. Heat to 50 °C. Sift D into ABC; mix until both polymers are fully dissolved. Increase temperature to 70 °C. Add E one at a time; mix well between each addition. Turn heat off when homogeneous. Maintain mixing. When temperature is at 55 °C, add F. Adjust to pH with C. When below 40 °C, add G.

Non-Silicone Conditioning Agents

A number of non-silicone conditioning agents have been used in shampoos, either alone or as secondary conditioners in two-in-one formulations. Because of their compatibility with anionic surfactants, a number of cationic polymers have been used as conditioners in shampoos. The two most widely used are polyquaternium-10 and polyquaternium-7. As was stated in the section on cleaning of cationic polymers, deposition of these two polymers from shampoos is greatly reduced as a result of formation of negatively charged polymer:anionic surfactant complexes. Significant conditioning can be obtained from cationic polymers in certain shampoo formulations. Care must be taken, however, to avoid buildup and a heavy, coated feel on the hair.

A patented shampoo formula (U.S. Patent. 5,747,436) based on the use of silicones and quaternaries follows.

Reduced Static Conditioning Shampoo

Ingredient	%
Polyquaternium-10	0.60
Sodium laureth sulfate	10.50
Cocamidopropyl betaine	7.80
Sodium cumene sulfonate	1.95
Disodium phosphate	0.45
Laureth-3-carboxylic acid	0.15
Isostearamidopropyl dimethylamine	0.21
Dimethicone copolyol (1500 cst)	0.10
Dimethicone copolyol (400 cst)	0.10
PEG-55 propylene glycol oleate	0.60
PEG-4-distearylethonium ethosulfate	0.20
Cetyltrimonium chloride	0.20
Water	q.s. to 100

Another patented (WO 99 02, 122) composition that contains a cationically modified cellulose and a silicone is included below for illustrative purposes.

Conditioning Shampoo*

Ingredient	%
3-Lauryldimethylammonium-2-hydroxypropyl PEG ether with cellulose	1.00
Polyquaternium-10	0.50
Dimethicone	1.00
Ammonium lauryl sulfate	6.00
Ammonium laureth-3-sulfate	4.00
Cocamidopropylbetaine	4.00
Lauramide DEA	2.00
Methylparaben	0.15
Propylparaben	0.05
Fragrance	0.05
Water	q.s. to 100

*Some of the ingredients listed have no INCI designation.

The use of quaternary ammonium compounds, such as CTAC in shampoos, is limited as a result of the incompatibility of most commercial quats with common anionic surfactants. Ethoxylated quaternaries, such as PEG-2

cocomonium chloride or PEG-15 stearmonium chloride, are more compatible with typical anionic detergents. Introduction of hydrophilic groups, however, greatly reduces the conditioning efficacy of these materials. It appears that other anionic detergent compatible quats are available, but they all suffer from the same types of conditioning limitations as the ethoxylated quaternaries. For additional conditioning shampoo compositions, refer to *Cosmet. Toiletries*, **113**(VI), 83–85, 1998.

ANTIDANDRUFF SHAMPOOS

In the United States shampoos and non-shampooos containing an antidandruff agent are considered drugs. Similar controls over these preparations exist in other legislative areas. Therefore antidandruff shampoos are included as OTC drugs in Chapter 19.

EVALUATION OF SHAMPOO ATTRIBUTES

Laboratory testing of shampoos is designed to measure performance and predict the consumer's response to a particular product. In some cases, laboratory tests are more sensitive than the consumer's assessment. Following laboratory assessments, prototype shampoo formulations are typically evaluated in the salon using half-head test methodology, which eliminates differences in hair diameter, density, and overall condition. Although again these are not consumer evaluations, they provide very useful side-by-side comparisons by a trained cosmetologist. Only after a potential product is screened in the laboratory and salon is consumer testing initiated. Various types of consumer testing have been described elsewhere [3].

Discussed next are several important shampoo attributes and commonly employed test methods.

Ease of Application

This attribute is related to shampoo viscosity. A shampoo should be viscous enough to remain in the palm of the hand during pouring, but should easily disperse over the hair during application.

Lather

Although not an indication of cleaning efficiency, the ability of a shampoo to provide a rich, copious lather is one of the first performance evaluations made by a consumer. A formulator should be aware that a consumer is likely to perceive a shampoo's lathering potential to reflect its efficacy. Therefore multiple facets of the lathering attribute should consider the speed with which lather is generated, the volume, the quality (i.e., loose or creamy), and the

stability of the lather on the hair. In vitro techniques for shampoo lather assessment have been published but have not been widely accepted [18,19].

Rinsing

Following lather generation, it is important that the shampoo easily rinse out of the hair. The rinsing ability of a shampoo is related to lather consistency, surfactant adsorption to the hair, water conditions, such as hardness, temperature and rinsing rate, and the amount of hair [3]. The surfactants should not precipitate onto the hair in hard water, nor should they leave a residual sticky or tacky feel on the hair surface.

Ease of Combing

Combing ease can be defined as the ease of aligning hair fibers in a parallel arrangement with a comb [20]. Evaluations of combing ease especially on wet hair are often used as the primary assessment for the broader consumer attribute of hair conditioning, which also includes hair softness and lubricity. Hair fiber properties that improve combing ease are increasing stiffness, diameter, and cohesion and decreasing curvature, friction, length and static charge. Studies have indicated how different types of hair treatments can affect combing ease. Shampoos can affect several of these properties depending on the particular formulation. For instance, high-cleaning shampoos can make the hair more difficult to comb by removing sebum and oily soils that can lubricate the hair, while conditioning shampoos can deposit materials on the hair that decrease friction and thereby make the hair easier to comb.

The ease of combing attribute includes ease of snag removal and ease of comb slip on both wet and dry hair. Methods to evaluate combing ease include both qualitative combing of tresses combined with statistical evaluation of the results and quantitative instrumental methods [20,21]. Instrumental methods involve the measurement of combing forces on tresses following treatment, using an Instron or Diastron tensile tester.

Softness

Hair softness is an attribute associated with a smooth feel, devoid of stiffness and stickiness. This attribute is evaluated on wet and dry hair as well as at the scalp and the ends of the hair [20].

LUSTER OR SHINE

Shine is an attribute of hair that is extremely important to consumers for aesthetic reasons. Consumers also tend to associate shine with hair that is in good condition, considering shiny hair (perhaps as a result of advertising messages) to be healthy hair. Both instrumental methods and subjective evaluations of tresses or heads of hair have been used to evaluate shine [1]. The

effects of shampoos on hair shine can vary. A cleaning shampoo that removes dulling deposits from hair will leave it in a shinier state. On the other hand, shampoos containing dulling ingredients, for example, soap or certain polymers, will leave hair with reduced shine. Finally, considerable dulling has been observed when the hair is washed with a shampoo that contains an ingredient that forms a complex with a material previously deposited on the hair.

BODY

The consumer attribute of body is both a visual and a tactile hair property indicative of fullness and volume combined with springiness and bounce. The effects shampoos have on hair body are formula-dependent. For instance, cleaning shampoos can provide an increase in hair body by removing surface oils that weigh down the hair. Alternatively, shampoos containing materials that can build up on the hair can reduce hair body. Straight fine hair is especially sensitive to the latter effects.

Several instrumental methods have been developed to evaluate parameters associated with hair body [22]. These approaches measure changes in fiber friction, stiffness, curvature, diameter, weight, cohesion, and length. Treatments that increase the hair's curvature or diameter increase the frictional forces between fibers, or make the hair stiffer increase body; those that increase the cohesion between fibers or weigh them down will decrease hair body.

MANAGEABILITY

Manageability is a measure of styling ease and style retention. It is a complex consumer attribute that is difficult to assess by any one hair parameter or method. It has been suggested that evaluators consider three types of manageability: style arrangement manageability, style retention manageability, and flyaway manageability. These properties can be assessed best by using a control treatment. As with other attributes, the effects that a particular shampoo has on manageability can vary. Any assessment of manageability is further complicated by factors involving the type of hair and style.

STABILITY

A shampoo should be stable for at least two to three years at room temperature in daylight conditions as well as at low or high ambient temperatures during warehouse storage. Although there are no industry standard aging or stability tests, each company has developed internal test methods to evaluate product stability. Typically, elevated temperatures are used to accelerate the aging of a product and predict its stability. Aging a product at multiple temperatures provides a more rigorous evaluation of stability, particularly for complex

emulsions. Freeze-thaw or temperature cycling indicates whether the product performance or aesthetics will be impaired in colder climates. Additionally, aging the product both in glass and in the actual packaging will indicate whether there is an adverse reaction between the product and the packaging materials. Shampoos sold in clear packaging should also be evaluated for color stability. As discussed in the section on shampoo ingredients, shampoos can be protected against degradation of color components upon exposure to light by incorporating a UV absorber such as benzophenone-2.

Safety of Shampoos

Shampoos are considered to be among the safest consumer products when used appropriately. Labels cautioning against accidental eye contact is included on most medicated and some cosmetic shampoo products. Adverse reactions to shampoos have been attributed to sensitization to medicated ingredients or preservatives [23].

Regulatory efforts have been made to ensure the safety of consumer products, such as shampoos. Considerable differences exist between major jurisdictions, such as the United States, the European Union, and Japan [24]. In some cases, ingredients are restricted or prohibited from use in cosmetic products.

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CHAPTER 30
Hair Setting Products

INTRODUCTION

A coiffure or hair style is created for many reasons including adornment, protection, convenience, temperature control, framing the face, coordination with clothing or apparel, and modification of the overall appearance or symmetry of the face, head, and body. Styling, fixative, and grooming products (referred to collectively as hair setting products in this chapter) are necessary to manipulate, hold, or adjust the configuration of the hair and to control durability, shine, or appearance of the hair arrangement and assembly throughout the day or week between shampoo and styling cycles. These products may also protect the hair during the styling process and subsequent grooming actions.

The hair style fails to hold its shape and appearance permanently for several reasons. These include increased relative humidity (atmospheric), compression during sleeping or from wearing apparel, wind, combing or brushing, manipulation with fingers, or other forms of distortion. Thus hair styling is an often repeated routine throughout the life span of the hair. For example, the hair is shampooed and conditioned to clean and prepare it for remolding by breaking hydrogen bonds with the water. Styling products are then applied to provide slip, detangling, and setting characteristics to the hair during the wet and dry stages of styling and finishing. The completed hair style may be fixed into place with a hair spray; the hair may be modified (before, after, or instead of the hair spray) with a shine or texture adjuster.

MECHANISM OF HAIR STYLING

The hair's tertiary protein structure is held together by hydrogen bonds, disulfide bonds, and salt bonds. As the humidity rises or the hair is wetted and the hydrogen bonds are broken, the hair becomes soft, is more easily stretched, and reverts to its permanent configuration established by the disulfide bonds, salt bonds, and other bonds during hair growth. In this softened condition,

the hair can be fashioned into a new shape by positioning and holding the hair in the new desired position or shape during drying. Typically, the hair is shampooed to remove sebum, corneocytes, previously applied styling products, dust, and other environmentally derived debris from the hair fibers and scalp. The shampoo process completely saturates the hair with water, thus breaking the hydrogen bonds of any previous "water set" retained by the hair. The hair can now be re-formed into a new style during a subsequent drying cycle.

This new "set" or curl pattern is permanent until the relative humidity rises, at which time the disulfide and salt bonds configuration pulls the hair back into its permanent configuration. Of course, this applies whether a curl is imposed onto straight hair or a curly hair is dried into a straighter pattern. In both cases, one of the purposes of styling products is to override the effects of the fluctuating relative humidity; another purpose is to provide curl memory after mechanical distortion. Since the cuticle scales are smooth and are all arranged pointing away from the scalp, the hair has a tendency to fall flat to the head under the influence of gravity (straight hair). Interfiber attachments created by styling products help to maintain the hairs in their place in the hair style. Newer products include thermal protection and protection from damage due to sun exposure. Hair fixatives such as hair sprays can supplement the styling product to hold the hair against the wind, to add additional resiliency to compression, or to increase the resistance to moisture or humidity. A group of other product types such as spray shines, pomades, and tonics confer additional modifications and effects to the look and feel of the hair style.

Protection

During the wet phase, the hair is softened and susceptible to stretching and abrasion damage. Therefore, protection from mechanical hair damage that may occur during the styling process is another benefit that a styling product can offer; this may be assessed as slip, detangling, or reduced friction between the hair and the styling devices during the entire process from very wet to the drying stage. Ever since the introduction of heated implements that were designed to dry and curl or straighten hair, thermal damage has been a concern. Recently, thermal damage has been quantified, and subsequently protection from thermal damage has been attributed to some polymers and conditioning agents [1].

Styles can also be retouched or refreshed throughout the day or daily between shampoos using thermal styling implements (curling irons). Sometimes certain sections of the hair style may be curled repeatedly to refresh the bounce or intensity of the curl. Many people shampoo infrequently for many reasons: convenience; because the hair style or hair type requires many

hours to complete the cycle of shampooing, drying, and styling; or to minimize hair damage, stripping of color, or even scalp irritation. In any case, the style may be refreshed or restyled without going through the entire cycle of shampooing, drying, and styling the hair. This creates a new type of styling products that contain very little water or that distribute readily onto dry hair for fast drying and with low tack to facilitate restyling dry hair—usually with thermal implements but possibly simply with the fingers at ambient conditions.

EFFECT OF STYLING PRODUCTS

Hair styling products may be classified by their rheological attributes, their spreading characteristics, and their dispensing mode of application, as well as the final attributes they provide to the hair. Depending on the hair style, styling technique, and type of hair, styling the hair may require a product with a particular spreading or distribution characteristic (rheology), degree of tackiness or wetness, a high enough molecular weight of polymer for crispness or slip (~500,000 to 1,500,000), low molecular weight of polymer for sprayability (~10,000 to 200,000), or a host of other additives for the required feel, shine, or hold characteristics specified by the consumer's need. Curly hair styled straight may have different and specific needs than straight hair styled curly.

Typically, the polymer provides many of the attributes during styling, as well as the final holding and texture characteristics. However, the total formulation determines functionality such as ease of application, distribution of polymer, absence of flaking, shine, longevity of hold, restylability, and removability. Product performance and efficacy is rarely a function of only one active ingredient. The entire formulation and package or delivery mechanism contribute to the characteristic effect developed on the hair.

FORMULATION PRINCIPLES

The number of hair styling products is large. To help in the identification of products, Table 30.1 is included.

PRODUCT COMPONENTS

A typical styling or fixative product might contain solvents, co-solvents and propellants, styling polymer(s), viscosity-increasing polymer, polymer modifier, preservative, color, fragrance, and solubilizer, and marketing concept additives.

Solvents

The solvent is typically water because of good solvency and clarity, low toxicity, low cost, high volatility, and efficiency for breaking hydrogen bonds.

Table 30.1 Overview of Hair Styling Products

Products used on wet hair

1 Liquids, lotions, splash-ons, spray gels (without gelling agent)
2 Glazes, lotions, spray gels (with gelling agent)
3 Gels, cream gels, emulsion creams
4 Ringing gels, pomades, styling sticks, aqueous liquid pomades, cream emulsions
5 Shaping sprays, mousses, postfoaming gel mousses

Products used on dry hair

1 Pump sprays, spritzes, shaping spray
2 Aerosols (pressurized cans)

Products used to create special effects on dry hair after styling is almost complete

1 Pomades, aqueous liquid pomades, ringing gels, and cream emulsions
2. Anhydrous silicone and nonsilicone shine drops and sprays, hair mascaras

It is the same solvent as that in freshly shampooed hair but is kept as low as possible in hair sprays.

Co-solvent and Propellant

Typically, ethanol or isopropanol helps to decrease the viscosity (to allow for spraying or penetration into the hair bundles) or increase drying. Propellants supply pressure to deliver product, improve dry time by quicker evaporation, and help to produce smaller particles. Hydrocarbons, dimethyl ether, and hydrofluorocarbon are the most common propellants today.

Polymer (Resin)

Historically, the most ubiquitous polymer in styling products has been PVP K-30 (~60,000 Kd). Its ready solubility in water or ethanol, ease of sprayability at low to high concentrations (1–8%), versatility in modifying its stiffness or brittleness (flaking), good adhesion to keratin, clarity of its film, and its nonionic character offering compatibility with cationic antistatic agents have made it the agent of choice. However, many other polymers have been or could be incorporated in addition to PVP K-30 or used alone.

For sprayable applications, low molecular weight polymers may be used up to 16% solids, whereas the higher molecular weight polymers must be kept low, ~0.2% solids depending on the polymer characteristics. For splash-on lotions, the high molecular weight polymers could be used at 2% solids or more.

Some examples of other polymers that have been used for styling or hair spray include PVP, PVP/VA copolymers, polyquaternium-11 (low and

high MW), PVP/dimethylaminoethylmethacrylate copolymer (low and high MW), vinyl caprolactam/PVP/dimethylaminoethyl methacrylate copolymer, polyquaterniums 2, 4, 7, 10, 11, 16, 28, 39, 46, and so forth, sodium polystyrenesulfonate, PVP/DMAPA acrylates copolymer, acrylates copolymer, corn starch/acrylamide/sodium acrylate copolymer, PVP/vinylcaprolactam/DMAPA acrylates copolymer, isobutylene/ethylmaleimide/hydroxyethylmaleimide copolymer, diglycol/CHDM/isophthalates/SIP copolymer, proteins and protein derivatives, ethyl and butyl esters of PVM/MA copolymers, VA/crotonates acid/vinyl neodecanoate copolymer, octylacrylamide/acrylates/butylaminoethyl methacrylate copolymer, acrylates/hydroxyesters acrylates copolymer, acrylates/C1-2 succinates/hydroxyacrylates copolymer, acrylates/acrylamide copolymer, polyvinylcaprolactam, adipic acid/epoxypropyl diethylenetriamine copolymer, polyurethane-1, polyester-1, VA/butyl maleate/isobornylacrylate copolymer, methacryloyl ethyl betaine/methacrylates copolymer, methacrylates/acrylates copolymer/amine salt, methacryloylethyl betaine/methacrylate copolymer, AMP-acrylates/diacetone copolymer, AMPD-acrylates/diacetone copolymer, acrylates/methacrylates copolymer, and others.

Depending on their solubilities, ionic character, molecular weight or size in solution, sprayability, compatibility with solvents or thickeners, stiffness, smoothness, or raspiness, these polymers will be chosen to deliver their special attributes for styling or fixative products.

Modifier

Usually very little modifier is required to make dramatic changes to the polymer character. Plasticizers, humectants, detackifiers, wetting agents, and antistatic agents make up the bulk of the modifiers. Propylene glycol, glycerin, and ethoxylated and/or propoxylated lipids or silicones have been the primary plasticizers because of their ability to bind moisture. They may also provide wetting or lower surface tension, which helps the polymer flow to attach to the keratin or hair surface. Since most polymers become less brittle as the water content rises, incorporating a water-like or water-binding molecule in the polymer film is a direct method of plasticization, as also observed with salts, polyols, or ethoxylated polymers. Preventing complete dryness or giving a medium to bridge the polymer to the atmospheric moisture also provides for a small amount of antistatic effect. Large waxy hydrogen-bonding polyol derivatives may also provide for some smoothness to the touch as you run your fingers down the tress of hair. It is considered significant that after adding the additives the dried film is still clear for maximum shine and minimum interference with the natural look of the hair.

Examples of polyols and wetting agents used as antitack and feel modifiers follow: propylene glycol, glycerin, 1,3-butane diol, PEG-8, oleth-20, laureth-23, PEG-60 almond glycerides, PEG-40 castor oil, dimethicone copolyol, PPG-12 buteth-16.

Water-soluble mono-alkyl quaternary salts (quats) have been used for reducing static, although larger and less soluble quats could be used, depending on the solvent mix and solubilizers present. Quats that are sprayed into a cloud around the head and are inhaled may induce coughing. Judicious formulation and control of quat choice and particle size (and placement onto the hair and not inhaled) will allow a properly balanced formula to be produced. Examples of antistatic agents are quaternium 22, 26, 52, cetrimonium chloride or bromide, steartrimonium chloride, and others in the family.

An old rule of thumb suggests keeping the modifier at <10% of the polymer solids level. Thus if 3% PVP K-30 is used, then 0.3% glycerin would be evaluated as a midpoint level to test the effect of this plasticizer on the system. From there, higher and lower levels can be evaluated for optimum performance based on the product profile. Very little antistatic agent is needed, but antistatic properties are very important since recent styling changes involve brushing or handling during the drying process. Brushing dry hair develops significant levels of static, which renders the hair unmanageable as the individual hairs repel each other and stand away from or stick to the head. Antistatic agents incorporated at 0.05–0.25% active levels together with the proper levels of the other modifiers can reduce the static levels to allow unhampered styling of the hair.

Dimethyl or diethyl phthalate is rarely used today as a plasticizer because of lack of solubility in alcohol-free systems. Most U.S. formulations are intended to be alcohol-free for marketing appeal and for regulatory reasons.

Using higher levels of polyol plasticizers or wetting agents can cause the styling product to take too long to dry, to stay in the tacky stage too long, or never to develop any stiffness. Since styles and techniques change over the years, or among age groups or countries, hard and fast rules for preferences cannot be made. Choice of levels of modifiers and final effect will depend on the current product profile and needs of the hair style.

Preservative

Aqueous solutions must be preserved. Even hot processing or pasteurization is rarely perfect, and most packaging allows for air or liquids to enter the package during normal use (and consumers also return unused portions of product back to the container). Some products may be adequately "protected" at levels >25% alcohol or >35% glycols, but this must be confirmed by microbial challenge tests (procedure available from CTFA). Preservatives are

used to prevent growth of organisms that may inadvertently be introduced to the product but are not intended to sanitize the product.

Color

Water-soluble colors may be used; if the alcohol level is high enough, it may be possible to use alcohol-soluble colors. Typically, certified colorants are used at low concentrations ($\sim<0.001\%$) so as to color only the product and not the hair. Some colors are more stable than others to degradation in the presence of light, especially UV or sunlight. UV absorbers have been placed in the packaging or dissolved in the product solution (such as benzophenone-4) with varying levels of success in preventing color fading. Sometimes Ext. D&C Violet #2 is used to counter the hint of yellow color imposed by higher levels of many polymers or increase in yellow color over time and with exposure to heat. Some products have been formulated with higher levels of color expressly to add or enhance the color of hair. Others have been colored brown with caramel coloring to minimize the visible effects of flaking on dark brown or black hair.

Fragrance and Solubilizer

Fragrance continues to exert a major marketing impact on hair care products. Spray-on products can use much less fragrance "oil" than splash-ons or gels because of the high surface area developed by the formation of fine droplets of the spray. The high surface area allows the fragrance to evaporate into the air at a faster rate; thus less fragrance is required. Since fragrances are typically insoluble "oils," they need to have a solubilizer to help incorporate them into the aqueous solution; if the alcohol content is high enough, the solubilizer level may be reduced significantly or eliminated completely. As stated earlier, solubilizers also affect the polymer film either in a beneficial or deleterious way, depending on the solubilizer type and level utilized. Popular solubilizers are polysorbate 20 and 80, PEG-60 almond glycerides, PEG-40 or 60 hydrogenated castor oil, oleth-20, laureth-23, PEG-75 lanolin, and any one of many that have a similar structure. The nonionics are more common, perhaps because of lower degree of foaming.

Marketing Concept Additives

These ingredients could be included as a marketing focus, even though they may be the primary actives. However, they could be used to create a unity for a family of products. Examples of this category of products are endless, but a few include fragrance, proteins and protein derivatives (from fatty acid condensates, or polymers, to silicones), sodium PCA, panthenol and derivatives, lactic acid, citric acid, botanical extracts, vitamins A, B, E, and, others, allantoin and derivatives, pearlaceous pigments, colors, UV absorbers (protection for

the product or for the hair), EDTA, minerals like magnesium sulfate, natural oils like jojoba or olive, silicones, glucosamine hydrochloride, hyaluronic acid, and many others. These may change with the cyclic consumer and marketing flavor or technical breakthroughs. They are used at levels according to their activity, impact, and costs, starting at 0.0001 to 10% wt/wt.

PRODUCTS FOR SETTING OR SHAPING THE HAIR STYLE (USED ON WET HAIR)

LIQUIDS, LOTIONS, SPLASH-ONS, SPRAY GELS (WITHOUT GELLING AGENTS)

This category represents low-viscosity formulations that derive most of their function, rheology, and ease of application and distribution onto and throughout the hair from the polymer type and concentration. Depending on the polymer and modifiers chosen, the resulting dried hair could be stiff and crunchy, moderately firm and flexible, or soft to the touch, and run the range of smooth to raspy feel. The viscosity of these liquid product forms ranges from <10 cps to 3,000 cps. These low-viscosity products could be dispensed from glass, aluminum, or plastic squeeze bottles into the palm of the hand or directly onto the hair. The product might be massaged uniformly throughout all the hair or only on the portion of hair that needs this particular styling aid. The hair could be combed into place, either straight or in wave patterns (finger waves). The hair is then wrapped and held on plastic rollers or fashioned in free-standing or flat curls, (with bobby pins or clips) until the hair and the styling aid are completely dry. Applying the product to the hands usually resulted in an undesirable feeling of stickiness as the solvent evaporated and the concentration of the actives increased on the hands. Molecular weights as high as 60,000 to 120,000 are easily employed at levels of 3–8% in low-viscosity aqueous sprays or lotions, and polymers up to 1,500,000 molecular weight can be sprayed at levels of 0.2% active or used up to 3% active in lotion types. Use of co-solvents and surfactants such as ethanol and nonionics or ionics, could allow much higher levels of various structured and high molecular weight polymers to be used in products in which a low-viscosity is desired.

Since these products are low-viscosity liquids and supply no physical structure, they do not hold the hair in place until it dries. These products are well suited for men's and women's hair styling, utilizing techniques such as wet setting (hair is wrapped around rollers or mandrels), wet look (combed through and allowed to dry without disturbing hair orientation, resulting in a shiny wet look when dry), and blow-drying. A number of prototype liquid

Formula III A 1 Setting Lotion

Ingredients	%Wt/Wt
Water	q.s.
PVP K-30*	2.0–8.0*
Glycerin	0.1–0.5
Cetrimonium chloride (25% aqueous)	0.1–0.8
Oleth-20 and fragrance	0.8
Diazolidinyl urea (and) iodopropynyl butylcarbamate	0.2

*PVP K-90 (1,300,000 MW) creates a significantly stiffer product than the K-30 version (60,000 MW). The K-30 form can be sprayed, whereas the K-90 form cannot be sprayed.

Formula III A 2 Blow-Dry Lotion

Ingredient	%Wt/WT
Water	q.s.
Polyquaternium-28 (20% aqueous)	5.0–10.0*
Quaternium-26 (50% in propylene glycol)	0.3
Propylene glycol	0.05–0.3
Other ingredients as in Formula III A 1	

*Other polymers can be used, e.g., PVP/dimethylaminoethyl methacrylate, polyxquaternium-4, and many others in the category.

setting lotions and spray gels follow to illustrate the use of diverse polymers in styling products applied to water-wet hair followed by drying. For preparation the ingredients are added with agitation in the order listed.

In general, the PVP family is crisp and produces a raspy feel on the dry hair. The related PVP/VA copolymer is a copolymer of the flexible and nonwater-soluble vinyl acetate with vinyl pyrrolidone. Increasing the vinyl acetate in the copolymer makes it more flexible, less affected by humidity, less tacky, and less soluble in aqueous systems.

The polyquaternium-28 provides much longer retention of curl under high humidity conditions than does PVP/VA or PVP; this is another criterion that is used in selecting a polymer for a styling product.

GLAZES, SCULPTING LOTIONS, SPRAY GELS (WITH GELLING AGENT)

These low- to moderate-viscosity styling products differ from the simple polymeric solutions because they have rheological attributes facilitating their use

Formula III A 3 Tack-Free Sprayable Lotion (Low-Viscosity)

Ingredients	%Wt/Wt
SD alcohol 40-B (anhydrous)	73.7
Water	6.25
Aminomethylpropanol	0.3
Butyl ester of PVM/MA copolymer (50% active)	12.0
Cyclomethicone (D5)	7.5
Dimethicone (5 cs)	0.05
Fragrance	0.2

Add components in order listed. Very thin and sprayable product; dries without tackiness.

Formula III A 4 Fibrous and Stringy Lotion (Forms Threads)

Ingredients	%Wt/Wt
Water	80.65
PVP K-90 (powder)	7.0
PVP/DMAPA acrylates copolymer (10% active, very high MW)	10.0
Quaternium-52 (25% active in water)	0.5
Lactic acid (88%)	0.05
Ceteth-20	1.0
Fragrance	0.2
Propylene glycol (and) diazolidinyl urea (and) iodopropynyl butyl carbonate	0.5

Add components in order listed. Clear product of moderate viscosity. Provides visual evidence of tack during drying.

in styling hair. A viscosity-increasing additive is added to the product to create body, to prevent dripping, or to allow for a different feel during distribution. Once on the hair, the product exerts a cohesive force to hold the hairs together.

Cellulose or carbohydrate-type derivatives are not subject to shear thinning. They yield styling products that exhibit slip, cushion, and detangling as they are distributed throughout the hair. Commonly used cellulosic types are hydroxyethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl guar, tragacanth gum, karaya gum, xanthan gum, and others. Synthetic nonionics are also available as in the preblend of polyacrylamide, laureth-7, and C13-14 isoparaffin. The nonionic types allow for ease of formulation with cationic polymers or cationic antistatic additives. As molecular weights or concentrations of these cellulosic thickeners increase,

Formula III A 5 Low-Viscosity Lotion (Thermal Protection and Split End Treatment)

Ingredients	%Wt/Wt
Water	85.475
PVP/DMAPA acrylates copolymer (10% active in water)	12.0
Glyceryl polymethacrylate (and) propylene glycol (and) PVM/MA copolymer	0.5
Acetamide MEA	0.5
Polysorbate 20	1.0
Fragrance	0.2
Methylchloroisothiazolinone and methylisothiazolinone,	0.075
Methyl paraben	0.15

Add in order listed. A low-viscosity product with high slip when wet and with a flexible natural feel when dry; can be used to seal and hide split ends.

the viscosity increases and the spreadability decreases. If there is difficulty in spreading the product to get uniform distribution throughout the hair, flaking or bridges may form between fibers. Generally, only the lowest viscosity grades or molecular weights of these cellulosics are barely sprayable.

For providing shear thinning, anionic polycarboxylate polymers are used. Products made with these thickeners spread easily but without cushion. Such gels thin when sheared, but the gel strength returns when agitation stops. This shear-thinning characteristic allows for very thin and uniform distribution throughout the hair. Common polyanionic gelling products include carbomer,

Formula III B 1 Non-Drip Lotion Glaze

Ingredients	%Wt/Wt
Water	85.4
Hydroxyethylcellulose (med. viscosity)	0.5
Polyquaternium-4 (powder)	0.5
Polyquaternium-11 (20% active in water, high molecular weight)	10.0
Glycerin	2.0
Sodium PCA	0.1
Polysorbate 80	1.0
Fragrance	0.2
Diazolidinyl urea (and) iodopropynyl butylcarbamate	0.2

Add hydroxyethylcellulose and polyquaternium-4 to water and mix until completely hydrated (40 minutes at 40 °C or 2 hours at RT). Add other ingredients in the order shown. Mix until clear.

Formula III B 2 Pourable Sculpting Gel

Ingredients	%Wt/Wt
Water	80.75
Hydroxyethylcellulose (high viscosity)	1.2
PVP/DMAPA acrylates copolymer (10% in water)	15.0
Quaternium 26 (~50% in propylene glycol)	0.75
Diazolidinyl urea (and) methyl paraben (and) propyl paraben (and) propylene glycol	1.0
PEG-20 stearate	1.0
Fragrance	0.2

Add hydroxyethylcellulose to water and mix until completely hydrated (40 minutes at 40 °C, or 2 hours at RT). Add other ingredients in order listed. Mix until clear.

Formula III B 3 Antifrizz Gel (High Humectant)

Ingredients	%Wt/Wt
Water	76.4
Hydroxyethylcellulose (med. viscosity)	1.2
Polyquaternium-28 (20% aqueous)	15.0
Propylene glycol	3.0
Glycerin	2.0
Gluceth-20	1.0
PEG-75 palm kernel glycerides	1.0
Fragrance	0.2
Panthenol (powder)	0.1
Diazolidinyl urea (and) methyl paraben (and) propyl paraben (and) propylene glycol	0.9

Add hydroxyethylcellulose to water and mix until completely hydrated (40 minutes at 40 °C or 2 hours at RT). Add other components in order shown. Mix until clear. Product weights hair, smooths, controls style, and prevents flyaway.

PVM/MA decadiene crosspolymer, acrylates/steareth-20 acrylates copolymer, acrylates copolymer and others. Each gelling polymer (anionic or nonionic) has a specific pH requirement for clarity, viscosity, and compatibility with polymers, salts, and additives [2].

A few prototype glazes and spray gels follow to illustrate the compositions of these types of products.

GELS, CREAM GELS (EMULSION FORMS)

These medium, to high-viscosity products employ high levels of gelling agents or a hybrid of several viscosity-builders to deliver a desirable holding and

Formula III B 4 Spray-Gel (Pump Spray)

Ingredients	%Wt/Wt
Water	73.29
PVM/MA decadiene cross-polymer	0.28
Diazolidinyl urea (and) methyl paraben (and) propyl paraben (and) propylene glycol	0.85
Water	20.0
PVP K-30	3.0
Triethanolamine (99%)	0.28
Oleth-20	1.0
Fragrance	0.2

Add the PVM/MA decadiene cross-polymer to the water in main kettle, heat to 70 °C, and mix for 45 minutes. Cool to 40 °C and add preservative blend. In side kettle, dissolve PVP in water and de-aerate; add TEA and preblended fragrance. Transfer side kettle to main kettle and mix 30 minutes after clarity is reached. Another thickening polymer is acrylates/steareth-20 methacrylate which is supplied as an emulsion. This formula could be packaged in a tube with small orifice or 2 ml-output cream-type pump.

fixative effect on hair. They are typically provided in squeeze tubes, open-mouth jars, or containers with a pump dispenser.

Gels

Gels are high-viscosity preparations based on carbomers, PVM/MA decadiene crosspolymer or acrylates/steareth-20 methacrylate copolymer or related styling polymers. These type of "thickeners" at higher viscosities (20,000–175,000 cps) offer wet-strength holding power. The product can be distributed through the hair, and the hair can now be fashioned into curls that will hold their own shape during drying with or without the aid of a pin or clip. The same rules as for lotions (cf. B above) apply for flaking in regard to uniform and thin distribution as well as plasticization. These gels use primarily PVP or PVP/VA polymers as hair-bodying agents. Several recent introductions have included blends of two or more of these polymers: PVP, PVP/VA, PVP/dimethylaminoethylmethacrylate, polyquaternium-11 or -4, PVF, PVP/DMAPA acrylates copolymer, and others to create just the right level of stiffness, raspiness, volume, body, flexibility, manageability, improved curl retention, feel and shine on the hair, and thermal protection. The viscosity is mostly dependent on the properties of the thickener, whereas the stiffness and bodying are mostly dependent on the styling polymer. However, the very high molecular weight and the cationic styling polymers do influence the viscosity of the thickener because of competition for the water or interactions with the anionic thickener. The shear thinning of the anionic thickeners

Formula III C 1 High-Viscosity Gel

Ingredients	%Wt/Wt
Water #1	72.23
Carbomer	0.5
Glycerin	0.5
Panthenol	0.05
Disodium EDTA	0.05
Benzophenone-4	0.02
Diazolidinyl urea (and) iodopropynyl butylcarbamate	0.2
Water #2	20.0
PVP K-90	2.0
PVP/dimethylaminoethylmethacrylate copolymer (20% active, high MW)	3.0
Oleth-20	0.8
Fragrance	0.15
Aminomethylpropanol	0.5

Disperse carbomer powder into water #1 in main kettle using a strong vortex with low-shear agitators (propeller types); mix until completely homogeneous and smooth (translucent gray). Add other ingredients in order. In side kettle, add PVP to water #2 and mix until dissolved. Reduce agitation to de-aerate; add other ingredients in order. Transfer side kettle to main kettle, increasing agitation as viscosity increases. Mix at least 30 minutes after gel reaches clarity. Check the pH and viscosity within an hour after mixing and again the next day. Tiny air bubbles create haze in a gel, and vacuum kettles work well to make these clear gels quickly without entraining air. It is best to prevent air from entering a gel; it is next to impossible to remove it from a gel short of using a Versator®.

is sometimes modified with cellulosic-type thickeners to give some slip or cushion after the gel thins down to facilitate distribution throughout rough hair.

Gels may contain high alcohol levels or may be alcohol-free. Alcohol levels of 10–30% facilitate use of polymers because of increased solubility, increase the clarity of the gel, and shorten dry times. A rapidly growing market in gels currently is the nonchemical relaxers. Some of these are styling gels that contain high levels of a silicone, oil, or wax that supply some slip to prevent damage during stretching or ironing. The oils give the hair some heaviness that helps the curl to hang out and perhaps add some hydrophobic character to the hair. Other formulas are utilizing polymers with better high-humidity curl retention, good slip properties, and thermal protection. Curly hair being styled straight suffers from the same problem as straight hair being styled curly: whenever the humidity rises, the hair returns to its original configuration. Therefore, the polymer and complete formulation should enhance resistance to humidity to maintain the style.

Typically, the wet curly hair is towel-blotted, hair is detangled, some water removed by blow-drying, and nonchemical relaxing gel or cream (sometimes called "relaxing balm") is applied and distributed. Then the hair is dried while

Formula III C 2 Styling Gel with UV Screen

Ingredients	%Wt/Wt
Water	85.68
Oleth-20	2.5
Dimethylpabamidopropyl laurdimonium tosylate (and) propylene glycol stearate (65% active in water)	0.5
PVP (K-30 powder)	3.0
Propylene glycol (and) diazolidinyl urea (and) iodopropynyl butylcarbamate	0.5
Triethanolamine (99%)	0.82
Water	3.0
Acrylates/steareth-20 methacrylate copolymer (30% aqueous)	4.0

Premelt and mix the dimethylpabamidopropyl laurdimonium tosylate (and) propylene glycol stearate and add to the oleth-20 at 60 °C; mix until clear and homogeneous. Add to 55 °C water and mix until clear. Cool to 25–40 °C. Add other constituents in order and de-aerate before adding the prediluted acrylates thickener. Mix at least 30 minutes after clarity is achieved.

Formula III C 3 Styling Cream (Reduced Oil Level)

Ingredients	%Wt/Wt
Phase 1	
Water	67.8
Disodium EDTA	0.1
PVM/MA decadiene cross-polymer	0.2
Glycerin	1.0
Phase 2	
Glyceryl stearate (and) behenyl alcohol (and) palmitic acid (and) stearic acid (and) lecithin (and) lauryl alcohol (and) myristyl alcohol (and) cetyl alcohol	5.0
Diisopropyl adipate	4.0
Isocetyl stearate	6.0
Octyl palmitate	10.0
Phase 3	
Sodium hydroxide (1.0% solution)	5.0
Phase 4	
Phenoxyethanol (and) isopropylparaben (and) isobutylparaben (and) butylparaben	0.5
Diazolidinyl urea (and) iodopropynyl butylcarbamate	0.3
Fragrance	0.1

Phase 1: Add PVM/MA decadiene cross-polymer to water and heat to 70 °–75 °C. Add glycerin and EDTA and mix for 40 minutes. Melt and mix phase 2 at 75 °–80 °C. Add phase 2 to phase 1 at 75 °–80 °C with high-shear homomixing. Add phase 3 with homomixing. Cool to 35°–40 °C with sweep agitation and add phase 4.

Formula III C 4 Cream Gel (Mechanically Dispersed Oil Phase Nonchemical Hair Relaxer)

Ingredients	%Wt/Wt
Water #1	59.6
Carbomer	0.5
Glycereth-26	3.0
DMDMH (and) iodopropynyl butylcarbamate	0.2
Diisopropyl adipate	3.0
Isocetyl stearate	5.0
Dimethicone (gum/low molecular weight blend)	1.0
Fragrance	0.2
Water #2	15.0
PVP/VA (70% VP type, 50% active in water)	12.0
Aminomethylpropanol	0.5

Prepare carbomer in water #1 in main kettle. Add other components; esters and silicones will float on top. Dilute PVP/VA in water #2 and add neutralizer and additives. Transfer PVP/VA phase to the main kettle and mix until gel is complete. As neutralization begins, the oils are pulled into the gel. Mixing will create a uniform mechanical dispersion of droplets of oil, which makes the gel opaque, and can be measured under the microscope to confirm uniformity throughout the batch.

stretching it with a brush and with heat from a blow-dryer. This dries the hair while it is in the stretched (straight) conformation. The smaller the section of hair used, the faster the drying process and the higher the pounds per square inch of force is applied to the hair section. This process may take from 30 minutes to 2 hours and has to be repeated every time the humidity rises. Special brushes are being marketed right now for this application.

Creams

Creams can simply be oil in water emulsions with a 10–25% oil phase. The cream gel is a hybrid of the clear gel and an oil treatment or the emulsion. It can be a polymer-stabilized cream or simply a dispersion of oils, esters, or fatty products in a gelling matrix. The emulsion-stabilizing polymer thickener and stabilizer can be shear thinning for easier distribution and a lighter feel on the hands and the hair. The choice and concentration of esters, oils, silicones, fatty alcohols, or waxes determines the final feel and look of the product after dry-down. The higher the viscosity, unctuousness, or melting point of the oils and waxes, the greasier the feel will be on the hair after dry-down and perhaps during the wet application. The converse is true as lighter feeling, easier spreading oils are used. Styling polymers are also used in these formulas to supply some hold and counteract the oily effect of the oil phase.

On curly hair or hair that has been permed, colored, or bleached, cream gels and cream styling products provide a softening effect. The architecture of kinky hair increases the difficulty in combing as the curls are caught on the comb. As the comb catches on the curls, the combing force may cause stretch damage to the hair and scrape the surface of the cuticle. These types of products provide slip and protection to the surface of the hair during wet and dry combing [3]. The cream gel or cream texture can make the hair feel softer and appear to be less curly during application. As such a cream gel or cream is combed through the hair, the force of the combing opens up the curl, and the yield value of the product helps the hair retain at least a portion of this "stretched out" conformation. For less curly and processed hair, these creamy formulas add some weight and cohesiveness that reduces the flyaway. Upon rinse-out, these creamy products feel like detangling conditioners.

RINGING GELS, POMADES, STYLING STICKS

Ringing Gels

Ringing gels are clear microemulsions that vibrate when tapped. They may contain 10–20% oil and 10–30% nonionic surfactants (low and high HLB combination); the remainder includes water, preservative, fragrance, and sometimes styling polymers. The effect of a ringing gel on the hair is similar to treating the hair with a pomade, except that because of the high nonionic surfactant load the product rinses out or shampoos out very easily. A ringing gel may be applied to wet or dry hair; in order to enhance hair holding, a hair styling fixative polymer like PVP or polyquaternium-11 is included.

Pomades

Pomades can be as simple as petrolatum and fragrance or as complex as blends of paraffin or natural waxes (to stiffen and to modify the melt point or spreadability), esters or organo-silicones (to detackify and to make spreading easier), organo-modified polymers for film-forming, low and high HLB surfactants (to aid wetting and removability), preservatives (to retard microbial growth when contaminated with trace water from multiple applications), actives like allantoin (to soothe the scalp), fragrance, and color or pigments (for visual enhancements).

Historically, these products were used on extremely curly hair to make it easier to comb, pick, or braid the hair, and to minimize breakage. Because of the viscosity of the pomade, the curl could be combed a little straighter, perhaps into rows of organized waves, and would be held in place by the cohesiveness of the pomade. The pomade would also make the hair feel softer to the touch, because the pomade coating the hair would provide lubricity between hairs as they slide across each other. Today pomades are also used

Formula III D 1 Pomade

Ingredients	%Wt/Wt
Petrolatum	60.0
PEG-20 stearate	4.0
Ozokerite	4.0
Carnauba	4.0
Microcrystalline wax	10.0
Lauryl lactate	4.0
Phenyltrimethicone	2.0
Jojoba oil	2.0
Myristyl myristate	4.0
PVP/hexadecene copolymer	3.0
Mineral oil	2.5
Fragrance	0.5

Melt all ingredients except fragrance with mixing until uniform. Cool. Add fragrance and fill before viscosity builds. Many pomades today contain preservatives. Can be sold in glass jars or plastic swivel packages.

on straight hair to give a conditioned feel and a little weight to control flyaway hair, especially damaged hair.

Styling Sticks

Styling sticks are now appearing in the marketplace. They are filled into similar packaging as underarm deodorant sticks and follow similar formulation style: water and propylene glycol for solvents, sodium stearate as the gellant, preservative, and styling polymer (PVP and PVP/VA). The product is applied to the hand or directly to the hair.

MOUSSES, SHAPING SPRAYS, POSTFOAMING GEL/MOUSSES

Mousses

Mousses made a major impact on the hair styling industry first in Europe and the United States and then worldwide upon introduction. A mousse is a setting lotion with a small amount of surfactant to emulsify some propane and butane propellant temporarily. It is stored in a can, shaken just prior to dispensing, and dispensed through a simple aerosol valve through a mousse actuator. The final product exits as a ball of foam into the palm of the hand. The product is used by distributing the foam throughout the hair before blow-drying or wet-setting. The mousse is an attractive form of delivery for the styling polymer: the consumer dispenses the product into the hand, crushes the foam, feels the glide of the formula as the hands are rubbed together, and senses hair detangling during the application to the hair. Most of the mousses

produced gave a conditioning natural feel with less drag in the dry stage than previous setting products. However, the entire spectrum of stiff to soft feel can be produced in mousse form, that is, by control of the propellant.

The Shaping Spray or Spritz

The shaping spray or spritz was another development during the 1980s. In most cases, it was merely a new name for a pump hair spray. In other formulations, it represented new formulations with higher levels of water and nonhair spray polymers and polymer blends with special additive packages for feel. These were styling products for damp or dry hair. Their introduction coincided with the popularity of the "spike" look in which the hair was made to stand on end and be very high and stiff; during this period, polymer solids levels rose from as low as 2% to as high as 16%.

The Postfoaming Gel/Mousse

The postfoaming gel/mousse is a hybrid of products that started in 1984 but did not become popular until about 1997. A simple type of postfoaming gel is a mechanical dispersion of propellant like *iso*-pentane and *n*-butane in a styling gel with a small amount of surfactant to aid in the dispersion and distribution of the propellant throughout the gel. This mix is placed in a so-called Sepro-can or bag-in-can container, which is then sealed and pressurized on the outside of the bag.

Formula III E 1 Styling Mousse

Ingredients	%Wt/Wt
Water	78.5
Oleth-20	1.0
Fragrance	0.2
Polyquaternium-11 (20% aqueous, high MW)	10.0
Preservative	0.3
80% isobutane and 20% propane (A-46 propellant)	10.0

Add in order listed. Fill 90 g concentrate and then vacuum crimp and pressurize. Preservatives are necessary to inhibit growth between the time compounding begins and actual vacuum crimping and pressurizing (up to 5 days at 30 °C, optimal conditions for growth). A few years ago, over 60% of mousses were based on polyquaternium-11, either as the sole polymer or in a blend with PVP, PVP/VA, or polyquaternium-4. There are several patents covering use of polyquaternaries in combination with polyanionics (including polymers like polyquaternium-11 and esters of PVM/MA copolymers) that produce special foaming characteristics, feel, or styling benefits.

Formula III E 2 Extra-Body Mousse

Ingredients	%Wt/Wt
Water	77.8
PEG-60 hydrogenated castor oil	1.0
Fragrance	0.2
PVP K-90	2.0
PVP/VA (70% VP type, 50% aqueous)	10.0
Glycereth-7	1.0
Preservative	q.s.
80% isobutane and 20% propane (A-46 propellant)	8.0

Add in order and fill as before (in Formula 30 E 1), noting the 92/8 ratio. The lower level of propellant gives a softer and easier to spread foam. The bodying PVP/VA plus an extra crisp high molecular weight PVP (which also adds a smoothness or cushion between the fingers and the hair) gives this mousse an extra-hold sensation because of the extra tackiness during drying and a good deal of dry comb drag compared to a polyquaternium formula (30 E 1).

Formula III E 3 Mousse (Creamy Foam)

Ingredients	%Wt/Wt
Water	78.2
Oleth-20	0.8
Glyceryl stearate and laureth-23	0.4
Isocetyl stearate	0.2
Quaternium-52 (25% active)	0.4
PVP/DMAPA acrylates copolymer (10% active in water)	10.0
80% isobutane and 20% propane (A-46 propellant)	5.0
Hydrofluorocarbon 152a propellant	5.0

Preblend the oleth-20, GMS/laureth-23, isocetyl stearate, and quaternium-52 at 60 °C and add to 60 °C water with mixing to form an emulsion (has to be stable for only a few days to facilitate filling into the cans and smooth enough to prevent lumps in the can). Add remaining components while cooling. The 152a propellant blended with the hydrocarbon usually produces whiter, shinier mousse foam.

New modifications in the marketplace are the nonaerosol mousse and the spray mousse, based on refillable finger-touch nonaerosol pumps. One of the key requirements for the nonaerosol mousse formulation is that the concentrate must be very fluid to pass through the aeration chambers and develop foam during the pump action (a single depression of an actuator button).

The amount of polymer required is difficult to determine and depends on rheological and distributional aspects of the final product. If a small drop of

Formula III E 4 Spray Mousse

Ingredients	%Wt/Wt
Water	82.4
Dimethicone copolyol	0.6
Isobutylene/ethylmaleimide/hydroxyethylmaleimide copolymer (40% active, in ethanol and water)	6.0
Amodimethicone (and) nonoxynol-10 (and) tallowtrimonium chloride (~35% aqueous)	1.0
A-46 propellant (80% isobutane and 20% propane)	4.0
Dimethyl ether (DME)	6.0

Add in order listed, fill into can, and pressurize as before. Uses less effective foamers and a blend of propellants: DME alone does not produce sufficient foam because of its high solubility in water; A-46 produces a stable foam. Together they produce a transient foam that dissipates rapidly on the hair. An aerosol valve with a narrow dip tube and a hair spray actuator yields a spray foam. If DME is used, the compatibility with packaging components must be examined.

thick gel must be distributed on wet hair, a very high level of active polymer will be used. If 15 g of gel is distributed, then a lower level of active polymer may be used. The quantity used also has to be coupled with the degree of the effect desired, such as stiff, soft, smooth, raspy, and so forth. The entire formula has to be balanced and in concert with the expected use by the end-user.

Volatile Organic Components (VOCs)

The U.S. Environmental Protection Agency (EPA) established a nationwide limitation (12/10/98) for VOCs in gels at 6% and mousses at 16%, which matches the 1993 California regulations. California is planning tighter restrictions for 2003 for mousses at 6%, which may be accomplished by reducing the alcohol to "0" and the propellant to 6% or by augmenting the 6% hydrocarbon propellant with hydrofluorocarbon 152a (an exempted propellant).

PRODUCTS FOR FIXING AND HOLDING THE STYLE (USED ON DRY HAIR)

PUMP SPRAYS AND SPRITZES

Changes in hair sprays that are delivered via a finger-pumped device are the result of VOC, chlorofluorocarbon, and methylene chloride regulations, as well as environmental concerns. Modifications in hair styles and frequent style changes have caused share shifts between aerosols (sprays containing propellant) and pumps (mechanically propelled sprays).

Formula III E 5 Nonaerosol Mousse

Ingredients	%Wt/Wt
Water	96.5
Oleth-20	1.0
PVP K-90 (powder)	1.0
PVP/DMAPA acrylates copolymer (10% aqueous)	1.0
Propylene glycol (and) diazolidinyl urea (and) iodopropynyl butylcarbamate	0.5

Add ingredients in listed order. The product is dispensed from a finger-touch pump. Oleth-20 at 1% performs as good or better than 2% or 3% oleth-20. Low viscosity and a good foamer are required and a low concentration of large polymers to enable the concentrate to move quickly through the aeration chambers. Lower molecular weight polymers like PVP/VA and PVP K-30 work well alone or in combinations with high molecular weight polymers.

Formula III E 6 Postfoaming Gel or Mousse

Ingredients	%Wt/Wt
Phase 1	
Water	69.55
Carbomer	0.35
Glycerin	0.5
Diazolidinyl urea (and) iodopropynyl carbamate	0.2
Phase 2	
Water	20.0
PVP K-90	2.00
Triethanolamine (99%)	0.3
Oleth-20	1.0
Fragrance	0.1
Phase 3	
70% isopentane and 30% butane	6.0

Disperse carbomer into water; when complete and homogeneous, add rest of phase 1. In a separate kettle, dissolve the PVP and then de-aerate; complete phase 2 and hold less than 1 hour. Add phase 2 to phase 1 and mix until the gel is completely clear. It is important to be free of bubbles—use vacuum kettle or Versator® to remove air. Phase 3 can be incorporated in two ways: (1) cool the gel to 0–4 °C and blend in phase 3 (propellant @ ~ 15 °C) with simple mixing until particle size is uniform (oleth-20 aids in dispersion)—the gel with propellant can now be filled into a "bag-in-the-can" container; or (2) the gel and propellant can be injected simultaneously through the valve stem into the "bag-in-the-can" container. In both cases, the void between the bag and the can must be pressurized with nitrogen, air, or propellant to maintain pressure on the gel to prevent premature foaming in the bag and to push it out of the can when the valve is actuated.

After the style is in place and all the manipulations and arrangements of the hair are complete, the hair style could be sprayed with a finishing spray. This spray completes the style by effectively creating a net over the hair, holding it in place to prevent separation or rearrangement of the parts of the hair style because of a slight breeze or wind or inadvertent contact by hands or clothing and so forth. Such sprays are available in a variety of holding strengths. Hold in this context refers to either the impression the user gets from the stiffness or crunch when touched, to the expectation of holding a long time in high humidity, to how fast it dries, or to a combination of these, and other marketing features.

In modern styling, the hair may be blown-dry, dry-set, or curled with electric curling irons or steam rollers, and then brushed or fingered into place to complete the style. For finishing, the hair may be spritzed (or sprayed) with a pump spray followed by pushing and pulling the hair into place with the fingers or comb and brush while the spray dries. This requires that the spray dry with minimal tackiness or stickiness in order not to impede the placement of the hair in the shape desired by adhering to the fingers or implements. This is accomplished by choosing polymers of limited tackiness and additives that do not make the hair spray film tacky. Examples of useful additives include cyclomethicone, diisopropyl adipate, dioctyl sebacate, triethyl citrate, and dimethicone. Lower VOC products may require additives that are soluble in the lower alcohol and higher water bases.

The level of polymer used depends—as in other hair styling products—on the polymer chosen, the desired feel, the spray pattern, the amount of product expected to be sprayed on the hair, the pump output, the quality or particle size of the spray (fine or coarse), and the mandatory concept ingredients that are included in the formula. The pump output could range from 140–210 μL/actuation; with formulations with lower VOC content (alcohol primarily), the output may be 140–160 μL at 55% VOC, and 160–180 μL at 80% VOC, and as high as 210 μL at anhydrous conditions (90%+VOC).

Formulators must attempt to work with the complex interactions of water and VOC, delivery levels, polymer concentrations, spray patterns, and the effect of diverse product components on the hair and the consumer. In principle, holding efficacy depends on the fate of the sprayed droplets after delivery and their coalescence or spreading on the sprayed hair [3].

Levels of polymer solids can range from 1% to 16% or higher. Usually the polyanionic polymers need to be neutralized at levels of 8% to 100% to be easily removable from the hair after drying [4]. Historically, the neutralizer of choice has been aminomethyl-propanol, because of minimal yellowing and minimum reduction in high-humidity curl retention and film clarity. However, several other neutralizers can be used.

The properties of the polymer also change depending on the stoichiometric neutralization levels. Increased neutralization makes the polymer more water-soluble, less resistant to high humidity, more interactive with the water in the formulation, and more viscous. The changes in surface tension may result in more difficulty in atomization or flowing on the hair surface. If the equivalent weight or acidity of the polymer is known, the amount of amine required for stoichiometric neutralization can easily be calculated using one of the following formulas:

1) Grams of Neutralizer =

$$\frac{\text{Grams of Resin(active)} \times \text{Acidity} \times \text{Equivalent Weight of Base} \times \%\ \text{Neutralization}}{1000 \times 100}$$

2) % Neutralizer =

$$(\%\ \text{Polymer solids}) \times \frac{(\text{Eq. Wt. Neut.})}{(\text{Eq. Wt. Polymer})} \times \frac{(\text{Desired \%Neut.})}{(100)}$$

Nonionic and amine types of polymers are popular; examples include PVP and vinyl caprolactam/PVP/dimethylaminoethylmethacrylate. These classes of polymers do not require neutralization to make them compatible with alcohol or hydroalcoholic solvents. Some are totally soluble in water. In contrast to PVP, the newer types of polymers produce dried films that are very humidity-resistant even though they are water-soluble. This phenomenon of resistance to humidity is probably because of the physical chemistry differences between water and water vapor.

During the selection and screening of polymers, some important attributes must be considered:

1. Level of neutralization required for compatibility with various solvent blends
2. Level of neutralization required for ease of removal from hair
3. Level of neutralization required for clarity of dry film. This needs to be checked again after ingredients have been added.
4. Softness; stiffness; flexibility; crunchiness; smoothness; raspiness or roughness; shine; flaking, tackiness during and after drying; sprayability at the necessary solids level; and especially high-humidity curl resistance (HHCR).
5. Compatibility with other ingredients and packaging components

AEROSOL HAIR SPRAYS

Aerosols, hair sprays delivered by pressure from propellants within the containers, differ significantly from pump sprays because the droplets exiting

Formula IV A 1 Pump Spray (Firm Hold)

Ingredients	%Wt/Wt
SD alcohol 40B (anhydrous)	73.80
Water	12.77
Butyl ester of PVM/MA copolymer (50% active, in ethanol)	12.0
Aminomethylpropanol	0.23
Cyclomethicone	1.0
Fragrance	0.2

Add in order listed with mixing.

Formula IV A 2 Pump Spray (Low-Tack)

Ingredients	%Wt/Wt
SD alcohol 40B (anhydrous)	55.0
Water	33.48
Aminomethylpropanol	0.78
Acrylates/C1-2 succinates/hydroxyacrylates copolymer (47% active)	10.64
Dimethicone copolyol	0.1

Add in order listed. Since the acrylates copolymer is an aqueous emulsion, it is important to have the neutralizer in the alcohol or water solution before adding the polymer. Clarity occurs quickly. High water content allows style modification of dry hair by spraying and agitation with hands. Extra low-tack polymer dries with very little tackiness during the dry-down period, a significant feature for a working spray. When used as a finishing spray, it yields a stiff final effect.

Formula IV A 3 Pump Spray (Extra Hold)

Ingredients	%Wt/Wt
SD alcohol 40-B (anhydrous)	72.75
Water	12.09
Ethyl ester of PVM/MA (50% active, in ethanol)	13.0
VA/butyl maleate/isobornyl acrylate copolymer (50% active, in ethanol)	1.5
Triisopropanolamine	0.46
Fragrance	0.2

The two resins used together create an extra-stiff feel.

the actuator are part concentrate and part propellant, in contrast to concentrate only in the case of pump sprays.

There are four main components of the aerosol: the concentrate (including solvent(s), polymers, neutralizers, etc.), the propellant, the valving, and the can [5]. In general, the composition of hair spray concentrates is very similar

to that of the pump sprays, by omitting some solvent to be replaced by the propellant.

The propellants can range from very polar (DME, dimethyl ether) to nonpolar (hydrocarbons like propane, *iso*-butane or *n*-butane). As the propellant exits the confined spaces and high pressure of the sealed container and enters the low pressure of ambient conditions, the propellant expands rapidly, which aids breaking droplets into smaller particles. Any propellant dissolved in the droplet after landing on the hair evaporates rapidly. Therefore, high propellant levels create a fast-drying hair spray. Drying is also affected by the pressure, which typically ranges between 31 and 70 psig at 21 °C. Since federal and California regulations have exempted propellant hydrofluorocarbon 152a from the VOC regulations currently in effect, formulators have substituted 152a for some or all of the water in the concentrate. DME has allowed compounding of high-propellant hair sprays with polymers compatible with high levels of nonpolar propellants. Because of its high solubility in water, DME has resulted in hair sprays containing moderate to high levels of water [6].

The valves (and actuators) control the rate of dispensing the concentrate (measured in grams per second), the droplet diameter (particle size in microns), spread of the particles (cone diameter in inches on paper or alcohol-sensitive chart paper), and can adjust the ratio of concentrate to propellant exiting the can (liquefied propellant versus gaseous propellant via a vapor tap). Features of commercial valves, including body, vapor tap, stem, and actuator, are described in Ref. 5 and in Chapter 17.

Formula IV B 1 Hair Spray (Anhydrous, High VOC)

Ingredients	%Wt/Wt
SD alcohol 40B (anhydrous)	49.32–69
Aminomethylpropanol	0.38
VA/crotonates/vinyl neodecanoate copolymer (granules)	4.0
Lauramide DEA	0.5
Dimethicone copolyol	0.5
Phenyltrimethicone	0.2
Fragrance	0.2
Propane and butane (LPG propellant A-46) or	25.0
Dimethyl ether or DME/LPG blend	30.0–45

Sift the polymer into the vortex after the aminomethylpropanol has been added to the alcohol. Mix until the polymer is completely dissolved and no polymer is visible on the bottom of the kettle. Add the rest in order listed; then fill and pressurize cans.

Formula IV B 2 Hair Spray (Anhydrous, Moderate VOC)

Ingredients	%Wt/Wt
SD alcohol 40B (anhydrous)	59.6
Butyl ester PVM/MA copolymer (50% active, in ethanol)	10.0
Aminomethylpropanol (95%)	0.2
Dioctyl sebacate	0.1
Fragrance	0.1
Hydrofluorocarbon 152a propellant	15.0
n-Butane	15.0

Add in order with mixing, fill, vacuum crimp cans, and pressurize. If the level of neutralization is increased, the polymer becomes more polar and needs a more polar solvent or medium to keep it in solution or the propellant levels must be reduced.

Formula IV B 3 Hair Spray (Hydroalcoholic, Moderate VOC)

Ingredients	%Wt/Wt
SD alcohol 40-B (anhydrous)	50.0
Aminomethylpropanol	0.98
Octylacrylamide/acrylates/butylaminoethyl methacrylate copolymer (granules)	5.0
Water	12.42
Lauramide DEA	0.5
Dimethicone copolyol	0.5
Phenyltrimethicone	0.1
Corrosion inhibitor q.s.	0.1–0
Fragrance	0.1
Dimethyl ether	21.0
Propane and butane (LPG propellant A-46)	9.0

Add polymer to vortex after adding aminomethylpropanol to alcohol. When completely mixed, add the rest in order. Vacuum crimp and charge propellant either as a 70/30 preblend or add the DME first followed by A-46.

The compatibility of the polymers with the propellant and its level can be affected by the degree of neutralization and the neutralizer chosen. The higher the neutralization, the more polar the polymer becomes, which in turn requires a more polar propellant. A fatty or more oil-soluble neutralizer can enhance polymer compatibility with the nonpolar propellant (propane and butane blend) as it attaches a nonpolar or "oily" component to the polymer. Dimethylstearamine is an example of a hydrophobic (or lipophilic) amine used to neutralize polymers to increase the propellant tolerance of a polymer. Addition of water to the concentrate increases its polarity and limits the choices of propellant and propellant levels. A hair spray with 15% water may dissolve no more than 15% of a propane/butane blend, depending on temperature. Such a 15/15

Formula IV B 4 Hair Spray (Hydroalcoholic, Single-Phase Hydrocarbon)

Ingredients	%Wt/Wt
SD alcohol 40B (200 proof, anhydrous)	60.6
Water	11.5
Isobutylene/hydroxyethylmaleimide/ethylmaleimide copolymer (40% solids, 35% ethanol, 25% water)	12.5
Fragrance	0.15
Aminomethylpropanol (for pH adjustment only: 7.5–8.5 for Al cans and 8.5–9.5 for tin-plate steel)	
Corrosion inhibitor package	q.s.
Propane and butane (LPG propellant A-46)	15.0

Add in order with simple agitation. Check pH of a 1:1 dilution in water, and then adjust with AMP to confirm pH is appropriate for the type of can being used. Propellant fill tolerances should be within ±1.0 % to prevent phase separation because of an imbalance of hydrophobic propellant and the polar solvent blend of water and alcohol.

Formula IV B 5 Hair Spray (Hydroalcoholic, 55% VOC)

Ingredients	%Wt/Wt
SD alcohol 40B (anhydrous)	20.0
Water	31.68
Aminomethylpropanol	0.97
Acrylates/C1-2 succinates/hydroxyacrylates copolymer (47% aqueous)	11.7
MEA borate and MIPA borate	0.25
Ammonium hydroxide (28%)	0.25
Fragrance	0.15
Dimethyl ether	35.0

The polymer is an emulsion, and the neutralizer should be in the alcohol or water solvent. Add all ingredients in order with mixing. Adjust the inhibitor package and pH according to the package type. Vacuum crimp and charge with propellant.

blend (with 65% alcohol and 5% solid polymer) is referred to as a single-phase hydrocarbon hair spray. Higher levels of water usually require the use of DME, forcing the formulator to study all types of incompatibilities and compatibilities during product development. Separation into distinct layers or precipitation of polymeric substances is not acceptable under normal circumstances. Storage conditions and local climate must be taken into account. Most stability studies require visual inspection, and transparent packaging components are required for these studies. Other concerns with propellants and the alcohol in aerosols include the rate of expansion upon heating, the internal pressure created, and the effects on headspace.

Finally, can corrosion has plagued formulators for years. Corrosion can result from diverse factors such as pH, dissolved oxygen, carboxylic acids (possible chelators), and tramp ions (chloride and others). Corrosion inhibitors may be nonvolatile or volatile. The former normally protect the metal from attack by the contacting solution; volatile inhibitors are required to protect the can interior from attack by volatile product components. The most commonly used materials include ammonia or aminomethylpropanol.

PRODUCTS FOR CREATING SPECIAL EFFECTS (USED ON DRY HAIR)

Many style changes have occurred over the years modifying the way styles are finished. Males relied on heavy grease for styling and controlling the hair; at the same time, dry, clean-looking controlled bouffants and "flips" were popular with females. Since then, a variety of fixed and rigid-to-loose uncombed and lived-in styles have become fashionable. Today shine and luster are signs of healthy hair, but they need to be restored to hair because of improperly processing or excessive exposure to sun, thermal styling, chlorine, and mechanical damage. Hair coloring, highlighting, and relaxing are popular, and the final treatment of the hair can give the hair the feel or look of natural and healthy hair. Of course, the same products can be formulated to give that not-freshly-shampooed look, referred to for a while as the "grunge" or slept-in look. Although some of these products may have the same composition as those used for styling, they may take on other marketing names, such as sculpting mud, cuticle coat, antifrizz, glossifier, butch wax, glaze, shine, or hair mascara if color is added.

Most of these products deposit nonvolatile oily or waxy materials on the hair to create a hair assembly (by lateral adhesion), to cover up a raspy feel, to add a luster or sheen, to give weight to reduce flyaway, to highlight by texture or color, and to add fragrance. Some of these are totally nonvolatile, whereas others are solutions of nonvolatiles in various solvents such as water, alcohol, volatile silicone, deodorized mineral spirits, or deodorized kerosene. These products are typically applied manually to the hair to create a polished look.

Some of the anhydrous waxy products are difficult to remove from the hair; they can be modified with emulsifiers or surfactants to aid removal during shampooing. The product types range from waxy pots or sticks to sprayable or splash-on liquids or silicone formulations and include creams, lotions, and cream gels.

Hair mascaras have become popular recently, both for cosmetic highlights and for touch-ups between hair color treatments (to cover up regrowth).

Formula V 1 Solid Brilliantine

Ingredients	%Wt/Wt
Petrolatum	75.0
Microcrystalline wax	10.0
Beeswax	5.0
Tricontanyl PVP	3.0
Phenyltrimethicone	7.0

Melt and mix until homogeneous. Cool to just before set point. Fill and cool.

Formula V 2 Liquid Pomade

Ingredients	%Wt/Wt
Water	58.2
Butylated PVP	1.0
PEG-40 hydrogenated castor oil	5.0
PEG-60 almond glycerides	5.0
Fragrance	0.5
Glycerin	10.0
Sorbitol	5.0
Dimethicone copolyol	5.0
PEG-75 shea butter glycerides	5.0
Methyl gluceth-10	5.0
Diazolidinyl urea (and) iodopropynyl butylcarbamate	0.2

Add premelted ethoxylates to water with moderate mixing. Warm water to 40–50 °C if necessary. Add all ingredients in order (premix fragrance with PEG-60 almond glycerides before adding to water).

Formula V 3 Liquid (Split End Control)

Ingredients	%Wt/Wt
Water	58.4
SD alcohol 40B (anhydrous)	30.0
PVP/DMAPA acrylates copolymer (10% active in water)	10.0
Acetamide MEA	0.5
Polyglyceryl methacrylate and PVM/MA copolymer	0.5
Oleth-20	0.5
Fragrance	0.1

Add in the order listed. This low-viscosity liquid dries rapidly to seal split ends.

Formula V 4 Gel Pomade (Water-Based)

Ingredients	%Wt/Wt
Water	87.9
Carbomer	0.5
Butylene glycol	0.5
Diazolidinyl urea (and) iodopropynyl butylcarbamate	0.2
Cyclomethicone and dimethicone/dimethiconol gum blend	5.0
Diisopropyl adipate	5.0
Fragrance	0.3
Aminomethylpropanol	0.5

Add in the order listed. Float the insoluble silicones, ester, and fragrance on the carbomer water phase. Add aminomethylpropanol; adjust agitation as necessary. Continue mixing until the insoluble ingredients are uniformly dispersed throughout the gel, as determined by microscopy.

Formula V 5 Hair Tonic (Liquid)

Ingredients	%Wt/Wt
Cyclomethicone	68.4
Diisopropyl adipate	1.0
Isocetyl stearate	1.0
Dimethicone (20 cs)	0.1
Fragrance	5.0
SD alcohol 40B (anhydrous)	25.0

Add in the order listed. This is a combination of volatile and nonvolatile emollients for detangling, shine, and taming of hair that can be used for fragrance delivery. The alcohol level can be reduced.

Formula V 6 Hair Mascara (Temporary Hair Color)

Ingredients	%Wt/Wt
Water	42.8
Hydroxyethylcellulose, high viscosity	0.8
Tetrasodium EDTA	0.1
Water	24.0
PVP/DMAPA acrylates copolymer (10% active in water)	12.0
Diazolidinyl urea (and) iodopropynyl butylcarbamate	0.3
Mica (and) titanium dioxide (and) iron oxides	20.0

Process the water, cellulose, and EDTA together at above 40 °C for 40 minutes or more. Dilute the PVP/DMAPA acrylates copolymer in water and then add to cellulose phase. Cool to 40–45 °C and add preservative and pigments with mixing.

EVALUATION OF PERFORMANCE

Methods of evaluation of hair fixative products are as varied as the intended purpose and function of the prototype. Two critical and typical studies are the high-humidity curl retention or resistance (HHCR) and hair characteristics. The HHCR allows comparisons of polymers, formulas, or additives on hair swatches at the selected humidity on the basis of their effect on retaining the set or curl. In one methodology, eight replicate 6.5″ long hair swatches are treated with styling product or hair spray, dried, randomized on graduated racks at 80% RH and 33 °C, and the length of the curl is then monitored from initial time through 4 or 24 hours. A graph or bar chart is generated to visualize the function of humidity and time on the curl retention.

Procedures can be varied depending on the way the product will be used by the consumer, for example, as applied to wet hair and dried on rollers or sprayed onto hair predried into curls. A typical graph of the HHCR of a setting gel is shown in Figure 30.1. This graph shows a comparison of four formulas when treated hair is exposed to 90% RH and 27 °C for four hours. Two formulas show rapid decline after 60 minutes, whereas the others still hold well at four hours.

Meaningful hair tests require that products are applied to tresses in a similar manner. After setting and drying on rods (Teflon® rods are commonly used for easy removal), the curled hair is examined, touched or combed and brushed, and evaluated for characteristics such as shine, stiffness, curl snap, comb drag, comb residue, hair residue (flaking), curl memory, static, and smoothness [7]. Other tests include initial curl droop, tackiness, clarity and shine on glass plates, and hardness. In vivo testing proceeds via salon half-head tests

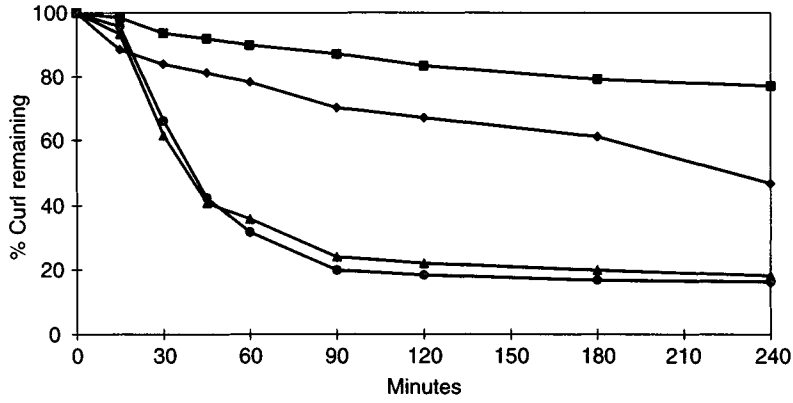

Figure 30.1. High-humidity curl retention (up to 240 minutes)

and consumer panel tests. Approaches to these and additional evaluations or screening tests may be found in suppliers' literature. Curl retention by hair treated with styling products is generally studied at 90% relative humidity and 27 °C.

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CHAPTER 31
Hair Colorants

INTRODUCTION

The coloring of hair is one of the oldest and most prevalent acts of adornment. Early Egyptians used henna (i.e., *Lawsonia inermis*) preparations for imparting reddish-orange highlights to hair, and still today henna, henna extract, and the actual color active lawsone (2-hydroxy-1,4-naphthoquinone) are recognized cosmetic ingredients. Modern usage of natural colorants is quite minor, however, because of the vastly superior performance of synthetic colorants.

It is estimated that today up to 50% of women in the industrialized countries are users of coloring products, either in the home or at the hairdresser. Enhancement of appearance remains the primary motivation for hair coloring, and extends from temporary color addition through more durable color highlights and gray coverage to lasting color changes. Each stage has its own set of dye types and chemistries, and discussion should begin with a general overview of the coloring systems.

This review will stress current technologies and will not address the majority of patent literature. The breadth of patents covering hair coloration is quite vast, yet only a portion has been reduced to practice. Only this applied knowledge is within the scope of this chapter.

HAIR COLORING SYSTEMS

Modern systems of hair coloring may be divided into three broad categories determined by the duration of color on the hair. However, new dyestuffs and improved formulations have somewhat blurred the distinctions between these categories. The market share of each of these categories is, perhaps not surprisingly, directly related to their degree of durability. The longest-lasting products are by far the most popular.

TEMPORARY COLORING

These are fugitive colors that can be removed at the first shampooing. Commercial products are frequently designated "color rinses." These products utilize ionic colorants of a high molecular weight that are in effect deposited on the surface of the hair without being able to penetrate the cortex. Additionally, these are acid dyes that have minimal affinity for hair that has an overall anionic character.

A second class of temporary colorants are cationic compounds. These are basic dyes with at least an ionic attraction for hair, but still only surface deposition and less durability than semipermanents.

Hair may also be colored temporarily with pigments, but usually has an unnatural feel, and this type of temporary is least durable and most subject to flaking and abrasion.

SEMIPERMANENT COLORING

These are colors that resist several shampooings (six to eight), but whose fastness is poorer than that of permanent colors. The colors used in this case are direct dyes of low molecular weight having a good affinity for hair keratin. Because of this, they are capable of penetrating the cuticle and diffusing throughout the cortex.

PERMANENT COLORING

As the name indicates, this category provides effectively permanent coloration, resistant to shampooing and other external factors such as brushing, friction, light, and so forth. This is the process most widely used and represents at least 80% of the hair coloring market.

In this system, uncolored precursors undergo a series of chemical reactions to produce the desired color in situ in the hair. The process is one of oxidation (almost always effected by hydrogen peroxide), followed by coupling and further oxidations. Thus this system is also called *oxidative coloring*. This is the only system in which the dyes are not preformed; the oxidative chemistry involved is somewhat similar to that used in color photography.

CHARACTERISTICS OF AN IDEAL HAIR COLORANT

The ideal hair colorant should possess the following properties:

Harmlessness

(1) It should not damage the hair structure and should color the hair without impairing the natural texture and gloss;
(2) It should possess no primary irritant action and be free from sensitizing properties.

The optimization of formulas to maximize dyeing efficiency while minimizing dye concentrations and oxidative damage have gone far to fulfill these goals.

Adequate Physical and Chemical Stability on the Hair
The color of the dyed hair should be stable to air, sunlight, friction (rubbing, brushing), sweat, and chlorinated water (municipal supplies and pool treatments).

Compatibility with Other Hair Treatments
It should not change color or bleach out on the application of any hair cosmetic preparation such as brilliantines, fixatives, hair lacquers, hair waving preparations, or conditioners. Shampoos should remove color completely for temporaries, gradually and on-shade for semipermanents, and not at all for permanents.

Stability in Solution
Colorants should be stable both chemically and physically (i.e., no precipitation) in formulated products, whether liquid, cream, gel, or solid.

Absence of Selectivity
Because it is always necessary to use a mixture of dyestuffs, selectivity is quite important. Hair is very heterogeneous both individually and in its "history" (the ends damaged by air and sun, previous perms or other treatments, roots compared with shaft, etc.). The ideal colorant avoids:

(1) significantly different coloration on different parts of the same hair;
(2) different fastness over time of different dyestuffs on the hair.

The problem of selectivity plays a most significant part in the technology of hair colorants. It is probably most critical in the semipermanents, which rely solely on physical diffusion into the hair of dyes with significantly different molecular sizes. Oxidative dyes are somewhat less prone to selectivity issues, since the precursors are generally small molecules and there is an evenness after reactive formation of the larger dye molecules. Additionally, there may be some leveling effects with peroxide.

Affinity for Hair Keratin
Hair dyeing is quite unlike the dyeing of any other fiber in terms of necessary conditions. Textiles and other fibers may be treated in very stringent environments of pH and temperature extremes, but hair must be colored in a physiologically acceptable manner. Thus the physicochemical characteristics of affinity of the dyestuff for, and its diffusabilty into, the hair shaft are quite significant in light of the limitations controlling hair dyeing. These include

low temperature (40 °C), short time of contact (5–40 minutes), minimum dye concentrations, and so forth. The formulator faces the difficult task of developing a product that initially solubilizes the dyestuffs, keeps them in stable solution, then gives optimum dyeing performance under these nonstringent conditions.

Affinity is the more significant factor for temporary colorants, which only adhere to the exterior hair surface to impart color. These molecules are far too large for any diffusion through the cuticle and into the cortex.

Conversely, diffusability is more critical for semipermanent and permanent colorants. At least part of the durability of these compounds is because of their complete distribution throughout the hair shaft; thus diffusion must be fast, even, and comprehensive.

Ingredients such as water, organic solvents, swelling agents, alkalis, conditioners, preservatives, and so forth must be well balanced to improve penetration and/or modify the partition coefficient between water and hair. It can easily be seen that the vehicle may be just as critical as the dyes for an effective product.

THE PROCESS OF HAIR COLORING

Hair colorants provide a range of commercial products capable of coloring the hair in various shades and tints, ranging from very light blonde to black and passing through a range of tones: golden, ash, reddish, mahogany, violets, and so forth. The number of shades constituting such a range can exceed 60, although most consumer products include only 20–30 shades in a given product line. All these products use and are based on strictly limited technical factors, a summary of which follows.

Commercial Products Are Mixtures

The dyeing solutions contain mixtures of several single dyestuffs, as few as 3 but usually 5 to 6 with a maximum of 10–12. In fact, each particular shade is the overall result of the blending of individual colorations (red, yellow, violet, blue, etc.) supplied by each of the dyestuffs or each intermediate or coupler combination.

Concentrations of Dyestuffs

The total quantity of all the dyestuffs used to obtain a shade is limited and can range roughly between 0.01% and 5% by weight of the tinting medium applied to the head. The concentration is a function of the dyestuffs used, shade desired, the procedure involved, and any regulatory considerations. For

instance, levels of specific dyestuffs in European products are regulated by COLIPA.

Duration of Coloring Process

The time of contact of the dyeing solution with the scalp and the hair is on the order of 5–40 minutes. Shorter dyeing times usually necessitate higher dye loads but do not have the durability of products with longer application times because of less thorough penetration. Additionally, shorter times allow only minimal bleaching of base color by peroxide-containing products.

Quantity of Solution Applied

The amount of dyeing solution applied varies between 15 and 100 ml.

Frequency of Application

Temporary colorants based on acid dyes are used generally only when desired, especially for a specific event or occasion. Their poor resistance to perspiration and precipitation, along with complete removal by shampoo, makes usage more episodic than routine. This includes products containing very low levels of violet colorants used to counteract the yellowness of completely gray hair. Although they are generally formulated as shampoos and meant to be used each time the hair is washed, the user customarily shampoos less frequently than the general population. Products based on the more substantive basic dyes can be used at every shampooing, usually to "freshen" a previously applied, more permanent colorant. Semipermanent products are formulated to last through six to eight shampoos rather than a specific time, so they are usually reapplied when needed. Oxidative colorants usually last a minimum of 24 shampoos, so the appearance of new hair growth (the "roots") determines the time for reapplication. Generally, this is three to six weeks, with once per month on average.

Treatment After Coloration

Colorants must be formulated to minimize the staining of the scalp while maximizing the hair dyeing. This is with semipermanent and permanent products, assisted by abundant rinsing with water that is obligatory after every application of dye and also by shampooing one or more times to wash away any dye that has not been absorbed.

Many products include a conditioning after-treatment to ease both wet and dry combability and enhance the feel of the hair. They must accomplish this task while not leaching out any of the colorant. In fact, after-treatments often embellish the durability of the color by helping to "close" the cuticle layer back to its preswollen configuration.

TEMPORARY HAIR DYES

DYESTUFFS

The dyestuffs used are generally acid dyes or basic dyes and may belong to any chemical class, although azo and anthraquinone compounds predominate. Table 31.1 lists some of the common temporary dyestuffs along with Color Index Number and Name, and FDA designation where applicable. This list is representative, not exhaustive. The names in boldface are the recognized International Nomenclature for Cosmetic Ingredients identifications; some colorants can have two identifications, depending on whether FDA certification is obtained.

TYPES OF COMMERCIAL TEMPORARY PRODUCTS AND THEIR FORMULATION

Temporary hair coloration products may be rinses, shampoos, or colored fixatives. In rinses the dyestuffs are used in the form of simple aqueous or aqueous-alcoholic solutions. To increase the substantivity to hair, various assistants (organic acids such as citric or tartaric, certain solvents such as benzyl alcohol or propylene glycol, etc.) are added, or the hair may be pretreated with cationic compounds. Alternatively, coloration may be achieved by precipitating the dye onto hair with a cationic polymer, although it should be noted that such tinting solutions may not be stable long term. These rinses are generally ready-to-use and are more fluid than the thickened products in other hair dye categories.

Table 31.1 Common Temporary Colorants

CI Name	CI Number	FDA Designation	Chemical Class
Acid Yellow 3	47005	**D&C Yellow #10**	Quinoline
Acid Orange 7	15510	**D&C Orange #4**	Monoazo
Acid Orange 24	20170		Disazo
Direct Red 80	35780		Polyazo
Food Red 1	14700	**FD&C Red #4**	Monoazo
Acid Red 33	17200	**D&C Red #33**	Monoazo
Acid Violet 43	60730	**Ext. D&C Violet #2**	Anthraquinone
Acid Blue 9	42090	**FD&C Blue #1**	Triphenylmethane
Acid Green 25	61570	**D&C Green #5**	Anthraquinone
Direct Black 51	31720		Disazo
Basic Yellow 57	13119		Monoazo
Basic Red 76	12245		Monoazo
Basic Blue 99	56059		Naphthoquinoneimine
Basic Brown 16	12250		Monoazo
Basic Brown 17	12251		Monoazo

Temporary colorants formulated solely with D& C and/or FD&C dyes have the significant advantage of not requiring a preliminary patch test, usually performed 48 hours prior to application of the product to hair, to check for allergenic response. Some products in this category have been claimed to be hypoallergenic.

The more substantive basic dyes have found a successful niche as treatments between application of longer lasting colorants. These "color refresher" products are usually formulated as shampoos and may be employed each time the hair is washed.

It should be noted that application of heat after treatment with temporary colorants may significantly increase the durability of the dyes.

The second approach, that of colored fixatives, consists in applying the dyestuffs to the hair in the vehicle of a setting or styling aid. This is usually in the form of a gel or aerosol mousse and is a leave-in product. Alternatively, insoluble pigments rather than more traditional colorants may be used as the coloring agents in this type of product. This should be thought of more as a deposition of particles rather than a dyeing and will be far more susceptible to flaking and abrasive removal. Also, formulation of a stable, homogeneous suspension may make formulation, especially of an aerosol, problematical.

Pigments may also be used as temporary hair colorants and are usually formulated in a waxy base and rubbed directly on hair. This type of product is quite simple to apply, but the result is not particularly natural-looking or appealing and suffers from the same drawbacks as other pigment deposition products. This is an extremely minor player in hair dyeing.

A typical formulation for a temporary coloring lotion follows:

Ingredient	Weight %
Propylene glycol	3.0
Hydroxyethylcellulose	1.0
Sodium hydroxide	0.04
Propyl paraben	0.3
Preservative	0.4
FD&C Blue 1	0.04
Ext. D&C Violet 2	0.05
D&C Orange 4	0.2
D&C Yellow 10	0.03
D&C Green 5	0.02
FD&C Red 4	0.05
Water	q.s.100

SEMIPERMANENT COLORANTS

Semipermanent colorants are the first step in hair coloring for many consumers. Positioned largely as "gray coverage" products, they offer the advantages of efficacy, simplicity, and reversibility. They require no mixing and contain no ammonia or peroxide—all appealing attributes to the newcomer who wants to cover the initial gray that appears with aging. Additionally, an undesirable result can be removed by repeated shampooings. These are usually called Level 1 products.

DYESTUFFS

Dyes used in semipermanent hair coloring are generally smaller molecules; most are classed as nitro dyes. Their colors are bright and sharp, and many also find use in permanent products in which vivid dyes in the yellow to orange range are difficult to obtain. Perhaps their only drawback is their very uniqueness: they are generally not useful in other dyeing applications, so the limited quantities required by the industry rarely result in economies of scale. Consequently, some of these compounds are quite expensive.

The great majority of these dyes belong to the following chemical classes:

Nitrophenylenediamines
Nitroaminophenols
Aminoanthraquinones

The first two classes provide yellow to violet colors, while the aminoanthraquinones are necessary for the violet to blue tints required to develop a comprehensive palette.

NITROPHENYLENEDIAMINES

Nitrophenylenediamines are by far the most important class of semipermanent dyes because of their ease of synthesis and, more significantly, the range of colors available. Depending on isomer and substitution, a spectrum of colors from yellow to violet with a range of 140 nm is available. Nitrophenylenediamines can be described by the general formula:

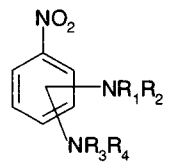
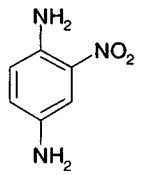


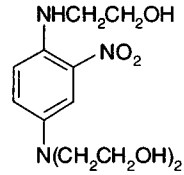
Table 31.2 Common Nitrophenylenediamine Semipermanent Colorants

Compound	Color
4-nitro-*m*-phenylenediamine	Yellow
HC Yellow No. 10	Yellow
4-nitro-*o*-phenylenediamine	Orange-yellow
HC Yellow No. 5	Orange
2-nitro-*p*-phenylenediamine	Orange-red
HC Red 14	Orange-red
HC Red 10	Orange-red
HC Red 11	Red
HC Red 1	Violet-red
HC Red 3	Violet-red
HC Red 13	Red-violet
N,N′-*bis*(2-hydroxyethyl)-2-nitro-*p*-phenylenediamine	Red-violet
HC Violet 2	Violet
HC Blue 2	Violet

where R_1-R_4 may vary considerably but are generally H, methyl, 2-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypropyl, and the like. Although there are six possible isomers, only three are used; the remaining three offer no advantages and are far more difficult to synthesize. In order of importance, the isomers utilized are 2-nitro-*p*-phenylenediamine, 4-nitro-*o*-phenylenediamine, and 4-nitro-*m*-phenylenediamine. The predominance of the 2-nitro ppd's is due mostly to the 65 nm range, from orange-red to violet, achievable from the unsubstituted parent **[1]** to the trisubstituted HC Blue 2 **[2]**. This particular isomer also has the advantage of an inexpensive and readily available starting material, 4-fluoro-3-nitroaniline. Numerous degrees and patterns of substitution are obtainable with this base skeleton.



1



2

Another factor in the wider popularity of this isomer is the capability of obtaining the shades provided by the 4-nitro-orthophenylenediamine (opd) and 4-nitro-metaphenylinediamines (mpd) with nitroaminophenols, a far more populous and useful class. This will be discussed in the following section.

Versatility and low cost also play a role in placing 4-nitro opd's next in order of significance. The high reactivity and minimal cost of 2,4-dinitrochlorobenzene make this an ideal starting material for reaction with many amines, which then is followed by the equally straightforward selective reduction of the 2-nitro group with sulfide.

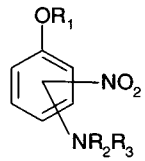
Finally, the less versatile and less easily manipulated 1,3-dichloro-4-nitrobenzene, the usual starting material for 4-nitro mpd's, make this isomer the least used of the nitrophenylenediamines.

Table 31.2 lists some of the available compounds (INCI names are used) in the nitrophenylenediamine series and their colors.

Nitroaminophenols

Nitroaminophenols also represent a widely used class of semipermanent hair colorants. The range of available colors is quite substantial, ~ 80 nm, even more than that of nitrophenylenediamines. The wide variety of isomers and substitution possibilities give the formulator wide leverage in obtaining the yellow to orange-red tints supplied by these compounds. While the nitrophenylenediamine series nominally includes the same spectral range as the nitroaminophenols, the extensive number of the latter compounds provides much more flexibility for these colors than the limited number of compounds in the former series. Thus the nitroaminophenols are quite necessary for semipermanent products, rather than simply being an enhancement. In fact, most of the yellow to orange dyes used are nitroaminophenols, with nitrophenylenediamines supplying orange to violet colors.

The generic structure is given below (including nitroaminophenolic ethers in this class).



As with the nitrophenylenediamines, R_1-R_3 may have many possibilities but generally use the same hydrogen, lower alkyl, and hydroxy- and dihydroxyalkyl moieties as the previous class. Unlike the nitrophenylenediamine class, which really uses only three starting materials, this class presents far more options for the synthetic chemist developing new colors for the formulator. There are numerous isomers of unsubstituted nitroaminophenol itself, and these lead to many reaction possibilities. Added to this, the usual stable of reactions such as replacement of activated halogens by amines, hydroxy or

Table 31.3 Common Nitroaminophenol Semipermanent Colorants

Compound	Color
2-amino-4-nitrophenol	Yellow
2-amino-5-nitrophenol	Yellow
HC Yellow No. 4	Yellow
HC Yellow No. 9	Yellow
2-nitro-5-glyceryl methylaniline	Yellow
2-amino-3-nitrophenol	Yellow-orange
2-nitro-N-hydroxyethyl-*p*-anisidine	Yellow-orange
HC Orange No. 2	Orange
HC Orange No. 3	Orange
4-amino-3-nitrophenol	Orange
4-hydroxypropylamino-3-nitrophenol	Orange-red
3-nitro-*p*-hydroxyethylaminophenol	Orange-red

hydroxyl compounds, nitration, and selective reductions, and the accessibility of many compounds becomes obvious. Table 31.3 lists some of these dyes; again, this list is representative, not exhaustive.

Aminoanthraquinones

Aminoanthraquinones (AQ) are used to complete the color palette of semipermanent dyes; they contribute the violet and blue colors and extend the spectrum approximately 100 nm. These molecules are significantly larger than the nitro dyes, but this is somewhat mitigated by their planarity and the nonbulky substituents of the AQs used for hair dyes. These dyes are used generally as disperse dyes, consisting of 40–60% colorant and the remainder a dispersing agent, usually a very hydrophilic lignosulfonate. There is some controversy over whether such dyes are truly in solution or in an ultrafine dispersion when in product, but certainly their use is necessary for the formulator since attempts to dissolve the solvent (i.e., nondisperse colorant) form of most AQs results in a nondissoluble residue in the bottom of the container. Interestingly, neither the large size nor the dispersant prevents thorough penetration and diffusion throughout the hair shaft.

The AQ colorants have traditionally been borrowed from other dyeing industries, especially textiles. Cost is thus minimal and the selection wide, although factors such as size and nature of the substituents usually restrict these choices. Recently, however, some AQs are being specifically designed and manufactured for hair dyes. This allows particular attributes, such as increased hydrophilicity, to be built into the molecule and removes dependence of the hair color companies on the vagaries of the textile dyeing industry.

Table 31.4 Common Aminoanthraquinone Semipermanent Colorants

Compound	Color
Disperse Red 15	Red-violet
Disperse Red 11	Red-violet
Disperse Violet 1	Violet
Disperse Violet 4	Blue-violet
Disperse Blue 3	Blue
HC Blue No. 14	Blue

The range of AQs used in hair dyeing need not be as extensive as those of other classes because of their high intensity and wider spectral bandwidth. Representative examples are listed in Table 31.4.

Other Dyes

The preceding three dye classes represent by far the most significant semipermanent hair colorants, but selected other dyes are also used for this application. Reasons generally include molecular size and hydrophilic character rather than unique color properties. Nitroanilines, dinitroanilines, and azo dyes are among these colorants; Table 31.5 lists some of these.

COMMERCIAL SEMIPERMANENT PRODUCTS AND THEIR FORMULATION

General practice among formulators of semipermanent hair colorants is to use several dyes of the same color but different molecular sizes. The smaller molecules will penetrate the entire hair shaft from root to tip, including the tighter, less porous area near the scalp, but will wash out of the more porous

Table 31.5 Miscellaneous Semipermanent Colorants

Compound	Color	Type
HC Yellow No. 6	Yellow	Nitroaniline
HC Yellow No. 15	Yellow	Nitroaniline
HC Yellow No. 2	Orange	Nitroaniline
HC Orange No. 1	Orange	Nitroaniline
HC Yellow No. 7	Orange	Monoazo
Disperse Black 9	Orange	Monoazo
2-Hydroxyethyl picramic acid	Red-orange	Dinitroaniline

tip end. Conversely, larger molecules will not enter the hair near the root but will permeate and remain in the tip end. Examples of this type of "color pairs" include HC Red Numbers 1 and 3 (both nitro-*p*-phenylenediamines, but the former having aromatic rather than aliphatic substitution, i.e., a diphenylamine), and HC Yellow Number 2/HC Orange 1 (the former a nitroaniline, the latter a diphenylamine).

Perhaps the most significant aspect of a semipermanent vehicle is its ability to temporarily swell the hair strand to allow penetration of the dyestuffs. The cuticle must open enough to allow thorough diffusion of the dyes into and through the cortex, then close back down to retain the dyes, and this must occur at ambient temperature and in a limited time. Optimum conditions for this process include mild alkalinity; thus most products are formulated in a pH range of 8.5–9.5. Ammonia is never used as the alkalizer, since it is too powerful and many dyes are not stable to NH_3. Secondary amines such as diethanolamine and methylethanolamine are generally avoided because of concerns about potential nitrosamine formation, and tertiary amines such as triethanol- or triisopropanolamine are not strong enough alkalizers. Thus primary amines, especially sterically hindered ones such as aminomethyl propanol and aminoethyl propanediol, are the alkalizers of choice.

Semipermanent products are usually lotions or aerosol mousses, and a cap may be used to slightly raise ambient temperature and thus enhance dyetake. Browns, reds, and blacks are by far the most popular shades since the gray hair that semipermanents are meant to cover appears most dramatically in these base colors. Product lines include, of course, tints for lighter shades and blondes, but these are not as popular because of the less noticeable nature of gray in these shades.

Most semipermanent products are applied to damp hair and then rinsed or shampooed off after 15–40 minutes; so formulations may contain mild surfactants in addition to solvents and swelling agents necessary for dye solubility and diffusion. This type of product does little or no damage to hair, but a conditioning agent may be added to the formula to enhance both the feel and the wet and dry combability of the hair. Such a conditioner may be alternatively included as an after-treatment.

One other application for semipermanent products is for tinting chemically treated hair that may not tolerate more rigorous oxidation dyeing. This includes hair that has been permed or relaxed, and formulations with low levels of semipermanent colorants and mildly alkaline pH are excellent choices for tinting such hair. The increased porosity of this hair will enhance dyetake but will also increase washout; in this case, however, gentleness is preferable to durability.

A typical semipermanent lotion formulation is given below:

Ingredient	Weight %
Ethoxydiglycol	3.2
PEG-8 tallow amide	1.5
Hydroxyethylcellulose	1.0
Cocamide DEA	2.0
Aminoethylpropanediol	1.5
Oleic acid	1.8
TEA-Dodecylbenzenesulfonate	0.9
HC Blue No. 2	0.4
Disperse Blue 3	0.3
Disperse Black 9	0.05
HC Yellow No. 4	0.1
HC Red No. 1	0.07
Disperse Violet 1	0.02
HC Orange No. 1	0.01
Water	q.s. 100

PERMANENT HAIR DYES

As stated previously, this class of hair colorants is by far the most popular. The advantages of these products lie not only in their durability but also in their versatility: these are the only products that allow the user to lighten the base hair color. Most products have traditionally done this to some extent, and the appeal of lightening remains strong. In recent years, however, a subclass of permanent products has arisen, frequently called demipermanents. These products rely on the same oxidative chemistry and have similar durability to permanents but lighten the base color little or not at all. Coverage of gray is not quite as thorough but the results are often more natural looking than the more evenly dyeing traditional products. Both types of products offer the user the most effective hair coloration and maximum flexibility. The general theory of oxidative dyeing holds that small colorless molecules are allowed to diffuse into and through the hair, then undergo a series of chemical reactions to generate large colored molecules incapable of being washed out. While this is simplistic, it is nevertheless accurate enough to describe the process.

Oxidative hair coloring chemistry requires three constituents:

1. An *ortho* or *para* substituted aminoaromatic, usually single ring, with the substituent being hydroxy, amine, or substituted amine. This is called the primary intermediate;

2. A second aromatic, again usually single ring, with at least one but usually two electron-donating groups arranged *meta* to each other. This is called the coupler or color modifier.
3. An oxidant, almost exclusively hydrogen peroxide but possibly perborate, percarbonate, and the like.

There are several similarities between oxidative hair dye and color photographic chemistries. Both rely on oxidative processes, silver salts being the oxidants in the latter case and peroxide in the former. Both use closely related primary intermediates, and some of the couplers, especially for blue tints, are also alike. The similarities mostly end there, however, and the different priorities dictate the variations. Hair dyes are periodically reapplied, so fastness to light is less crucial (although fastness to aqueous surfactant washing, insignificant to the photographic chemist, is more so). Photographic chemistry occurs in discrete layers sandwiched between protective layers; therefore, competing reactions in mixtures need not be considered. Nor are the chemistries completely alike: some of the couplers and/or finished dyes of color photography are not stable to alkaline peroxide. This is especially unfortunate, since some of the photographic colors would be excellent tools for the hair colorist.

DYESTUFFS

Many of the compounds in this hair dye class, perhaps more accurately called dye precursors rather than dyestuffs, are used in large quantities in other, often unrelated, industries. Thus they can frequently be obtained in very high purity for very low cost. Examples include *p*-phenylenediamine itself, used in other dyeing applications but also as an antioxidant and as a monomer for synthetic polymers, and *p*-aminophenol, precursor to the analgesic acetaminophen. Several compounds, however, are unique to hair dyeing and thus are custom-manufactured.

Primary Intermediates

These compounds are easily oxidized to form an intermediate reactive species, hence the name. There are many theoretical possibilities for this class, but almost every compound used is a *p*-phenylenediamine, *p*-aminophenol, or some variation thereof. The most common compounds are shown in Figure 31.1.

Although all of the examples above are *para* disubstituted benzenes, *ortho* compounds such as *o*-aminophenol have been used for many years and, more recently, heterocycles such as pyridine and pyrimidine compounds have gained wider acceptance.

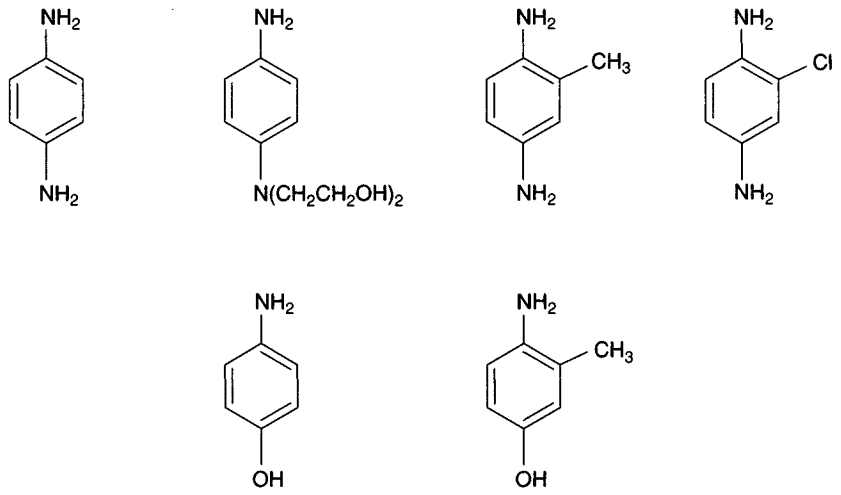


Figure 31.1. Common primary intermediates

Couplers

These compounds are the substrate to which the oxidized intermediate attaches, or couples, to give a colorless diphenylamine, the leuco form of the final indo dye. There are also many possibilities for this class, but almost all are resorcinols, *m*-aminophenols, *m*-phenylenediamines, or naphthols. The common ones are shown in Figure 31.2.

Heterocycles and fused ring compounds such as 2,6-dimethoxy-3,5-pyridinediamine, 6-hydroxyindole, and hydroxybenzomorpholine are also growing in usage.

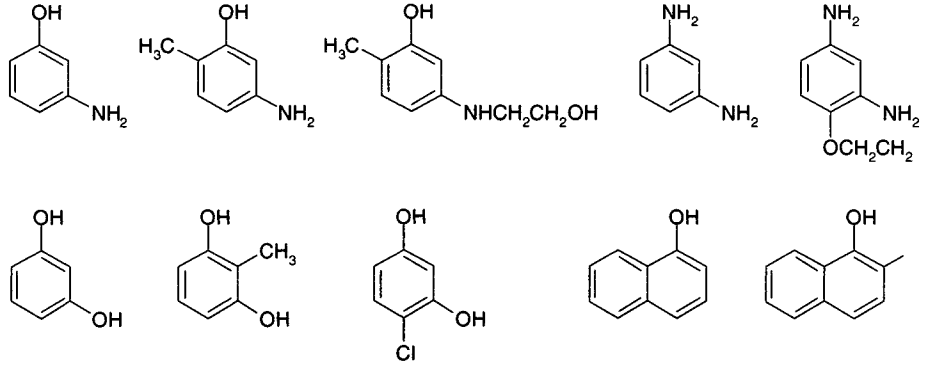


Figure 31.2. Common oxidative couplers

FORMATION OF COLORS IN THE HAIR

Oxidative hair dyeing relies on a three-step process to form the final dyes from the colorless precursors:

1. Oxidation of the primary to form a reactive intermediate, either a quinonediimine (from diamines) or a quinoneimine (from aminophenols), by alkaline peroxide. This is a slow step;
2. Addition of the imine to the coupler to give a colorless diphenylamine, referred to as the leuco form of the dye;
3. Oxidation of the diphenylamine to the final dye; this is quite rapid. These dyestuffs are called indo dyes and bear a structural similarity to the azomethine class.

This sequence can be exemplified by the reaction of *p*-phenylenediamine and resorcinol, shown in Figure 31.3.

The chemistry is not quite as simple as might first appear, however. Further coupling can occur, giving rise to tri- and multinuclear species of different tints. This effect may be enhanced, if desired, by manipulating the relative amounts of each compound or class. Also, rates of reaction, both of the initial oxidation and coupling, will vary considerably between each intermediate and each intermediate or coupler combination.

Additionally, the imines can self-couple to form multinuclear compounds; the trimer formed by *p*-phenylenediamine in known as Bandrowski's base.

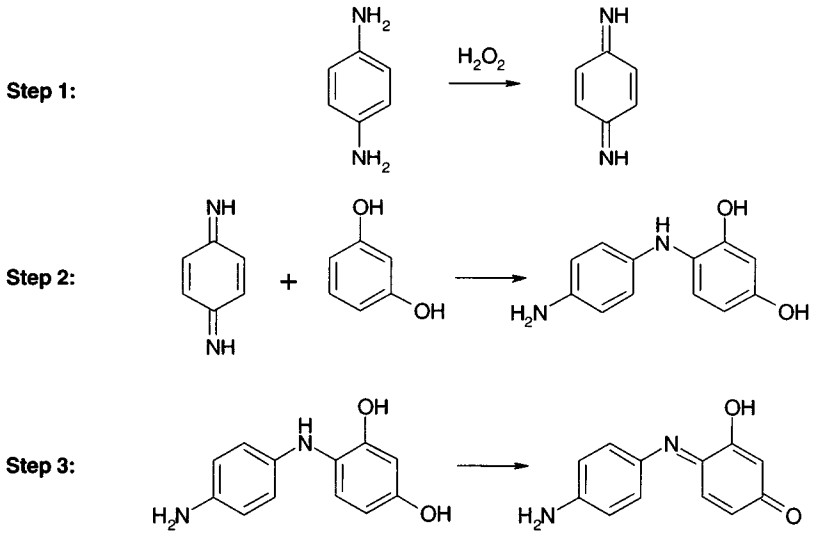


Figure 31.3. Formation of an oxidative hair dye

However, this sequence is far less favored in the presence of couplers than straightforward addition to form the diphenylamine, so it is of no consequence.

It can be clearly seen that quite a range of colors is attainable by the formulator who has four to six primaries and six to eight couplers available. In fact, many products contain a combination of two to three primaries and three to five couplers, the resulting shade being a smooth blend of color and nuance.

Shade descriptions of just 12 combinations, two primaries and six couplers, are given in Table 31.6.

The attainable color range of oxidative hair dyes does have some limitations. Neither a bright yellow nor a bright orange is available. This lack is somewhat mitigated by a number of factors: first, peroxide will lighten, to some extent, the natural color of hair. This has a brightening effect that lessens the need for yellow and orange colors. Second, semipermanent dyes that are stable to ammonia and peroxide may be used to add these colors. This is not an elegant solution, however, since the nuances and brightness they add will be less durable. Their levels must be kept low to prevent significant shade changes over short time periods. Standard oxidative dyes with this coloration would be useful additions to the palette, rather than the "band-aid" addition of semipermanent colorants.

TOXICOLOGY

Some of the oxidation dye precursors, notably *p*-phenylenediamine but also some couplers, are known to be potential sensitizers. Although the occurrence of dermatitis or other allergic response is quite rare with respect to the use of hair dye products, many countries have introduced laws or regulations requiring users to carry out prophetic patch tests before dyeing and specifying limits to concentrations of ingredients in the formulae, and so forth. For example, products in the United States must show in a prominent and conspicuous place the statement: "Caution. This product contains ingredients that may

Table 31.6 Shade Descriptions of Various Primary or Coupler Combinations

	***p*-phenylenediamine**	***p*-aminophenol**
***m*-Phenylenediamine**	Blue	Violet
***m*-Aminophenol**	Red-brown	Orange
4-Amino-2-hydroxytoluene	Red-violet	Orange-red
Resorcinol	Green-brown	Yellow-brown
2-Methylresorcinol	Violet-brown	Orange-brown
1-Naphthol	Blue-violet	Red-orange

cause skin irritation on certain individuals, and a preliminary test according to the accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness." The safety of hair dye ingredients of all classes is thoroughly reviewed in the United States by the Cosmetic Ingredient Review (CIR), and the findings are published in the *International Journal of Toxicology*. Further discussion of the safety and toxicology of hair dye compounds can be found in Kalopissis [1] and Corbett, et al. [2].

TYPES AND FORMULATION OF PERMANENT HAIR DYES

Oxidative hair coloring products come in many forms: liquid, creme, gel, powder, and aerosol. Except for a powder that uses a solid oxidant, all other types require separation of the dye-containing portion usually called the dye base, and the oxidant usually called the developer. In the case of an aerosol, this is accomplished with separate compartments whose contents are mixed when dispensed.

The concentration of hydrogen peroxide is measured in *volume* rather than percentage and refers to the volume of oxygen liberated on peroxide decomposition. This nomenclature is somewhat archaic but is firmly entrenched; therefore it is used here. For hair dyeing purposes, concentration usually varies between 3% (10 volume) and 9% (30 volume), with up to 12% (40 volume) available to the professional colorist.

The selection of alkalizing agent and peroxide concentration are the most significant factors in determining the product character. Traditional products, often referred to as Level 3 colorants, use ammonia and 30 volume H_2O_2; these are both the longest lasting and most complete gray coverage products. They also offer significant lightening during the coloring process, which increases both the brightness and the levelness of the final result. These advantageous properties require a somewhat longer application time to achieve, 20–45 minutes, but generally 20–30 minutes suffice. Effective results rely on application near the roots first, to allow more exposure time for this undyed new growth, followed by application to the remainder of the hair. These products comprise the largest share of this category and thus the largest selling types of hair colorants. Recent improvements to this category include the use of an alkanolamine, usually monoethanolamine, to replace some of the ammonia. This significantly reduces the strong ammonia odor to where it can be almost completely masked by fragrance without decreasing the amount of lightening. Present technology still requires the use of some ammonia to lighten, with peroxide, the base hair color.

Recent years have seen the introduction and fast growth of a related series of hair colorants generally referred to as demipermanents or Level 2 colorants. The chemistry and precursors remain the same, but the peroxide concentration is lower (10–12 volume) and a nonammonia alkalizer, typically monoethanolamine or aminomethylpropanol, is used. Little or no lightening is achieved and gray coverage is somewhat less thorough, but this lack of complete evenness gives the appearance of highlights and thus may be a more natural result. They may be thought of as gray-blending rather than gray-covering, dyeing the gray hair to a tone quite similar to the base hair color rather than an even dyeing of all the hair. An additional advantage is a shorter dyeing time, usually ~10 minutes, since no extended bleaching period is required. However, these products do not perform very well on hair with extensive amounts of gray or on hair that may be more resistant to dyeing and thus requires the enhanced swelling that ammonia provides. Also, the less rigorous dyeing may require more frequent application. Colorants of this type also find use in professional salons as mild, longer lasting hair dyes used after a strenuous hair treatment (e.g., bleaching, relaxing). These products are used to tone rather than heavily dye the bleached hair.

One final type of oxidative product is designed to have an application time of five minutes; these are usually but not exclusively targeted at the men's market. These usually contain high levels of dye precursors to obtain significant color formation in the abbreviated time, and lower concentrations of peroxide, since no lightening is achievable anyway. Alkalizer is alkanolamine and/or ammonia. Although the shorter time has great appeal, the results are not as aesthetically pleasing as those from other oxidative products. Dyetake may be quite uneven and significant washout, because of less complete dye penetration, usually occurs in the first few shampoos. Durability is also sacrificed, again because of less thorough diffusion. These products have therefore not generated mass appeal.

Formulation of oxidative hair colorants has shifted in recent years from vehicles with high levels of organic solvents to those that are largely aqueous. Problems with dye solubilization and long-term emulsion stability have been overcome, and new products make far more efficient use of the dyes. Optimization of the vehicles has given equal or better coloring results with lower dye concentrations and has allowed development of products with shortened dyeing times. The most convenient medium for coloring the hair is a shampoo; thus many products are formulated around an aqueous surfactant composition modified to contain the dye precursors and the required adjuvants. These include antioxidants, generally sodium sulfite and erythorbic acid, for protection during initial solubilization or manufacture and long term in product. Another necessary additive is EDTA or one of its salts, used to chelate any metals that

would catalyze peroxide decomposition upon mixing with developer. This is, in fact, found often in both the dye base and the developer. Biological preservatives are usually not required because of the high pH. Similarly, products in creme, gel, and lotion forms may be devised with other additives such as fatty alcohol sulfates or ether sulfates, fatty acid alkanolamides, nonionic, cationic, or amphoteric surfactants, fatty alcohols and/or amines, amine oxides, alcoholic solvents, thickeners, and so forth. Generally, the only required property of a hair dye formulation is a thick viscosity after mixing with developer, such that the applied colorant will not drip down out of the hair and onto the face and neck of the user.

Conditioners are frequently included in hair dye products and offer smooth combability, both wet and dry, and enhanced feel and luster. Modern permanent dye formulations keep oxidative damage to a minimum, but conditioners add improved aesthetics of high value to the user. Conditioners may be included in the dye base or as a separate package after-treatment. While this later option requires another formulation and more packaging components, it may offer multiple uses to the consumer and could therefore be perceived as an added benefit. The developer formulation may be as simple or as complex as the product chemist desires. It may consist of only peroxide and water, it may have a stabilizing acid, such as phosphoric or etidronic, or it may be a complicated mixture in its own right. Ingredients may include thickeners, silicon-based conditioners, surfactants, and so forth. Developers containing acrylate-based thickeners have become especially popular in recent years.

A sample formulation found in Brown and Pohl [3] is as follows:

Ingredient	Weight %
Oleic acid	21.0
Sodium lauryl sulfate	2.0
Oleyl alcohol	10.0
Ammonia (28%)	12.0
Isopropyl alcohol	10.0
Propylene glycol	4.0
Sodium sulfite	0.2
EDTA	0.05
p-Phenylenediamine	0.2
Resorcinol	0.3
4-Amino-2-hydroxytoluene	0.2
m-Aminophenol	0.1
Water	q.s.100

Another exemplary formulation, that gives a dark brown color on hair, is in U.S. 5,851,237 [4]:

Ingredient	Weight %
Cocamidopropylbetaine	10
Monoethanolamine	2
Citric acid	1
Ammonium hydroxide	10
Sodium sulfite	0.1
1-(4-aminophenyl)pyrrolidine sulfate	1.0
m-Aminophenol	0.5
Resorcinol	0.5
1-Naphthol	0.1
Water	q.s. 100

OTHER DYES FOR HAIR

Hair coloring products based on other technologies have been developed to fill specific consumer needs; some of these have been available for many years. Although such products continue to be sold, improvements on and expansions of common hair dye technology, especially permanent colorants, have largely fulfilled these needs. Additionally, the fact remains that modern hair coloring products are better than anything else in accomplishing that goal. The limited appeal of niche materials pales beside the performance and convenience of today's colorants based on synthetic dyestuffs. Thus the market for products using alternative approaches is quite small.

AUTOOXIDATIVE DYES

This class of dyes relies quite heavily on standard oxidation dyestuffs but uses the slow oxidation by air rather than the fast peroxide oxidation to cause reaction. "Autooxidative" is a somewhat misleading term, since it is atmospheric oxygen that is the active oxidant. Color development is therefore very slow, on the order of days, and appeals chiefly to the user who wants gradual color change. These products are for gray coverage only, generally come in shades of medium or light brown and darker, and are usually aimed at the men's market. Dyestuffs include the same primary intermediates and many of the same couplers as permanent products and some tri-substituted compounds. These later compounds are benzenes with oxidizable groups in the 1,2,4-positions. Two are most common: 2,4-diaminophenol and 1,2,4-trihydroxybenzene. The development of five-minute products targeted at men,

and especially of demipermanent products, has largely pushed this class out of the market.

VEGETABLE HAIR DYES

As noted in the introduction, henna has a long history of use in tinting hair. It is still used in some areas today, often in combination with one or more other plant materials. Little or no product formulation is required: ground or powdered plant material is prepared in a poltice, using usually hot water and a mild acid for pH adjustment at the time of application. The plant material may include other species, such as indigo, for additional nuances. The paste is applied to the hair for some period of time and then rinsed off. This type of product has the appeal of a purely natural colorant, but the severe disadvantages largely outweigh this. These include highly variable results, limited shades, and messiness. Far superior and controllable results could be obtained by simply incorporating synthetic lawsone into a commercial hair dye formulation.

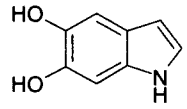
METALLIC HAIR DYES

Hair colorants based on metals have been around for decades. These are usually based on lead and rely on the slow formation of lead sulfide from the lead acetate salt in the product. As with autooxidative colorants, the appeal is gradual color formation over several days. Disadvantages include limited shades, potentially variable results, uneven shade development, and possible sulfide odors. This technology, as with the other alternative methods, has become even less appealing with the advent of modern coloring formulations.

INDOLIC DYES

The natural hair and skin colorant for non-red shades is eumelanin, a biopolymer whose structure is not strictly defined. Its monomeric precursor in the biological pathway is dihydroxyindole **[3]**:

3



Products seeking to mimic eumelanin coloration have included this indole and/or its analogues and usually rely on air oxidation of this unstable compound. Despite intensive effort, the structure and characteristics of eumelanin are not yet completely understood, so attempts to imitate it have been

premature. Products formulated around **[3]** have demonstrated poor fastness properties, with severe off-shade wearing. Even a successful indolic product, however, would suffer from the same drawbacks seen in other alternatives, namely, limited shade range, slow color development, potentially variable results, and no lightening possible. Additionally, **[3]** is difficult to synthesize and is therefore quite expensive. A protected, stable precursor that generates **[3]** in situ may be used. The claim of a natural melanin-based colorant, the presumed market hook for such a product, might be suspect in light of the chemically synthesized active component. For now technical limitations preclude an effective indole-based hair colorant.

HAIR DYE REMOVERS

The removal of hair dyes is sometimes necessary because of either a mistake or an undesirable result. The degree of difficulty in removal is directly related to the intended durability of the product.

Temporary products can be removed by one or more shampoos. Semipermanent products can be removed by multiple vigorous shampooings. These products are designed to last anywhere from four to eight shampoos, depending on the specific formulation. Complete removal will require at least this number, since there is no environmental wearing between the shampoos.

Oxidative products, whether permanent or demipermanent, cannot be removed by shampooing. There are two options for corrective action: chemical treatment, or redyeing with another shade, usually using a demipermanent, to obtain the desired tonality. Chemical treatments will not remove oxidative colorants completely but will significantly reduce color. The result may be acceptable to the user or, if not, more conducive to corrective recoloration. Treatment with ascorbic and/or isoascorbic acid will accomplish this [5]. More stringent chemical treatments, such as those using strong bleaching agents, will also bleach both the dyes and the underlying hair color but will risk damaging hair already treated with an oxidative dye.

Corrective recoloration, preferably with a demipermanent and with or without a prior nonrigorous chemical color reduction, remains the treatment of choice. Either approach should only be undertaken by a professional.

BLEACHING AND LIGHTENING

The depth of shade of color is often described by a range of 12 levels, with level 1 being black and level 12 being ultralight blonde. This nomenclature is not to be confused with the Level rating of a product, which is a measure of

its durability. This repetition of term is unfortunate, but the designations are generally accepted by the industry.

Temporary and semipermanent products do not lighten the natural color at all. It may sometimes appear that this is the case, but the effect is because of lighter, brighter dyes that give the impression of highlighting, or selective lightening.

Demipermanent products usually lighten the natural hair color about 1 level. These products can be formulated not to lighten at all, or possibly up to 2 levels.

The highest amount of lightening that can be achieved with simultaneous dyeing is about 3–4 levels; these require higher concentrations of ammonia and peroxide and longer application times.

Thus rigorous lightening cannot be achieved with simultaneous dyeing and requires a separate procedure. This is "double process" an initial bleaching followed by dyeing, usually with a mild demipermanent. A semipermanent might also be appropriate, but the greater porosity of the treated hair would result in faster, and possibly uneven, washout. In practice, bleaching is rarely followed by an intense dyeing, and the coloration is more of a toning with a product containing low dye concentrations.

Bleaching the hair more than 3–4 levels allows the user to produce blonde shades from darker hair, although a reduction of 6–7 levels is the maximum practicable. This strong bleaching is only accomplished with ammonia, high, volume peroxide, and peroxy salts. These are sodium, potassium, and ammonium persulfate, and most bleaching formulations have at least two and usually all three. Ammonium persulfate is the ammonia source. Peroxide and persulfate work synergistically in the bleaching process, which seems to be a two-step sequence: breaking apart of the melanin granules ("melanosomes") followed by chemical decolorization.

The practice of bleaching usually consists of mixing peroxide with the preblended persulfate (often containing silicates for flow characteristics) powder to the consistency of a thick paste, then application to the hair for a period of time that depends on the desired result. The degree of lightening is controlled by the peroxide concentration, contact time, and to some extent the amount of ammonium persulfate. A variation of this procedure is the application of the mixture only to selected portions of hair, followed by the wrapping of these portions in foil. This results in highlighting rather than overall lightening.

Recent improvements in this area have focused on making the persulfates easier to use. Especially noteworthy is the addition of an inert oil to the powder to prevent dusting [6]. Lightening kits are available to the home user, including usually a mild shampoo and a conditioning after-treatment. However, most

bleaching and/or lightening, especially if followed by dyeing, is performed by a trained professional in the more controlled salon environment. This is because of the somewhat rigorous nature of the bleaching process, the possibility of damage if done incorrectly, and the convenience of having it done by a professional.

Very mild lighteners consisting of low-level peroxide are also available to the consumer. These are meant to mimic the lightening effects of sun exposure and are leave-in products, usually aerosols.

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6. U.S. Patent 5,698,186 Methods of controlling dust and compositions produced thereby, Weeks, G., December 16, 1997; Assignee: Clairol.

CHAPTER 32

Permanent Waving, Hair Straightening, and Depilatories

INTRODUCTION

From the time when early Egyptian women curled their hair by means of wet mud, and through the Roman and Grecian era up to the present day, the desire of all women has been to possess an attractive and beautiful coiffure. In general, even allowing for the vicissitudes of fashion, curly or at least wavy hair is more attractive than straight hair and at the same time provides more opportunities for rearrangement into suitable and fashionable styles. Hence any process by which curls or waves could be introduced into hair was bound to affect, to a very marked degree, the trend of modern hairdressing.

Until about 1910, hair was always curled by means of a curling iron or by steaming. This, however, never resulted in a lasting wave. The hairdressing pioneers of the early twentieth century found that the addition of chemicals such as borax to the water before steaming would curl hair so that the curl survived several washings. From these early beginnings, investigators created chemical methods of heating moist hair and identified chemical modifiers of human hair at room temperature.

The configuration of the hair is determined during the keratinization stage, as the almost fluid cells produced by the papilla are shaped by the follicle wall and converted into keratin (see Chapter 2). The shape of the hair is thus a very deep-seated structural characteristic, not easily altered by subsequent treatments of the fully keratinized shaft. Hence all the processes described in this chapter, although they are called "permanent," are subject to gradual

relaxation, as the hair returns to its normal straightness or kinkiness. The time taken for this relaxation varies with the process, the hair, and the environment, and may require a few weeks to many months.

The process of straightening hair involves deformation of wavy hair to an uncurled condition and depends on chemistry similar to that of the waving process. It is largely confined to one section of the consumer market and is discussed later in this chapter.

Finally, depilation or hair removal also relies on chemical processes similar to those required for waving or straightening.

HAIR WAVING

CHEMISTRY OF HAIR WAVING

The important chemical processes for changing the configuration of straight or excessively curly human hair were discussed in Chapter 2. In principle, the keratin fiber is softened, reshaped in the desired way, and finally hardened to retain the new shape.

Reduction Step

In modern hair waving or hair straightening practices mercaptans are more frequently employed than either sulfites or alkalis. Each of these reagents softens the keratin and makes it more plastic. The use of thiols is widely practiced, and it will be recalled that the presence of mercaptan (–SH) groups in hair is essential for the reconfiguration of hair and also for relaxation as a result of the so-called sulfide or disulfide interchange. Mercaptans (or thiols) are weak acids but form (sulfide mercaptide or thiolate) ions as the pH is raised. To achieve the required disulfide (cystine) bond breakage, the levels of RS^- ions must be raised by increasing the pH. Raising the pH of the waving preparation always presents the possibility of lanthionine formation, which is difficult to modify or remove from the hair. Thus formulators strive for products exhibiting low pHs.

Like all chemical reactions, the rate of disulfide bond breakage by mercaptides is temperature-dependent. The mechanism of reaction is a typical equilibrium reaction with mixed disulfide formation, as demonstrated by many investigators (Scheme 3, Chapter 2). A comprehensive review of this chemistry can be found in Reference 1. The equilibrium nature of the reaction explains why breakage of as few as about 20% of all cystine bonds suffices to effect waving. During the time of contact with the mercaptide-containing product, the sulfide or disulfide interchange reaction proceeds continuously. Although only 20% of keratocystine may be broken at a given time, it is likely

that many more disulfide bonds are opened and re-formed during processing. Finally, it should be understood that a keratocystine bond under stress is more likely to undergo the interchange reaction than an unstressed disulfide bond. It is significant to note that excessive stress because of bending or pulling of hair fibers is a common cause of hair breakage.

In practice, the reduction level ranges between 19% and 43% [2]. In common practice, such levels of reduction are reached with 0.5 to 0.9 *M* thioglycolic acid near pH 9. A decrease in pH enhances formation of the mixed disulfide, while the addition of disulfide (e.g., dithiodiglycolic acid) tends to displace the equilibrium of step one toward formation of the mixed disulfide.

The nature of the thiol compound, especially its pK, and the pH of the solution, are therefore critical to the rate at which the above equilibria are established and to any competitive reactions, which could occur as a result of the elevated pH. Some typical thiol waving compounds are shown in Table 32.1. Those containing carboxylic acid functions require a high pH for mercaptide formation because the carboxylate anion interferes with the ionization of the thiol group.

In accordance with the common pattern of dissociation constants of organic compounds, the mercaptan groups of carboxylic acids have a pK of about 10.4; the esters of these substances have a pK of about 7.8, as do most neutral mercaptans; keratocysteine, that is, peptide-bound cysteine, reportedly has a pK near 8; and cystamine's pK is likely to be lower (about 7.5). Efficient hair waving with thioglycolic or thiolactic acid requires a pH above about 9.1; simple esters including glyceryl thioglycolate can wave hair near neutrality. The same is true of thioglycolamide and cysteamine. Some of these and more obscure mercaptans tend to split off hydrogen sulfide, which makes them unsuitable for use in hair waving preparations.

Hydrolysis of the esters may alter the efficiency of the compounds, and there seems to be some inverse relationship between potential irritation to the scalp and the pK of the thiol compound. Despite its disadvantages (odor, only average efficacy, used for alkaline pH), thioglycolic acid remains as the most dependable thiol since it offers an excellent compromise between activity and tolerance. However, it is not necessarily irreplaceable; for example, some dithiol compounds such as Cleland's reagent may be used at low concentration and at neutral or even acidic pH. Their efficacy depends on their ability to form a cyclic disulfide by oxidation, which results in a complete displacement of the equilibrium thiol-disulfide toward formation of keratocysteine through an internal thiol-disulfide exchange reaction on the mixed disulfide. Some patented thiol compounds and other reducing agents are listed next:

Polymeric Mercaptan	U.S. Patent 3,693,633
Reducing Enzymes	German Patents 2,141,763 and 2,141,764
	U.S. Patent 4,853,215
Reducing Agents	U.S. Patent 2,403,937
	Brit. Patent 771,627
	U.S. Patent 2,600,624
	Brit. Patent 766,385
	U.S. Patent 3,256,621
	German Patent 2,345,621
	U.S. Patent 5,260,054
	U.S. Patent 5,362,487
	U.S. Patent 5,382,426

There is only limited evidence that any of the patented substances has been used successfully in hair care.

Reoxidation Step

The oxidation of hair after any of these softening (reducing) treatments is a necessary stage in hardening the structure into the new imposed shape (straightened, curled, or waved). The basic process is a simple reoxidation of keratocysteine to keratocystine, but at the same time it should induce the formation of cross-linked fibers and restore the former mechano-physical properties of hair. For this type of reaction to occur, two keratocysteine residues must be in a favorable position to each other to reestablish a disulfide bridge under the action of the oxidant; otherwise, keratocysteine may undergo peroxidation to sulfinic or sulfonic acids. Side reactions during the reducing step may also form compounds that may produce substances of different oxidation levels. In fact, the oxidation process is complex because it is performed with an excess of oxidant (H_2O_2, bromate, iodate, etc.). Despite these complications, the currently practiced two steps in the cold waving process under mild conditions transforms 95% or more of keratocysteine into disulfide without keratolytic effects, either with "6 volume" hydrogen peroxide at pH 3 or with 18% sodium bromate solution at near neutral pH. Any lanthionine formed during the reduction phase—which may represent 30% of the hair cystine—is oxidized to sulfoxide and sulfone; the same applies to the hair methionine. On the whole, permanent wave processing with thioglycolic acid shows a modest loss of cysteine because of transformation into lanthionine and its oxidation derivatives.

Sulfite-reduced hair is usually hardened through the same procedure; Bunte salts and thiol groups are transformed into disulfide by hydrogen peroxide at a much slower rate and therefore not completely.

Cross-linking of reduced hair may be effected by other means than through peroxides, which may involve a risk of lightening the hair; thus polythionates (French Pat. 1,309,816) allow the rebuilding of keratocysteine without the side effects mentioned because of oxidation. A formaldehyde-releasing agent such as hexamethylene tetramine may lead to another kind of cross-linkage: "methylene dithio" linkage, as does azadioxabicyclooctane derived from tris(hydroxymethyl) aminomethane; even formaldehyde has been recommended for this purpose (U.S. Pat. 4,013,409).

Alkylene dihalides can also yield dithioethers, and some metallic salts have been suggested for cross-linking: triethanolamine titanate (Brit. Pat, 745,179), the zirconium salt of an organic hydroxy acid (U.S. Pat. 2,707,697), and barium salts (Brit. Pat. 453, 701) have been recommended for cross-linking. In fact, the patent literature on this subject is overwhelming. Nevertheless, there is no evidence that these inventions were ever commercialized for cosmetic purposes.

HEAT WAVING PROCESSES

The procedure adopted by the professional hairdresser in heat waving is as follows:

1. Any grease is removed from the hair by shampooing.
2. The hair is then divided and wound around a suitable roller under slight tension.
3. A sachet or absorbent strip dipped in a suitable solution is wound over the hair, the whole is encased in an electric heater, and the hair is steamed for the required period.

It must be understood that this method is modified somewhat according to whether *sachet* waving or *oil* waving is being employed, and according to the particular type of wave desired. Usually, heat is supplied to the rollers electrically; in the wireless system the heaters are preheated; finally, chemical heating methods are also used, in which moisture from the wrapper induces an exothermic chemical reaction in contact with a chemical mixture.

This type of permanent waving demands, in addition to suitable reagents, considerable professional skill and experience. The selection of suitable methods of winding, of strengths and types of reagents, times of steaming, and so forth (according to the type and condition of hair treated) are of paramount significance.

Hairdressers have claimed, without scientific proof, that the success of permanent waves can be affected by the state of health of the subject. This generalization is probably invalid: hair that has been keratinized and has erupted beyond the limits of the hair follicle is not affected by anything taking place inside the body. In addition, hair care is practiced widely in hospitals.

Permanent Waving Solutions

Permanent waving solutions are almost invariably strongly alkaline, since the presence of alkalis considerably shortens the time necessary to produce a satisfactory wave. Recommended alkalis include lithium hydroxide, sodium, potassium, ammonium carbonates, borax, ethanolamine, or neutral or alkaline solutions of sulfites (sodium, ammonium, mono- or triethanolamine, morpholine sulfites).

The following formulas 32.1–32.3 reportedly give good results on average hair after about 10 minutes steaming time:

Formula 32.1 Heat Waving Lotion

	%
Monoethanolamine	6.0
Potassium sulfite	1.5
Potassium carbonate	1.5
Ammonium carbonate	2.5
Borax	0.5
Sulfonated castor oil	1.0
Water	87.0

Formula 32.2 Heat Waving Lotion

	%
Ammonium hydroxide (s.g. 0.88)	20.0
Sodium carbonate	4.0
Potassium sulfite	2.0
Water	74.0

Formula 32.3 Heat Waving Lotion

	%
Monoethanolamine or ammonium hydroxide (s.g. 0.88)	14.0
Borax	4.0
Potassium sulfite	2.0
Water	80.0

The use of agents that enhance the lanthionine formation (sodium chloride, sulfates, and cationic surfactants), and of boosters (urea, amides, and lithium bromide) helps to reduce the concentration and to lower the pH.

A gel to be applied at 40 °C for 30 minutes is given in Formula 32.4. Today hot waving, because it is aggressive to the hair and uncertain in its results, is

Formula 32.4 Heat Waving Gel

	%
Hydroxyethylcellulose WP 4400	4-0
Lithium hydroxide	2.0
Sodium chloride	17.5
Water	q.s. to 100

no longer widely used. Theoretical and practical reasons have mandated the use of sulfites in hot waving and of thio-compounds in cold waving. Nevertheless, successful cold products for the achievement of "soft" permanent waves are available, which employ sulfite at high pH (about pH 10) and hydrogen peroxide neutralization. Such products were discussed in 1979 [3].

Chemical Heating Methods (Heating Packages)

Chemical heating methods have been introduced, in which the heat required for the normal waving process is obtained without the aid of electricity. Such methods depend on heat evolved by the reaction of an exothermic material with a moistening medium as a result of one of oxidation and reduction, hydration, or neutralization.

This method originated in England in 1923 with the use of quicklime to generate the heat. Since that time numerous chemical mixtures have been recommended and patented, including active agents such as aluminum and its chloride and sulfate, ammonium salts of various organic acids, barium salts, copper carbonate or nitrate, iron filings and other salts, and so forth [4].

COLD WAVING PROCESSES

Acid and alkaline cold waving have to a large extent replaced the older hot waving process, particularly in the more sophisticated parts of the world where the replacement is complete. There is some confusion between acid and alkaline perms, because the pH of most acid perms is between 7 and 8. Originally, acid perms had a pH of 6–7 but required heat to enhance performance. To eliminate the need for heat the pH was increased to a range of 7–8, but the acid name has remained as a way of differentiating between glyceryl thioglycolate (GMTG) perms and alkaline perms containing salts of thioglycolic acid. Also, GMTG-based perms must be mixed with a basic lotion prior to use, because GMTG breaks down in the presence of water. Acid perms are only available for professional use.

The cold waving operation is performed at room temperature for alkaline waves and for acid waves. The hair is shampooed thoroughly and divided into

sections for ease of handling. Locks of hair of such size as to give 35–50 curlers (6–14 mm diameter) per head are moistened with the waving lotion and then wound on to circular curlers with the aid of endpapers. Because the nape hair needs a good curl to stop it from "wisping" and because it also seems rather resistant to perming, it is usual to start at the nape and work forward.

After winding is complete, the hair is remoistened with more lotion and left to "process" for 10–40 minutes. Some manufacturers recommend set times for various types of hair, while others advise the examination of a test curl by the user, who then decides how much longer to leave the lotion on the hair. Hairdressers usually use the test-curl method. After the processing with reducing agents, the hair is rinsed and neutralized by application of an oxidizing solution to the wound curls. After 5–10 minutes the curls are unwound, and usually a further application of neutralizer is made. The hair is then rinsed and set into the desired style.

During the processing time, diffusion of the waving agent into the hair shaft occurs from the outside in. The oxidized waving agent (dithiodiglycolic acid) is expected to diffuse outward in accordance with concentration-controlled Fickian diffusion. At the same time, the wave is formed via the well-documented thiol or disulfide exchange. It should be clearly understood that wave formation occurs during the processing period, that is, while the hair is wound on the curler. The longer this exchange is allowed to progress, the tighter the resulting wave. If the hair is reduced straight and then wound on curlers and promptly reoxidized, the resulting wave is not well-developed.

The Reducer in Cold Waving

Permanent waving formulations are based on thioglycolic acid, salts, esters of thioglycolic, and salts of thiolactic acid. The simplest lotions contain ammonium thioglycolate at pH 9.2–9.8. In practice, pH 9.3–9.5 is used for concentrations of thioglycolic acid between 7.5% and 11%, but the strength of the lotion is essentially dictated by the quality of the hair to be waved; the average thioglycolate concentrations for use in commercial salons are as follows [5]:

Thioglycolic Acid	%
Difficult to wave (fine) natural hair	9–11
Easy to wave (medium to coarse) natural hair	7
Slightly bleached hair	5
Medium bleached hair	3
Strongly bleached hair	1

For use at home, concentrations are commonly decreased by about one-third.

The pH of mercaptan-based waving agents depends on the ratio of mercaptide ion (RS^-) to mercaptan (RSH). The former, RS^-, is generally believed to be the active reactant in hair reduction. It should be remembered that thioglycolic and thiolactic acids contain carboxylic acid groups that are neutralized by alkalis at pHs much below those required for RS^- function. The pH required to form RS^- in sufficient concentration to effect waving is critically dependent on the mercaptan's pH. Table 32.1 lists the pKs of the most commonly used mercaptan waving agents. It is apparent that the presence of a free carboxylic acid group raises the pK of the SH group by about 2.5 to 3.0.

The use of bases other than ammonia has been much discussed. Sodium and potassium hydroxides have been said to render the hair too soft to take a good wave [6]; ammonia and organic amines have been shown to hydrolyze peptides less than alkali. Only monoethanolamine seems to be as good as ammonia, and this is used together with ammonia to reduce the odor. The main problem is to maintain the mercaptide level during the whole softening phase, that is, to maintain the pH high despite the volatility of ammonia. Buffering with ammonium carbonate, sesquicarbonate or bicarbonate is often employed, and this also allows the reduction of the pH to about 8.8 to 9.1. The persistent employment of ammonia in mercaptan waving products suggests that NH_3 or NH_4OH can facilitate hair waving.

Another method of ensuring a steady supply of alkali, obtaining more uniform curling, and reducing aggressiveness is to generate ammonia in situ under controlled conditions by introducing urea and urease into the product. Other bases have been suggested, for example, arginine or guanidine or its carbonate, for neutralizing thioglycolic acid and for enhancing the swelling of hair by disrupting hydrogen bonds [7,8].

Table 32.1 Dissociation Constants of Mercaptide Waving Agents

Mercaptan	pK
Cysteamine	7.5 (?)
Cystine	10.5 (?)
Mercaptopropionic acid	10.4
Mercaptopropionic acid esters	7.8
Thioglycerin	7.8
Thioglycolic acid	10.4
Thiglycolic acid esters (ethyl, methyl, butyl, *i*-propyl, glyceryl)	7.8
Thiolactic acid	10.4
Thiolactic acid esters	7.8

Also, the use or generation of dithiodiglycolate in waving systems prevents overprocessing of the hair. This type of system is called a stop-action perm. The stop-action perm is perfect for home use and for inexperienced hairdressers.

The Neutralizer in Cold Waving

Most hairdressers use hydrogen peroxide as neutralizer because it is not expensive and is easy to handle. Usually, agents such as polyoxyethylene ethers of fatty alcohols or cationic compounds are added to improve wetting, and silicone emulsions help to improve condition.

To speed up the neutralizing step, activators of the decomposition of inorganic percompounds have been suggested. Self-warming systems have also been proposed; for example, the addition to hydrogen peroxide of either sulfite or thiourea or of anhydrous calcium chloride or magnesium sulfate elicits an exothermic reaction, producing a warmed oxidizing bath.

Catalase was suggested to degrade the potential hair-decoloring excess of hydrogen peroxide. As in the reducing stage, cationic polymers and surfactants are added to enhance the setting and condition of the hair.

Other oxidants that have been used are dry persalts, for example, sodium perborate or percarbonate, and sodium or potassium bromate. Bromates can be formulated into stable aqueous solutions; they are extremely toxic on ingestion and should be labeled "Poison." Bromates are used primarily in Japan, with some use in United States, but their use is prohibited in Europe.

Air oxidation was once practiced to oxidize reduced hair. This was accomplished by waving the hair and then rinsing it and allowing the hair to be oxidized by air in the presence of metal catalysts. Evidence now exists to show that air oxidation is not fully effective.

FORMULATION OF COLD WAVING SYSTEMS

For the preparation of thiol-based cold waving products, all glassware must be clean and free from any metal contamination. Also, all contact material must either be glass, plastic, or passivated 316 stainless steel. Cleansing is very important because metal contamination, especially iron, turns the waving solution purple and accelerates autooxidation. One passivation process for 316 stainless steel includes the following: Prepare a 10% nitric acid solution; submerge all 316 stainless steel contact parts for at least three hours; rinse passivated 316 stainless steel parts well with deionized water; check run-off with a dilute ammonium thioglycolate solution. Repeat process if purple discoloration is observed. Sample waving and neutralizing formulas are provided next; these are prototype formulas that can be modified to meet the formulator's objective.

Formula 32.5 Acid Cold Waving Lotion

Activator	%
Glyceryl thioglycolate	98.0
Thioglycolic acid	2.0
pH-balancing solution	
Monoethanolamine (iron-free)	4.00
Ammonium thioglycolate (50%, aqueous)	3.83
Diammonium dithiodiglycolate (40% aqueous)	3.66
Sodium lauryl sulfate	2.43
Fragrance	0.15
Water	QS 100

Mixing directions: At the time of application, 10 parts of the activator is mixed with 80 parts of the pH-balancing solution.

Formulas 32.6 and 32.7 Alkaline Cold Waving Lotions

	%	
	Tinted hair	**Normal hair**
Ammonium thiolactate (50% aqueous)	18.00	25.00
HEDTA	0.20	0.20
Laureth-23	2.00	2.00
Ammonium hydroxide (28%)	to pH 8.7	to pH 9.2
Fragrance	0.15	0.15
Water	to 100	to 100

Formula 32.8 Buffered Cold Waving Lotion

	%
Ammonium thioglycolate (60% TGA)	14.00
Ammonium hydroxide (28%)	1.70
Ammonium bicarbonate	5.00
Urea	2.50
Soluble lanolin	0.50
Fragrance	0.15
Water	to 100

PERFUMING OF THIOGLYCOLATE LOTIONS

A comprehensive review of this subject was prepared by Sagarin and Balsam [9], who list the results of their own tests with over 200 materials. Unfortunately, it is impossible to mask the smell of thiols completely, particularly during the application stages when they are spread over the whole head, and the inherent

Formulas 32.9 and 32.10 Stop-Action Cold Waving Lotions

	%	
	Tinted hair	**Normal hair**
Ammonium thioglycolate (60% aqueous)	14.00	11.00
Diammonium dithiodiglycolate (40 aqueous)	10.00	10.00
HEDTA	0.20	0.20
Wetting agent	0.50%	2.00%
Ammonium hydroxide (28%)	to pH 9.0	to pH 9.2
Fragrance	0.15%	0.15%
Water	to 100	to 100

Formula 32.11 Cysteine Cold Waving Lotion

	%
Cysteine HCl	7.50
Ammonium hydroxide (28%)	2.00
Ammonium carbonate	2.50
DTPA 41 (chelating agent)	0.50
Wetting agent, perfume	
Water	to 100

Formula 32.12 Peroxide Cold Wave Neutralizer

	%
Hydrogen peroxide (50%)	4.0
EDTA	0.2
Wetting agent	q.s. to 2.00
Phosphoric acid (85%)	to pH 3.0
Water	to 100

Formula 32.13 Nonperoxide Cold Wave Neutralizer

	%
Sodium bromate	8.0
Urea	9.0
Polyquaternium-22	2.00
Dibasic sodium phosphate	2.00
Sodium hydroxymethylglycinate	0.20
Water	to 100

smell of the thiol is enhanced by the odor of the reduced hair. Another difficulty is choosing perfumes that are stable in the ammoniacal-reducing medium. The cosmetic industry and the public are still awaiting new methods of permanent waving using completely odorless materials.

EVALUATION OF PERMANENT WAVING

It is apparent from the foregoing that the chemistry of the waving process is extremely complicated. Therefore any investigative method, however sophisticated, cannot fully identify all the physicochemical modifications, particularly the state of hair after treatment. As with many other hair processes, permanent waving is best assessed in vivo. This is accomplished by recruiting volunteers for salon testing under control of a competent beauty operator.

A number of in vitro techniques may, however, give some valuable information on the evolution of the mechanophysical properties during and after the process [10–12]. Other techniques that can provide insight to the damage caused by permanent waving are electron spectroscopy [13], Fourier tranform infrared spectroscopy [14], and fluorescence microscopy [15].

Some major factors controlling variations in permanent waving are briefly discussed in this section.

Choice of Lotion

This is the most significant factor; it is independent of the degree of curling desired but depends on the quality and structure of the hair to be treated. It may even be chosen according to whether it is applied to the root or to the tip of the hair (bleached hair).

Temperature Variation

The ambient temperature has a considerable effect on the cold waving process. In addition, heat of the hair and heat loss because of evaporation should be carefully controlled during any testing.

Processing Time

This should be short, since if it is prolonged the result may be excessive softening of the hair without enhancing the efficacy of the treatment. Some manufacturers offer stop-action permanent waves that prevent overprocessing by incorporating dithiodiglycolate or by forming dithiodiglycolate in situ.

In the usual method of cold waving, the hair is wetted with lotion before and after winding the curls. A salon operator cannot wind a head of hair in much less than 30 minutes, and the home user may take as long as 90 minutes. In view of the time interval between the application of lotion to the first and last curls, the so-called processing time after rewetting may become far less significant. The equilibrium between cysteine in the hair and thiols in the

lotion is reached after about four minutes when the hair is immersed in a large volume of lotion. This equilibrium is reached much later during the actual head waving. Therefore most of the lotions are studied at setting times, varying between 10 and 20 minutes after winding on natural hair.

Penetration Rate

This depends not only on the presence or absence of wetting agents, and so forth, but also on the type of thioglycolate used and the nature of the hair to be waved. An acid wave composed of glyceryl ester of thioglycolic acid has a slow penetration rate compared to alkaline waves composed of ammonium thioglycolate. Penetration through fine hair should be more rapid than that through coarse hair, but this does not account for the tensional differences during winding [1] or for the porosity of the hair. After bleaching, for instance, the hair has usually lost some cross-linkages and cell membrane complexes and swells much more rapidly than normal hair, thus taking up the waving lotion more completely. Washing the hair with a shampoo beforehand removes sebum, which might hinder penetration, but some detergents are strongly absorbed on the fiber and may be capable of changing the permeability; for example, some cationic detergents show a definite inhibiting effect when present at concentrations as low as 1% in the waving lotion.

Choice of Curlers

The curl diameter obviously depends on the diameter of the curler. Some methods make use of very large diameter curlers or rollers, and some depend on making a pincurl with the aid of a waving lotion. Another factor is the amount of hair on each curler, which depends on the number of curlers per head and the amount of hair on the head, as the outside layer of hair has a curl diameter equal to the curler diameter plus the thickness of hair.

Neutralizing Step

This is a rather significant operation since it determines the set of the permanent wave and the rebuilding of keratin. Hair must be very carefully rinsed beforehand to eliminate reducing lotions. Then the setting lotion must be applied in two separate stages: first, two-thirds of the lotion is applied to the wound hair, impregnating each curl for five minutes and left for five minutes; then, after the hair has been unwound without stretching, the remaining lotion is applied to the tips and left for five minutes before being carefully rinsed out.

HAIR STRAIGHTENERS

Hair straighteners are needed by those consumers who want tightly curled hair made straight or very gently waved or who want essentially kinky hair opened

up and made more controllable. Hair straightening preparations on the market include hot comb–pressing oil methods, caustic preparations, and keratin-reducing relaxers. The chemical and physical processes for hair straightening are very similar to those used for hair waving.

HOT COMB METHOD

In the hot comb method, hair is straightened by the use of petroleum jelly and a hot metal comb. This procedure is referred to as "hot pressing." Alternatively, a mixture of petrolatum and paraffin may be used, in which petrolatum is the major component, acting as a heat transfer agent between the comb and the hair and lubricating the latter to allow the comb to slide through it without drag. The hair is washed and dried before the pressing oil is applied, and the repeated combing with the heated metallic comb is used to straighten the hair.

Quite apart from the fact that considerable stress is applied to the hair, causing a high incidence of breakage, the set is not very permanent and tends to be destroyed by rain or even by perspiration so that the hair reverts to its original state. Silicone-containing sprays have been marketed as barriers against moisture, but they do not appear to provide any significant improvement.

CAUSTIC PREPARATIONS

The chemistry of caustic straighteners is primarily that of lanthionine formation, as described in Chapter 2.

$$K\text{–}S\text{–}S\text{–}K + NaOH \longrightarrow K\text{–}S\text{–}K + Na_2S + H_2O$$

The sodium hydroxide identified in this equation can be replaced with lithium, potassium, or guanidine hydroxide. Caustic alkali preparations, usually in cream form, are the second type of hair straightening preparation still fairly widely employed. The use of caustic products involves risks such as irritation of the scalp and even accidental eye damage. Caustic relaxers are classified in two groups—lye and no-lye. A lye relaxer's active ingredient is sodium hydroxide, and no-lye relaxer's active ingredients are generally derived from calcium hydroxide and alkali metal or guanidine carbonates (Formula 32.14).

The viscosity of caustic products varies according to the softening and melting points of the cream base. The amount of active constituent employed is between 2% and 9%, most frequently about 4–5%. The more alkali present, the more rapid the action; but at the same time there is a greater risk of hair damage, and additional care is required in using the product. The addition of activators of lanthione formation helps to reduce the temperature, the time, and the pH value of treatment.

The selection of ingredients for the cream base vehicle for the caustic obviously requires considerable care to avoid incompatibility. The emulsifier should be neither an acid nor an ester, nor should it be an anionic of a type that might be salted out by the caustic alkali, such as soap. The fatty phase should be neither an acid nor an ester and is best formulated from waxlike fatty alcohols with mineral oils and petroleum jelly as protecting agents and, for example, ethoxylated lanolin as an emollient. Generally, the cream base also contains some sodium lauryl sulfate or lauryl ether sulfate as wetting agent and emulsifier despite the potential for hydrolysis.

Multicomponent caustic straighteners generally include five components:

(1) A soft pomade based on mineral oil–petrolatum wax applied to the scalp as a protective pretreatment.
(2) The "relaxer," which consists of an oil-in-water emulsion containing about 3–5% caustic material and about 40% fatty material on the same general lines as the simple straighteners described. For a no-lye relaxer, the relaxer base contains calcium hydroxide and is mixed with an activator containing guanidine carbonate. This mixture generates guanidine hydroxide as the active in situ.
(3) A cream shampoo that is used to follow the relaxing step. Its constitution is conventional, with some unspecified emulsified fatty material.
(4) A dilute oil-in-water emulsion containing about 2% fatty esters and a cationic wetting agent referred to as the "neutralizer," preferably slightly acid.
(5) A stiffer pomade containing petrolatum, fatty ester, and lanolin to provide the final set and dressing.

CHEMICAL HAIR REDUCING AGENTS

Hair straightening preparations of the third type contain a keratin-reducing agent as the "relaxer" that effects the softening and straightening of the hair. The active agents are frequently thioglycolates, that is, the same compounds that are used in the opposite process of permanent waving but usually at a slightly lower concentration.

Unlike permanent waving, where the hair is kept in curlers throughout the treatment, in hair straightening the hair is kept straight during combing by virtue of the high viscosity of the product. As a result, a cream like formulation is no longer a disadvantage but becomes highly desirable, so that the majority of the preparations are oil-in-water emulsions, gels, or thickened liquids. This type of straightener requires two preparations, one the viscous reducing agent or relaxer, the other the neutralizer.

Relaxer

In most existing examples, the relaxer is based on ammonium thioglycolate at a pH of about 9.0–9.5. Organic bases such as monoethanolamine and an

alkali salt of a basic amino acid may partly replace ammonia. Cream products are based on glycerol, glycol stearates, or on cetyl and cetyl or stearyl alcohols emulsified in water by ethoxylated (usually 20 to 25 EO units) cetyl or oleyl alcohols. Gels or viscous liquids are obtained by means of carboxyvinyl polymer or copolymers. The use of less potent reducers such as sulfites provides a good product for home use.

Neutralizer

Commonly neutralizers are acidic hydrogen peroxide solutions or sometimes alkaline solutions for sulfite straightener.

Formula 32.14 No-Lye Hair Straightener

	%
Component I:	
Part A	
Polawax	8.00
Cetyl alcohol	0.50
Stearyl alcohol	0.30
PEG-75 lanolin	2.00
Petrolatum	15.78
Mineral oil	19.32
Laneth-15	0.40
PEG-24 hydrogenated lanolin	0.20
PEG-25 soy sterol	2.00
Part B	
Water	45.40
Polysorbate 20	1.00
Oleth-3	0.30
Calcium hydroxide	2.80
Polyquaternium-2	2.00
Component II:	
Propylene glycol	56.00
Lithium carbonate	40.00
Silica	3.00
Titanium dioxide	1.00

Procedure: Part A is emulsified into Part B at elevated temperature to create Component I. Component II is prepared by adding propylene glycol to the kettle and begins with moderate agitation with a high-speed Cowls disperser blade. Add lithium carbonate slowly. Continue disperser action and add silica and titanium dioxide. Continue mixing for 30 minutes.

Application

It is important to remember that hair that has already been damaged during hot combing treatment or by the use of lye straighteners should not be subjected to a thioglycolate straightener until several weeks have elapsed. The thioglycolate cream is applied liberally to the hair, which is then combed rapidly until the hair no longer has a tendency to curl. When the hair is sufficiently straight, the cream is rinsed off, and the neutralizer is applied to give a permanent set. Care should be taken to ensure complete neutralization so as to avoid hair damage. Preferably a finishing cream or hair dressing is used to weigh down the hair and improve the maintenance of a straightened shape.

FORMULATIONS

The activated relaxer cream is prepared by mixing 250 grams of Component I with 20 grams of Component II. Accurate dispensing is required. The relaxer is ready for use about 15 minutes after mixing. Moreover, the relaxer can be safely used without fear of irritation for at least one year after mixing.

Formula 32.15 Self-Heating Hair Straightener

	%
Part A	
Ammonium bisulfite (45% aqueous)	10–18
TEA-cocoyl hydrolyzed collagen	0.5–2
Ethanolamine	to pH 6.8–10
Urea	5–15
Sodium carbonate	0.5–3.5
Water	QS to 100%
Part B	
Methylparaben	0.05
Hydrogen peroxide (35% w/w)	8.5–16 (3–5.6% w/w)
Disodium phosphate	0.02
Phosphoric acid, 85%	to pH 3.0–4.5
Water	to 100%

Formula 32.15 makes no provision for enhancing the viscosity by the inclusion of a gum or other means; instead this product is used by winding on large diameter plastic rods and ultimate use of an oxidizing neutralizer, as described in Formulas 32.12 or 32.13.

DEPILATORIES

INTRODUCTION

Preparations for the removal of unwanted hair have been known for thousands of years. Among them was rhusma, a mixture of quicklime and arsenical pyrites in a ratio of 1:2, or orpiment. Inorganic sulfides in strongly alkaline media were widely used, as were diverse abrasives, for example, pumice stone. In modern times, however, a rapidly increasing interest in depilatories has resulted from changes in fashions, clothing, and social customs.

While the term "depilatory" has been applied to any preparation designed for the removal of superfluous hair (in particular hair occurring on the face and legs, as well as in the axilla) without causing injury to the skin, a distinction must be drawn between the mechanical removal of hair either by plucking it with tweezers or by embedding it in an adherent material that can then be pulled away from the skin, bringing the hair with it (a process referred to as epilation), destruction of hair papillae by electrolysis, and the removal of hair after it has been sufficiently degraded by chemical means.

EPILATION

Epilation has some following because the effect may be slightly longer lasting since the epilated hairs also remove the hair bulbs or the hair papillae. This may create a relatively long pause before the hair starts growing in the follicle and reaches the surface of the skin. It is, however, not painless and can often cause serious skin damage and subsequent infection and is therefore frowned upon by physicians.

For many years epilatory preparations were based on mixtures consisting essentially of rosin and beeswax, modified in some instances by the addition of mineral oil and/or waxes. The following two simple examples are illustrative:

Formula 32.16 Epilating Wax

	%
Rosin	75.0
Beeswax	25.0

In addition to rosin and waxes, mineral or vegetable oil may be included (for example, at a level of about 15%). Camphor is often included for its cooling

Formula 32.17 Epilating Wax

	%
Rosin	52.0
Beeswax	25.0
Paraffin	17.0
Petrolatum	5.0
Perfume	1.0

Procedure: Melt the rosin and waxes, mix, and add the petrolatum; when the temperature drops to about 60 °C, add the perfume and pour the melted mass into suitable molds. When this wax is used it is melted and painted over the surface to be dehaired.

effect which reduces the discomfort experienced when the hair is pulled off. A local anaesthetic, for example, benzocaine or butyl PABA, can enhance this effect, and an antibacterial compound will reduce the chance of infecting the skin after damage or exposure.

There has been no dramatic development of a "painless" epilatory in the industry. The few and limited developments have been concerned with modifications in the method of application, such as the provision of a flexible backing strip, and the provision of a preparation that does not require melting prior to use but can be applied cold, the preparation being based on a mixture of glucose and zinc oxide or a honey, sugar, and citric acid mixture. The use of a "rubber solution," in which the solvent evaporates and the rubber film is stripped off, is covered in a U.S. patent.

An epilating wax in strip form from a French patent cites the following composition as an example:

Formula 32.18 Epilating Wax

	Parts
Rosin	1700
Vegetable oil	900
Triethanolamine	100
Benzoin gum	10
Balsam tolu	10
Lemongrass bouquet	5
Butyl PABA	10
Alcohol	5

The wax is spread on the rough side of a strip of kraft paper, the smooth side of which is silicone-treated.

The patent literature includes numerous patents; some of them are briefly reviewed in Reference 16. Gallant has given a detailed account of professional techniques for depilatory waxing treatments [17].

ELECTROLYSIS

The mechanical waxing methods mentioned earlier are temporary and not often only fully effective since the papillae are not always removed and hair soon reappears. The most effective method of hair removal is undoubtedly electrolysis, which entails inserting a needle into the hair follicle and completely destroying the hair root by means of a weak DC current. This method is practiced in beauty salons and by some dermatologists but is expensive and time-consuming since every hair must be treated individually, and even a competent operator can only deal with 25–100 hairs per sitting.

CHEMICAL DEPILATION

The term "depilatory" as used nowadays refers to a preparation intended for the chemical breakdown of superfluous hair without injury to the skin. The advantage of such preparations is that they preempt any danger of cutting or abrading the skin in regions such as the underarms, where it is difficult to see the area clearly and even more difficult to guide a razor over the complicated contours. There is also a widespread belief that shaving increases the rate of hair growth or the coarseness of the hair. Although these beliefs are unfounded in fact, chemical depilatories have the apparent advantage that they discourage the regrowth of hair if they are applied regularly. There seems to be no scientific explanation for this, but possibly it arises from a gradual removal of keratinous debris from the mouth of the hair follicle, which allows removal of the hair at a deeper level.

Since the hair shaft is of composition similar to that of the skin (both are derived from keratin), a small degree of local damage may occur as the result of applying such preparations, particularly if the depilatory is kept in contact with the skin for any length of time and the pH is sufficiently high to allow attack on the horny layer of the skin. The principle of chemical depilation depends on extensive swelling of hair fibers because of disulfide bond reduction and the effect of high pH on hydrogen bonding. The final dehairing of skin is achieved by scraping with a blunt instrument or rubbing with terry cloth of the depilatory-treated skin area.

Provided that the skin is reasonably healthy, the time of application of the depilatory is not too long, and the depilat is correctly formulated, very

little if any skin damage will result. In formulating depilatory preparations, therefore, care should be taken to ensure that they will react with the hair preferentially and that their effects will be sufficiently rapid to cause disintegration of the hair before they cause any damage to the underlying and surrounding skin.

With these aims in mind, the desirable requirements of a depilatory may be defined as follows. The product should:

(1) be nontoxic and nonirritant to the skin
(2) remove hair rapidly, preferably in 4–6 minutes
(3) preferably be odorless
(4) be stable on storage
(5) be harmless to clothing
(6) exhibit cosmetic elegance

In line with the requirement for a rapid depilation, depilatory preparations usually contain as their active component a strongly alkaline reducing agent. The latter causes the hair fibers to swell and produces cleavage of the cystine bridges between adjacent polypeptide chains as a preliminary to the complete degradation of the hair.

Sulfides

The use of sulfides has been known, as pointed out at the beginning of this chapter, for a very long time; patents covering the use of barium polysufide for removing hair are more than 100 years old. Compositions based on alkali and alkaline earth sulfides are capable of producing rapid depilation, particularly if used together with a suspension of lime. The alkali sulfides such as sodium sulfide were, however, found to be too drastic in action. Their depilatory action is linked to their hydrolysis and the formation of sulfhydrates and sodium hydroxide. The latter acts as a primary irritant and will produce erythema. Even a dilute (2%) aqueous solution of sodium sulfide will have a pH of 12. Although it will disintegrate hair within 6–7 minutes, it may simultaneously damage the stratum corneum. It is, therefore, no longer used in marketed depilatory preparations.

Strontium sulfide is a much milder depilatory but must be used at a higher concentration than sodium sulfide to produce an equivalent dehairing action. Preparations containing strontium sulfide, although largely replaced today by those based on thioglycolates, are still available. They are very effective and work within 3–5 minutes after application.

While some people are sensitive to such preparations, the products appear to be innocuous if used according to the directions of the manufacturer. The main reason for their loss in popularity is that, in common with other sulfides, they generate the odor of hydrogen sulfide on application (and not infrequently on storage). This odor is most intense when the product is washed off, owing to hydrolysis of the sulfide. It is advisable, therefore, to remove the bulk of the product with a spatula before washing, and it is the usual practice to include such a spatula, made of wood or plastic, in the pack. It also serves to apply the product in the necessary thick layer (1–2 mm). Under no circumstances should the final washing be omitted.

In addition to the active agent, a depilatory preparation may contain a humectant such as glycerin or sorbitol. A thickening agent (e.g., methylcellulose) may sometimes be incorporated, so as to thicken the solution sufficiently to allow it to remain in contact with the hair as long as necessary.

For a sulfide depilatory, the following formula will be found effective:

Formula 32.19 Sulfide Depilatory

	%
Strontium sulfide	20.0
Talc	20.0
Methylcellulose	3.0
Glycerin	15.0
Water	42.0

A similar composition may be prepared using an emulsion base for smoothness and stability.

Despite their disadvantages, sulfide-based depilatories are preferred by many African American men for removing facial hair because of their comparatively rapid action. This subject is covered later in this chapter.

Stannites

In the 1930s considerable attention was devoted to the use of "soluble stannites." Several patents describe sodium stannite solutions as depilatories. Despite their acceptable low odor, they have been largely abandoned because of their instability, forming stannates in the presence of water. Many proposals

for stabilizing stannites with water-soluble organic compounds can be found in the extensive patent literature, as reviewed in Reference 16. Nevertheless the recommended stabilizers were not found to be effective and did not produce stable preparations.

Substituted Mercaptans

The majority of depilatories available today are based on substituted mercaptans, which are used in the presence of alkaline-reacting materials (e.g., calcium thioglycolate) in conjunction with calcium hydroxide. These preparations possess less odor than the sulfide type but take longer to act. They are safer on the skin than sulfides and can therefore be used on the face—an area where superfluous hair can cause great distress and where women have a strong psychological aversion to using a razor. In general, thioglycolate preparations are more attractive than the sulfide types. However, their slowness in attacking the coarse and resistant hair of the underarm has left a market open for sulfide depilatories for this specific purpose. It is often said that depilatories can be used for smoothing the legs, but the amount required to cover the leg makes it uneconomical for most users.

Thioglycolates

Thioglycolate-based preparations are nontoxic and stable at use concentrations, that is, between 2.5% and 4%. At common use concentrations (about 4%), they may produce depilation in 5–15 minutes, this again depending on the pH of the preparation. This should not be less than pH 10 and should preferably be about pH 12.5 to produce depilation within a fairly short time and without irritating the skin.

The use of thioglycolate in depilatories stemmed from the research conducted on the dehairing of animal hides and resulted in patents, issued in France (French Pat. 824,804), Britain (Brit. Pat. 484,467), and the United States (U.S. Pat. 2,352,524, Ref. 18).

The U.S. patent [18] issued in 1944 to Evans and McDonough covered the use of substituted mercaptans (thioglycolic acid) in conjunction with an alkaline-reacting material and a perfume. Substituted mercaptans having polar groupings are preferred. The patentees claim that in order to obtain a desirable depilating action, the depilating product must meet a number of requirements:

(1) The pH should be between pH 9.0 and pH 12.5.
(2) The mercaptan concentration should be between 0.1 and 1.5 mol per liter.
(3) The alkaline ingredient must have an ionization constant greater than 2×10^{-5}.

(4) To prevent skin damage it is desirable that the concentration of the alkaline material in solution be not greater than twice the equivalent concentration of the mercaptans.

Basic formulations for preparing cream, semifluid, and powder depilatories were provided more than 30 years ago [19]:

Formula 32.20 Depilatory Cream

	%
Coconut alcohol	6.5
Calcium thioglycolate	5.4
Calcium hydroxide	7.0
Sodium lauryl sulfate	0.02
Sodium silicate	3.43
Perfume	q.s.
Water	to 100

Procedure: Heat the water to 70 °C. With stirring add the lauryl sulfate and fatty alcohol; continue stirring until melted and dispersed. Discontinue heating and cool, stirring until room temperature. Add the calcium hydroxide and perfume. Add the calcium thioglycolate and stir until uniform.

Formulas 32.21 and 32.22 Semifluid Depilatories

	%	%
Cream base		
Water	60.0	60.0
Cetyl alcohol	6.0	6.0
Laureth-23	1.0	1.0
Final product		
Water	17.3	17.2
Calcium thioglycolate	5.4	5.4
Calcium hydroxide	6.6	10.4
Strontium hydroxide	3.7	—
Perfume	q.s.	q.s.
Cream base (as above)	67.0	67.0

Procedure: Prepare the cream base at 70 °C and allow to cool to room temperature. Add the calcium thioglycolate to the bulk of the water and mix well; add the calcium hydroxide slowly with stirring, followed by the strontium hydroxide and any remaining water. Combine the two parts and stir well, adding the perfume at this point.

Formula 32.23 Powder Depilatory

	%
Calcium thioglycolate	20.0
Calcium hydroxide	23.1
Strontium hydroxide	8.9
Sodium lauryl sulfate (powder)	1.5
Hydroxyethylcellulose	1.0
Magnesium carbonate	45.2
Perfume	0.3

Procedure: Mix the calcium thioglycolate, calcium hydroxide, strontium hydroxide, sodium lauryl sulfate and hydroxyethylcellulose. Blend the perfume thoroughly with the magnesium carbonate. Add the latter to the former and blend thoroughly. (This formula contains a much higher level of thioglycolate than is currently permitted for sale within the EEC.)

The slow activity of calcium thioglycolate–based products has led to many attempts to accelerate the depilatory action by incorporating substances that cause swelling of the hair fibers. Urea was at one time considered for this purpose but could not be used since it decomposes at the normal pH of depilatory preparations. The patent activity in this field has been extensive, and space does not allow a more detailed discussion. Some patented additives are listed below.

Melamine	U.S.P. 3,271,258
Lithium thioglycolate	U.S.P. 3,384,548
Silicates, thiourea	U.S.P. 3,981,681

Other forms of depilatories have been described, including

Sticks	U.S.P. 3,194,737
Aerosols	British Patent 1,142,090 and British Patent 1,296,356

The EEC Cosmetics Directive and the other regulations limit the use of thioglycolic acid in depilatories to a maximum of 5% with a pH value not to exceed 12.65.

Other "Thio" Compounds

Thioglycolic acid is the most economical and effective active agent of this type. However, legal limitations on the home use of thiglycolates resulted in the introduction of products in which thiolactic acid, 3-mercaptopropionic acid, or thioglycerol replace thioglycolate.

Enzymes

Nonirritating and odorless depilatory preparations based on the enzyme keratinase have also been developed. A keratinase, isolated from *Streptomyces*

fradiae, was found to be capable of digesting keratin (U.S. Pat. 2,988,488). The extremely slow depilatory action interfered with the commercial success of these preparations.

FACIAL DEPILATORIES FOR AFRICAN AMERICAN SKIN

The facial hair of the black male is often curly and wiry. Shaving leaves the exposed ends of the hairs with sharp points, and as the hairs regrow these sharp points can actually turn back onto and penetrate the skin, causing a clinical condition called pseudofolliculitis barbae. For this reason some black men prefer to use a depilatory that not only gives a closer "shave" but also leaves the hair tip soft and blunt so that it does not puncture and reenter the skin.

Conventional thioglycolate-based depilatories take 15–20 minutes to remove beard hair, which is regarded as far too long. Effectiveness outweighs cosmetic elegance, and the tendency is to use a powder depilatory that must be mixed with water before use but which provides adequate hair removal in 3–7 minutes. In the United States the active ingredient commonly used in powder depilatories is calcium thioglycolate, which exhibits low odor and is easily perfumed (Formula 32.23).

EVALUATION OF DEPILATORY EFFICACY

Yablonsky and Williams [20] described a procedure for determining the efficacy of depilatories. It involves the measurement of the cross-sectional diameter and the length of a hair immersed in a solution of a depilatory and observing the time of maximum hair swelling. Sigmoidal curves are obtained when both the length and the width of swelling hair are plotted against time. The slope maxima of these sigmoidal curves may be used to define an index of depilatory effectiveness in vitro. No test results were given.

Elliot [21] designed a depilometer to simulate practical use conditions as closely as possible. In-use tests gave good correlation, and rapid screening of formulation variables is possible using this technique. His depilation time represents the "time to break" of 10 fibers exposed to the depilatory at a load of 50 g. No adjustments were made for the mercaptide dissociation constant or for its molarity. A summary of his extensive data is difficult. He found considerable variation in depilating times between individuals, but in general, leg hair is easier to remove than axillary hair, which is similar to head hair. Some of Elliot's data are summarized in Tables 32.2 and 32.3.

Table 32.2 Relative Efficacy of "Mercaptans" (5% Concentration at pH 11.0–12.0)

Mercaptan	Average depilation time* (min)
2-Mercaptoethanol	4.0
Thioglycerol	6.5
Thioglycolic acid	7.5
3-Mercaptopropionic acid	8.0
2-Thiolactic acid	11.0
Thiodiglycol	15.0
Thiomalic acid	15.0

*Average of times for various alkalis used for neutralization

Table 32.3 Relative Efficacy of Various Alkalis

Hydroxide	Average depilation time (min)*
Sodium	5.7
Lithium	5.7
Potassium	6.5
Barium	6.5
Calcium	7.1
Strontium	8.3

*Average of times for the different mercaptans studied at pH 10.0 to 11.0. (Lowering the pH to 9.0 from about 10.0–11.0 lengthens the time for depilation.)

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CHAPTER 33
Oral Care Products

This chapter includes brief discussions of dentifrices, toothbrushes, denture cleansers, and mouthwashes, with emphasis on the first. Readers requiring more information are urged to consult the general reference and specific references. The formulation of oral care products is as much an art as it is a science. The formulator of these types of products must use the senses of sight, taste, smell, and feel in the ongoing evaluation of compositions, and integrate this input with costs, availability, claim support, stability, and safety testing results in order to finalize a formula.

DENTIFRICES

BASIC REQUIREMENTS

The minimum requirements for a marketable dentifrice have changed in emphasis and in content in recent years. Modern dentifrices meet all of the listed requirements:

1. When used properly with a toothbrush they should clean the teeth adequately; removing food debris, pellicle, plaque, and stains.
2. They should leave the mouth with a fresh, clean sensation and freshen the breath.
3. The cost to the consumer should not be prohibitive.
4. They should be safe, pleasant, and convenient to use.
5. They should be capable of being manufactured and packaged economically.
6. They should conform to accepted standards in terms of their abrasivity to enamel and dentin.
7. When drug claims are made, they should be substantiated by properly conducted clinical trials and meet all regulatory requirements of the countries in which the product is to be marketed.
8. They should be stable in storage throughout their anticipated shelf life.

BACKGROUND

Over the past four decades toothpastes have been in a transition state between cosmetic and drug products. At present the vast majority of toothpaste sales

fall into the drug category since in most countries fluoride is considered a drug active. Recently toothpastes are being viewed as drug-delivery systems aimed at gum disease and other diseases of the mouth.

The resulting changes and accompanying monetary pressures have made development more difficult for the formulation chemists; they now have the problem not only of formulating an acceptable cosmetic product but also of incorporating into it an active ingredient or ingredients, which may be incompatible with the other materials used, as well as being concerned with the financial implications of ingredient choice.

During this time period, television advertising has become the norm for all but the smallest brands. Television networks normally require that both cosmetic and therapeutic claims be fully substantiated. This has forced dentifrice manufacturers to move into the areas of consumer product preference testing, cosmetic efficacy testing, and clinical research in order to provide support for their claims.

The question in today's toothpaste market is whether there is still a niche for a purely cosmetic product. Such a product, if properly used, might have some anticaries effect by removing plaque and would help to prevent gum diseases by improving oral hygiene. Oral products have appeared in many physical forms, but in terms of convenience the most important is a semi-solid paste/toothpaste packed in a tube or pump. Powders, solid blocks, and liquid products can be made but have not achieved the high degree of consumer acceptance of a toothpaste.

TOOTHPASTE INGREDIENT FUNCTIONS

The primary function of a dentifrice is to remove adherent soil from a hard surface with minimal damage to that surface. This common cleaning situation is normally solved by using a mildly abrasive powder with an added surface-active agent. The function of the surface-active agent is to aid in the penetration and removal of the adherent film and to suspend removed soiling matter. The foam produced also has a psychological effect by making tooth cleaning more pleasurable. This cleaning function must be achieved in a short time, under a minute, and at body temperature.

The requirements of convenience during packaging and during use provide the reason for making this basic product into a paste. It thus becomes necessary to add liquids, some of which should have humectant properties, to prevent the toothpaste from drying out at the tube nozzle. In order to maintain a stable high-solids suspension, it also becomes necessary to increase the viscosity of the liquid phase by the addition of a thickening or gelling agent(s). For consumer acceptance it is necessary to add a flavor and possibly color(s).

For microbiological stability it may be necessary to add a preservative(s). For anticaries effect it is probably necessary to add fluoride. For other claimed functions "active ingredient(s)" may be added. All of these components must be nontoxic and nonirritant under the conditions of use and should not interfere with the activity of a dentifrice.

The final product should maintain its consistency over a temperature range from 0 °C to 37 °C, that is, its viscosity should be independent of temperature. It should also exhibit adequate storage stability without noticeable physical or chemical changes over the same temperature range. Most large manufacturers have international sales and may have to take into account local conditions in many countries.

From the manufacturer's point of view the product should be made from the least expensive abundantly available raw materials that will yield good product quality and high consumer acceptance. If an active ingredient is incorporated, the product becomes a delivery vehicle for the active ingredient, and this may impact other ingredients that can be used in the base formulation.

TOOTHPASTE PRODUCT PARAMETERS

A properly formulated toothpaste should, on discharge, produce a ribbon which:

(1) Can easily be extruded from its package
(2) Does not run off of a toothbrush
(3) Holds its shape to a large extent after extrusion
(4) Is uniform
(5) Is not overly stringy
(6) Disperses readily while the teeth are being brushed
(7) Has a shiny surface

Furthermore, the toothpaste formulation should be of an appropriate pH. A pH range of 4.0 to 9.0 is proper and should cover most formulation situations. The possible exceptions are dual-phase products that are mixed on the toothbrush; in these systems, too, the end mixture will still fall into the pH range given above. The general appearance of the toothpaste should be pleasant. If it is meant to be a gel, it should be of reasonable clarity. Its color, if any, should be attractive and possibly reinforce the type of flavor used.

INGREDIENTS

An acceptable (safe, stable, and cosmetically pleasing) formula can only be achieved by considering all the ingredients together, since many of them may have a dual function or may interact with one another. Other factors such as

processing limitations and compatibility of available packaging components can play an important role in the development of an acceptable formulation. Cost and availability of raw materials, local regulations, and even local habits/tastes may be reasons for formulation variability.

The list of ingredients that follows is by no means exhaustive. Many other materials have been used for specific purposes or may be currently in usage for specific functions.

Abrasives

The abrasive (or abrasives) used in a dentifrice is the workhorse of the formulation with regard to cleaning the surface of the teeth. The abrasivity of a toothpaste should be a compromise between the ability to clean the surface and the necessity to avoid damage to the tooth surface. The Council on Dental Therapeutics of the American Dental Association states that: "a dentifrice should be no more abrasive than is necessary to keep the teeth clean—that is, free of accessible plaque, debris, and superficial stain. The degree of abrasivity needed to accomplish this purpose may vary from one individual to another." The degree of abrasivity is usually measured by Radioactive Dentin Abrasion testing [1].

The abrasivity and cleaning action of abrasives are related to abrasive particle size, shape, brittleness, and hardness. The most commonly used abrasives are hydrated silica, calcium carbonate, calcium pyrophosphate, and dicalcium phosphate dihydrate. Other materials include sodium bicarbonate, tricalcium phosphate, sodium metaphosphate, and alumina or aluminum hydroxide. Particles of plastics and waxes may also be used either individually or in combination with other abrasives.

Hydrated silica (or silica as it is sometimes called) has become the most widely used abrasive in the United States and many other countries over the last 25 years. Hydrated silica used as an abrasive is manufactured by either gellation or precipitation. A xerogel is manufactured by drying the gel formed by gellation with subsequent milling to obtain the desired particle size. The precipitates are collected and dried. Use of these hydrated silica abrasives is the basis for clear gel toothpastes; their use is practical in opacified gel toothpastes as well. The advantages in using hydrated silicas as abrasives include high degree of compatibility with fluoride salts, flavors, and other materials, as well as higher efficiency in cleaning tooth surfaces as compared to most other toothpaste abrasives. Hydrated silica is available in many grades from various suppliers worldwide and ranges in abrasivity from fairly low to quite high. The precipitates tend to give somewhat lower abrasion than the xerogels at the same usage level. Particle sizes used for abrasives range

from about 5–35 microns. There also are dual-function hydrated silica grades available that also serve as toothpaste thickeners.

Calcium carbonate or chalk (or precipitated calcium carbonate as it is normally referred to) is available in a number of grades varying in crystalline form, particle size, and surface area. Calcium carbonate is one of the earliest abrasives used and is still in use today, mainly due to its innately low cost. By varying the conditions of precipitation, precipitated chalks of different densities and crystal structure may be obtained. The two common crystal types are aragonite (orthorhombic) and calcite (rhombohedral). Particle sizes in the range of 2–20 microns are normally used.

Calcium carbonate is an efficient cleaner but tends to not polish teeth well (i.e., does not produce good luster on teeth) and may not leave a smooth feel on the teeth. Grades containing particles over 20 microns in size can also produce scratching on enamel surfaces. All grades of calcium carbonate contain a finite amount of water-soluble calcium salts. These water-soluble calcium salts may cause problems in some formulations. In particular, fluoride-containing formulations normally exclude calcium carbonate. All calcium carbonate toothpastes are alkaline, and therefore it may be necessary to protect unlined aluminum tubes from corrosion by adding sodium silicate or tetrasodium pyrophosphate.

Calcium phosphates include diverse chemicals, such as dicalcium phosphate dihydrate, dicalcium phosphate, tricalcium phosphate, calcium pyrophosphate, and synthetic apatites, all of which are used as toothpaste abrasives.

Dicalcium phosphate dihydrate (DCP-D) is the calcium phosphate most commonly used in dentifrices. The pH of a toothpaste made with DCP-D normally ranges from about 6 to 8. The taste of DCP-D–based toothpastes tends to be better than that of calcium carbonate–based products, and flavor stability is usually less of a problem. DCP-D is in a metastable state and reverts to the anhydrous form with consequent hardening of the paste. This hardening is accelerated in the presence of fluoride ions. DCP-D may be supplied with a stabilizer to delay or prevent this change. Trimagnesium phosphate, tetrasodium pyrophosphate, and other pyrophosphates are common stabilizers.

Dicalcium phosphate anhydrous (DCP-A) is much more abrasive than the dihydrate and should be used only in smaller quantities. It is less soluble than the dihydrate, and this can be an advantage in fluoride-containing pastes.

Tricalcium phosphate (TCP) is not used to a large extent. It is also less soluble than DCP-D.

Calcium pyrophosphate (CPP) was originally developed as the abrasive of choice for products containing sodium or stannous fluoride. The particular form used was patented in many countries. It was claimed that the low availability of soluble calcium ions contributes to the stability of the fluoride.

Sodium metaphosphate or insoluble sodium phosphate (IMP) is a useful abrasive for fluoride dentifrices since it contains no calcium ions. It can, however, contain low levels of soluble phosphates that lead to some taste problems and other interactions.

Sodium bicarbonate or baking soda has been used as an abrasive in the United States since the early 1960s. Although water-soluble, usage of a high level in a low-free-water toothpaste yields abrasive cleaning action. Its advantages are price and compatibility with fluorides. Its drawbacks can be saltiness and high product pH, which may lead to some incompatibilities. It serves a second function since it can neutralize some odors in the mouth. In the United States, it has a mystique of being an odor reducer and a mild/gentle cleanser.

Alumina or aluminum hydroxide was originally developed as a toothpaste abrasive due to the perceived need for a calcium-free and therefore more fluoride-compatible abrasive. Alumina, technically alpha alumina trihydrate, was also thought to be an ideal toothpaste abrasive since it has a Moh's hardness of about 3.5, which is roughly the same as that of human dentin. Grades of varying particle size from 0.5 to 25 microns are available from various suppliers. The cost of alumina has risen rapidly over the last 15 years. This, along with the potential for soluble aluminum salts (as impurities), decreasing soluble fluoride ion content upon storage, and other factors, is responsible for its being used less frequently as a toothpaste abrasive. The typical pH of an alumina-based toothpaste is essentially neutral (dependent to a large extent on the purity of the feedstock used for its manufacture).

Calcium peroxide finds some usage as an abrasive; under acidic conditions in the mouth it may release hydrogen peroxide.

Detergents

Tooth cleaning is partially a detersive process, and almost all toothpastes incorporate a surface-active agent. Soap was the earliest surface-active agent used, but the obvious disadvantages (high pH, off-taste, and incompatibility with other components) led to its replacement by synthetic detergents (Chapter 9). The ideal detergent should be tasteless, nontoxic, and nonirritant to the oral mucosa, while producing a large volume of dense but nongagging foam. Foam quality is important since it has a significant influence on the subjective assessment of toothpaste performance.

Sodium lauryl sulfate (SLS) is the most widely used detergent for oral products and satisfies almost all the requirements of the ideal detergent. Various grades are available from manufacturers, and particular attention should be paid to purity and taste, which are influenced by the unsulfated alcohol content. A low content of inorganic salts is also desirable. Recrystallized grades exhibit excellent quality but are more costly. There exists some negative publicity

concerning the safety of SLS. However, a reasonable level of SLS as used in most toothpastes should not lead to any safety problems.

Sodium lauroyl sarcosinate had been widely used in accordance with a patent that claimed antienzyme properties. Its foaming properties are somewhat different from those of sodium lauryl sulfate, and it is not widely used today.

Although not in wide usage, some other anionic detergents, *sodium lauryl sulfoacetate* and *sodium methyl cocoyl taurate*, have found limited usage in toothpaste. In addition, *poloxamer 407* and similar nonionic block copolymers have been included in toothpaste formulations.

Water

In order to form a semisolid toothpaste a liquid must be added to the solid abrasives and surfactants. Water is included in most toothpastes intentionally due to its low cost and indirectly in other ingredients (some humectants contain 30% water). High purity, usually deionized or distilled, water, is added directly. Keeping the overall water level low enough so as to not allow microbial growth is important. Measurements of water activity have been developed to help in formulating a microbiologically safe product without the need for using strong preservatives (Chapter 14).

Humectants

It is necessary to incorporate a component with humectant properties to prevent toothpastes from drying out. This is most likely to happen if the cap is not replaced on the tube. Alternatively, if toothpaste is allowed to build up on the tube nozzle threads, the cap can become locked in place.

Glycerin was the only humectant used 55 years ago in the form of a 50% aqueous solution of glycerin. This was the perfect humectant in the sense that it is stable and nontoxic, has some solubilizing properties, and contributes some sweetness. Today glycerin is available in natural and synthetic grades at 96% and higher levels. The natural product can be animal- or plant-derived.

Sorbitol and hydrogenated starch hydrolysate have replaced glycerin as a humectant due to its almost steady price increase since the late 1970s. Partial or total replacement by sorbitol syrup 70% has been found useful since it has some properties similar to those of glycerin. It is available in crystallizing and noncrystallizing grades. The crystallizing grades are made by the hydrogenation of glucose. The noncrystallizing grades contain low levels of other hydrogenated sugars such as polymers of glucose (with up to about 10 glucose units). Hydrogenated starch hydrolysate is manufactured by a route suggested by the name, primarily from corn starch. Hydrogenated starch hydrolysate is available in 70% and 75% grades and is very similar in most properties to the noncrystallizing sorbitols.

Propylene glycol has also been used as a component of the humectant system. The drawback here is that of a burning sensation at high usage levels and a tendency to be somewhat bitter.

Xylitol is manufactured from xylose and is noted for its pleasant coolness in the mouth when used at high levels. It has a positive reputation of having anticaries properties. While it is noticeably sweeter than sorbitol, it is also more expensive as of the time of writing this text.

Polyethylene glycol or PEG is one of the dual functional materials that can be used in toothpaste. The lower molecular weight materials, such as PEG-8, exhibit some humectant-like effects and act as lubricants to some degree and as processing aids to disperse some of the thickening agents that require hydration. In hydrated silica-based products even the low molecular weight PEGs act as thickening agents, with a more pronounced effect resulting from higher molecular weight PEGs up to PEG-20M. Problems related to their usage include the fact that the low molecular weight PEGs may be bitter and that those larger than PEG-18 require heat during processing in order to facilitate incorporation.

Thickening Agents

A thickening or gelling agent is necessary in order to maintain the stability of a high-solids suspension. The thickening agent also modifies the dispersibility, foam character, and "mouth feel." Thickening agents used in toothpastes can be natural or synthetic gums that thicken when hydrated or inorganic materials such as hydrated silica or magnesium aluminum silicate.

Tragacanth gum was widely used some time ago to prepare entirely satisfactory pastes. Due to its natural origin, significant variations in toothpaste viscosity may occur; it is rarely used today.

Carrageenan is the generic name given to gums derived from the seaweed *Chondrus crispus* or Irish moss. Commercial carrageenans are standardized products of uniform and reproducible quality. Though very commonly used 20 years ago, they have been largely replaced by the cellulose derivatives.

Cellulose gum or sodium carboxymethyl cellulose (SCMC) is prepared by the action of sodium chloroacetate on alkali cellulose. The physical properties may be controlled by adjusting the degree of breakdown of the cellulose before substitution, and by the degree of substitution. Cellulose gum gels are anionic and sensitive to pH values outside the range 5.5–9.5. They are reasonably stable in the presence of electrolytes and calcium ions and in general are suitable for most toothpaste formulations. Cellulose gum is the most commonly used gum for toothpastes. It imparts little color and is nontoxic and relatively tasteless.

Because it is anionic, SCMC is not suitable for toothpastes containing cationic agents, especially certain antibacterials. For these pastes a nonionic

cellulose derivative such as *hydroxyethylcellulose* or *hydroxypropyl methylcellulose* may be used.

Xanthan gum and *gellan gum* are both bioengineered fermentation products and can be used as thickeners in toothpaste. Xanthan gum has been used widely in the United States and elsewhere in toothpaste products and is available in various grades for specific applications. It might be the ideal thickener for toothpaste except for its relatively high cost. Gellan gum is a relatively new introduction that has been suggested for usage as a toothpaste thickener.

Hydroxypropyl guar has also been used as a sole gum or in combination with other thickeners in toothpastes.

Carbomer is available in various grades that have been used in toothpastes as a thickening agent. Their efficacy and utility depend on the pH of the system.

The *clays*, in particular *magnesium aluminum silicate* and *sodium magnesium silicate*, continue to find usage as thickening agents in toothpaste.

Hydrated silica, discussed previously as an abrasive, exists in both gel and precipitated forms that are widely used as toothpaste thickeners. The average particle sizes used range from submicron to about 5 microns. Fumed or pyrogenic silica is rarely used. All forms of silica are highly compatible with fluorides and can yield a rapidly dispersing and highly consumer acceptable toothpaste or gel.

Flavor

The perceived flavor of a toothpaste is one of the most important characteristics influencing consumer acceptance. Consumers expect a fresh clean mouth after brushing. Flavor also plays a large role in delivering fresh breath either by masking or modifying the perception of malodors. The flavor oils used are usually the highest cost ingredients in a toothpaste. For these reasons it is essential to choose a flavor wisely. Since this is largely a consumer acceptance area, a sound knowledge based on the experience of the formulator or an experienced flavorist of what works and what does not in the intended marketplace or country is necessary to choose the "right" flavor. Flavor may also be treated as if it were a perfume for the mouth, in which case a trained perfumer or breath odor judge might be employed in the flavor selection process.

So-called universal pleasant-tasting flavors such as fruit, chocolate, coffee, (even whiskey has been suggested!) have not been widely accepted in a toothpaste. There are products using flavors such as fruit or bubblegum for children, but in general the consumer demands a flavor that is conventionally acceptable (this varies in different countries) and leaves a fresh sensation in the mouth and a lasting awareness that the mouth has been cleaned.

In the United States, flavors have usually been based on spearmint, peppermint, and to a smaller degree wintergreen. Menthol is sometimes added, as are

other cooling materials, to increase the cooling effect. Flavors can be modified with clove, eucalyptus, aniseed, cinnamon, and so forth. Other flavor modifiers such as woody, herbal, medicinal, and floral notes are used in different countries, and some are quite successful.

Various other ingredients of the toothpaste formulation can contribute to the perceived flavor; for example, dicalcium phosphate dihydrate–based pastes usually have a flavor preferred over those based on calcium carbonate. The hydrated silica-based toothpastes or gels are noted for having less of a base note than any of the other abrasive systems used. The flavor may also be modified by the presence of an active ingredient and even by the pH or electrolyte content of the product. The nature of the foam and the dispersibility of the paste can also modify flavor perception in the mouth. For these reasons, consumer acceptance of a given flavor should only be judged in the intended full base formulation.

Sweeteners

Most flavor oils are inherently bitter, as are some other toothpaste ingredients. This leads to the requirement of an added sweetener. Even though most humectants are somewhat sweet, most final toothpaste formulations are not very palatable without an added high-intensity sweetener. Since sugars should not be used due to their cariogenic nature, artificial sweeteners are employed.

Saccharin is the sweetener of choice; *sodium saccharin* (due to its high solubility) is used in preference to the acid form.

Potassium acesulfame is gaining wider acceptance but remains more expensive than sodium saccharin at the time of writing this text.

Preservatives

The use of preservatives is rare today primarily as a result of safety concerns. *Sodium benzoate* is not very effective at neutral and higher pH values but is used fairly widely for in-process control of microorganisms. *Potassium sorbate* and the various *parabens* also find limited usage. Some flavor components themselves exhibit antibacterial activity, as do some of the "active" ingredients now used. Careful formulation using the proper ingredients should allow for an almost or completely preservative-free toothpaste.

The product should be manufactured in conditions such that the final product has a plate count below 10 organisms per gram. It should also be subjected to water activity and bacteriological challenge testing.

Corrosion Inhibitors

Once in wide usage in products packed in unlined aluminium tubes, the advent of the less expensive laminate or plastic tubes has virtually eliminated the need for these materials. *Sodium silicate* was often added to high

pH chalk-based toothpastes to prevent corrosion in aluminium tubes. Some phosphates also reduce the corrosion risk with alumina-based toothpastes. Increasing the humectant level might often reduce the risk of this type of corrosion.

Colorants

Colors are often added to toothpastes, sometimes to mask an off-color from the base formulation either initially or upon storage. The range of colors available is restricted somewhat by food or drug additive regulations. In the United States, the predominantly used colorants are FD&C and D&C approved dyes and lakes, as well as a few allowable natural colorants.

Titanium dioxide is widely used in hydrated silica-based toothpastes as an opacifier and in other abrasive system toothpastes to impart a bright white color to the products.

The range of toothpastes available today is quite varied. These can be opaque, white, or colored pastes, "water white" or colored clear gels, striped products, different colored toothpastes, and gels delivered from two-compartment pumps or tubes. There are even products containing colored specks composed of agglomerates of abrasive or encapsulated oils. While some of this (e.g., dual-compartment containers) may be required for technical reasons (incompatability of two phases), it is apparent that consumers have an interest in new visual effects in toothpaste products. History repeats itself even in toothpastes; in the early 1960s it was the novel development of a striped toothpaste in which white and red pastes were delivered from an ingenious nozzle fitment. Today the multicolored striped products still exist, but the "news" is two-compartment tubes and pumps delivering two different phases (in some cases clear and opaque).

Bleaches

To enhance the whitening effect of toothpastes and to assist in the removal of stains, oxidizing agents have been added to toothpastes. *Hydrogen peroxide* and *urea peroxide* are in usage today. In order to deliver either of these materials in an active form, great care must be given to the choice of other formulation ingredients and in the case of hydrogen peroxide in the manufacturing process.

Anticaries Actives

Fluoride ion delivered from a compatible toothpaste base has been shown in numerous clinical trials to reduce the incidence of carious lesions in both children and adults. It acts by reducing the acid solubility of tooth enamel. Fluoride has also been shown to aid in the remineralization of white spot carious lesions.

Sodium fluoride, sodium monofluorophosphate, and *stannous fluoride* are the anticaries actives of choice. In the United States the Final Monograph [2] defines the allowable levels of soluble fluoride ion from each salt in each allowable abrasive system for anticaries active drugs. In a broad sense the only significant change from the earlier "accepted" target of 1,000 ppm of fluoride is the addition of an allowable 1,500 ppm of soluble fluoride ion from sodium fluoride and sodium monofluorophosphate. Also, since toothpaste is volume-dosed, the allowable level of total fluorine has been widened to 850–1,150 to account for the varying specific gravities of toothpaste products. This document goes on to describe other test criteria that must be met, including animal caries reduction, enamel solubility reduction, and fluoride uptake testing [2].

Anticalculus Agents

Zinc chloride and *zinc citrate* are used as anticalculus agents. Other zinc salts have been used, but these two are most frequently employed; they also possess some antiplaque activity. Zinc citrate has been used in combination with *triclosan* for enhanced activity against plaque and gingivitis. Consumer acceptance of zinc chloride–containing toothpastes is low because of its astringency, even at low levels. Due to its much lower solubility, zinc citrate can be formulated at a higher level without undue astringency.

Tetrasodium pyrophosphate, tetrapotassium pyrophosphate and *disodium pyrophosphate* are used more widely as anticalculus agents than the zinc salts. They are somewhat easier to formulate and are less expensive than the zinc salts at comparable usage levels. The pyrophosphates may also have some antiplaque activity. Both of these families of ingredients can be delivered efficiently from a hydrated silica-based formulation.

Desensitizing Agents

Potassium nitrate (5%) is a relatively new desensitizing agent, 5% of which has now become the widely accepted standard for application in toothpaste formulations containing fluoride [3]. Potassium nitrate exhibits a "salty" taste but otherwise is easily formulated and is compatible with fluoride. It has essentially replaced strontium chloride for this application in the United States.

Antimicrobials/Antiplaque/Antigingivitis Agents

Triclosan is the most widely used of the small number of antimicrobials that can be delivered from standard toothpastes. Triclosan was allowed by the United States Food and Drug Administration for use in an approved New Drug Application (NDA) toothpaste, although it has been used overseas in combination with or without zinc. The variations as marketed in the United States also contain fluoride and PVM/MA copolymer to enhance the activity of the formulation.

There are other ingredients mentioned elsewhere in this chapter that have clinically demonstrated antiplaque and antigingivitis activity, in either a toothpaste or a mouthwash. These actives include *chlorhexidine, stannous fluoride, cetylpyridinium chloride*, and a mixture of phenolics and essential oils at specified levels (*thymol, eucalyptol, methyl salicylate, and menthol*).

Sanguinaria canadensis extract or *sanguinaria* (also known as bloodroot extract) has been reported to be an active antiplaque and antigingivitis agent.

Enzymes of various sorts have been used in toothpastes with claims for stain removal, whitening, antiplaque activity, and bad breath reduction. They can be denatured readily by some formulation ingredients and temperature extremes and therefore create formulation problems.

FORMULATION OF TOOTHPASTES

General formulations for a clear gel hydrated silica toothpaste and an opaque dicalcium phosphate dihydrate toothpaste are presented side by side in an effort to show differences.

Hydrated silica	Dicalcium phosphate
Clear gel toothpaste	Dihydrate opaque toothpaste

Ingredients	%	%
Cellulose gum	0.35	1.00
Glycerin	10.00	10.00
PEG-32	5.00	
Sorbitol (70%)	50.00	30.00
Hydrated silica abrasive	15.00	
Hydrated silica thickener	8.00	
Dicalcium phosphate dihydrate		50.00
Flavor	1.20	1.20
Sodium saccharin	0.30	0.30
Sodium monofluoro phosphate	0.80	0.80
Sodium lauryl sulfate	1.30	1.40
FD&C Blue No. 1	0.0001	0.0001
Water	q.s. 100.0	q.s. 100.0

Toothpaste Manufacture

Two basic processes are involved in toothpaste manufacture: the hydration of the gum and the dispersion of the abrasive and possibly any inorganic thickening agent. The hydration of the gum is normally carried out by adding

the dry gum to glycerin (or other essentially nonaqueous liquids), dispersing the gum, and then hydrating the mixture with part of the aqueous portion of the toothpaste under conditions of moderate agitation. Heating the mixture may not be necessary to hydrate the gum but may be of help bacteriologically. Over-shearing of cellulose gum gels may result in an irreversible drop in viscosity and should be avoided.

Gum hydration can also be accomplished by means of an eductor in which the gum is introduced gradually into a stream of cold water that is then forced through a nozzle. The vigorous agitation produced gives a smooth uniform gel.

The powder addition may be done in a variety of mixers capable of heavy-duty mixing. It is the usual practice to add the active ingredient (if present) late in the mixing cycle and to add the surface-active agent and the flavor late. This is done to avoid excessive foaming and to reduce loss of flavor during vacuum mixing. Final mixing is usually performed under vacuum to deaerate the product, or a vacuum centrifuge may be used for final deaeration. Vacuum mixing aids in delivering a uniform product ribbon and ensuring uniform fill weights. The degree to which deaeration is complete can be checked by visual means in clear gel products or by specific gravity measurement in clear and opaque products.

TOOTHPOWDERS

Toothpowder is the original, the simplest, and the least expensive form of oral care products. It is a blend of an abrasive or abrasives, a surfactant, a flavor, and a sweetener. Formulation problems are less troublesome than those with a toothpaste since interactions between ingredients are unlikely in the absence of water. Fluorides and oxidizing agents, for example, are likely to retain their effective concentration longer than in a water-containing paste formulation. Formulation problems of concern are physical characteristics such as the preparation of ingredients of fairly uniform size so as to prevent segregation on shaking and in ensuring that the product does not cake on storage. A typical formulation is given below:

Prototype Toothpowder

Ingredient	%
Dicalcium phosphate dihydrate	77.35
Calcium carbonate	20.00
Sodium lauryl sulfate	1.00
Flavor	1.25
Sodium saccharin	0.40
	100.00

Manufacture

The manufacture of a toothpowder is relatively simple. The sweetener and flavor, together with a little alcohol if desired, are made into a premix concentrate with a part of the abrasive powder. This is then mixed with the rest of the powders in a conventional powder mixer.

SOLID DENTIFRICE

Solid dentifrices are today primarily of historical interest. They consist of a soap into which an abrasive powder and other ingredients such as a flavor, glycerin, and sweetener are mixed. As a rule, a high level of flavor is used, and the product is usually colored. Solid dentifrices, like toothpowders, have been replaced by toothpastes.

Typical Formula

Ingredient	%
"Dental soap"	18.0
Calcium carbonate	76.5
Glycerin	3.0
Color	q.s.
Flavor	2.0
Sodium saccharin	0.5

Manufacture

The soap and abrasive materials are milled with the glycerin and sufficient water to give a plastic mass. The color and flavor are added, and the product is then plodded and extruded in a conventional soap plodder, cut into billets, and stamped.

DENTIFRICE TESTING

Consumer Testing

The first one to test the acceptability of a new formulation is usually the formulator. In the course of toothpaste formulation development a great deal of toothbrushing is done. The taste, aftertaste, mouth feel, dispersibility, foaming, appearance of the extruded ribbon of toothpaste, and any other targeted cosmetic effects can be judged rather rapidly. If successful, the formulation will most likely be consumer tested by larger panels of employees and possibly large-scale consumer panels. Large-scale targeted consumer trials will be necessary if a competitive cosmetic claim such as "makes the mouth feel cooler longer than X" is to be made.

Safety Testing

As with any product that may be accidentally ingested, at least an LD 50 acute toxicity study should be performed on any toothpaste. Due to the presence of a surfactant and flavor, irritation and sensitization testing should also be conducted.

Performance Testing

The claims made for dentifrices and the tighter restraints placed on advertising have increased the volume of work devoted to the performance of dentifrices in recent years. Biological materials in the form of extracted human and animal teeth are readily available, and some experimental work can even be done on teeth or gums in the mouth. Large- and small-scale clinical trials are being run continually by the major toothpaste marketers. Chemists, physicists, clinicians, and dental researchers have all contributed to the vastly increased knowledge of the performance of oral products. While the following paragraphs cover the general testing performed on toothpastes, there are many claims for toothpastes based on "custom-designed" in vitro and in vivo clinical trial tests crafted to support these specific claims.

Abrasiveness

The cleaning properties of a dentifrice depend primarily on the qualities and quantities of abrasive present; the design of the toothbrush and even the detergent may play a part, but their effects are insignificant compared with that of the abrasive. During cleaning, food debris, plaque, acquired pellicle, stains, and possibly calculus should be removed from the tooth surface, if possible without damage to the underlying enamel or dentin. Dentifrice abrasives are a compromise between the demand for perfect cleaning and the desire to avoid excessive wear to tooth surfaces; evaluation methods and the standards adopted reflect this compromise.

The most obvious method of measuring abrasion would be by weight loss, but this requires excessive abrasion and would lead to wear far in excess of the real-life situation. A variety of techniques were proposed for the measurement of the abrasive quality of toothpastes. The technique most nearly approximating real-life conditions is the radio tracer method first described by Grabenstetter et al. [4] This test method is termed *radioactive dentin abrasion* or simply RDA [1].

With the aid of RDA it is possible to assess the relative wear rates of different particle sizes of different abrasives or of different toothpaste formulations. For a series of toothpaste formulations using the same type of abrasive there is an almost linear relationship between (1) particle size and wear rate, (2) percentage concentration of abrasive and wear rate, and (3) product abrasiveness and cleaning.

Hardness, crystallinity of particles, porosity of particles, the agglomeration or lack thereof of particles, and particle shape all play some part in determining abrasiveness, but with the knowledge available from past experience and abrasive suppliers' data it is now possible to essentially preset the abrasivity of a toothpaste within fairly narrow limits. However, the RDA of the final formulation should still be determined for confirmation. There is no evidence to show that any marketed conventional toothpaste today, when properly used, causes excessive wear of enamel or dentin.

Luster (Gloss or Polish)

Unlike RDA, which measures abrasiveness, there is no standardized method for measuring tooth luster. There is no agreement even in the oral care industry on whether the term *luster* is the correct one; the terms *tooth polish, tooth gloss*, and even *whitening* have all been used. The meaning of the term, however, should be the amount of light reflected off tooth surfaces or the shiny look of teeth. The measurement of luster is complicated by a number of factors. Hunter [5] pointed out that it is impossible to measure specular reflectance and diffuse reflectance as separate entities in any but an approximate way, and he describes six different kinds of gloss:

1. *Specular gloss*—shine
2. *Sheen*—surface shine at grazing angles
3. *Contrast gloss*—contrast between specular reflectance of different areas
4. *Absence-of-bloom gloss*—absence of reflection haze or smear adjacent to highlights
5. *Distinctness-of-reflected-image gloss*—distinctness of images reflected in surfaces
6. *Absence-of-surface-texture gloss*—lack of surface texture and surface blemishes

Such a sophisticated analysis of luster is too complex for measurement on human teeth. Instead the simplest assessment of luster on teeth is a subjective one; what is required is a simple objective procedure that can duplicate subjective assessment. Tainter and coworkers [6,7] modified an apparatus used in the paint industry for measurements of gloss on teeth.

It has been found that the depth of scratches measured by profilometric techniques (the deeper the scratches, the lower the luster) correlates with polishing power. Probably the simplest assessment of polish and cleaning power is the technique described by Wilkinson and Pugh [7], who showed that there is a direct relationship between abrasion and cleaning power. Based on their work, it should be possible to devise an abrasive system to give both adequate cleaning and minimum abrasion. A mixture of large (10 micron) soft crystals with a minor proportion of small (1 micron) hard crystals should achieve this result.

Demineralization/Remineralization

Anticalculus claims are considered to be "cosmetic" in the United States. Thus demineralization/remineralization testing is sometimes equated with safety testing. A strong calcium sequestrant has the potential to demineralize teeth. Even a milder sequestrant, such as the pyrophosphates, might under the wrong conditions interfere with the remineralization by a fluoride-containing toothpaste of white spot lesions that is normally expected. Due to these potential problems, it is the usual practice to evaluate toothpaste products having anticalculus activity in demineralization/remineralization tests.

Cleaning

There exist many test procedures for measuring the cleaning or stain removal properties of toothpastes. Most rely on an exaggerated number of brush strokes on extracted teeth on a brushing machine. The teeth are usually artificially stained prior to brushing. The amount of cleaning can be judged by trained technicians or by instrumental means. The most definitive test of cleaning is a clinical trial of a few months' duration or more, with trained technicians judging the relative cleaning of two products, or the maintenance of a "clean state" from a professionally cleaned (prophylaxis) starting point.

Breath Freshening

The breath-freshening potential of dentifrices can be judged directly by trained/calibrated judges or instrumentally. This property of toothpastes can be tested against various insults and at various points of time after usage. Examples of insults that have been used are "morning mouth odor" or food odors such as onion or garlic.

Clinical Trials

Large-scale human clinical trials have been and continue to be run to assess the anticaries effects of fluoride- and nonfluoride-containing toothpastes. Large-scale clinical trials are being run on a variety of antiplaque and antigingivitis agents/toothpaste formulations. Due to the high cost and long duration of these trials (anticaries trials of 3 years' duration are not uncommon), preliminary testing in animal models or short-term human panel tests are routinely run prior to the commitment to the larger trials.

TOOTHBRUSHES AND TOOTHBRUSHING

The toothbrush and the mechanism of toothbrushing play an important part in oral hygiene. Toothbrushes produced today employ nylon bristles with a plastic handle. Here is where the commonality ends. Bristle texture, bristle length, number of bristles per tuft, number of tufts, angle of tufts to the brush

head, rows of tufts, uniformity of bristle length, head length/width, angle of the head relative to the handle, whether the handle flexes and so forth can all vary. Claims for most new toothbrush designs include better plaque removal than competitive products. These claims need to be substantiated in much the same manner as claims for toothpastes.

Surveys of toothbrushing habits in the United States show that up to 85% of adults claim to brush their teeth twice a day, usually on waking and before going to bed, and that women are more conscientious than men. Children usually have a lower frequency of usage. However, the statistics of toothpaste and toothbrush sales in different countries show clearly that a large number of people either do not brush their teeth at all or do it rarely, and people do not purchase a new toothbrush every three months as recommended.

It has never been shown unequivocally that toothbrushing alone is instrumental in reducing dental decay. Researchers have shown, however, that regular brushing with a cosmetic dentifrice reduces the incidence of decay among susceptible subjects. It is also clear that regular toothbrushing is effective in reducing or preventing periodontal disease. The removal of food debris and the massaging of the gums are part of good oral hygiene.

The introduction of the mechanical toothbrush stimulated tests designed to show whether mechanical brushing is superior to hand brushing. Unfortunately, there are no accepted criteria for evaluating the effectiveness of a toothbrush. Prevention of the formation or the removal of plaque and calculus, the gingival index, and the absence of staining are all common criteria. An evaluation of this type is further complicated by the large variety of designs available for toothbrushes.

Other devices have been suggested for cleaning teeth, such as water jet rinsing devices and water jets containing abrasives or other ingredients.

It can be assumed that most brushes, properly used, have some effect in improving oral hygiene and therefore reduce periodontal disease, but no case can be made for their having any anticaries effect. In general, professional dental care, proper diet, the use of a fluoride dentifrice, and education in brushing technique are essential factors in the prevention of oral diseases.

DENTURE CLEANSERS

Denture cleansers are marketed either in paste form or in tablet form. The tablet and earlier powder forms are yielding some market share to the newer paste products. Regardless of the product form, the functions of a denture cleanser are removal of debris, plaque, calculus, and surface stains from the denture.

Denture Tablets

Although the tablet products may differ widely in composition, they contain an oxidizing agent, a flavor, an electrolyte, and an alkali.

Sodium perborate or *sodium percarbonate*, are the oxidizing agents normally used, although hypochlorites, trichloroisocyanuric acid and its salts, and persulfates have also been used. Sodium percarbonate is more soluble in water than sodium perborate but is not quite as stable, although in the solid form its stability is adequate.

Tablet products are dissolved in water to form a solution in which the denture is soaked. After a suitable period of soaking, the deposits should be easily brushed away. In addition, the denture may be "sterilized," and surface stains are removed. Whatever the type of oxidizing agent used, care must be taken to ensure that the product does not alter the color of the denture. Modern plastic dentures normally retain their color well. The amount of sodium perborate or percarbonate used is usually in the range of 20–50%; corresponding amounts of other oxidizing agents may be employed, but chlorine-generating compounds should be used at such a level that leaves the denture without an unpleasant chlorine aftertaste after rinsing.

Sodium chloride is the electrolyte used, and the alkali is most commonly anhydrous trisodium phosphate.

A typical denture cleanser tablet formulation is provided below:

Prototype Denture Cleanser

Ingredient	%
Sodium percarbonate	88.0
Sodium chloride	10.0
Sodium silicate and other binders	2.0
Flavor, color	q.s.

It is common to promote effervescence in tablet products. This helps in the disintegration and dissolution of tablets and reinforces the concept of activity. Effervescence may be provided by the addition of conventional carbonate acid mixtures (tartaric or citric acids). The inclusion of proteolytic and amylolytic enzymes in denture cleansers has been practiced.

The manufacture of these products is not as simple as it appears. It is vital to keep moisture out of the product and to protect it from atmospheric humidity. Tablets should dissolve quickly. Stringent storage testing should be performed on the packed product, and the continued performance of the stored product under usage conditions should be monitored.

Denture Cleanser Paste

Paste denture products are used with a denture brush or toothbrush for cleansing the denture. They are essentially formulated like dentifrices, with care being taken to avoid causing excessive abrasion of the denture material. Formulation latitude exists here for the use of strong oxidizing substances and other ingredients (which cannot be used in dentifrice due to their inherent safety problems if ingested) since these paste denture cleaners are meant to be thoroughly rinsed off the denture prior to placement in the mouth.

MOUTHWASHES

BACKGROUND AND FUNCTION

Mouthwashes should be the ideal product form to deliver active ingredients to the mouth, the gums, or the teeth. Mouthwashes have been defined as pleasant-tasting solutions (containing germicides) that are used for freshening the mouth. Mass-marketed ready-to-use mouthwashes will be the primary focus of this section.

In general, a mouthwash may belong to any of four types (there may be overlap between these types driven by claims or marketing):

(1) Antibacterial, which contain a germicidal agent of some sort to decrease the bacterial population of the mouth
(2) Fluoride, which help strengthen the enamel of teeth
(3) Cosmetic, which freshen the breath
(4) Prebrushing rinses, which loosen plaque to render it easier to remove with a toothbrush and toothpaste

Antibacterial products can further be broken into two types: those based on phenolics, sometimes called antiseptic mouthwashes, and those based on other antimicrobials. American mouthwashes have been formulated to be ready for use, while European mouthwashes are more concentrated and are intended to be used after dilution. Mouthwashes were historically marketed on the basis of a social necessity for fresh clean breath. Newer developments have led to antiplaque or antigingivitis claims and even anticaries properties.

A mouthwash should be a liquid of reasonable viscosity when used (not too thin or too thick), with a "pleasant" flavor. It should be safe to use on a daily basis and not support bacterial growth. Preferably, it should be clear and single phase. It may foam to reinforce the concept of cleaning. It should be stable over the temperature range likely to be encountered during its distribution and anticipated shelf life. A mouthwash may be a ready-to-use liquid, a liquid concentrate, or a powder to be added to water.

A mouthwash should perform several basic functions: (1) clean debris from the oral cavity, (2) freshen the breath, and (3) leave a fresh feel. In addition, mouthwashes, depending on type, may (1) decrease the number of microorganisms in the mouth, (2) deliver an active ingredient such as a fluoride, and (3) loosen dental plaque.

MOUTHWASH INGREDIENTS

There is a large overlap in the ingredients used and their functions in toothpastes and mouthwashes. The approach taken in this section is to mention only those ingredients in fairly wide usage in mouthwashes.

Solvents

Water is the first ingredient in all ready-to-use and most concentrate mouthwashes. High-quality purified, distilled, or deionized water is normally used to avoid interactions with other ingredients and to provide a neutral starting base for the mouthwash.

Alcohol or alcohol denatured is used in the majority of ready-to-use mouthwashes. Ethanol is usually purchased in the United States as 190 proof (95%) SD alcohol (specially denatured) in one of various formulations. One of the more widely used alcohols for mouthwash is SD alcohol 38-B since it allows for the usage of various flavor oils as the denaturant(s). Alcohol helps to deliver the required fresh mouth feeling, and even at low levels aids in the solubilization or emulsification of the flavor, and depresses the freezing point of the formulation. It also helps to stabilize the product against microbial growth. Alcohol adds a "lift" to the flavor and has been claimed to aid in decreasing oral malodor.

Flavor

Flavor is the reason for choice of a mouthwash by most consumers. They expect either a "pleasant" or a "medicinal/antiseptic" taste during usage and a corresponding breath odor after usage. Predominant flavor types for cosmetic type mouthwashes in the United States are mints such as spearmint, peppermint, and to a lesser extent wintergreen. These are not usually just straight oils such as peppermint (*Mentha piperita*) oil but compounded flavors with possibly many modifiers. Herbal, woody, floral, and medicinal (or phenolic) type notes are routinely added to these compounded flavors.

Flavor preferences vary widely from country to country and even by sections of the same country. Due to this, and the relatively high cost of some flavor oils, it is necessary to carefully consider the flavor used for a product. The best test of this is most likely using a target group of consumers for the product with the product concept.

Beyond just the taste of the flavor, the flavor may act to mask or modify the perception of bad breath or an intended insult such as "morning mouth" or garlic odor. In that case, studies should be run to determine the effectiveness of candidate flavors in masking or altering the perception of that target odor. This is probably best tested by using consumers, the target odor, and trained/calibrated odor judges.

The "Phenolics"

The phenolics include thymol, eucalyptol, methyl salicylate, and menthol. Many people consider these ingredients to add a "medicinal" or "antiseptic" character to the flavor of a mouthwash. These materials have been used in products at set levels with an American Dental Association accepted claim of "Kills germs that cause bad breath, plaque, & the gum infection gingivitis."

Menthyl lactate and related esters of menthol have been used in a few products to increase cooling while not having some of the strong taste effects of menthol itself.

Methyl salicylate as well as phenyl salicylate and other phenolics have been used either as individual ingredients or as part of a compounded flavor.

Synthetic sweeteners are usually added to mouthwashes to make them more acceptable. The two most widely used are sodium saccharin and potassium acesulfame.

Humectants

Humectants are used in mouthwashes to aid in the solubilization of flavors, to modify the mouth feel, to add sweetness, and to increase the osmotic pressure of the mouthwash to decrease the risk of microbial growth. Humectants that have been used in recently marketed products are essentially the same as those used in toothpastes: glycerin, sorbitol, hydrogenated starch hydrolysate, propylene glycol, and xylitol. Higher levels of humectant are usually used in nonalcoholic mouthwashes.

Solubilizers/Emulsifiers

In order to obtain a clear end product, mouthwash formulations employ an emulsifier or solubilizer to incorporate the flavor of other non–water-soluble ingredients. These emulsifiers may also contribute to the mouth-cleansing effect of the mouthwash. Combinations of the emulsifiers listed are often necessary to obtain a clear end product. In order to evaluate these materials, the formulation is made up and checked for clarity and lack of phase separation both initially and upon low and high temperature storage.

The *poloxamer* types of surfactants have been used fairly widely, and their usage is increasing. The more widely used members of this series include poloxamer 407, poloxamer 338, and poloxamer 124. Other members of this

family of materials have been suggested for usage in mouthwashes and may be worth evaluating in formulations in which the previously mentioned ones do not function adequately.

Polysorbates, for example, polysorbate 20, polysorbate 60, polysorbate 80, and steareth-20, also are used widely as the sole emulsifiers in mouthwashes. PEG-40 hydrogenated castor oil is being used as an emulsifier as well as part of a tobacco tar removal mixture in a patented product. Other similar ingredients may be used as emulsifiers or stabilizers.

Cationic emulsifiers were used in a few products in the past but have not been used recently, mainly due to the off-flavors of these materials.

Anionics, for example, sodium lauryl sulfate and sodium lauryl sulfoacetate, have been used in mouthwashes, usually in combination with a nonionic. They are, however, not used in formulations containing cationic materials due to their incompatibility.

Antimicrobials

Beyond killing "germs" the antimicrobials function to decrease bad breath, plaque, and gingivitis. The "phenolics" were discussed earlier as flavors.

Cationic quaternary antibacterials currently in usage are limited essentially to cetylpyridinium chloride (CPC) and domiphen bromide. While CPC is sometimes used as the sole antibacterial, domiphen bromide is used only in combination with CPC. Chlorhexidine is noted for its strong broad-spectrum antimicrobial activity and strongly substantive nature. It is used in a prescription drug mouthwash in the United States for its antiplaque and antigingivitis effects.

Sanguinaria canadensis extract or *sanguinaria* has been incorporated into mouthwashes for its antibacterial and therefore antiplaque and antigingivitis effects.

Triclosan is currently not allowed to be used in the United States, but mouthwashes with this active, which deliver antiplaque and antigingivitis activity, have been formulated overseas. These mouthwash formulations may also contain PVA/MA copolymer or a pyrophosphate to boost activity.

It is neither possible nor desirable to aim for complete sterility in the mouth. The use of antibiotics, for example, might destroy normal bacteria and thus permit the overgrowth of undesirable opportunistic organisms. It is possible, however, to reduce the bacterial population and maintain it at low levels by the use of antibacterials that are substantive. Cationic antibacterials normally have this property to some degree, as do other materials. The buccal tissue scraping test can serve as a standard technique for assessment [8].

The total antimicrobial effect of a formulation is a combination of various factors: the mechanical effect of rinsing debris and microorganisms from the mouth, possibly enhanced by a surfactant; the effect of the antibacterial agent on the oral flora; and the possible effects of the flavor components and the alcohol, if present at a high level. Synergistic effects may also occur and should be evaluated.

Other "Actives"

Hydrogen peroxide (1.5%) can be used as an oxidizing agent in mouthwashes. Hydrogen peroxide, of course, is quite reactive and may react with other formulation ingredients, and products containing it require great care in processing.

Chlorine dioxide, or its source in practice, sodium chlorite, is used as an oxidizing agent in mouthwashes. These oxidizing materials are used primarily to decrease bad breath but could also provide some antibacterial effect if properly formulated.

Zinc salts, such as zinc chloride and other soluble zinc salts, have been in use in mouthwashes for many years as astringents to tighten bleeding gums. Zinc salts are known to react with volatile sulfur compounds and therefore contribute to breath freshening. There are data to indicate that they also have some antiplaque activity. Formulations containing zinc chloride require a pH of about 4.5 or below to keep this salt from precipitating.

Buffers

Buffers are used in some products to maintain the pH within a narrow range to help stabilize or improve the efficacy of certain products. Typical examples are benzoic acid and sodium benzoate, sodium phosphate, and disodium phosphate.

Fluoride

In the United States, fluoride-containing mouthwashes are regulated by the FDA as over-the-counter drugs [2]. Limits on the level of fluoride and permissible claims are given in this regulation and should be reviewed carefully before the start of formulation development. Sodium fluoride is easily formulated with other normal mouthwash ingredients and should not present a problem when added to most mouthwashes.

Miscellaneous Ingredients

There are many other ingredients that occasionally find use in mouthwashes. These include a long list of surfactants, other antibacterials, preservatives,

and even biological extracts. Two materials worthy of note since they are used in a widely marketed prebrushing rinse are tetrasodium pyrophosphate and xanthan gum. Tetrasodium pyrophosphate is normally used in dentifrice for its anticalculus effect but in this case is employed for its antiplaque effect. Xanthan gum is being used for its film-forming properties to stabilize the foam from the surfactant and possibly to increase debris (plaque) removal.

Sodium bicarbonate or baking soda is used in a few marketed mouthwashes for its malodor-reducing properties.

FORMULATION EXAMPLES OF MOUTHWASHES

Cosmetic Alcohol-Free Mouthwash

Ingredient	%
Water	86.01
Benzoic acid	0.04
Sodium benzoate	0.15
Poloxamer 407	1.25
Glycerin	12.00
Sodium saccharin	0.05
FD&C Blue No. 1	0.0002
Flavor	0.25
Polysorbate 20	0.25
	100.00

Antimicrobial Alcohol-Containing Mouthwash

Ingredient	%
Water	76.18
Glycerin	8.00
Sodium benzoate	0.10
Benzoic acid	0.04
Sodium saccharin	0.08
Cetylpyridinium chloride	0.05
FD&C Blue No. 1	0.0002
SDA alcohol 38-B	15.00
Flavor	0.25
Polysorbate 80	0.30
	100.00

Prebrushing Rinse

Ingredient	%
Water	72.60
Sorbitol	15.50
Benzoic acid	0.05
Sodium benzoate	0.20
Xanthan gum	0.10
Sodium lauryl sulfate	0.20
Tetrasodium pyrophosphate	1.50
FD&C Blue No. 1	0.0002
SDA alcohol 38-B	8.70
Flavor	0.15
Poloxamer 407	1.00
	100.00

Mouthwash Manufacture

Most mouthwashes are prepared in three steps. In step one, a phase containing the water-soluble ingredients is prepared; in the next step the non–water-soluble ingredients plus an emulsifier are combined. These two phases are then mixed together. From a manufacturing standpoint it is best if the smaller phase (the nonaqueous) can be added to the larger (aqueous) phase. The final step in production is filtration through a series of filters, ending with a submicron cartridge type of filter. It is believed that a very clear sparkling product is better received by the consumer.

Packaging

Both ready-to-use and concentrate mouthwashes are packed in bottles. Historically most mouthwashes were packed in glass with a resealable cap; this was viewed as the perfect package for many years. Glass was considered to be nonreactive and provided "perfect" barrier properties. The trend in the beverage industry toward lighter weight, more break-resistant plastic containers and toward the use of fluorides influenced the marketers of mouthwash to adopt plastic bottles. Today the majority of mouthwashes are sold in plastic bottles with a resealable plastic cap. The resins of choice for the bottle are polyethylene terephthalate (PET) and polyvinyl chloride (PVC). Some high-density polyethylene and some exotic resins and coextruded bottles are also used. PET offers better surface contact clarity than PVC.

A FDA regulation in the United States [9] requires "tamper-evident" packaging for mouthwashes. The tamper-evident features used are usually

shrink-bands over the cap and part of the bottle or an induction heat-seal over the neck of the bottle that must be peeled off or broken prior to use of the product.

MOUTHWASH TESTING

Consumer Testing

Consumer acceptance testing of mouthwash formulations usually starts at the laboratory bench with the formulator tasting his formulations. This acceptance testing may go to great lengths, employing hundreds of target consumers, particularly if a "tastes better" claim is to be made.

Safety Testing

As with any product subject to accidental ingestion, the acute toxicity or the LD 50 product must be tested prior to human exposure. Also suggested due to the presence of flavor, surfactant, and possible other active ingredients are irritation and sensitization testing.

Bacteriological Testing

While all mouthwashes should be evaluated to determine that they will not support microbiological growth, the antibacterial products must also be tested to support the exact antibacterial claim made (e.g., kills germs for x hours).

Mouth Odor Reduction Testing

Many instrumental test procedures based on gas liquid chromatography, odor detectors based on them, and other detection methods are available. The usage of consumer panels with trained odor judges specifically designed to assess the target insult odor (be it morning mouth or garlic-containing food) have gained wide acceptance over the past 20 years for claim support, particularly for television network approval since they better reflect real-life situations.

Clinical Tests

The type of clinical tests performed on today's mouthwashes are as varied as the claims made for the various products. They range from traditional anticaries trials to the loosening of plaque by a prebrushing rinse. The test's design should be such that it will clearly support the intended claim. This is much easier said than done. Potentially a lot of time, money, and energy will be expended in preliminary screening trials prior to finalizing the design of the clinical trial(s) used for claim support.

Mouthwash Concentrates

This category is not widely marketed to the consumer in the United States but is in Europe and a few other countries. Essentially these products employ

the same ingredients as those found in the ready-to-use products but at two- to four-fold levels. The main concern in formulating a mouthwash concentrate is the quality of the water for dilution prior to usage. The presence of excessive amounts of water hardness can lead to clarity problems or to precipitation of some ingredients. A very bad tasting water used for dilution will most likely yield an unpleasant tasting end product. The formulator should be aware of these water quality issues and attempt to compensate for them during formulation development.

Mouth Fresheners

Aerosol and pump spray mouth fresheners are a natural extension of mouthwash and are marketed fairly widely worldwide. They are recommended for freshening the breath after eating, drinking, or smoking, and may contain only flavoring agents, although antibacterials could be added. The basic formulation can be an exaggerated concentrate of a mouthwash. The significant advantage of this form is that the container is small enough to be carried in a handbag or pocket, so that its use is not confined to the home.

Some manufacturers market breath freshener liquid drops. One drop placed on the tongue is claimed to produce instant freshness and control breath odor. These formulations are essentially the same as the aerosol products but are only dispensed differently.

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CHAPTER 34

Safety and Performance

INTRODUCTION

This chapter discusses the various aspects of safety and performance of cosmetics and skin care products. Marketed products must be tested to avoid adverse reactions such as irritant contact dermatitis, allergic contact dermatitis, phototoxic dermatitis, photoallergic dermatitis, and contact urticaria. Furthermore, damage to the skin barrier, heightened neurosensory input, or increased immune responsiveness must not occur following initial or repeated product application. The adverse reactions can be prevented by employing the proper safety testing methodologies in in vitro, animal, or human models. Finally, product performance must also be assessed through the use of bioengineering techniques, specialized user panels, and qualified observers. This logical approach to product safety and performance will help ensure that cosmetics and skin care products are safe for use by millions of people.

NATURE OF ADVERSE SKIN REACTIONS FROM COSMETIC USE

The skin has a surprisingly limited repertoire of reaction patterns, given the extensive number of substances that may cause potential problems. Interestingly, the responses are remarkably similar regardless of the evoking chemical. These responses may be divided into those resulting from a breakdown in the barrier function of the skin, known as irritant contact dermatitis, and problems involving the immune system, known as allergic contact dermatitis. Sometimes the reaction pattern is characterized by welts instead of a dermatitis, in which case it is called contact urticaria. If light is operative in the reaction pattern, a photodermatitis is produced. However, some reactions involve only abnormalities induced in the sensory aspects of the skin, and no visible

abnormalities are present, yet an adverse reaction has occurred. Each of these reactions patterns will now be discussed in detail (Table 34.1).

IRRITANT CONTACT DERMATITIS

Irritant contact dermatitis, the most commonly encountered adverse reaction to cosmetics and skin care products, is manifested as erythematous, warm, pruritic skin. Mild irritation, which may occur following use of some cosmetic preparations, results in redness and mild itching or stinging, without swelling or warmth. Such dermatitis usually progresses to an accumulation of dry scales, fine surface fissures, and slight thickening of the skin. The redness is a manifestation of the increased flow of blood through the superficial dilated vessels, and hence the greater number of red cells in the tissue. The subsequent desquamation of scales and thickening of the skin results from the shedding of the damaged surface corneal squames. The mild swelling is due to leukocytes and

Table 34.1 Cutaneous Reaction Patterns

Reaction Pattern	Immune System Activated	Dermatologic Appearance	Possible Causes
Irritant contact dermatitis	No	Erythema, desquamation, erosions, inflammatory papules	Soaps, detergents, strong acids, strong alkalis, solvents
Allergic contact dermatitis	Yes	Erythema, edema, vesicles, serum crusting	Poison ivy, methacrylate, formaldehyde, nickel
Nonimmunologic contact urticaria	No	Erythema, welt	Alcohol, acetic acid, balsam of Peru, sorbic acid
Immunologic contact urticaria	Yes	Erythema, welt	Benzoic acid, formaldehyde, menthol
Phototoxic contact dermatitis	No	Erythema	Sun, psoralens
Photoallergic contact dermatitis	Yes	Erythema, inflammatory papules, vesicles	Methylcoumarin, musk ambrette, PABA esters
Sensory irritation	No	No cutaneous findings	Lactic acid, propylene glycol, benzoyl peroxide

serum infiltrating the dermis. Within two weeks, the appearance of the skin returns to normal, although there will still be histologic evidence of the irritant contact dermatitis. The epidermal and dermal changes associated with irritant contact dermatitis are summarized in Table 34.2.

The most important aspect of irritant contact dermatitis is the presence of stratum corneum damage without immunologic phenomena, so that vesicles (blisters) are generally not present. The irritancy may be due to the presence of chemical factors with excessively high or low pH or to volatile vehicles that dissolve protective sebum [1]. Irritants may be classified as primary or secondary. A primary irritant induces an inflammatory response on first contact with the skin, although the contact may be of several hours' duration. For example, contact with hydrochloric acid produces an immediate, acute, primary contact dermatitis. A secondary irritant is a substance that is outwardly harmless on first contact but produces skin disease on repeated application. For example, repeated water contact, which induces household hand dermatitis, may take weeks to develop.

Physical factors may also contribute, including stroking the skin to apply cosmetics or abrasive particles within the cosmetic. Environmental conditions, temperature, relative humidity, and exposure to sunlight also influence the susceptibility to irritation. Essentially, any activity or substance that damages the stratum corneum barrier will ultimately result in irritant contact dermatitis.

Table 34.2 Epidermal and Dermal Findings Associated with Irritant Contact Dermatitis

Epidermal Findings
Decreased surface lipids (sebum)
Decreased intercellular lipids
Protein denaturation
Vacuolation (cell damage)
Desquamation (skin scale)
Hyperkeratosis (skin thickening)
Dermal Findings
Erythema (redness)
Edema (swelling)
Leukocyte, polymorphonuclear leukocyte, and mononuclear cell migration (white blood cells)
Fibrin deposition (framework for healing)
Granuloma formation (tissue reaction to damage)
Capillary proliferation (new blood vessels to heal skin)
Fibrosis and scar

This is the case in people with chronic skin disease, such as atopic dermatitis, xerotic eczema, or neurodermatitis. These people frequently describe numerous products that produce "allergic" symptoms. In actuality, there is no immunologic basis to the dermatitis but an irritancy heightened by a damaged stratum corneum. Any cosmetic or skin care product applied to dermatitic skin may produce irritation; therefore, cosmetics or unnecessary personal care items should be discontinued until the dermatitis has resolved.

The changes in irritated skin are induced by the physical and chemical toxic actions of the irritant and by the pharmacologic mediators released or activated in the inflammatory response. Thus solvents may extract lipids from the stratum corneum, macerate the cells, impair the water barrier function, and damage or kill some of the underlying keratinocytes. These changes are a direct effect of the applied substance. During the ensuing inflammatory response, lysosomal, proteolytic, and other enzymes from infiltrating leukocytes and damaged epidermal cells degrade tissue elements and activate other pharmacologically active systems (e.g., complement and cytokines). These mediators attract more leukocytes and release other active substances (e.g., histamine and proteolytic enzymes from mast cells). The complex cascade of inflammatory events results in more tissue change than that induced directly by the toxic substance.

Among the changes induced in the stratum corneum by applied substances are removal of lipids, soluble proteins, and other cellular substances; denaturation of soluble proteins; and unfolding of fibrillar proteins such as keratin. These result in impairment of physiologic function, for example, loss of the water barrier or water retention properties; impaired resistance to penetration by microorganisms or environmental substances; and loss of plasticity or elasticity, which may lead to fine ruptures and desquamation. More important, the defective barrier no longer protects the underlying nerve endings resulting in the noxious stimuli of itching, burning, tightness, and stinging. These are the sensory perceptions that accompany irritant contact dermatitis.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis is less frequent but more severe than irritant contact dermatitis. It is a complex immune response involving allergens, also known as antigens, and antibodies. An antigen is a substance that stimulates the formation of an antibody or alters the reactivity of certain immune cells. Some substances found in skin care products can act as antigens by themselves, but other low molecular weight chemicals must combine with a protein, known as a hapten, before they become antigenic. An important property of antigens is specificity. Antibodies or sensitized lymphocytes react with a specific

antigen resulting in sensitization. However, some cross-reactions with other antigens may occur if the substances are chemically similar in structure. Thus a person sensitized to one antigen may react to another of similar chemical form, although the cross-reaction is usually weaker.

Allergic contact dermatitis can be difficult to differentiate clinically from irritant contact dermatitis, but the distinction is important. Both conditions may appear with skin redness; however, acute allergic contact dermatitis is characterized by vesiculation and blistering. In some cases, late-stage allergic and irritant contact dermatitis cannot be differentiated. This can be confusing, since healing skin appears the same on visual and histologic examination regardless of the source of the injury. Allergic contact dermatitis is an immunologic phenomenon requiring antigen-presenting and antigen-processing cells, without regard to the condition of the protective stratum corneum. Therefore, an intact stratum corneum cannot prevent development of allergic contact dermatitis in sensitized individuals.

The only reliable method of preventing allergic contact dermatitis is avoidance of the allergen [2]. It is technically impossible to "desensitize" people from a strong allergen. The most common cosmetic-induced causes of allergic contact dermatitis, as determined by the North American Contact Dermatitis Group, are listed by product category in Table 34.3.

CONTACT URTICARIA

Contact urticaria (hives) is a transient erythematous eruption, with edema mainly in the dermis, at the site of application of a topical substance. The edema results from the release of mast cell histamine, which increases the permeability of the cutaneous vessels, augmented by the activation of kinins with similar activity. The spectrum of clinical presentation ranges from itching and burning to generalized urticaria to anaphylaxis.

Contact urticaria can be divided into nonimmunologic and immunologic categories, based on the cutaneous and systemic effect of the substance

Table 34.3 Relative Incidence of Allergic Contact Dermatitis Due to Defined Categories of Cosmetic and Skin Care Products

1. Skin care products	28%
2. Hair care products	24%
3. Facial cosmetics	11%
4. Nail cosmetics	8%
5. Fragrance products	7%

Data from R. M. Adams and H. I.'Maibach, A five-year study of cosmetic reactions. *J. Am. Acad. Dermatol.*, 13:1062–1069, 1985.

(Table 34.4). Nonimmunologic contact urticaria is induced by direct contactant release of histamine from the mast cells, the chemical responsible for the redness and swelling. It is more commonly encountered than immunologic contact urticaria, in which immunologic mechanisms, such as an antigen (allergen) reacting with an antibody are involved in histamine release, so the phenomenon can only be elicited in sensitized individuals. However, there are some chemicals that produce contact urticaria due to uncertain mechanisms, such as persulfate and *p*-phenylenediamine. Testing for contact urticaria should be carried out under carefully controlled conditions with nearby resuscitation facilities, since anaphylaxis due to topically applied chemicals has occurred in sensitized individuals.

PHOTOTOXIC AND PHOTOALLERGIC DERMATITIS

Phototoxic and photoallergic dermatoses are limited to areas exposed to light. Phototoxic reactions are based on nonimmunologic mechanisms and usually appear as a sunburn that may be followed by hyperpigmentation and desquamation. The molecules that produce phototoxicity are generally of low molecular weight and possess highly resonant structures that readily absorb mainly UVA radiation [3]. Photoallergic dermatitis, on the other hand, is less common, is immunologically mediated, and generally requires repeat exposure. It is characterized by erythema, edema, and vesiculation. Photoallergens are generally low molecular weight lipid-soluble substances that possess highly resonant structures absorbing energy over a wide range of wavelengths, but again predominantly in the UVA spectrum. The light energy photochemically converts the photosensitizer into its active forms [4]. Less UV radiation energy is required to elicit a photoallergic reaction compared

Table 34.4 Cosmetic Ingredients That May Cause Contact Urticaria

Nonimmunologic	Immunologic	Uncertain
Acetic Acid	Alcohols	Persulfate
Alcohols	Benzoic acid	*p*-phenylenediamine
Balsam Peru	Benzophenone	
Benzoic acid	Diethyltoluamide	
Cinnamic acid	Formaldehyde	
Cinnamal	Henna	
Formaldehyde	Menthol	
Sodium benzoate	Parabens	
Sorbic acid	Polysorbate 60	
	Salicylic acid	

with a phototoxic reaction. Differentiating between the two many be difficult, however, especially if a severe phototoxic reaction results in vesiculation.

There are several substances that are, or previously were, used in cosmetics, which induce phototoxicity or photoallergy. Eosin, once used in lipsticks, is a much-quoted example of a phototoxic substance. Other examples are *p*-aminobenzoic acid derivatives and digalloyl trioleate in sunscreen preparations, bithionol and hexachlorophene in toilet soaps and deodorants, and the halogenated salicylanilides, for example, the bacteriostatic substance tetrachlorosalicylanilide (T4CS). Perfumes compounded with essential oils from some plants, for example, bergamot and particularly the psoralens contained in this oil, are a potent source of phototoxins.

Substances selected for cosmetics and skin care formulations should be examined for their ability to absorb light at wavelengths longer than 290 mn. Any substance capable of doing so should be considered suspect until tests show that it is free of photobiological activity or that such activity is not relevant to its intended use.

MECHANISMS OF SKIN SENSITIVITY

All of the previously described adverse reactions from cosmetic use ultimately result in increased skin sensitivity. Skin sensitivity may clinically present as stinging, burning, pruritus, and/or tightness, regardless of the environmental stimulus or underlying medical cause. These symptoms may be noticed immediately following product application or may be delayed by minutes, hours, or days. Furthermore, the symptoms may result only following cumulative product application or in combination with concomitant products [5]. It is important to note that these symptoms may be present, even though there is no visible sign of skin disease. Cosmetic manufacturers have reported that 1–10% of facial cosmetic users experience these subjective perceptions without clinical findings. Table 34.5 lists those ingredients that are likely to cause stinging in this select group of individuals. The most reliable predictor of sensitive skin appears to be prior history of dermatologic disease, especially eczematous dermatoses related by dry skin.

It is important to understand the physiologic changes that accompany both visible and invisible adverse reactions to cosmetics. The first change that occurs is within the nerve endings, primarily in the dermis, but extending to a lesser degree into the epidermis. Skin damage causes a heightened neurosensory input. This may be due to stratum corneum or epidermal damage allowing direct access of the cosmetic or skin care product to the nerves. Noxious sensory stimuli found in patients without barrier damage could be due to altered nerve endings, increased neurotransmitter release, unique central information processing, chronic nerve ending trauma, or slower neurotransmitter

Table 34.5 Substances That Induce Stinging

Slight Stingers	Moderate Stingers	Severe Stingers
Phenol	Sodium carbonate	Crude coal tar
Salicylic acid	Trisodium phosphate	Phosphoric acid
Resorcinol	Propylene glycol	Hydrochloric acid
Lactic acid	Propylene carbonate	Sodium hydroxide
	Dimethylsulfoxide	Cinoxate
	Diethyltoluamide	
	Dimethyl phthalate	
	2-Ethyl-1,3-hexanediol	
	Benzoyl peroxide	

Table adapted from Frosch PJ, Kligman AM: A method for appraising the stinging capacity of topically applied substances, *J. Soc. Cosm. Chem.* 28:197–209, 1977.

removal. It is the human variability in sensory perception that is difficult to assess when formulating cosmetics and skin care products.

Dermatologists generally characterize people as those who prefer the stimulus of rubbing the skin and those who prefer the stimulus of scratching the skin. Persons with atopic tendencies (including asthma, hay fever, and dry skin or eczema) universally prefer the stimulus of scratching over rubbing. Somehow the nerve endings and the central brain processing find the sensation of scratching pleasurable. Most nonatopic individuals find scratching to be a painful, undesirable cutaneous stimulus. Other examples of variability in neurosensory response include the tremendous flushing induced in patients with rosacea upon the application of topical volatile vehicles, such as low molecular weight alcohols or other solvents. Atopic individuals and people with rosacea present product formulation and testing challenges.

Immune reponsiveness is a second contributing component of adverse reactions to cosmetics and skin care products. It is immune responsiveness that allows the production of antibodies in response to an allergen. Heightened immune responsiveness is found in people with multiple episodes of immunologic contact urticaria, allergic contact dermatitis, or atopic dermatitis. Such people demonstrate increased positive reactions to patch and prick testing, with the height of immune responsiveness occurring around age 30 and progressively decreasing thereafter.

Finally, defective barrier function is an important component of adverse reactions to cosmetics and skin care products. Lack of an intact barrier can result in heightened neurosensory input by inadequately protecting nerve endings, as discussed previously, and may contribute to enhanced immune responsiveness through altered percutaneous absorption. This facilitates access

to increased levels of antigen in the dermal vasculature and antigen-presenting cells. The permeability barrier resides in the stratum corneum of the epidermis and requires the presence of intercellular lipids, such as cholesterol, ceramides, and free fatty acids, acting as liquid crystals. Perturbed barrier function is manifested by many measurable physiologic changes, including altered calcium levels in the stratum granulosum, increased cytokines, elevated levels of interleukin 1-alpha, and growth factor production. Thus, a well-organized multilayered lipid structure between the corneocytes is essential to barrier function. It is alterations in this basic structure that cause people with dermatologic disease to present with sensitive skin.

HUMAN VARIABILITY IN SKIN SENSITIVITY

Much research has been conducted to aid the cosmetic chemist in assessing the variability of human skin reactivity. Data have been collected from the standpoint of gender, skin type, and prior dermatologic history to attempt to identify populations at risk for sensitive skin. The findings from these numerous studies have been organized in Table 34.6.

It was thought at one time that women reacted more intensely to irritants than men because female skin had a higher pH with less buffering capacity. This thinking was refuted by Bjornberg, who demonstrated no difference in susceptibility to irritancy between men and women by evaluating the cutaneous effects of an anionic detergent, cationic detergent, soap, acid, alkali, and other common skin irritants [6]. Lack of gender difference was confirmed by Lammintausta et al., who examined transepidermal water loss (TEWL) and dielectric water content (DEWC) following sodium lauryl sulfate application [7]. Work by Reed et al. demonstrated that skin type, but neither race nor gender, influenced the epidermal permeability barrier function through tape stripping analysis [8]. Thus the increased reporting of adverse reactions to cosmetics and skin care products by females may simply reflects the greater number of products used by this population.

Further studies have investigated the effects of skin type and race on cutaneous sensitivity. Studies to determine differences have focused on barrier permeability, barrier recovery, epidermal lipid composition, dermal vasodilatation, TEWL, and stratum corneum thickness and cohesiveness. It appears that fair skin, especially skin type I (white skin that burns easily and never tans), is the most reactive to all types of irritancy, and black skin is the most resistant. There appears to be no difference in thickness of white and black skin; however, there are a greater number of cell layers in black skin, assessed by tape-stripping techniques, due to greater intercellular cohesion, thus furnishing superior protection. Additional protection may be afforded to black skin by

Table 34.6 Racial and Age-Related Cutaneous Differences

Evaluated parameter	White skin	Hispanic skin	Asian skin	Black skin	Aged skin
SC Thickness	7.2 Microns			6.5 Microns	Epidermis becomes more compact with age
SC Layers	17			22	
Tewl following SLS exposure		Higher than white following 2% SLS		Higher than white following preoccluded skin, 0.5% SLS	Lower in healthy aged skin
Tewl following tape stripping			Higher than white	Higher than white	
Corticosteroid penetration	Higher permeation than black			Lower permeation than white	
Vessel reactivity	Highest	Same as white skin		Less	No age-related difference
Stinging susceptibility	Greatest			Possibly less	Possibly less
Response to irritation	Erythema	Erythema and hyperpigmentation		Hyperpigmentation	Possibly less
Sweat glands	Fewer apocrine-eccrine glands			More apocrine-eccrine glands	
Ceramide levels	Intermediate	Intermediate high	Highest	Lowest	Decreased with age

increased epidermal lipids. Interestingly, tape-stripped white skin and black skin demonstrate an equal predisposition to irritancy.

Skin type differences in vasodilatation are somewhat ambiguous [9]. Application of methyl nicotinate followed by observing erythema and employing laser Doppler velocimetry yielded varying results depending on the assessment

technique [10]. It is believed, however, that black skin demonstrates a different vascular reactivity than fair skin when exposed to potent topical corticosteroids [11].

PRODUCT SAFETY AS A MANDATORY REQUIREMENT

The preceding discussions have pointed out the complexities of formulating cosmetics and skin care products given the tremendous variability in human response, yet product safety remains a mandatory requirement. Certainly, substances without an established safety profile should not be included in products without careful testing. Furthermore, cosmetic ingredients that may act as penetration enhancers should be carefully screened, since they can alter the safety profile of other ingredients. Ingredient combinations may become problematic even though the individual components have an established safety profile.

A number of phrases are currently used as marketing terms to engender consumer safety confidence, such as hypoallergenic, safe for sensitive skin, allergy tested, dermatologist tested, clinically tested, nonirritating, nonsensitizing, fragrance-free, preservative-free, all-natural, and so forth. These phrases must be regarded primarily as marketing claims, however, since no standard testing methodologies exist for claim substantiation [12]. One proposed approach for testing and evaluating skin products is presented in Table 34.7.

Safe formulations must avoid inducing both visible and invisible manifestations of skin disease. This means objective findings such as erythema, xerosis, edema, and vesiculation must be avoided along with subjective symptoms such as tightness, itching, stinging, and burning. Furthermore, the skin must not undergo physiologic changes such as dehydration, barrier damage, lipid alterations, decreased corneocyte adhesion, protein denaturation, stratum corneum

Table 34.7 Approach for Formulating Safe Skin Products

1. Review of ingredients to minimize known irritants and sensitizers
2. Elimination of unnecessary ingredients
3. Stability evaluation of ingredients as formulated
4. Utilization of in vitro methods to predict final formulation skin and eye irritation
5. Utilization of in vivo methods to predict final formulation skin irritation and sensitization, considering weather conditions and casual UV exposure
6. Utilization of sensitive skin panels to confirm results of in vitro and in vivo testing, considering weather conditions and casual UV exposure
7. Premarket monitored consumer large scale testing
8. Postmarket monitoring of consumer responses and adverse reaction reporting

swelling, removal or denaturation of water-soluble constituents, enzyme denaturation, or cytokine or mediator release. Safe skin products should meet the formulation criteria:

1. Common allergens and irritants must be eliminated from the formulation or, if this is nor possible, reduced in concentration.
2. High-quality, pure materials without contaminants should be selected. If it is impossible to eliminate highly allergenic contaminants, a suitable binding agent should be added.
3. Autooxidation products, which may be responsible for hypersensitivity reactions, should be prevented through the use of suitable antioxidants.
4. Volatile vehicles and substances producing cutaneous stimulation should be eliminated or reduced.
5. Solvents that promote skin penetration should be avoided.
6. Surfactants, used either for cleansing purposes or as emulsifiers, should be carefully selected.
7. Preservatives with a low sensitizing potential should be selected over those with a higher sensitizing potential.

It is the responsibility of the manufacturer and the cosmetic chemist to ensure that a cosmetic or skin care product is unlikely to cause irritant contact dermatitis, allergic contact dermatitis, contact urticaria, phototoxicity, or photoallergy. Certainly, this goal may be unachievable given the variation of human response, yet testing must be performed to document that the possibility of an adverse reaction is extremely small. Testing methodologies have been developed to aid in the detection of problematic formulations. This is the next topic of discussion.

SAFETY ASSESSMENT METHODS

Numerous methods have been developed to predict the safety of both individual ingredients and final formulations by assessing the potential activity of substances to induce irritation or sensitization in humans. Most predictive procedures are performed in vitro or an animals, although in some laboratories tests are made on humans. Predictive tests, properly made, have been very effective for many years in detecting substances or products likely to be harmful to humans, enabling the rejection of harmful products or the appropriate warning on the label if the product has weak activity for a particular tissue (e.g., the eyes). It should be understood that, despite all care in examination of products, such is the diversity of human susceptibility that a few people will show adverse reactions if sufficient numbers are exposed to the products. Nevertheless, predictive tests for safety in use have ensured that products are

harmless to the majority. The more common predictive safety tests are listed in Table 34.8.

IN VITRO TESTING

In vitro testing assumes paramount importance when developing products with irritant potential. The largest, most commonly used class of irritants are surfactants found in products to cleanse the skin, hair, and hand, as well as dishes, clothes, sinks, and so forth. Three common in vitro screening tests to evaluate the irritant potential of soaps are collagen swelling tests [13], pH rise test, and zein test. There are many more tests in this category, but these three have been chosen for discussion because they represent different methodologies of evaluating products [14].

The collagen swelling test employs a 1-cm^2 collagen sheet that is incubated for 24 hours at 50 °C with a solution of the finished cleanser product at 1% of

Table 34.8 Important Testing Methodologies for Product Safety and Performance

1. In Vitro Safety Testing
   a. Collagen swelling test
   b. pH rise test
   c. Zein test
2. Animal Safety Testing
   a. Draize test
   b. Eye irritancy
   c. Guinea pig maximization testing (GMPT)
3. Human Safety Testing
   a. Patch testing
   b. Modified soap chamber test
   c. Forearm controlled application technique (FCAT)
4. In Vitro Product Performance Testing
   a. Evaporimetry
   b. Polysulfide rubber replicas
   c. Squametry
   d. Chromametry
   e. Laser Doppler flowmetry
   f. A-scan ultrasound
5. In Vivo Product Performance Testing
   a. Lactic acid facial sting test
   b. Chloroform: methanol (20:80) test
   c. Dimethyl sulfoxide (DMSO) test
   d. Erythema following sodium lauryl sulfate occlusion test
   e. Nicotinate test

the dry extract at its own pH. The collagen is weighed before and after exposure to determine the amount of swelling, more swelling indicating increased product irritation. Another approach to irritation assessment is to examine pH rise by incubating equal volumes of a 2% solution of bovine serum albumin at a pH of 5.6 with a 2% solution of the finished product at room temperature for one hour. The pH of the solution is measured with greater pH rises indicating increased product irritation. The last method, or the zein test, uses a protein that is insoluble in aqueous solution until denatured by irritating surfactant products. The more protein that is solubilized, the more irritating the product.

ANIMAL TESTING PROCEDURES

After in vitro testing has been conducted to evaluate the safety of strong irritants, a variety of animal tests can be performed to obtain further safety information. Commonly used animal tests to be discussed include the Draize test, eye irritancy test, and guinea pig maximization test (GPMT).

Draize Test

The Draize test is an evaluation of dermal irritation using an animal model. Semiocclusive patch tests of the evaluation substance are placed at 100% concentration on both intact and abraded albino rabbit skin. Readings are performed at 24 and 72 hours after leaving the skin uncovered for 30 to 60 minutes to allow local effects to subside. The sites are evaluated for erythema and edema to determine the degree of irritancy on a numerical scale. This test is required by law for cosmetics and skin care products under the Federal Hazardous Substances Act to predict the toxicity of chemicals to humans in a manner that overestimates the risk [15].

The skin of the rabbit is more susceptible to irritation than that of humans, so that it is possible to identify any substance likely to have an effect on humans. However, the method of assessing results may lead to false-positives and rejection of materials harmless to humans. There are also laboratory variations in technique and recording results. It is preferable to compare the effect of the test substance with that of a similar substance known to be harmless to users, rather than to use the scoring system incorporated in the test procedure.

Eye Irritancy Test

The eye irritancy test, also developed by Draize, is important for cosmetics and skin care products, since accidental entry into the eye may occur. This test assesses the irritant effect of substances on the conjunctiva, cornea, and iris of Albino rabbits. This is similar to patch testing, but 0.10 ml of the test substance is instilled into the eye. In one group of rabbits the treated eyes are left unwashed; in the second group the treated eyes are washed with 20 ml of

lukewarm water after 2 seconds; and in the third group the eyes are washed with 20 ml of lukewarm water after 4 seconds. Evaluation of the eyes is performed at 24 hours, 48 hours, 72 hours, 4 days, and 7 days after treatment, or for as long as the injury persists [16].

Guinea Pig Maximization Test

The guinea pig maximization test (GPMT) is designed to assess the sensitizing potential of a particular ingredient, such as those found in cosmetics or skin care products. Freund's complete adjuvant, as an immune enhancer, is injected intradermally into the guinea pig followed by topical application of the ingredient under occlusion. The tests are read at 24 hours [17].

HUMAN TESTING PROCEDURES

Human testing is generally the third stage in ingredient or final formulation evaluation to ensure human safety. Human studies include patch testing, repeat insult patch testing (RIPT), cumulative irritancy testing, the chamber scarification test, the modified soap chamber test, and the forearm controlled application technique (FCAT), to name a few of the more popular methodologies.

Patch Test

Patch testing is the most popular dermatologic test to determine the allergenicity of a given substance or final formulation [18]. Table 34.9 lists the standard substances used for patch testing by the dermatologist. These substances have been selected because they cover the most common allergens found in topical preparations, industrial facilities, and articles worn on the body. Not all of these allergens are pertinent to the skin care industry. Generally, the appropriate substances for patch testing are selected from the patch test tray or individually formulated and applied to filter paper discs affixed to a strip of polyethylene-coated aluminum foil (A1-test) or placed in 8 mm aluminum chambers (Finn chambers) affixed to a nonwoven textile tape (Scanpor tape). A newer product provides a variety of preselected allergens in hydrophilic vehicles already applied to polyester patches (T.R.U.E. test, Glaxo). The healthy skin of the upper back is selected and marked for placement of the tape strips, which are worn for 48 hours. During this time, the subject should not get the patches wet or engage in activities that induce heavy sweating. The tests are initially evaluated at 20 minutes after removal and again at 2 to 7 days [19]. Excellent references are available regarding the preparation of customized patch test materials. [20,21]

There are two other methods of patch testing that are useful in patients with suspected cosmetics or skin care product sensitivities: open patch tests

Table 34.9 Substances on American Academy of Dermatology Standard Patch Test Tray

1. Benzocaine 5% petrolatum
2. Imidazolidinyl urea 2% aqueous
3. Thiram mix 1% petrolatum
4. Lanolin alcohol 30% petrolatum
5. Neomycin sulfate 20% petrolatum
6. P-phenylenediamine 1% petrolatum
7. Mercaptobenzothiazole 1% petrolatum
8. P-tert-butylphenol formaldehyde resin 1% in petrolatum
9. Formaldehyde 1% aqueous
10. Carba mix 3% petrolatum
11. Rosin (colophony) 20% petrolatum
12. Black rubber mix 0.6% petrolatum
13. Ethylenediamine dihydrochloride 1% petrolatum
14. Quaternium-15 2% petrolatum
15. Mercapto Mix 1% Petrolatum
16. Epoxy resin 1% petrolatum
17. Balsam of Peru 25% petrolatum
18. Poassium dichromate 0.25% petrolatum
19. Nickel sulfate 2.5% petrolatum
20. Cinnamic aldehyde 1% petrolatum

and provocative use tests. Open patch testing is useful when the test chemical is suspected of being a cutaneous irritant. The chemical is applied to the skin on the outer aspect of the arms above the elbow unoccluded twice daily for two or more days without washing the test site. False-negative results may occur with this method, however. Provocative use testing is valuable in confirming positive reactions to cosmetic products containing ingredients that were previously found to be sources of allergic contact dermatitis with standard patch testing. The product is applied twice daily to the skin 3 cm in diameter above or below the antecubital fossae for one week. A modification of this test for eye cosmetics is application to the skin lateral to the eye twice daily for one week. Care must be taken, however, not to induce a state of hyporeactivity [22].

Photopatch Test

Photopatch testing is performed when photosensitivity evaluation is required. Two patch tests are placed with the suspected chemical: one on a site to be irradiated and the other on a protected site. The patch tests are placed on the skin for 48 hours. One site is subjected to ultraviolet radiation of the wavelength desired and read in 24 and 48 hours. This process may be repeated if desired. A phototoxic reaction consists of erythema and usually arises within 6 hours.

A photoallergic reaction is characterized by erythema, papules, and vesicles. If only the irradiated site is positive, a diagnosis of photoallergy can be made. If both the irradiated site and the protected site are positive, a diagnosis of allergic contact dermatitis can be made. If the irradiated site is more positive than the protected site, a diagnosis of allergic contact dermatitis and photoallergy can be made. Substances that cause photoallergic dermatitis found in cosmetics are tested as follows: methylcoumarin 5% in petrolatum, musk ambrette 5% in petrolatum, and *p*-aminobenzoic acid esters 10% in petrolatum.

Repeat Insult Patch Tests (RIPT)

Repeat insult patch testing (RIPT) evaluates sensitization by repeating chemical exposure at the same site on the body. Ten patches are applied to the same site at 48-hour intervals for a three- to four-week period. The skin is allowed to rest for two weeks and then a repeat challenge of the same chemical to the skin is applied for 48 hours and read. This method is commonly used to evaluate ingredients and final products for minor sources of sensitization prior to large scale manufacturing.

Cumulative Irritancy Test

The cumulative irritancy test is designed to assess the irritancy of an ingredient or a final product. The test involves daily application of the same substance to the test site under occlusion for 21 days. The repeat application is designed to maximize irritant reactions.

Soap Chamber Test

The soap chamber test was devised because of the other evaluation methods previously described did not produce the irritation known to occur with certain soap, lotion, and cream products. The test is performed by applying small aluminum chambers containing the test product to the forearm of human volunteers with occlusive tape. The test product is applied daily to the same site and worn continuously for 24 hours. This procedure is repeated each weekday for one week with a rest period over the weekend. The materials are then reapplied on the following Monday for a few hours and the final readings are made in terms of erythema, scaling, and fissuring. This test is generally only used for cosmetics and skin care products or individual ingredients that may not have shown their true irritancy with other test methods.

Eye Irritancy Test

Human subjects are also used to assess the irritant capacity of products introduced into or around the eye. Cosmetics and skin care products should be tested in this manner to ensure human safety.

Noxious Sensory Stimuli Testing

A relatively new focus in human testing is the assessment of noxious sensory stimuli, which should not occur following application of cosmetics or skin care products. These stimuli can be assessed by assembling panels of subjects who demonstrated a heightened neurosensory input to sensations such as stinging, burning, itching, and vasodilatation. This discussion details sensory testing methodologies.

Stinging

Certain individuals experience stinging several minutes after application of cosmetics or skin care products, with intensification of symptoms over 5 to 10 minutes and resolution after 15 minutes. These subjects are known as "stingers" and will not tolerate certain cosmetic products even though patch testing for allergic contact dermatitis is negative and no evidence of irritant contact dermatitis is present. Subjects who are stingers can be identified by inducing sweating (110 °F and 80% relative humidity or exposure to a desktop facial sauna machine) and applying a 5% to 10% aqueous solution of lactic acid to the nasolabial fold [23]. Those who develop stinging lasting for at least 5 to 10 minutes are identified as "stingers."

The stinging experienced is rated by the subject at 2.5 and 5 minutes after application on an ordinal 4 point scale (0 = no stinging, 1 = 1 slight stinging, 2 = moderate stinging, 3 = severe stinging) with a cumulative stinging score (sum of the 2.5- and 5-minute evaluation) of 3 or higher classifying the subject as a "stinger," implying sensitive skin. Even though this test is quite artificial, it appears to correlate well with those individuals who experience heightened neurosensory input during actual cosmetic and skin care product use, but this remains controversial. These individuals can then be used as test panel subjects to evaluate the stinging capacity of cosmetic ingredients or finished products. Substances that can induce stinging are listed in Table 34.5.

Interestingly, there is seasonal variability in stinging scores assigned to sensitive skin subjects with more intense responses during the winter than the summer. This observation suggests that the increased cutaneous stinging noted must be due to the cumulative effect of a heightened neurosensory input combined with defective barrier function, possibly associated with the xerosis of winter. Furthermore, increased stinging is found in light-complected people of Celtic ancestry who sunburn easily and in people with a history of sensitivity to soaps, cosmetics, and drugs [24].

Vasodilatation. A different approach to identifying sensitive-skin subjects relies on vasodilatation of the skin, as opposed to cutaneous stinging, burning, or itching. Many investigators prefer this approach since objective changes can

be visually and biomechanically assessed. These two tests are the nicotinate test and erythema assessment following sodium lauryl sulfate exposure. In the first test, methyl nicotinate, a potent vasodilator, is applied to the upper third of the ventral forearm in concentrations varying between 1.4% and 13.7% for a period of 15 seconds. The vasodilatory effect is assessed by observing the erythema and employing laser Doppler velocimetry. Similar studies can be performed following application of various concentrations of sodium lauryl sulfate to the forearm. This method of skin analysis relies on the use of engineering equipment and principles to assess the skin, the next topic of discussion.

PRODUCT PERFORMANCE

One of the themes emerging from this discussion is the tremendous variability in human skin response to topical substances, considerably complicating cosmetics and skin care product development. This reality has resulted in development of variety of in vitro and in vivo testing protocols designed to assess product performance.

IN VITRO TECHNIQUES

Analysis of cosmetics and skin care products performance should reproducibly and accurately assess small cutaneous changes and preclinical disease without altering the underlying skin condition. This has led to great interest in the development of noninvasive mechanistic skin assessment. This section examines bioengineering methods of assessing cosmetic and skin care product performance based on profilometry, squametry, elasticity, impedance, evaporimetry, capacitance, thickness, colorimetry, blood flow, and sebum assessment [25].

Profilometry

Profilometry is a method of assessing changes in skin surface contour, such as wrinkling and scarring [26]. It involves analysis of silicon rubber replicas of the skin surface. These replicas service as negatives from which are cast plastic positives mirroring the three-dimensional topography of the skin in a selected area. For example, the upper cheek is typically used as the replica site for the assessment of decreased wrinkling following application of a moisturizing treatment cream. These plastic positive are evaluated with the aid of a computerized stylus or laser, producing a contour tracing of the skin surface. Dramatic two-or three-dimensional topograms can be created for the evaluation of fine lines and wrinkling of the skin. Unfortunately, this method can be

inaccurate, since application of silicone rubber to the skin decreases TEWL and skin wrinkling while flattening the desquamating skin scale.

Squametry

Another technique, known as squametry, is used to assess the amount of desquamating corneocytes. Squametry involves analysis of skin squames harvested by pressing a round sticky tape against the skin (D-Squame, Cu-Derm, Dallas, Texas). The outermost, loosely adherent skin scale is removed on the tape, which is attached to a black background. The tape provides a specimen that retains the topographical relationships of the skin surface and the pattern of desquamation. Image processing is then used to evaluate the scaliness of the skin [27]. This technique is valuable to document claims regarding skin scaliness.

Elasticity

The skin can be modeled and studied as an elastic material, investigating its ability to withstand forces of stress and strain. This is an indirect manner of assessing the moisturization of the skin, since well-moisturized skin is more elastic than dry skin. Reduced elastic properties are seen in aged skin. This technique uses a torsion machine, known as a Twistometer (L'Oreal, Paris, France), a Dermal Torque meter (Dia-Stron, Andover, Hampshire, U.K.), or a Cutometer (Courage-Khazaka Electronic GmbH, Cologne, Germany), to twist the skin. A computer is used to assess the ability of the skin to recover its original state, generating stress-strain curves. This noninvasive technique can substantiate claims of skin moisturization through improved elasticity [28]. Inaccurate data can be obtained, however, by repeated stretching of the skin, which increases extensibility unrelated to product application.

Impedance (Conductance)

The skin can be assessed in terms of its mechanical properties, such as elasticity, but it also can be evaluated for its electrical properties, such as impedance or conductance. The impedance of the skin is the total electric resistance of the skin to an alternating current. The noninvasive technique involves use of a dry electrode consisting of two concentric brass cylinders separated by a phenolic insulator operating at 3.5 Mhz (Skicon, IBS Ltd., Hamamatsu, Japan). The electrode is placed in contact with the skin. Impedance measurements have been found to directly correlate with skin hydration [29]. This technique can evaluate the efficacy and duration of the effect of moisturizers.

Capacitance

Another electrical skin property that can be analyzed is capacitance. This technique utilizes two metal plates electrically insulated by a medium that

acts as a dielectric, such as the skin. An electron excess, or negative charge, is built up on one plate and an electron depletion, or positive charge, on the other (Corneometer, Courage-Khazaka Electronic GmbH, Cologne, Germany) [30]. The capacity of the skin is reported to change as a function of its water content. This is another electrical noninvasive method of assessing skin moisturization.

Evaporimetry

Evaporimetry is a noninvasive technique assessing cutaneous TEWL, as opposed to skin water content. This computerized instrument employs a handpiece with two probes designed to measure changes in water vapor above the skin surface (Evaporimeter, ServoMed, Stockholm, Sweden). TEWL is increased in skin exhibiting a damaged stratum corneum barrier. Evaporimetry can be used to assess barrier dysfunction and recovery following ingredient or finished product application. It can also measure skin porosity, indirectly predicting the rate of loss of topically applied substances from the skin surface. This technique must be used under careful subject environmental control, since perspiration can make TEWL readings incorrect [31].

It is critical to recognize that noninvasive assessment data can be easily manipulated. For example, most moisturizers show a marked reduction in TEWL immediately following application, but this benefit may be lost within five minutes if the product is not carefully formulated. Useful assessments of moisturizer function should be performed after at least six hours have elapsed following product application. Furthermore, a product may demonstrate a 25% decrease in TEWL, but this may not translate into clinical efficacy.

Thickness

Sometimes it is interesting to evaluate the thickness of the skin without performing a biopsy procedure. This can be accomplished through the use of A-scan ultrasound [32]. Sound waves are transmitted through the skin and received with the aid of a transducer to provide a graphic picture of the skin. Different structures within the skin reflect and absorb sound waves to varying degrees, allowing separation of the epidermis, dermis, and subcutaneous tissues, depending on the type of transducer used.

Colorimetry

An assessment of skin color can be obtained through a technique known as colorimetry (Chromameter, Minolta, Osaka, Japan) [33]. This is a compact tristimulus color analyzer that measures color. It can be used to evaluate color changes in the skin, such as sunburn, erythema due to irritation, basic skin color, and the effect of pigmenting or depigmenting agents. This technique is useful for substantiating claims of improved skin color or decreased sallowness.

Blood Flow

Colorimetry can be influenced by the erythema present due to the underlying blood vessels. Vasodilatation can increase the red tones perceived by the computer, requiring a method of assessing blood flow. This can be accomplished with the aid of a laser Doppler flowmeter [34]. The laser sends light waves into the skin that bounce off red blood cells and are then received and processed by a computer. The Doppler shift is more dramatic when the red blood cells are moving rapidly, allowing calculation of a blood flow rate. Assessment of blood flow is valuable for determining the ability of a product to induce or reduce inflammation.

Sebum Assessment

It may be necessary to assess alterations in the amount of sebum on the face or to substantiate a claim regarding reduced sebum production. This can be done with a microporous, white adherent tape (Sebutape, CuDerm, Dallas, Texas) or a machine (Sebumeter, Courage and Khazaka, Cologne, Germany). The tape contains a hydrophobic film about 2.5 mm^2 that is pressed on the part of the body where a sebum measurement is desired. The site must be thoroughly cleaned prior to application to remove surface lipids, cell debris, or residual cosmetics. The sebum appears as transparent spots on the tape that are viewed against a black background. Image analysis is used to collect and compare data. This method provides data on the total sebum production, the number of active sebaceous follicles in an area, and the amount of sebum produced by each gland [35].

The sebumeter allows overall sebum assessment in a given area by using a handheld cartridge consisting of a measuring head covered with 0.1 mm thick, matte-finished, plastic strip to absorb lipid. The plastic strip becomes translucent as it absorbs lipid. The amount of light that is transmitted through the strip is then measured by a computer to indirectly determine the amount of sebum absorbed from the skin [36].

IN VIVO TECHNIQUES

Even though sophisticated noninvasive methods of cutaneous evaluation sound appealing, there is no substitute for the opinion of a trained unbiased observer for evaluation of cosmetic and skin care product effectiveness. Computers cannot accurately synthesize all the tactile and visual information that can be obtained through human evaluation. Furthermore, slight changes apparent with image processing techniques may not significantly alter clinical skin appearance. Thus noninvasive techniques are another tool for assessing product performance but should be used in combination with in vivo testing [37].

This section discusses methods used to clinically assess the performance of a cosmetic or skin care product in a human population utilizing a trained observer. Methods discussed include regression analysis, in vivo image analysis, in-use studies, and dermatologic assessment questionnaires.

Regression Analysis

Regression analysis, a method developed by A.M. Kligman, evaluates cosmetic and skin care product efficacy under clinical conditions. Subjects are selected and treated by an objective observer with the test products at a predetermined test site for two weeks. The test site is evaluated on days 7 and 14. If improvement is noted, product application is discontinued and the test site is evaluated daily for two weeks, or until the baseline pathology has reappeared [38]. This method is particularly valuable for efficacy assessment since product performance may be excellent immediately following application, but true effectiveness can only be assessed with the passage of time.

In Vivo Image Analysis

In vivo image analysis is accomplished by analyzing video or photographic images with the aid of a computer image processing system. This technique is used to evaluate skin surface features [39]. Care must be taken to standardize lighting and camera angles to ensure accurate data for analysis. Differing exposures can lead to erroneous image processing and faulty data. In vivo image analysis is only as good as the photographic image.

Clinical In-Use Studies

Clinical in-use studies are the final and most important step in evaluating product performance. Instrumental analysis, sensory testing, patch testing, irritancy testing, and so forth evaluate only one aspect of a cosmetic or skin care product. The consumer, however, evaluates all aspects of a product simultaneously to include the appearance, smell, feel, and efficacy. A successful product must create a favorable impression in the short period of time it takes for the brain to integrate the various pieces of information submitted by all of the senses.

Some individuals, however, have sensitive skin and experience adverse reactions that cannot be characterized by traditional analysis. For these individuals, the following dermatologist-controlled regimen is recommended [40].

1. Discontinue all topical cosmetics, over-the-counter treatment products, skin care items, cleansers, toiletries, and so forth. Allow the patient to use a syndet soap and a bland moisturizer for two weeks.
2. Discontinue all topical prescription medications for two weeks, especially those that contains benzoyl peroxide, tretinoin, glycolic acid, volatile alcohols, or other drying, irritating ingredients.

3. Eliminate all sources of skin friction by recommending loose, soft clothing and discontinuation of sports or other activities in which repetitive skin rubbing occurs for two weeks.
4. Evaluate the subject at two weeks to determine if any underlying dermatoses are present, such as seborrheic dermatitis, eczema, psoriasis, acne, rosacea, perioral dermatitis, and the like. If a dermatosis is present, treat as appropriate for at least two weeks beyond visible disease resolution to allow both clinical and histologic (subclinical) resolution.
5. Patch and photopatch test patient to elucidate any common sources of allergic contact dermatitis. Test for contact urticaria. Determine which positive reactions are clinically relevant to the subject's sensitive skin difficulties and advise the subject appropriately.
6. Perform the facial sting test on the subject by applying 10% lactic acid to the nasolabial fold or malar eminence.
7. Evaluate the subject's mental status, noting any signs of depression or other neuropsychiatric disease.
8. Allow the subject, if female, to add on facial cosmetic of low allergenic potential per week in the following order: lipstick, face powder, powder blush.
9. All other cosmetics that are more common sources of difficulty in sensitive-skin subjects should be individually provocative use–tested by applying them nightly, for at least five nights, to a 2 cm^2 area lateral to the eye. They should be tested in the following order: mascara, eyeliner, eyebrow pencil, eye shadow, facial foundation, any other colored facial cosmetics.
10. Over-the-counter treatment products and miscellaneous skin care products designed for leave-on use should be individually provocative use–tested by applying them nightly, for at least five nights, to a $2cm^2$ area lateral to the eye.
11. Skin care products designed to be rinsed off shortly after application should be individually use-tested nightly, for at least five nights, in the manner recommended by the manufacturer.
12. All data, both positive and negative, should be analyzed by the dermatologist and presented to the subject in the form of products or ingredients to avoid and those appropriate for continued use.

In-use testing is important in assessing product performance in both the general population and special need groups. The first step in performing a clinical in-use study is to design the experiment. What are the anticipated results? How should the study be controlled? How many subjects are needed to obtain the desired confidence in the results? A study should always be designed to compare the performance of the product under study with that of another product, either the market leader, a previous formulation, or a bland vehicle. One product must serve as the "placebo" to represent baseline. This provides data for comparison to determine whether the formulation under evaluation was better or worse than a preexisting product.

Next it is important to eliminate observer and subject bias. The observer may have a preconceived notion of which product is better, and the subject may be easily influenced by attributes, such as packaging and color, that may not correlate with product efficacy. The test product and the placebo should be identical in smell, feel, packaging, appearance, and so forth to the greatest degree possible. It is wise to blind the observer to the identity of the products, which is a single-blind study. In more critical studies, known as double-blind studies, both the observer and the subject are blinded. Eliminating bias to the greatest degree possible increases the reliability of the data and the reproducibility of the study.

The number of subjects required to generate data of a given confidence level, known as the power of the study, must be determined with the aid of a mathematical calculation that is beyond the scope of this chapter [41]. Some general rules of thumb are worth mentioning, however. Generally, at least 20 data points are required to generate statistically significant data when studying biologic systems. Forty data points are required when the data are not clustered. Two hundred data points are required when looking for data that are representative of the population as a whole. There is no doubt that more data points yield better, more reliable data.

Sometimes it is possible to reduce the number of subjects required in a given study by allowing each subject to function as his or her own control. For example, the study product is applied to the right side of the body, whereas the placebo product is applied to the left side of the body. These split body trials require an educated subject to properly apply the product and randomization of left vs. right application to blind both the observer and the subject. Split body trails are somewhat controversial. Some researchers argue that the products tend to be cross-contaminated, making all data from such studies subject to question. Others argue that human variability is such that only split body studies guarantee an ideal control. Whether split body studies are suitable depends on the product under study. As a rule, split body studies are well suited for the evaluation of nondrug cosmetic and skin care products.

Clinical in-use studies are only as good as the selection and compliance of the subjects. Many study centers maintain lists of professional study participants who are skilled in properly carrying out study responsibilities. While these subjects may be extraordinarily compliant, they do not represent the population as a whole. Individuals with sensitive skin and multiple allergies are certain not to be frequent study participants. Professional subjects generally have skin of low reactivity and no prior history of dermatologic disease. It is for this reason that many products that have demonstrated a lack of irritancy on well-performed repeat insult patch testing (RIPT), encounter problems when marketed to the general population.

Finally, the investigator must be skilled in evaluating the subjects' symptoms and findings. A well-trained investigative dermatologist can greatly improve the study results. The dermatologist not only can evaluate the skin of the subjects entering the study but also can identify and treat any side effects.

Dermatologic Assessment Questionnaires

The dermatologic assessment questionnaire is key to collecting accurate data. It is also key to capturing information regarding all aspects of the study and illuminating possible adverse effects. The questionnaire can be designed to assess multiple aspects of efficacy and to provide guidance for product reformulation, thereby leading to improved performance.

The type of questionnaire developed depends on the study. For example, a study designed to evaluate the aesthetics of two different hand creams, one applied to the left hand and one applied to the right hand, is presented in Table 34.10. Here the subjects must choose a preference, which provides clean data for analysis but does not capture subtle differences. Table 34.11 is a second subject questionnaire designed to assess the efficacy of a skin treatment/barrier cream, where the active product was used on one side of the body and a bland moisturizer was used on the other side. Here an ordinal scale of 0 to 3 is used to allow subjects to quantify their responses. The corresponding questionnaire to be completed by the dermatologist investigator (Table 34.12) also uses an ordinal scale. This provides data that can easily be statistically analyzed for significance.

It is important to be consistent during objective evaluation of changes in the skin during a study. This is best accomplished by selecting one blinded dermatologist to do all the patient examination and rating. The same questionnaires should be used for assessment throughout the study to increase the consistency of subject responses.

Table 34.10 Sample Aesthetic Assessment Questionnaire

Aesthetic Attribute	Right Hand Product	Left Hand Product
Less greasy		
Better thickness for application ease		
Less sticky		
Easier to rub into the skin		
Better fragrance		
Better overall application		
Better absorption		
Better overall product appearance		
Better skin feel		
Better overall aesthetic appeal		

Table 34.11 Sample Subject Assessment Questionnaire

Criteria	Right Side	Left Side
Pain		
Roughness		
Irritation		
Redness		
Open wounds		
Skin sensitivity		
Damage		
Skin dryness		

Ordinal rating scale:
0 = none
1 = mild
2 = moderate
3 = severe

Table 34.12 Sample Investigator Dermatologic Questionnaire

Criteria	Right Side	Left Side
Erythema		
Desquamation		
Barrier disruption		
Serum crusting		
Wound inflammation		
Wounding		
Skin sensitivity		
Skin roughness		

Ordinal rating scale:
0 = none
1 = mild
2 = moderate
3 = severe

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PART FIVE

Production

The final pages of this revision are devoted to the important steps required to ensure that newly developed products can be manufactured and marketed efficiently. Readers are reminded that problems of packaging are commonly the result of choices made by marketing personnel and are rarely controlled by development personnel. On the other hand, formulators should always make sure that stability issues are addressed during and after product development.

CHAPTER 35

The Manufacture of Cosmetics

INTRODUCTION

The successful commercialization of all new cosmetic products is vitally important in delivering the intended benefits to the consumer and in helping the company to improve its business. This objective is best achieved when the formulator is knowledgeable of scale-up techniques and the use of both pilot and production equipment. Armed with this knowledge, the formulator can best simulate the plant process and plan bench work effectively to ease the scale-up process and help ensure a smooth transition from bench to full production.

This chapter begins by providing a brief understanding of the more important unit operations, namely, mixing, heat transfer, and mass transfer. This is followed by a treatment of equipment, procedures, and principles commonly used in the cosmetics industry to manufacture and fill both wet and dry products. This background, combined with time spent in both the pilot plant and the manufacturing plant, will equip the formulator to carry out successful new product introductions. The sections on scale-up of both wet and dry products are particularly important as the product quality and stability may be adversely affected as the process progresses from bench to production. For this reason it is recommended that the formulator plan the use of bench equipment and procedures carefully with pilot and full-scale limitations in mind.

UNIT OPERATIONS

When studying scale-up operations, wherever they originate and no matter how complex, one considers a limited number of physical phenomena. These are separated into discrete yet interdependent events called "unit operations." The manufacture of cosmetics can be described in terms of four operations:

fluid flow/mixing, heat transfer, mass transfer, and filtration. All phases of manufacture involve aspects of each.

Fluid flow attempts to define operations involving movement of fluids and solids exhibiting fluid-like behavior. Mixing and agitation, pumping, and metering of liquids are typical operations studied in fluid flow.

Heat transfer involves the movement of thermal energy in a gradient from areas of higher temperature to areas of lower temperature. Heating and cooling of cosmetic bulk by conduction, convection, and radiation are studied.

Mass transfer operations define phenomena that involve movement of components of a mixture in a concentration gradient from areas where the concentration of a component is high to areas where it is lower. Cosmetic processes can make use of mass transfer by absorption (e.g., addition of binder to a cosmetic powder) and diffusion (e.g., migration of an active ingredient). The formation of an emulsion itself can be described in terms of mass transfer.

Filtration is not usually a unit operation of major importance in cosmetics manufacture except in the production of spirituous preparations (astringents/toners, colognes, aftershaves, and perfumes). It is possible to regard filtering as unmixing, and certainly the flow characteristics of the filtered product are again of prime importance. Filtration is usually included in the process to ensure clarity. The use of submicron filters for the sterilization of water is discussed elsewhere in this book.

Each of these four unit operations involves mathematical treatments that are inappropriate for this book and not pertinent to our practical use of the operations. Their theoretical treatment can be found in any chemical engineering textbook, such as *Unit Operations of Chemical Engineering* by McCabe and Smith. Mixing and heat transfer are the most critical operations and will be discussed in some detail [1].

MIXING

The subject of bulk cosmetics manufacture evolves around satisfactory mixing. There are several types of mixing employed, as indicated in Table 35.1.

Table 35.1 represents a convenient way of classifying the mixing processes most commonly found within the cosmetics industry. Almost every cosmetics manufacturing process includes at least one mixing operation, and often more than one type is involved. For example, the manufacture of a pigmented emulsion-based foundation cream may include:

(i) Preliminary dry blending of pigments and excipient (type 4b-i)
(ii) Dissolution of oil-soluble and water-soluble materials separately in their appropriate phase (type 3a-i and type 2Aa-ii)
(iii) Dispersion or suspension of pigments in the oil or water phase (type 3a-ii)

Table 35.1 Scope of Mixing Operations Within the Cosmetics Industry

Type of Mixing	Examples
Cohesive mixing—natural or forced combining of particles during blending Segregative mixing—natural or forced separation of particles during blending Distributive mixing—controlled or uniform diffusion of particles during blending	
1. Gas/Liquid	
(a) Cohesive	(i) Dispersion (aeration and gasification)
(b) Segregative	(i) Deaeration or degassing
2. Liquid/Liquid	
(A) Miscible	
(a) Cohesive	(i) Chemical reactions (formation of salts from acid and base)
	(ii) Blending (spirituous preparations, clear lip gloss products)
	(iii) Pumping (low-viscosity system)
(b) Distributive	(i) Blending (flow controlled)
	(ii) pH control or soap formation from fatty acid and base
	(iii) Pumping (high-viscosity system)
(B) Immiscible	
(a) Cohesive	(i) Emulsion formation (dispersion—addition rate is not critical)
(b) Distributive	(i) Emulsion formation (dispersion—addition rate is critical)
(c) Segregative	(i) Coalescing/settling (phase separation)
3. Solid/Liquid and Liquid/Solid	
(a) Cohesive	(i) Dissolution (of water-soluble dyes, preservatives, powder surfactants, etc.)
	(ii) Suspensions and dispersions (mascara, pigments in castor oil and in other liquids)
	(iii) Hot pour products (lipsticks, etc.)
(b) Distributive	(i) Controlled addition of liquid binders or actives to powders
(c) Segregative	(i) Filtration, sedimentation, decantation
4. Solid/Solid	
(a) Segregative	(i) Free-flowing powders discharged from hoppers, etc.
(b) Cohesive	(i) Face powders, eye shadows, and all dry mixing

(iv) Mixing of the two phases to form an emulsion, possibly with the formation in situ of soap as part of the emulsifier (type 2Ba and 2Bb)
(v) Adjustment of pH (type 2Ab-ii)
(vi) Deaeration of the bulk (type 1b-i)
(vii) Shade matching (type 3a-i or -ii and iii)
(viii) Pumping into a storage vessel (type 2Ab-iii)

Not only are all these operations different from each other, but also at each stage the characteristics of the bulk are quite different and require a different set of processing characteristics to achieve an optimal economic process. Not surprisingly, the optimum is rarely achieved throughout the process.

The subject of pumping is not clearly separated from that of mixing since the pumping process implies the forced flow of product. Any flow will naturally introduce an element of mixing if the product is not already homogeneous. Furthermore, since flow is a common element of both processes, the same product characteristics (e.g., rheological behavior) must be taken into account in each process. Different types of pumps provide different quantities of shear to the product and thus provide different degrees of mixing. The "standard" in the industry is the positive displacement pump, which imparts little shear and thus little mixing to the product. The centrifugal pump works similarly to a propeller mixer in a frame. This pump can impart a great deal of shear and produce vigorous mixing. It is typically used with lower viscosity materials.

QUALITY OF MIXING

Mixing can only occur by relative movement between the particles of the constituent components. Three basic mechanisms for achieving this relative movement are bulk flow, convective mixing, and diffusive mixing. Bulk flow (which includes shear mixing, cutting, folding, and tumbling) occurs in pastes and solids when relatively large volumes of mixture are first separated and then redistributed to another part of the mixing vessel. Convective mixing involves the establishment of circulation patterns within the mixture (e.g., propeller mixing). Finally, diffusive mixing occurs by particle collisions (e.g., thermal diffusion and concentration diffusion). In miscible liquids of sufficiently low viscosity, the thermal energy of the constituent molecules may be enough to achieve good mixing by thermal diffusion without additional energy.

It is incorrect to assume that the relative movement between mixture particles brought about by these mechanisms always results in an improved mixture quality. Many mixing problems arise from the tendency of mixture particles to segregate or aggregate during attempts to mix them, particularly with powders.

Segregation is defined as the preference of the particles of one component to be located nonrandomly in one or more sites in a mixture. The size of the nonuniformities in an imperfect mixture is sometimes referred to as the "scale of segregation," and the difference in composition between neighboring volumes is the "intensity of segregation." Segregation is fortunately not a major problem in cosmetics manufacture although it does manifest itself occasionally (e.g., the flotation of pigments during lipstick processing).

Aggregation is defined as the preference for the particles of one component to join with another component or components and then travel through the batch as a group. The aggregation can be physical (mixing of different viscosity materials) or physical bonding (powder agglomerations). To best control the distribution of some raw materials, aggregation may be required; cohesive powders may be included in the formula, or the process may be used to develop an aggregation that is easily controlled.

MIXING RHEOLOGY

Apart from the "dry" powder processing discussed later, the processes listed in Table 35.1 involve mostly liquids present in sufficiently large quantities as to impose fluid characteristics on the mixture. Although there are similarities between the flow of powders and the flow of liquids, it is easier to set up and sustain flow patterns in the latter. This makes liquid mixing processes easier to perform with a much larger variety of equipment to choose from. However, even for liquids the science of mixing has not yet been sufficiently developed to enable the optimum mixer to be designed for a given process from purely theoretical calculations. Much of the knowledge we have is empirical and has been accumulated from trial and error practical experience. Application of computational fluid dynamics (CFD), a method of mathematically modeling moving systems, promises to enhance the theoretical understanding of how forces are transmitted through a fluid by a given mixer design. The use of tomography provides actual measurements that can be used to verify CFD results and designs.

By definition, fluid mixing occurs when an applied force (e.g., a moving mixer blade) creates a velocity gradient, also known as the rate of shear, in the fluid. The "layers" or "particles" that make up the fluid are moving at different velocities relative to each other while the mixing blade is exerting the force. On the other hand, agitation occurs when the fluid particles and blade are moving at the same velocity, much like droplets of cream swirling around in a cup of coffee. In the coffee and cream example, mixing does not occur until blade speed is increased sufficiently to create a velocity gradient that breaks up the cream droplets into a fine dispersion that we know as "café-au-lait."

There is not only a great variation in the physical form and properties of substances that the cosmetics industry needs to mix but also a divergence of purpose. As indicated by Table 35.1, it is convenient to consider separately the case in which the liquid components are all mutually soluble (miscible liquids) and the case in which some or all of them can coexist as separate phases (immiscible liquids, at best partly soluble in each other). Some mixing operations involve simple blending of miscible ingredients, for example, the

blending of color solutions into miscible liquids and the blending of oils, alcohol, and water in perfumes and colognes. Mixing of miscible liquids represents the simplest mixing operation in cosmetics manufacture and is achieved by developing bulk flow throughout the vessel. On the other hand, the formation of an emulsion from two immiscible phases, the suspending of a gelling agent, and the distribution of pigment agglomerates in a viscous liquid all require hydraulic shearing to break up the constituents of the mixture into finer particles during the mixing process. For this reason, it is referred to as high-shear mixing to distinguish it from simple blending.

On the industrial scale, mixing occurs as the result of forced bulk flow within the mixing vessel. Two types of flow can be distinguished—laminar and turbulent. Laminar flow occurs when the fluid particles move along streamlines parallel to the direction of flow. The only mode of mass transfer is by molecular diffusion between adjacent layers of fluid (Brownian motion). Heat transfer is accomplished by the same type of mechanism—conduction from layer to layer. In turbulent flow, the fluid elements move not only in parallel paths but also along erratic and random paths, thus producing eddies that transfer mass from one layer to another. For this reason, turbulent mixing is rapid compared with other mixing mechanisms. Heat transfer is also influenced by forced convection—moving heat from higher to lower temperature areas along eddies created by turbulent mixing.

When a liquid at rest is slowly stirred the flow is laminar, but as the liquid's velocity increases flow will eventually become turbulent. A valuable aid in describing the critical point at which laminar flow becomes turbulent is credited to Osborne Reynolds, who in 1883 first characterized turbulence. The dimensionless number that bears his name, N_{Re}, can be calculated for an impeller mixing in a tank as follows:

$$N_{Re} = \frac{CD^2N\rho}{\eta} \tag{35.1}$$

Where N_{Re} = Reynolds number in dimensionless units
D = Diameter of the impeller in centimeters
N = Impeller speed in revolutions per minute
ρ = Density of liquid in grams per cubic centimeter
η = Viscosity of liquid in centipoise
C = Conversion constant of 1.67×10^{-4}

Experience has shown that the onset of turbulence occurs at Reynolds numbers above 2,000. For fully developed turbulence, Reynolds numbers greater than 10,000 are required and are found in many cosmetic mixing processes. As shown in Equation 35.1, it becomes more difficult to achieve turbulence as the viscosity

(η) increases. Between 1,000 and 10,000 centipoise, the viscosity range of many cosmetic products, turbulent flow can be achieved without the need for an excessive amount of power. For highly viscous creams and pastes, mixing raises certain problems since the flow pattern in the mixer is invariably laminar. Under these circumstances, distributive mixing (cutting and folding) is more applicable than turbulent mixing. Turbulence not only provides rapid mixing but also influences dispersion (mass transfer) and heating/cooling (heat transfer).

As can be seen by examining flow through a pipe (Fig. 35.2), there is a velocity gradient between the layers of moving liquid. A similar gradient can be found with the movement of all materials. When Newtonian (or ideal) liquids flow, the relationship between the force causing the movement (F) and the velocity gradient (η) between the layers of moving liquid is shown in Figure 35.3.

F/A is commonly referred to as the "shear stress" and the velocity gradient (v) as the "rate of shear." Assuming an ideal fluid, as velocity of flow increases, so does shear stress. This is the force that breaks up the weak bonds holding together pigment aggregates or other immiscible phases into droplets. Shear forces are also produced when liquids flow under laminar conditions, but under these circumstances the energy used to generate flow is dissipated largely as heat. During turbulent flow, the energy is dissipated in disorder; eddies are produced whose size and intensity depend on the viscosity of the liquid and on the force F. For a liquid of a given viscosity, the droplet size of an emulsion or the fragmented size of dispersed pigment agglomerates depends primarily

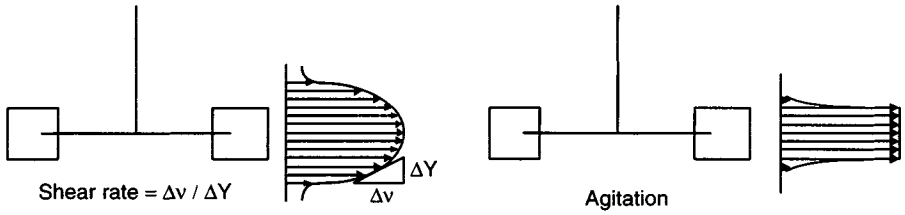


Figure 35.1. Shear rate and agitation profiles [2]

Figure 35.2. Velocity gradient of flow through a pipe

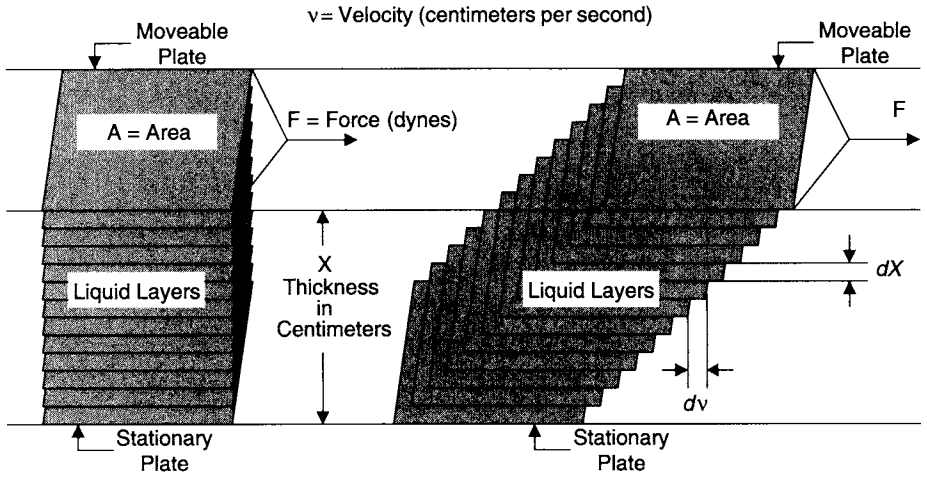


Figure 35.3. Newtonian flow [3]

on the energy input from the agitator, the velocity gradient, and the nature of the forces holding together the disintegrating entities. Unfortunately, the simple model shown in Equation 35.2 has limited application in cosmetics manufacture.

$$F = \eta \times A \times v \tag{35.2}$$

Where F = Force in gram-centimeters per second squared
η = Coefficient of viscosity of liquid in gram per centimeter-second squared
A = Cross-sectional area of the liquid in square centimeters
v = Velocity gradient in centimeters per second

The majority of products exhibit nonideal (non-Newtonian) behavior, which can often be more appropriately described by Equation 35.3.

$$F = (\eta_{app})^n \times A \times \mu \tag{35.3}$$

Where: F = Force in gram-centimeters per second squared
η_{app} = Apparent viscosity of liquid in gram per centimeter-second squared
n = exponent
A = Cross-sectional area of the liquid in square centimeters
μ = Velocity gradient in centimeters per second

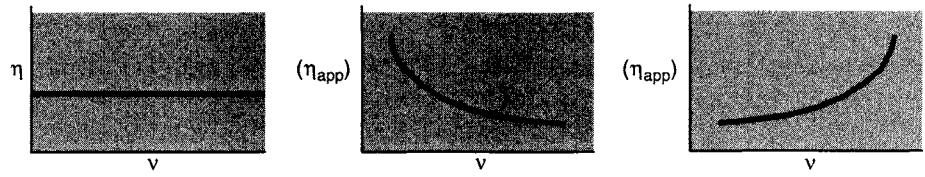


Figure 35.4. Rate of shear (μ) plotted against viscosity (η) or apparent viscosity (η_{app})

In the case where the exponent, n, has a value between zero and one, the type of behavior is "pseudoplastic." The basic difference between materials exhibiting this property and ideal or "Newtonian" fluids is illustrated in Figure 35.4(b). As can be seen, pseudoplasticity is manifested by a fall in viscosity with increasing shear rate at constant temperature. Many cosmetic liquids exhibit this behavior, especially emulsions and suspensions of particles 1 μm or less in size. Pseudoplastic viscosity loss is usually reversible to some extent; thus when left unstirred long enough, the fluid will recover some or most of its original viscosity. The magnitude of the pseudoplastic effect is variable with the identity of the fluid, although a fall in viscosity of 25% when the rate of shear is doubled is not unusual.

Three other types of rheological behavior are also worth noting, although they are less frequently encountered in cosmetics processing. A truly "plastic" fluid exhibits viscosity versus shear rate curves similar to those of pseudoplastic materials, but a certain force must be applied before any shear (or flow) takes place. "Dilatant" materials show the opposite effect, viscosity increasing with shear rate, Figure 35.4(c). The term "thixotropic" is often used erroneously to describe pseudoplastic behavior. Thixotropic liquids exhibit a fall of viscosity with time at constant shear rate, not with increasing shear rate as Figure 35.4(b) shows for a pseudoplastic material. However, like the pseudoplastic material, the thixotropic liquid recovers most of its original viscosity after the mixing force is removed.

In the mixing of fluids, all three mixing mechanisms—bulk flow, turbulent diffusion, and molecular diffusion—are usually present. As viscosity increases, however, and turbulence becomes more difficult to establish, the parts played by turbulent and molecular diffusion become less important. Mixing equipment can be divided into two categories, depending on whether turbulent conditions prevail, as shown in Table 35.2.

Control of mixing parameters and of the rheological characteristics of the bulk allows the manufacture of products with optimum homogeneity and stability.

Table 35.2 Types of Mixing Equipment

Laminar shear/distributive mixers	Turbulent mixers
Helical screw/ribbon blenders	Turbine-agitated vessels
Two-blade mixers	Pipes
Kneaders	Jet mixers
Extrusion devices	Sparged systems
Calenders	High-speed shear mixers
Static mixers: low N_{Re}	Static mixers: high N_{Re}
Contrarotational and planetary side-wiping blades at low speed	Contrarotational and planetary side-wiping blades at high speed

Heat and mass transfer are functions of the mixing process. The same mixing parameters that achieve ingredient homogeneity also influence heat and mass transfer. Good heat transfer, as well as good mass transfer, are consequences of good mixing.

HEAT TRANSFER

The topic of heat transfer in cosmetic operations does not require mathematical treatment as much as methodologies for its use and control in processing and scale-up. Heat can be used to one's advantage in a formulation. One must be aware of the fact that what can be done on the laboratory bench may not be achievable in production. The process team must be aware of the capabilities of available production-sized kettles and of the amount of heating and cooling capacity available to them.

The manufacture of most cosmetic creams and lotions involves the formation of an emulsion in which an oil and/or wax phase is combined with a water phase. As noted in Chapter 10, this combination is made most often at higher temperatures. The even distribution of temperature is of major importance in the formation of a good emulsion. Control of the rates of heating and cooling is required in order to scale properly from bench to production and if the formulation is to be reproducible from batch to batch.

The relationship of heat and mass transfer to mixing is similar and can be treated as analogous phenomena. The degree of heat transfer depends on a relative temperature difference (temperature gradient), which provides the driving force toward equilibrium. Equilibrium means that the temperature difference between transfer medium and product is zero. In reality, the maintenance of a gradient is required to meet the desired end point in heating or cooling the product, namely, the "set point temperature." At this temperature we want to stop the heating or cooling process, and this is done by making the gradient zero.

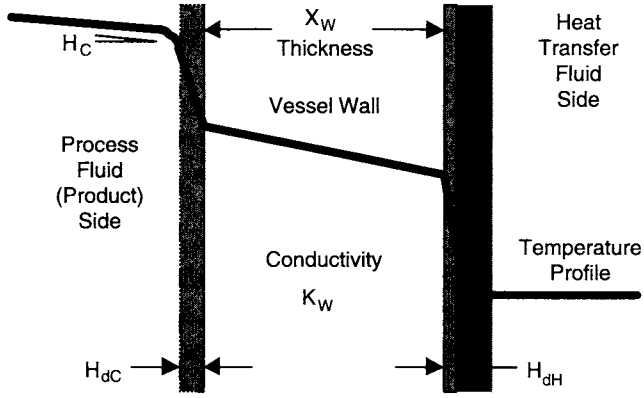
The mathematical relationship between heat transferred (Q) and temperature gradient ((T_{LM}) is expressed below.

$$Q = U_o A_o \Delta T_{LM} \tag{35.4}$$

Where: Q = Heat transfer in watts
U_o = Overall heat transfer coefficient in watts per square meter °C
A_o = Heat transfer area in square meters
ΔT_{LM} = Log mean temperature gradient between the product and the heat transfer fluid (difference) in °C

ΔT_{LM} takes into account the multiple heat transfer losses in the process system. The amount of heat transferred is directly proportional to the size of the temperature gradient, the contact area between heat transfer surfaces, and the magnitude of the heat transfer coefficient.

U_o is composed of a number of factors and is expressed as follows:



$$\frac{1}{U_o} = \frac{1}{H_C} + \frac{1}{H_{dC}} + \frac{X_W}{K_W} + \frac{1}{H_{dH}} + \frac{1}{H_H} \tag{35.5}$$

Where: U_o = Overall heat transfer coefficient in watts per square meter °C
H_c = Individual heat transfer coefficient between the process fluid (the product) and surface—based on the area and Δt (temperature gradient) between the surface and the fluid—in watts per square meter °C
H_{dC} = Individual heat transfer coefficient between the process fluid and surface—when that surface is fouled—in watts per square meter °C
X_w = Thickness of vessel wall in meters

K_w = Thermal conductivity of vessel wall in watts per meter °C
H_{dH} = Individual heat transfer coefficient between the heat transfer fluid (steam or cold water) and surface—when that surface is fouled by scale—in watts per square meter °C
H_H = Individual heat transfer coefficient between the heat transfer fluid (steam or cold water) and surface—based on the area and δt (temperature gradient) between the surface and the fluid—in watts per square meter °C

As the individual heat transfer coefficients increase, the overall heat transfer coefficient (U_o) increases. Fouling of either surface acts to decrease U_o. The fouling that occurs on the heat transfer fluid side of the vessel is usually caused by boiler steam scale or scale from untreated cooling water. This can be corrected by regular cleaning of the vessel jacket and by use of water additives to minimize scaling.

The fouling that occurs on the process fluid side of the vessel is caused by buildup of the product due to its own viscosity and lack of turbulence (mixing), which makes this "boundary layer" thicker, preventing good heat transfer. The factors H_{dH} and H_{dC} are referred to as "film coefficients." The thin layer of fluid that is in immediate contact with the surface of the vessel, both on the process side and on the heat transfer fluid side, represents the "film," which is essentially at rest. The film coefficient is a measure of the thermal conductivity through this resting fluid.

The importance of mixing as a unit operation is clearly demonstrated by its effect on the product film coefficient, H_{dC}. Higher mixing decreases the thickness of this film layer and permits more rapid heat transfer between the surface of the vessel and the bulk product. During heating, the film can be lower in viscosity than the product, which will improve heat transmission. It is during cooling that the product is subject to a significant decrease in heat transmission due to the increase in viscosity at the cool surface of the vessel. The mixing speed may need to be increased in order to produce the turbulence necessary to make the film thinner so that the bulk can be cooled at a satisfactory rate. The increased shear may be detrimental to the product, which may force a trade-off between cooling rate and shear rate. A side-wiping agitator can remove this film and replace the cold bulk with warm fresh bulk to be cooled. The removal of the cold layer is of prime importance in providing the proper shear in mixing and the specified cooling rate. The relationship between mixing and heat transfer is important information needed for scale-up.

The mass transfer coefficient has a mathematical form similar to the heat transfer coefficient. Its units are in kilogram moles per square meter second in

the MKS system. Qualitatively it is a measure of how much mass is transferred per unit of available surface per second. The heat transfer coefficient is a measure of how much heat is transferred per unit of available surface per second. The driving force for heat transfer is the temperature gradient, ΔT. The driving force for mass transfer is δC, the concentration gradient. Mixing both influences in the same way. The formulation team must consider both when developing and scaling a process.

TYPES OF REACTORS AND THEIR USE IN COSMETICS

The most frequently used "reactor" in the cosmetics industry is the continuous stirred tank reactor (CSTR). This is typically a jacketed stainless steel vessel with agitation provided by propeller blade, anchor blade, side-wipe, homogenizer, or any combination of these. This type of reactor is used in batch processing. Jacketing the vessel allows a heat transfer medium (cooling water, glycol, steam, hot water, etc.) to circulate. Heat transfer is accomplished by conduction from the inner surface of the vessel, which is heated or cooled by the medium, to the batch. Mixing the batch in the vessel increases the efficiency of heat transfer by forced convection. In batch processing, all raw materials are added to the vessel in a specified order, and the reaction mixture should be homogeneous after each operation. Ideally, each incremental sample of the batch, from any location, should be the same as others. Proper mixing will ensure homogeneity of the batch (mass transfer) as well as efficient heating or cooling.

In semicontinuous or continuous processes, it is more common to use a "plug flow reactor," which is also called a pipeline reactor. Unlike the CSTR, the contents of the pipe are not homogeneous throughout the length. Each incremental cross-section of the pipe is different in concentration (contents), and in temperature, from all others. Heat transfer in this type of process is attained by use of a jacket around the pipe similar to the CSTR. Increments of the pipe are heated or cooled as required by the process. As each increment, or plug, moves along the pipe it is subjected to a different set of concentration and temperature conditions. Each increment is homogeneous within itself but is different from all others along the pipe.

Batch reactors are suitable for use in small-scale operations using expensive raw materials. This is more typical of the cosmetics industry where quality control is performed on a discrete batch-to-batch basis. When deviations occur, they occur in a particular batch and can be easily isolated. Continuous processes lend themselves to large-scale operations. When deviations occur, they can be harder to isolate and correct due to the overall variations along the reactor. Both systems require instrumentation to record and control

process parameters. The batch process parameters to measure and control are heat/cool rate and times, mixing speeds and times, and degree of vacuum (if a vacuum kettle is used). Plug-flow reactor parameters to measure are rates of addition (to measure and control concentrations at any point in the pipe), temperature at each critical point in the reactor, mixing speeds (if dynamic pipeline mixing is used), pH, viscosity, conductivity (for complex emulsion systems), pressure/vacuum, and overall rate/product formation. The plug flow reactor makes up for its advantages by requiring precise measurement and control devices, as well as alarms to alert operators to process variations. The choice of the particular reactor type depends on quantity of product to be made, complexity of formulation, sensitivity to reaction parameters of heat and mass transfer, fluid flow, and regulatory issues (e.g., over-the-counter, or OTC, drugs versus nondrug product).

EMULSION PROCESSING EQUIPMENT—HEAT TRANSFER

The most common heat transfer method used in the cosmetic industry is jacketing of a vessel/pipe. The jacket may be used for either heating or cooling with steam, water, or other heat transfer medium (specially designed oils and glycols). Most liquid products can be made using this type of cooling regardless of viscosity. Because of the necessity to mix the batch uniformly, excess mixing may occur during long cooling cycles, which can cause viscosity and stability variations.

It is important in scale-up to keep the overall heating and cooling rates the same through the changes in batch size. In heating, manufacturing will typically use steam. It is not recommended that the steam pressure on the kettle be higher than 15 psig (pounds per square inch gauge, or 1 bar). Saturated steam at a pressure of 15 psig creates a jacket and kettle wall temperature of 250 °F (121 °C). Pressures greater than 15 psig give higher temperatures that could cause degradation of ingredients on the walls of the kettle (particularly oxidation at the liquid-air interface). Other than the issue of burning material—cooling is typically a more critical process than heating. This is particularly true of emulsion products or products containing waxes. If this type of product is cooled in the laboratory in 20 minutes but requires a cooling time of 120 minutes in manufacturing, the resultant batches will not be identical. The microstructure of the emulsion or waxes could be totally different, affecting viscosity, feel, absorption, appearance, and stability.

To overcome this problem, colder cooling media will be used in manufacturing than in the laboratory. The problem caused by this solution is that the product will be exposed to a much colder temperature at the wall of the kettle. This can result in premature solidification of waxes. To determine whether

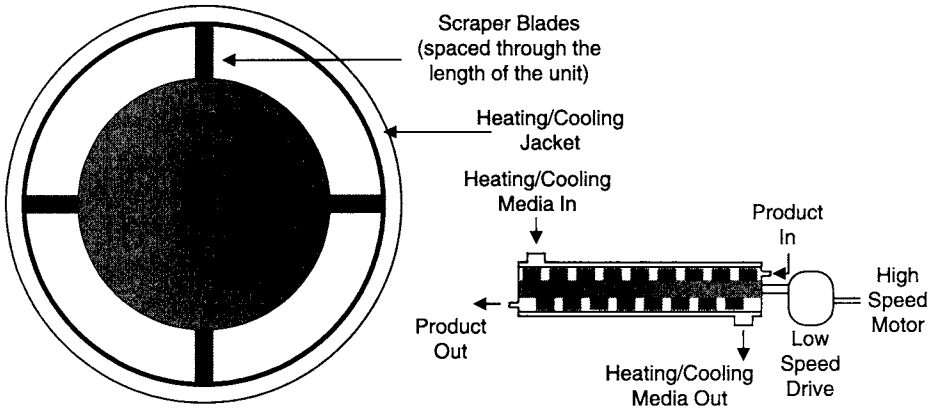


Figure 35.5. Scraped wall heat exchanger

this is a concern, batches should be made in the laboratory or pilot plant using both fast and slow cooling rates.

Tube-and-shell or plate-and-frame heat exchangers can be used with some low viscosity products, which are sensitive to shear. The larger ratio of surface area of cooling to product volume inherent in the design of this equipment allows heat transfer to be achieved quickly and efficiently. Only testing on the pilot or production scale will determine whether the product can be acceptably processed by this method. There are no simple laboratory systems available. Heating or cooling media, supply hopper, product transfer pump, and the heat exchanger must all be designed to work together for the product.

Products that are viscous can be pumped through a scraped wall heat exchanger, (Fig. 35.5). This piece of equipment has a surface area to volume ratio that is less than the last two pieces discussed, but which can provide cooling at rates four times or more higher than those in a CSTR. The disadvantage is that it can add considerable work to the product at lower temperatures. If the product requires a faster cool than can be achieved in a CSTR, and it can withstand shear at lower temperatures, the scraped wall heat exchanger may be the process equipment of choice. Other heat exchanger designs are available; some are more compact or of sanitary design to aid in the cleaning and sanitization process.

WET SYSTEMS—SINGLE PHASE (MISCIBLE) SYSTEMS

The science of mixing is far from complete. Designers of mixing equipment are not yet able to produce, from simple design principles, the optimum piece

of equipment for a specific job even if they are given the necessary parameters and fundamental characteristics of the process and formula. One of the reasons for this is that the complete mathematical description of the flow pattern of fluid within each mixing vessel is extremely difficult and complex to achieve. Progress, however, is being made using the mathematical tools of dimensional analysis and modeling [2,5]. As an illustration of the practical usefulness of the data that can emerge from this analytical approach, a brief description of the relationship between some of the relevant parameters follows.

FLOW PATTERNS: FLUIDS WITH LOW OR MEDIUM VISCOSITY (<5,000 CENTIPOISE)

Flow patterns in agitated vessels can be resolved into three principal types: tangential flow, radial flow, and axial flow.

Tangential Flow

In tangential flow the liquid moves parallel to the direction of the impeller. Movement of liquid into the surroundings is small and there is little movement perpendicular to the blades except in eddies near the tips. Tangential flow may be observed in paddle mixers operating at low speeds or in liquids of sufficient viscosity to prevent centrifugal flow from being developed (Fig. 35.6(a)).

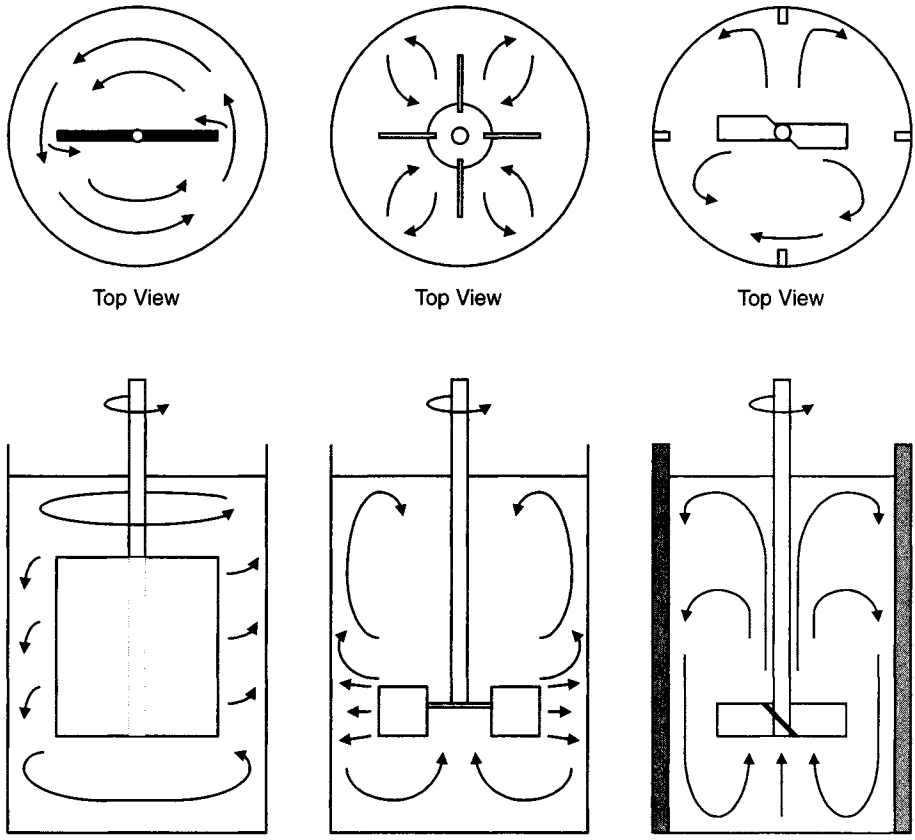
Radial Flow

In radial flow the liquid is discharged outward from the impeller by centrifugal force. If the moving liquid strikes the wall of the vessel, it splits into two sections, circulating back toward the impeller where it is re-entrained. The splitting of the flow at the wall induces further turbulence and mixing. There is usually some element of radial flow in all stirred vessels, but flat-blade turbines and disks with radial paddle blades or teeth are specifically designed to produce flow patterns that are primarily radial (Fig. 35.6(b)).

Axial Flow

As the name implies, axial flow takes place parallel to the axis of rotation. Usually the impeller or propeller blades are pitched so that liquid is discharged axially—the direction of flow may be from top to bottom of the vessel or vice versa (Fig. 35.6(c)). Generally speaking, the most difficult flow pattern to maintain is one of axial flow.

By far the most common form of mixing in liquids of low or medium viscosity (5,000 centipoise) is achieved by forced convection in stirred vessels. The motion of the liquid produced in the vessel must be sufficiently intense to sustain turbulence. Since it is unlikely that turbulence can be generated uniformly throughout the whole content of the vessel on the production scale,



(a) tangential, around the circumference of the vessel
(b) radial, or centrifugal off the peripheral tips of the blade
(c) axial, in the direction of the impeller shaft (baffles in vessel)

Figure 35.6. Flow patterns with different agitators

the liquid must be circulated continuously around the vessel so that all of it passes through those regions where turbulence develops. Thus the number of important basic mixing parameters to be considered is two: the extent of turbulence and the circulation rate of the contents.

Viscous liquids showing shear-thinning characteristics present considerable problems to the cosmetics processor. The fluid close to the rotating impeller of a mixer is sheared at a high rate and so becomes relatively mobile, but as this is pumped away from the impeller, regions of less intense flow, and hence

of much higher viscosity, are encountered. Turbulence is rapidly damped out, decreasing the turnover in the vessel and slowing down the mixing process. Scraper blades are often included on an anchor sweep, or contrasweep to ensure good agitation along the vessel walls as the batch viscosity increases during cooling.

IMPELLERS FOR LIQUIDS OF LOW AND MEDIUM VISCOSITY

Paddle Mixers

Paddle mixers produce mainly tangential flow and are usually mounted centrally because of their large diameter compared with that of the tank. For viscous liquids, the paddle is often of an anchor design equipped with scraper blades that remove product from the walls of the vessel.

Marine-Type Propeller Mixers

Marine-type propeller mixers are restricted to use with low viscosity fluids, since their pumping capacity becomes very localized at viscosities above 5,000 centipoise. They have pitched blades whose angle varies along the length from center to tip. Flow patterns developed by propeller mixers have a high axial component, and the rate of circulation around the vessel is high. Although the ideal impeller diameter to tank diameter ratio (D/T) is 0.33 ± 0.05, propeller mixers are usually of relatively small diameter, typically three-bladed, and are used at speeds between 150 and 2,500 RPM. Such stirrers are used extensively in the cosmetics industry for simple blending operations. Alternate propeller mixer designs are available. These are commonly called axial flow impellers (Fig. 35.7(a)).

Many portable mixers are of the propeller type. If the mixer is mounted centrally in the mixing tank (Fig. 35.8(a)), the surface becomes depressed and a vortex is formed. This is because of the natural movement of liquid to be drawn from above the impeller and toward its center. Generally, vortices are to be avoided because of the low order of turbulence and likely air entrapment. Thus propeller mixers should be mounted eccentrically, that is, offset from the center of the vessel at an angle other than perpendicular to the batch surface (Fig. 35.8(b)). Offset propeller mounting improves mixing efficiency by eliminating vortices, increasing turbulence, and improving batch turnover in the vessel. If the mixer must be mounted centrally, an alternate method of minimizing the formation of a vortex is through the addition of baffles (Fig. 35.8(c)). The baffles are normally equally spaced (e.g., four at 90° separations) and fixed to the vessel walls for efficiency. To improve cleanability of the vessel, the baffles may not be fixed, but they will not be sized the same to maintain the flow pattern required.

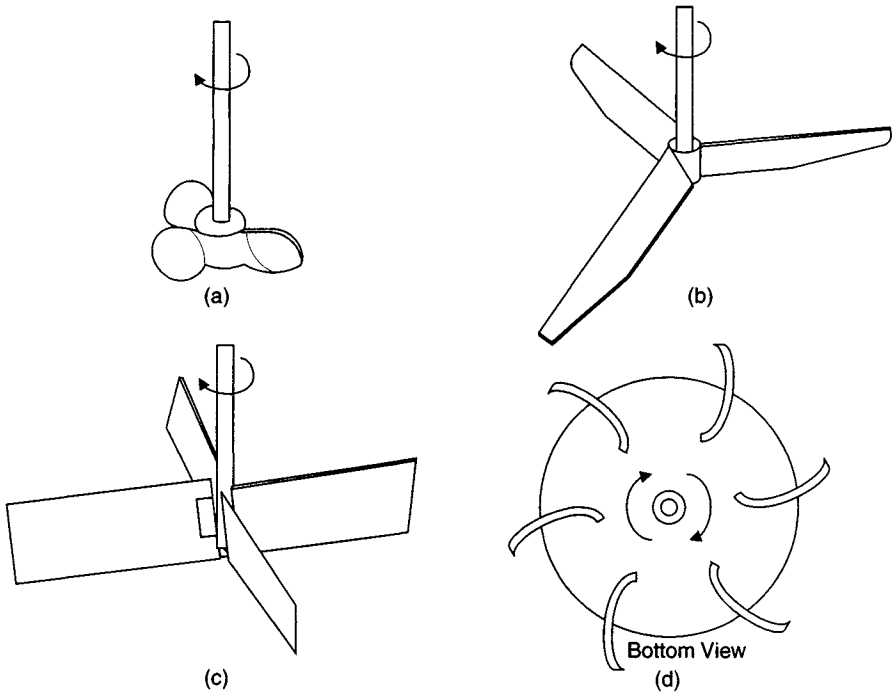


Figure 35.7. Designs of turbine impeller

Turbine

A turbine is a common impeller type used in cosmetics processing since it can cope with a wide range of viscosity and density. For liquids of low viscosity, the flat blade, axial flow impeller is sometimes used (Fig. 35.7(b)). Slightly more viscous fluids are more efficiently mixed using the axial flow, flat blade turbine shown in Figure 35.7(c). For very viscous materials, multiple radial flow turbine blades, curved backward in the direction opposite to the rotation, may be used (Fig. 35.7(d)). These require a lower starting torque and seem to give better energy transfer from impeller to liquid. Turbines produce a large flow of liquid with minimal shear and horsepower. They are normally mounted perpendicular to the top of the vessel with three or four baffles attached to the vertical vessel wall to reduce tangential and radial flow. Baffles help to induce and control the flow in both axial and radial directions. Used without baffles, the axial component generated by turbines remains secondary to the radial flow component, and the turbine does not efficiently turn over the entire batch. Typically, impellers of this kind are used at rotational speeds of 100–2,000 revolutions per minute (RPM) as compared with the low speeds of 15 to 50 RPM for paddles.

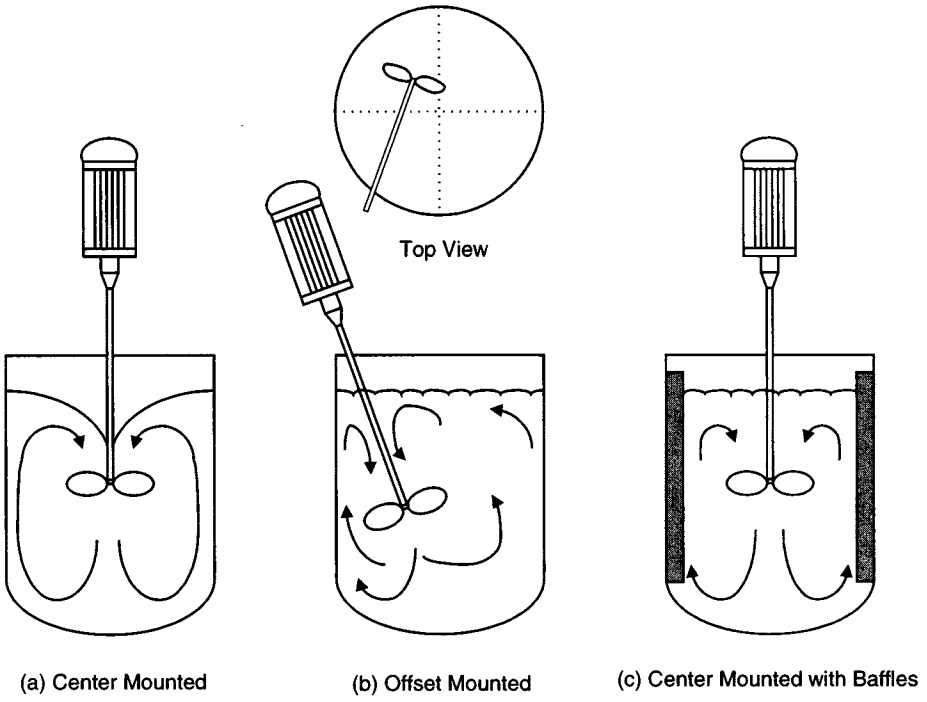


Figure 35.8. Portable mixer positioning

POWER CONSUMPTION

Power consumption is of great relevance to the economics of the mixing process. The choice of the wrong equipment can lead to the consumption of vastly greater quantities of power than are necessary to achieve the desired end result. On the other hand, sufficient power must be available and applied to the fluid to ensure that the endpoint of the mixing process can be achieved in a sensible time.

As can be seen in Equation 35.6, a change in impeller diameter has a more significant effect on the power required than a change in impeller speed. This is emphasized in the design of most drop-in homogenizers through their small head design powered by a large drive motor.

$$P \propto N^3 D^5 \tag{35.6}$$

Where: P = Power in watts
N = Impeller speed in revolutions per minute
D = Impeller diameter in meters

PUMPING CAPACITY AND VELOCITY HEAD

Perhaps the most powerful concept to arise from the analytical approach to mixing concerns the way that power provided by each type of impeller is actually transmitted to the fluid. This relationship can be expressed generally as:

$$P \propto QH \tag{35.7}$$

Where: P = Power in watts
Q = Pumping capacity in liters per minute
H = Velocity head in meters

Q is the pumping capacity of the impeller (the volume of fluid displaced directly by the impeller in liters per minute) and H is the velocity head—this is related to the shear rate experienced by fluid leaving the impeller. A large slow-moving impeller might produce, for example, a large pumping capacity and a low velocity head, while a small impeller operating at high speed might produce a lower volume of fluid pumping but at a much higher velocity head. Most cosmetics production processes require high pumping capacity, while others require high shear rate. It is useful to know the parameters that affect both these functions and how they interrelate.

For simple blending operations (e.g., the manufacture of shampoos or colognes,) pumping capacity of the impeller is often of the greatest significance. Under conditions of laminar flow, the number of complete recirculations of the bulk (batch turnover) required to bring about homogeneity is approximately three. For a turbine operating in turbulent conditions, this is reduced to about 1.5. However, given that only a fixed amount of power is available from the motor, it is not likely that a relatively small turbine will have sufficient pumping capacity to push a fairly viscous product around by even this amount. Not surprisingly, the factor that determines whether power is used as pumping capacity or velocity head is the ratio of impeller to tank diameter (D/T).

Examining the relationship between power consumption and D/T ratio for equal process results in a given vessel completes the picture (Fig. 35.9). The use of a D/T ratio larger than 0.6 lowers the power required to achieve the same end result. At the same time, this implies the use of lower impeller speed, and this inevitably means that the torque required to drive the mixer increases dramatically. The amount of torque that a given mixer is able to generate depends largely on its construction. It becomes a question of economics whether to invest in a more substantial (and expensive) mixer in order to reduce the power consumption needed to achieve a given mixture quality.

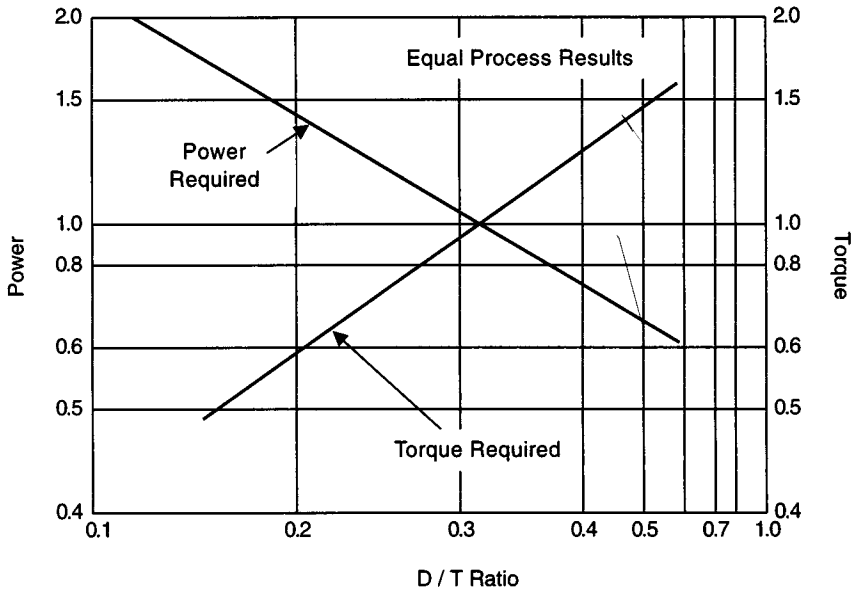


Figure 35.9. Power and torque relationship for equal process results [9]

MIXING TIME

Another important measurable parameter is mixing time, t_m. This is the time taken to achieve the desired degree of homogeneity in the mixture. There are many methods by which this characteristic may be measured but perhaps the most obvious is the time taken for a soluble dye to become uniformly dispersed throughout the mixing vessel (e.g., in the manufacture of a colored shampoo). The relationship between mixing time, t_m, and the degree of uniformity can clearly be shown if some index of mixing level can be established.

A simple example of this would be the ratio of color intensity between the top and bottom of the vessel contents at intervals after dye is added to the top (so that uniformity is achieved as the mixing index, M, approaches unity). This comparatively simple experiment should give rise to a curve similar to that shown in Figure 35.10. Since the approach of M to unity is asymptotic, t_m is difficult to measure accurately unless a colorimeter or other optical measuring device is available.

Once t_m has been established, however, more useful insight into the parameters controlling mixing rates may be gleaned from relationships such as that illustrated in Figure 35.11 [5]. In Figure 35.11(a) (which relates to a viscous liquid in which turbulence is not established), t_m, the mixing time, has been replaced by the product of rotational speed N and t_m, that is, by the number

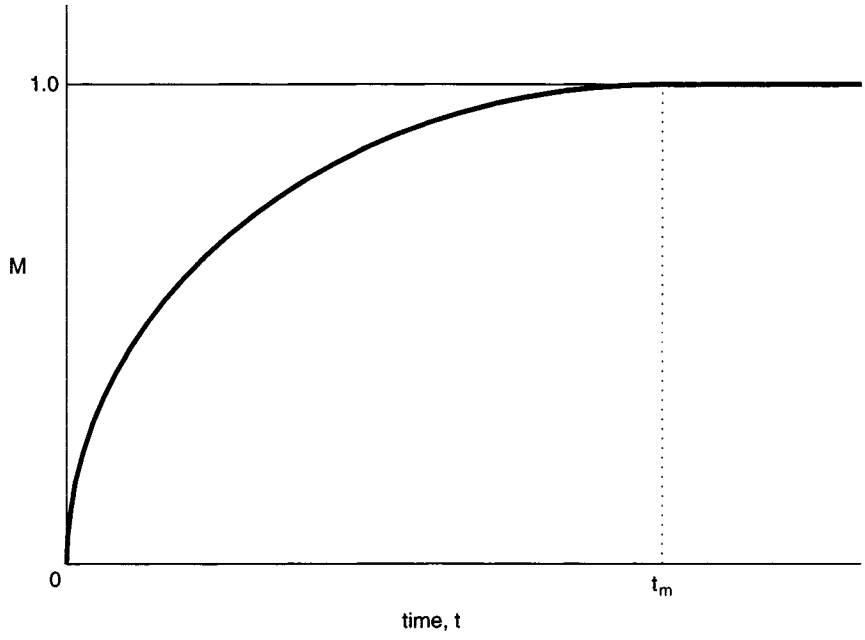


Figure 35.10. Mixing index, M, plotted against time to give mixing time, t_m

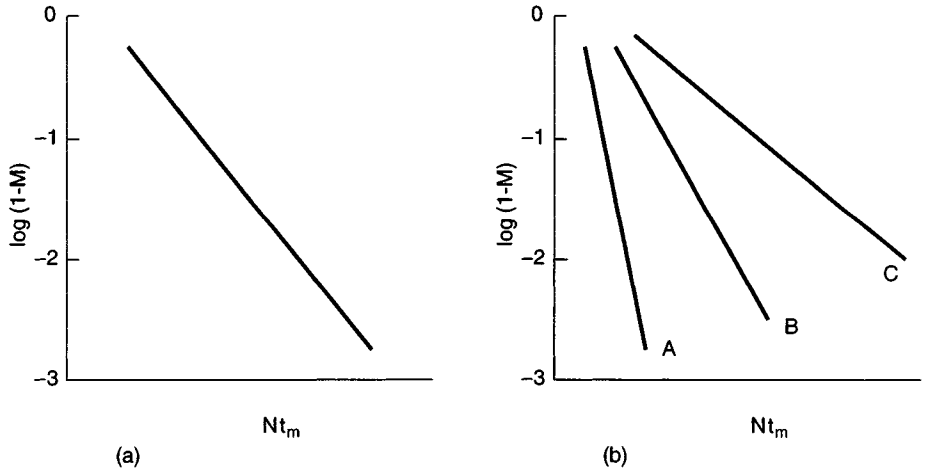


Figure 35.11. Mixing index, M, plotted against number of revolutions, Nt_m (a) Newtonian fluids (b) non-Newtonian fluids

of revolutions of the impeller. M, the mixing index, has been replaced by log (1-M) to linearize the plot.

It is interesting to note that for Newtonian fluids (ideal response between stress and strain) precisely the same plot is produced whatever the viscosity of the medium and speed of the impeller. In other words, only the number of impeller revolutions determines the change in mixing index. This is not true of non-Newtonian fluids—plots A, B, and C in Figure 35.11(b), which represents liquids showing increasing divergence from Newtonian behavior. This illustrates the difficulties of mixing non-Newtonian media in which flow is damped out rapidly by regions of high viscosity away from the vicinity of the impeller blade.

INFLUENCE OF VESSEL SHAPE

The ratio of tank dimensions can be an important factor in determining the efficiency of any mixing process. It is sensible to perform a simple blending, such as alcohol-water, in tall cylindrical vessels of small cross-section using a propeller or turbine mixer with two or three sets of blades located two to three blade diameters apart on the same shaft. This stirred tank setup allows the capability to make variable batch volumes with high axial flow. For low viscosity lotions, a hemispherical kettle often replaces the dished bottom conical tank to maximize the batch turnover achieved with an offset mounted propeller mixer. Normally the ratio of kettle diameter to kettle height is close to 1:1. In the production of an emulsion of medium viscosity, it is desirable to keep the height of the vessel between 1 and 1.5 times its diameter.

FLOW PATTERNS: FLUIDS OF HIGH VISCOSITY

As the viscosity of the mixture increases, it becomes increasingly difficult—and eventually mechanically impossible—to produce turbulent flow within the mixing vessel. At viscosities of 100,000 centipoise or above, flow is inevitably laminar, power consumption high, and the rate of mixing exceedingly low. In such systems, the input power should be used to create disorder (mixing) but is used to create heat. The rate of temperature rise is dependent on the energy input, the thermal conductivity of the mixture, and the efficiency of the cooling surfaces; but the range 1 °C to 3 °C per minute would include many cosmetic mixing processes of this kind. Generally it is difficult or impossible during industrial mixing of highly viscous materials to dissipate heat faster than it is generated. This is particularly true if the mixing vessel is of large capacity (in which the ratio of volume to heat exchange surface is high) and if appreciable films of chilled liquid are allowed to build up on the walls of the vessel, thereby insulating the contents from further

cooling. The increase in temperature associated with such processes has both advantages and disadvantages. On the one hand, a rise in temperature might cause a decrease in viscosity, making mixing more efficient, and might also help in the melting or dissolution of some of the components of the mixture. Taken too far, on the other hand, the decrease in shear stress caused by the fall in viscosity can decrease the efficiency of stress-dependent processes. This can be seen when breaking up and dispersing pigment agglomerates. The rise in temperature may damage the product by causing the thermal degradation of heat-sensitive components such as actives, preservatives, and perfumes. The relatively high energy input required while mixing viscous materials also influences the mechanical construction of the mixing machinery and the method by which mixing is achieved.

IMPELLER TYPES AND MIXERS FOR HIGH VISCOSITY FLUIDS

Propellers and turbines, as already mentioned, work best under turbulent conditions at relatively high rotational speeds. In viscous products (given that such speeds are attainable), flow is confined to the regions very close to the impeller. Large stagnant regions in the vessel exist where no mixing can occur without the employment of some secondary mechanism. To eliminate these stagnant regions, large impellers such as paddles, gates, anchors, and leaf impellers may be used. These sweep a much greater proportion of the vessel and produce more extensive flow. Usually such impellers are designed to have close clearances with walls, giving a degree of wall scraping. This helps to eliminate buildup of unmixed materials at the walls, provides a region of high shear for dispersing aggregates and lumps, and may improve the wall heat transfer to and from the bulk.

Such impellers provide extensive flow but only of the tangential and radial variety. Axial flow, and therefore top-to-bottom mixing, is almost totally absent. This is a limitation of the design. Several suppliers have developed agitation techniques that include special baffles (often of variable pitch) that induce flow in both the downward and upward directions. For this reason, recycling the batch either externally through a pump or with time using the pitch of the sweep blade becomes an important consideration.

An alternative approach to the problem created by lack of flow in viscous media is the use of impellers that progressively sweep the whole contents of the vessel while the mixture remains stationary. Examples of this include the mixer in which a helical screw sweeps the wall of a conical mixing chamber (Fig. 35.12). Equipment that exhibits a greater degree of distributive mixing may be utilized for more viscous products such as mascaras and toothpastes. Such mixers are designed to produce bulk flow and laminar shear by spatial

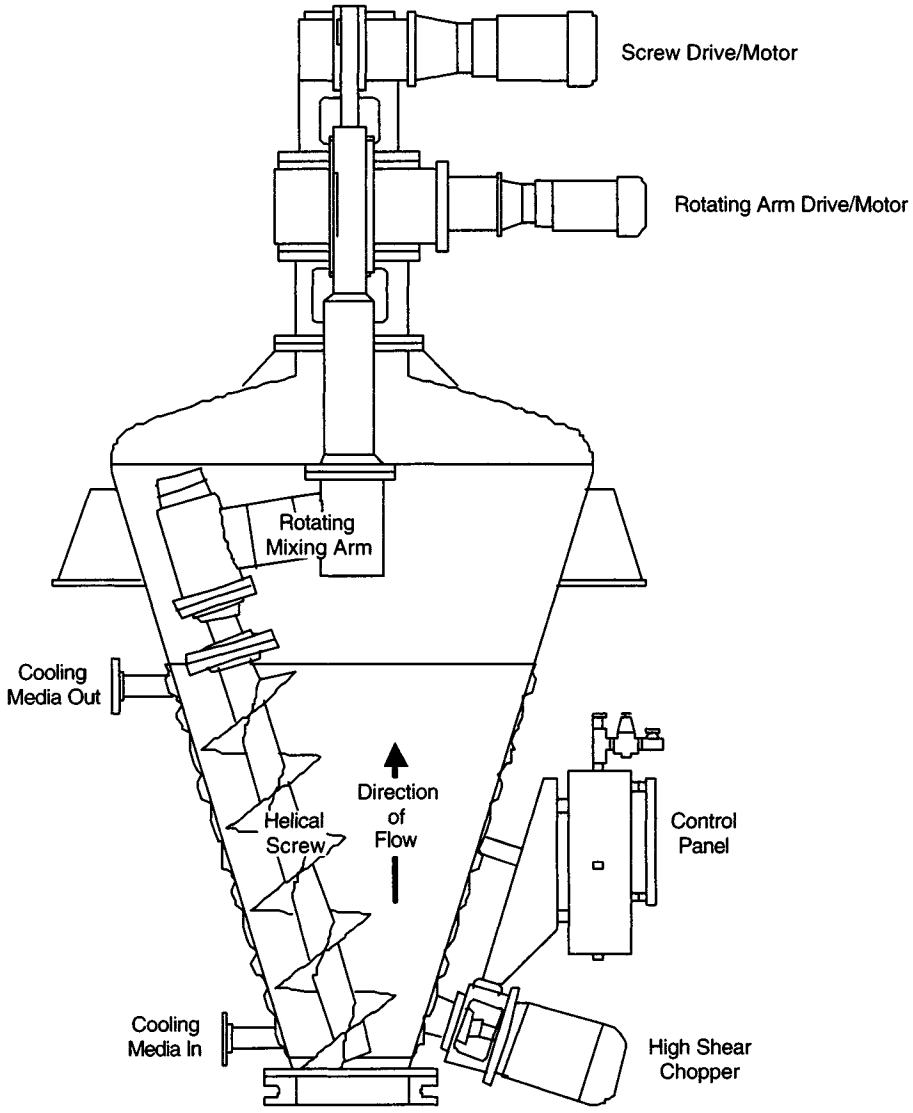


Figure 35.12. High solids blender; courtesy of Charles Ross and Son Company, Hauppauge, New York.

redistribution of elements of the mixture. Perhaps the most commonly encountered mixers of this type are of the single-or-double action planetary type or the two-blade "dough" mixer. Their essential feature involves the cutting and folding of a volume of the mixture and the physical replacement of it into another part of the mixture where it is cut and folded again.

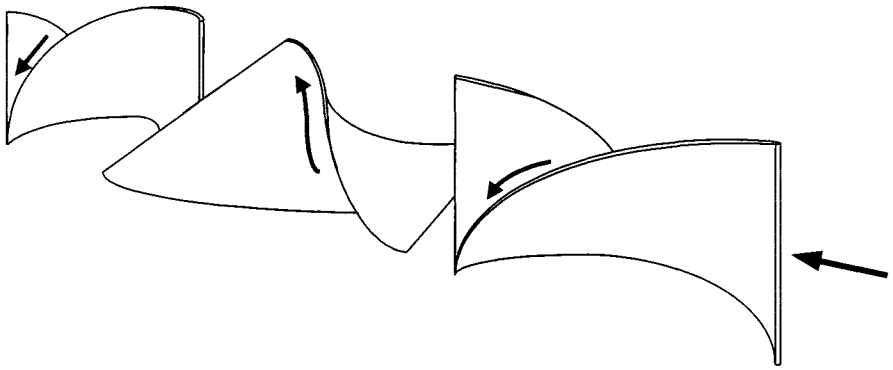


Figure 35.13. Static mixer elements

The static mixer is essentially an in-line mixing device in which mixtures flowing through a pipe are cut and folded by a series of helical elements in a circular tube (Fig. 35.13). These elements (which do not move—hence the name "static") turn the flowing mixture through an angle of 180°. Since alternate elements have opposite pitch and are displaced 90° to each other, this causes the bulk flow to reverse direction at each junction. The leading edge of each element becomes a cutting device, splitting and refolding the mixture in and on itself. This type of static mixer works well with thick materials. Other static, or motionless, mixer designs utilize the divergence and convergence of flows to induce mixing with some control as to the shear developed. This type of static mixer works well with thin materials. It can be seen that with both high and low viscosities, excellent mixing can be achieved in a relatively short length of pipe and with relatively few static elements. Each element splits the product stream in two and combines the two new streams with parts of the previously split streams. Other styles of static mixers are also available that offer specialty features such as adjustable gap settings and lower pressure drops.

Finally, mention must be made of extruders, in which a helical screw forces the bulk mixture to flow down a tube. Here the pressure generated can be enormous, as in soap plodding, and such energy can cause materials with high viscosity to undergo laminar flow and change structure. The actual flow pattern produced is complex, being a combination of pressure and drag flow within the tube [6].

WET SYSTEMS—MULTIPHASE SYSTEMS

THE EMULSIFICATION PROCESS

Two major immiscible phases (referred to as "oil" and "water") together with the emulsifier are brought together to form an emulsion. If the chemistry is

favorable, very little energy is needed to produce a stable product. To minimize the level of emulsifier, it may be possible to use energy to force the emulsion to a stable end point.

The level of energy required will be formula-dependent. Under turbulent conditions, one phase (usually the discontinuous or internal phase) is broken up into droplets (predominantly by the action of shear stress imparted by turbulent eddies). The droplets are distributed throughout the other phase (the continuous or external phase).

While the droplets remain larger than the majority of the flowing particles, they will continue to break up into ever-smaller droplets. Eventually a point is reached in this process when the available power creating the turbulence cannot provide the shear stress necessary to reduce the droplet size any further. At this stage an emulsion exists containing droplets of a certain mean diameter but ranging from d_{min} to d_{max}. Provided that it is correctly chosen, the emulsifier prevents the rapid coalescence of these droplets, and a stable emulsion may be formed.

In order to obtain products of maximum stability that can be made consistently from batch to batch, it is generally desirable to keep the droplet size distribution as narrow as possible. In a CSTR, droplet size is smallest near the impeller in the region of greatest turbulence, whereas the maximum droplet size is to be found in any quiescent region of the tank. Thus it can be seen that d_{min} is fixed by the power available to generate turbulence, and d_{max} depends on the efficiency of the mixing in the tank to produce a good circulation rate, to bring all the contents through the region of maximum turbulence. This will minimize the distribution range between d_{min} and d_{max}.

Superimposed on the effect of circulation patterns in the vessel is a further factor affecting the particle size range of the droplets. For a given vessel and impeller the effect of increasing the mixer speed should be to reduce the particle size range to a minimum, after which a further increase in speed could give rise to instability and coalescence. In practice, coalescence does not take place if a sufficient quantity of emulsifier is present; nevertheless, it is important to attain the correct impeller speed to reduce the particle size range to a minimum.

ORIENTATION OF PHASES

In any emulsion the orientation of the phases (i.e., whether the oil or the water phase is continuous) is determined principally by the choice of emulsifier and the volume ratio of oil to water. Usually there is a range of volume ratios over which either phase may be dispersed, depending on the method of manufacture.

Initially only one phase is present in the mixing vessel containing the impeller. The second phase will form the dispersed or discontinuous phase

upon its addition. If the second phase is combined with the choice of emulsifier that eventually leads to a volume ratio at which the system is more stable with the second phase being continuous, then the emulsion will spontaneously invert and the continuous and discontinuous phases will switch. When an inversion takes place, it is very often accompanied by a change in droplet size. When this droplet size change is a decrease, the inversion leads to a more stable emulsion and gives rise to a valuable method of manufacture. This inversion process is often an effective method of producing a uniform, fine droplet size and may stabilize the emulsion.

ADDITION OF SURFACTANT

In a batch manufacturing process for emulsions, there are four possible methods of adding the emulsifier.

1. dissolving or dispersing an emulsifying agent in water
2. dissolving or dispersing an emulsifying agent in oil
3. dissolving or dispersing an emulsifying agent in water and oil
4. adding the water and oil phases alternately to an emulsifying agent

Normally the emulsion process starts with a water phase to which the oil is added. An oil-in-water emulsion is initially produced, but an inversion to a water-in-oil emulsion may take place if sufficient oil is added. If the emulsifier is added to the oil phase, this mixture may be added directly to water to form an oil-in-water emulsion; if the water is added to the surfactant/oil mixture, a water-in-oil emulsion is formed initially.

Some emulsions are stabilized by soaps that are formed at the interface between the two phases. In this case, the fatty acid is dissolved in the oil and the alkaline component is dissolved in the water. The two phases can be brought together in any order. The neutralization reaction, which forms the emulsifier, takes place as the phases are combined.

A less used method is one in which water and oil are added alternately to the emulsifying agent. Usually the small improvement in product quality obtained by the use of this method does not warrant the complication it causes in the manufacturing procedure.

EMULSION TEMPERATURE

The primary reason for operating above room temperature during manufacture of an emulsion is to ensure that both phases are in the liquid state. In particular, the oil phase may contain fats and waxes that are solid at room temperature. The water phase is customarily heated slightly above the temperature chosen for the oil phase so as not to cause any sudden solidification upon

blending. There is, however, an interesting variation: emulsification between a hot oil phase and a cold (room temperature) water phase. An illustration of this procedure in which mixing and homogenization of the phases take place simultaneously is shown in Figure 35.14. The advantage of such a method is the saving of time and energy by not having to heat the aqueous phase and by reducing the time and energy required to cool the product to room temperature.

EMULSION PROCESSING EQUIPMENT—MIXING

It is evident from the discussion so far that there are two important elements of emulsion processing: shear for emulsification and particle size reduction and flow for circulation of vessel contents through the region of maximum shear. Flow is also important in the heating and cooling of the emulsion. Most emulsion processing vessels are equipped with a jacket through which steam

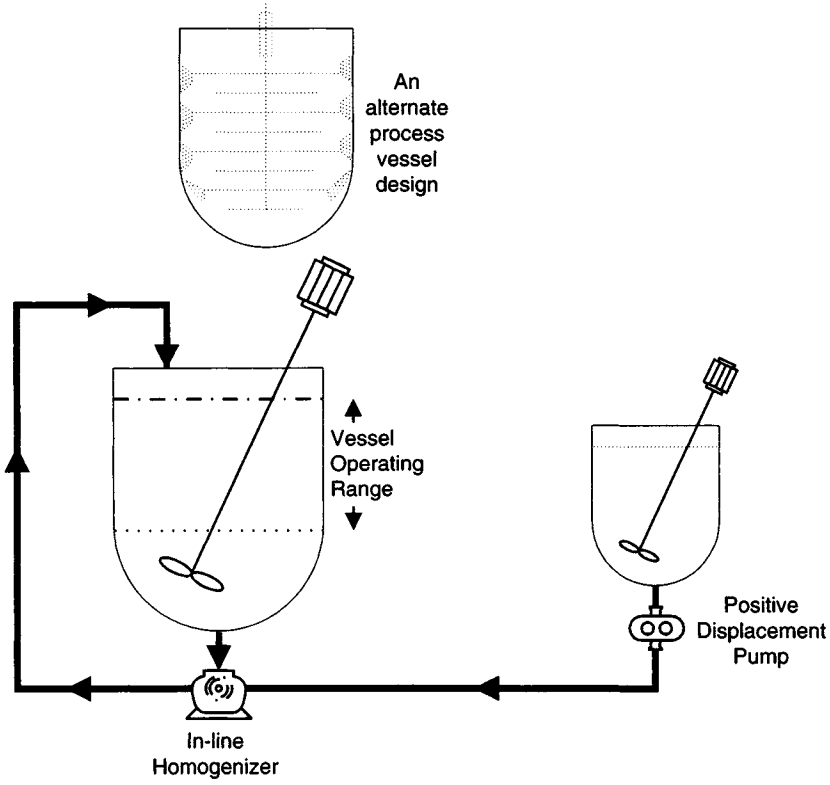


Figure 35.14. Hot/cold processing emulsion system

or hot water or cold water can be circulated for temperature control. To be effective, the mixing mechanism must include adequate flow to and from the vessel walls, as discussed earlier in this chapter.

For these reasons, most emulsion batch processing vessels contain a high shear turbine or rotor-stator homogenizer (typically bottom, side, or top entry). High flow in one design (Fig. 35.15) is provided by a paddle-style anchor agitator with scraper feet that meshes with two fixed baffles. The agitator can be run intermittently in either direction to provide a complete mix. In another design (Fig. 35.16), concentric central shafts carry blades that turn in opposite directions and sweep the area in-between. A frame holding the

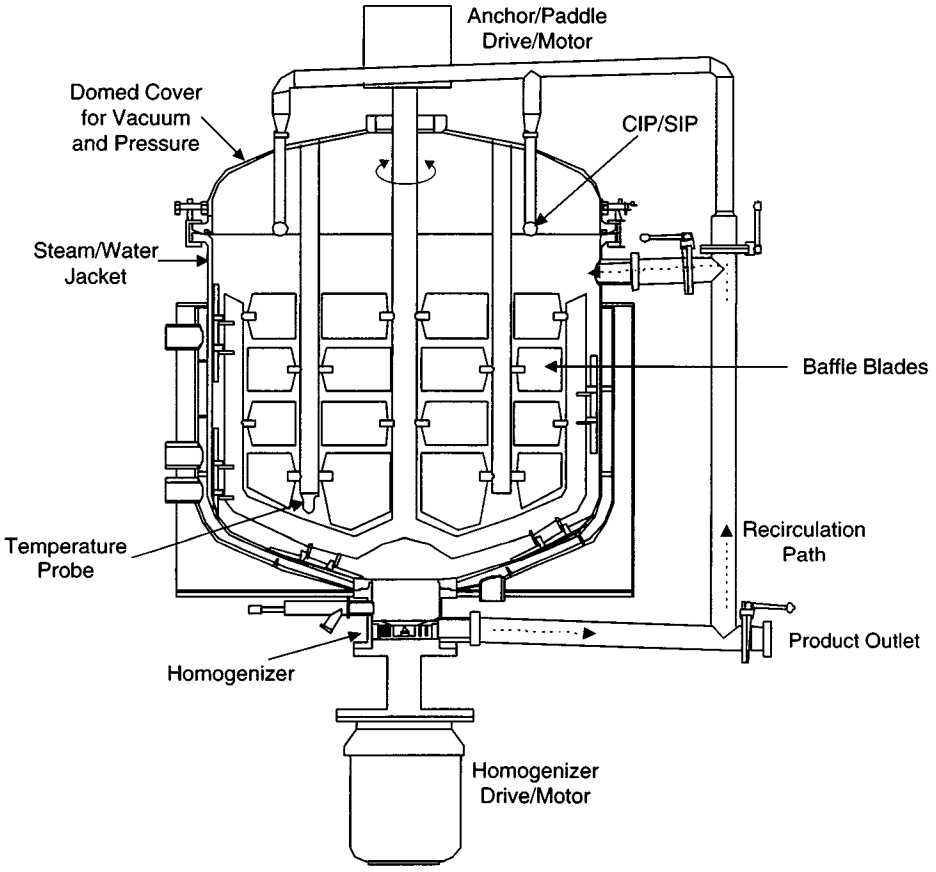


Figure 35.15. Batch emulsion processing vessel—SYMEX® Style—homogenizer in the down position; courtesy of Schröder and Boos, Misch & Anlagentechnik GmbH & Co. KG, Bremerhaven, Germany.

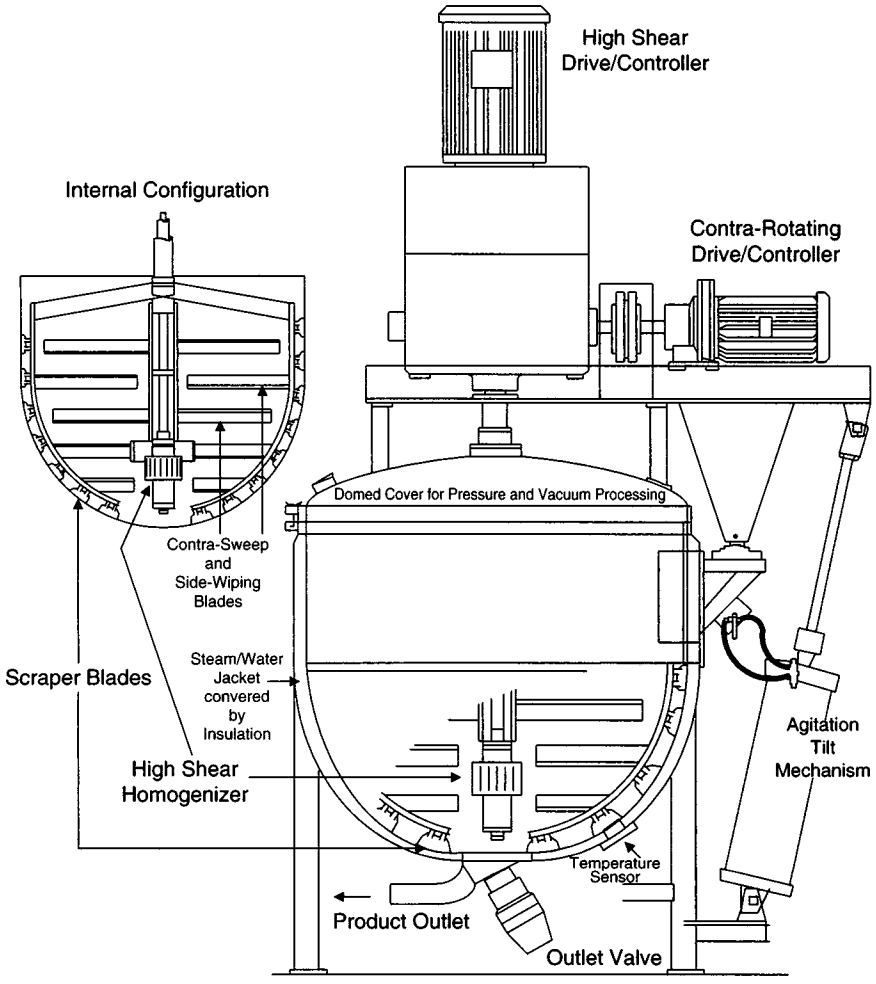


Figure 35.16. Batch emulsion processing vessel—•Lee® Tri-Mix •Turbo-Shear® Style; courtesy of Lee® Industries, Philipsburg, Penn.

outer blades carries spring-loaded or product-pressure scraper blades in both designs to prevent buildup of product on the vessel wall, while mixing in the higher viscosity region is thus enhanced. Mixing can be further enhanced by recirculating the batch through the homogenizer and depositing it on the top of the batch to enhance plug flow. The recirculation piping may be an integral part of the vessel design (as shown in Fig. 35.15) or an added feature in the production facility utilizing an external pump.

The need to combine all of these mixing capabilities into one vessel has led to the design shown in Figure 35.15. The following capabilities are available with no additional piping or equipment needed:

1. Universal in application. It is capable of handling the entire viscosity range from light lotions to heavy ointments.
2. Efficient presentation of the batch to the homogenizer for all batches. Efficient mixing ensures that all parts of the batch will see the same quantity of energy.
3. Vacuum capable for maximum production efficiencies (high mixing speeds without aeration) and specific gravity control capabilities. Product integrity is not compromised during processing since aeration during mixing is not a factor.
4. Clean-in-place and sanitize-in-place capable. The system is designed to be sanitary and maintain appropriate controls to meet the requirements for food, drug, and cosmetics manufacture.

Alternate designs are available from many suppliers in an effort to meet the above requirements (e.g., Fig. 35.17). It is important for personnel purchasing equipment to understand the flexibility that is available in light of the processing requirements of new and upcoming products.

HIGH SHEAR MIXERS AND DISPERSION EQUIPMENT

The mixing equipment that has so far been covered in this chapter is designed primarily to produce bulk flow patterns of sufficient intensity to allow mixing. In the majority of cases, the pattern of shear and turbulence developed within the mixture varies according to the viscosity of the bulk, the method of producing flow, and the volume within the mixture under consideration. For certain applications, however, it is desirable to generate a very intense degree of shear stress in the mixture, and for this purpose specialized equipment is available. The uses to which such machines are put in cosmetics processing include the breaking up of pigment agglomerates and their dispersion in liquids, the rapid fracture and dispersion of gelling agents (e.g., bentones, cellulose derivatives, and alginates), and the size reduction of internal phase droplets in emulsion products.

BATCH HOMOGENIZERS

All three types of batch homogenizers (top mounted, bottom mounted in the kettle with or without recirculation, and in-line) operate under the same principles. Liquid is drawn into the inlet by the suction created by the rotating blades, or teeth, of the rotor (centrifugal force). The liquid is then forced through the stator configuration, subjecting the fluid to high mechanical shear at the rotor/stator,

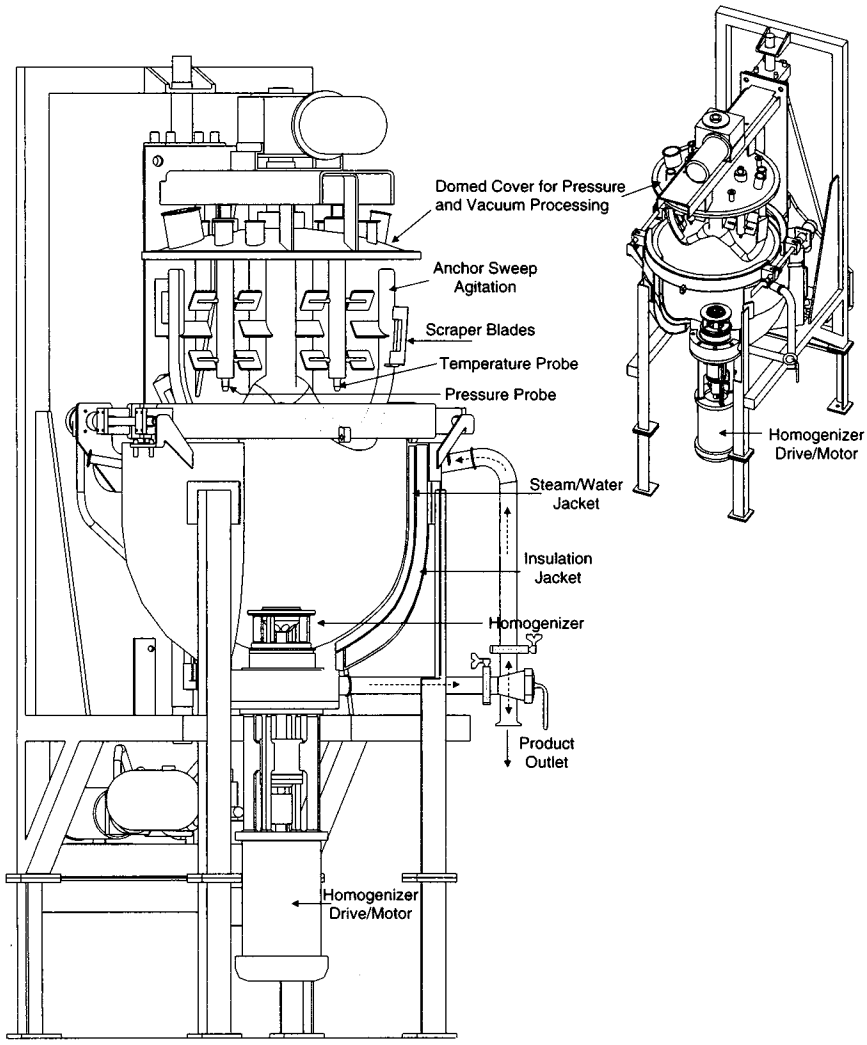
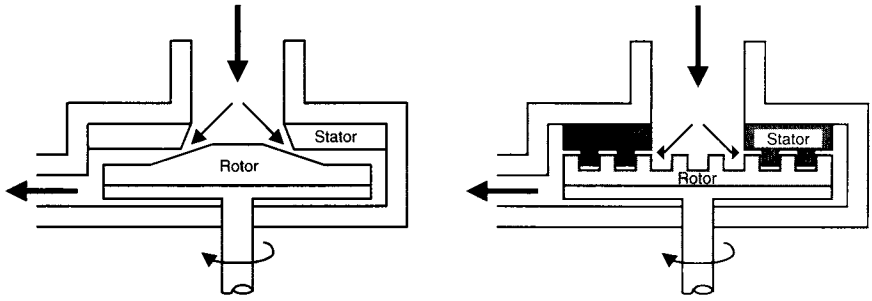


Figure 35.17. Batch emulsion processing vessel—AGI™ Mixer Triple Shaft, homogenizer in the up position; courtesy of Chemineer®-Greerco, North Andover, Mass.

interface. After the fluid enters the stator, it is subjected to high hydraulic shear as it returns to the vessel or pipeline. The design of the rotor and the stator dictates the magnitude of shear stress developed by the homogenizer. *High flow/low shear homogenizers* normally employ a flat or pitched design with an open stator design (Fig. 35.18(a)). The stator will have slotted, round, or other discharge port configurations and discharges radially or axially.



(a) High Flow Rotor/Stator Homogenizer (b) Low Flow Rotor/Stator Homogenizer (Higher Shear)

Figure 35.18. Rotor/stator designs

Major applications of the high flow design are for traditional creams and lotions and other low to medium viscosity products in which frequent particle interaction with low shear rates is required. *High shear/low flow* homogenizers are typically characterized by an intermeshing toothed rotor/stator design (Fig. 35.18(b)). The rotor and stator frequently have multiple rows of teeth, which operate at a gap range of 0.005″–0.015″ (0.127–0.381 mm). The close tolerance increases the shear stress but has the effect of reducing the batch turnover rate. Major applications for this design are makeup pigment dispersion, mascara production, and low emulsifier cream and lotion formulations that depend on mechanical energy for emulsification. Some vessels may allow interchangeability between high flow/low shear and high shear/low flow homogenizing heads. These units provide maximum flexibility for the production of a wide range of finished products ranging from thin lotions to thick ointments.

A disadvantage of the top-entering homogenizer is the tendency of the mixer to cause aeration due to vortex formation. For this reason, high shear devices are often incorporated into the bottom of the processing vessels. Additional advantages to the bottom-mounted design include the following: low volume processing with minimal aeration, consistent agitation throughout the mass, virtually no minimum batch size, and fewer seal problems and less wear due to shorter shaft length. If the homogenizer is the primary mixer in the vessel, the outer tips of the rotor may wear rapidly, leading to increased clearance and decreased efficiency. Since no adjustment is possible, worn rotors must be replaced at considerable cost.

Generally high shear rotor-stator mixers may be used either for batch processing in a mixing tank (as a drop-in unit) or as in-line devices when encased in a suitable chamber. Used as batch mixers, they are capable of generating considerable turbulence because of the great velocity with which fluid is pumped out

of the mixing head. In the high viscosity region pumping capacity decreases significantly. In this situation, use as an in-line device can be more effective. A positive displacement pump should be used to minimize viscosity effects during homogenization. The in-line homogenizer routinely has a significantly lower batch turnover rate than a drop-in homogenizer due to the restrictions of the recirculation arm especially as batch sizes increase. This limitation may be overcome since it is highly effective as a finishing step for products during discharge. It should be remembered that mixing time is required to ensure that every part of the mixture has passed through the shear head at least once.

CONTINUOUS HIGH PRESSURE HOMOGENIZERS AND MIXERS

High-pressure homogenizers require a continuous process. This may be part of a recirculation line for a one-kettle operation or it may involve multiple kettles with a single pass or multiple passes through the device. The problems with most high-pressure systems are the high initial and operating costs and the low production processing rate. The advantages lie in the small particle sizes that can be created during processing of both emulsions and solids dispersed in liquids.

Perhaps the highest shear stress is generated by the valve homogenizer, which is still extensively used in the production of emulsions with very fine

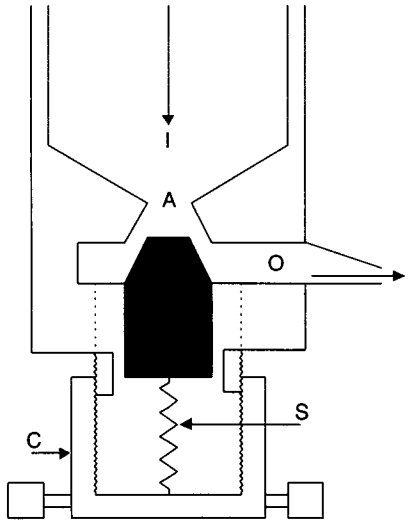


Figure 35.19. Valve homogenizer. The roughly premixed product at I is forced through the valve seating at A and leaves via O. T is a tapered shaft whose position can be adjusted with screw head C. S is a powerful spring against which the product is pushed through the narrow valve orifice.

internal phase droplets. A valve homogenizer (Fig. 35.19) consists of a high-pressure pump, which forces product through a small orifice at pressures of up to 30,000 psi (2,000 bar). Rapid expansion of the product after traveling through the orifice produces very fine emulsion and dispersion particles that are smaller than those produced by most other equipment.

An alternative to the valve homogenizer is the ultrasonic homogenizer. When high-intensity ultrasonic energy is applied to liquids, a phenomenon known as "cavitation" occurs. Cavitation is complex and not fully understood. As ultrasonic waves are propagated through the fluid, areas of compression and rarefaction are formed, and cavitation is produced in these rarefied areas. When the ultrasonic wave passes on, these cavities collapse and change to an area of compression. It has been demonstrated that the pressure in these cavities, just before their collapse, can be as high as several thousand bars. Most of the effects of ultrasonic homogenization in liquids are attributed to the powerful shock waves produced immediately following the collapse of such cavities. One design of an ultrasonic homogenizer is illustrated in Figure 35.20. The

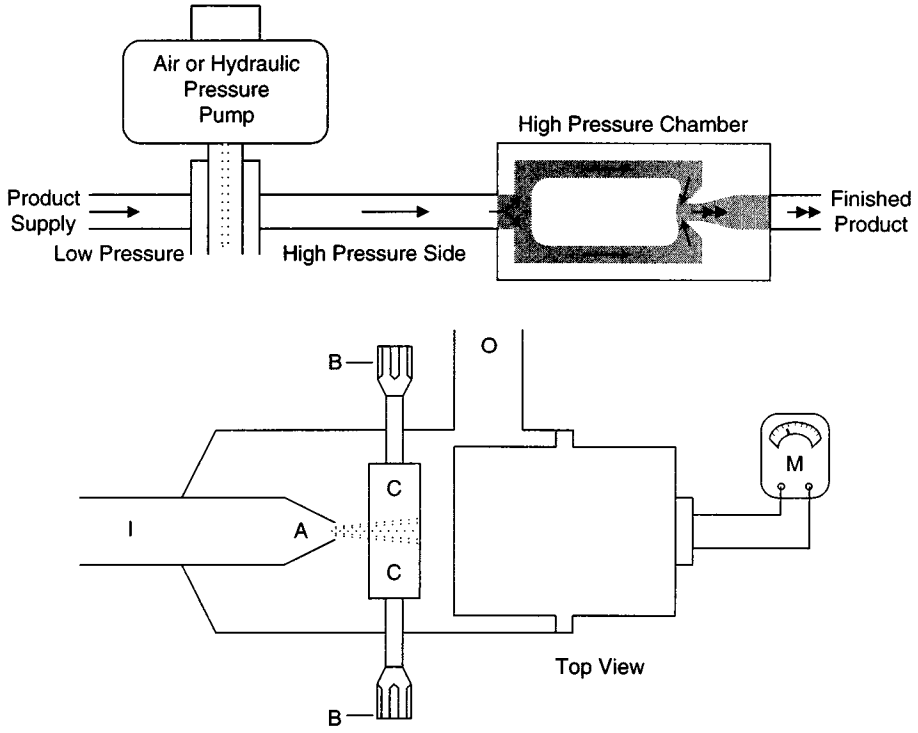


Figure 35.20. Ultrasonic homogenizer

energy developed through the cavitation process will wear specific components. These will need regular replacement to maintain process efficiency.

A third alternative to the valve homogenizer is a design that forces fluid, at high pressure, through an orifice into an expansion and impingement chamber (Fig. 35.21). These systems can usually achieve higher pressures than the other designs described, from 15,000 psi (1,000 bar) to 40,000 psi (2,757 bar) and higher. These systems are often used in the processing of liposomes and special dispersions. Costs of these dispersions are high and production flow rates are low.

PROCESSING OF WATER IN SILICONE EMULSIONS

Advances in silicone technology have offered an alternative set of synthetic chemicals to the hydrocarbon compounds that have traditionally been used in the cosmetics industry, both as emulsifiers and as oil phase ingredients. In the case of emulsifiers, many specialty products can be derived by selective block copolymerization with hydrophilic materials along the siloxane backbone of the chain. The result of this block copolymerization is a molecule with a strongly hydrophobic Si–O–Si backbone with a 130° bond angle that allows a series of hydrophilic sites to rotate freely about that backbone with minimal steric restriction.

In working with silicone emulsifiers, the key processing step in forming a stable emulsion is by allowing enough time for the randomly oriented hydrophilic sites to uncoil and become oriented in the water phase with the less polar and highly flexible Si–O–Si backbone following the curvature of a single water droplet. Failure to allow time for this orientation and coating action to progress to completion usually leads to a less stable emulsion that loses viscosity over time and can lead to syneresis (separation of the phases) as the water droplets coalesce. Thus normal processing of water-in-silicone (W/S) emulsions involves introducing the water phase into the silicone phase

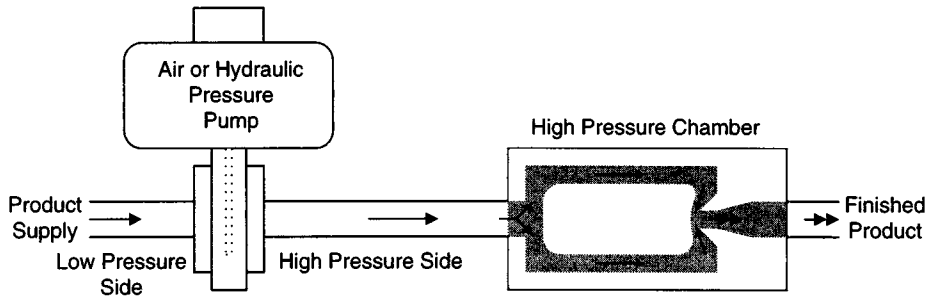


Figure 35.21. Multistream high pressure homogenizer

very slowly with low-shear agitation to produce a "crude" emulsion that, after a mixing period, is "finished" by a high-shear mixing step. Failure to follow the above process can yield an emulsion that meets initial viscosity specifications and looks fine but deteriorates in two to four weeks into a low viscosity product that may even bleed (syneresis).

Low-shear turbulent mixing can be accomplished with a turbine, sweep, or propeller blade turning with a "tip-speed" below 900 feet per minute (4.57 meters per second). Gentle mixing is essential in order to allow the silicone emulsifier molecule to uncoil from a random orientation. The implication is that excessive hydraulic shear can interfere with proper orientation of these large molecules. The slow water transfer under low-shear mixing results in a "crude" emulsion of large water droplets suspended in the oil phase.

"Slow" water transfer is a relative term that is very dependent on the chemicals involved. Thus slow transfer can mean transferring a water phase, which is normally between 35% and 65% of the batch, into the oil phase over a period of 40–220 minutes. Another way to help the silicone emulsifier uncoil is to "seed" the oil phase with 5% to 10% of the water phase. The seeding step involves the slow transfer of a small percentage of the water phase into the oil, followed by a mixing period before the slow water transfer is resumed. In either case, a gentle mixing period follows the water transfer, with the batch sometimes showing a 1,000–5,000 centipoise build in viscosity indicating that it is ready to be finished.

The finishing step involves converting the large water droplets of the "crude" emulsion into fine droplets that make up the internal phase of the W/S product. High-shear mixing is normally needed in this step. It can be applied as a single pass through a high-shear device with the shear applied via an orifice plate, colloid mill, or in-line rotor-stator homogenizer. Production of water-in-silicone emulsion systems requires as much attention to the "crude" emulsion step as it does to the finishing step. The water transfer time cannot be cut short. Cold emulsion formation eliminates cooling time and provides a faster batch cycle time, provided the production equipment can match the shear energy applied in the lab. These are the two keys to successful w/s processing.

LIPOSOME PRODUCTION

Liposome formulation in the cosmetic industry normally utilizes phospholipids and produces either single or multilamellar vesicles. High-pressure homogenization is the main method for liposome processing. There are two processes commonly employed for manufacture. Both methods are used to achieve a uniform-sized single or multilamellar vesicle. The first utilizes a piston/valve homogenizer at an 8,000–10,000 psi (551–689 bar) operating

pressure. Production requires four to five passes to achieve a uniform size distribution of the vesicles. Additionally, a temperature reduction step is required between passes to avoid degradation of active materials and destruction of the vesicles. This method produces vesicles in the range of 300–500 nanometers in diameter. The second method uses two product streams that impinge at 20,000–30,000 psi (1,333–2,000 bar). For specialized applications, pressures up to 60,000 psi (4,000 bar) are available. This method also requires four to five passes, with temperature reduction between passes. It will result in much smaller vesicle sizes, typically 50–200 nanometers.

Non-phospholipid liposomes can also be produced. High pressures are not usually required for their formation. They are formula-specific and temperature sensitive, and may require specific agitation for their formation. Special controls may be required during their production. Typical vesicle sizes are in the 100–500 nanometer range, with process pressures of 200–1,000 psig (13–67 bar).

WET SYSTEMS—Liquid-Solid Systems

The production of a cosmetic product often involves the incorporation of a powdered solid material into a liquid. The objective may be to dissolve the powder completely (as with true solutions like salts or preservatives in water), to produce a colloidal dispersion of water-swellable particles (as with bentones and other gelling agents), or simply to disperse insoluble materials, such as pigments. To do this efficiently with a wide range of powder particle sizes, surface characteristics, and liquids of varying viscosities, a variety of mixing equipment is available.

Perhaps the easiest of these processes to carry out is the dissolution of a fairly large, smooth-faced solid, such as salt. The initial incorporation of each crystal into the liquid involves the complete replacement of the air-solid

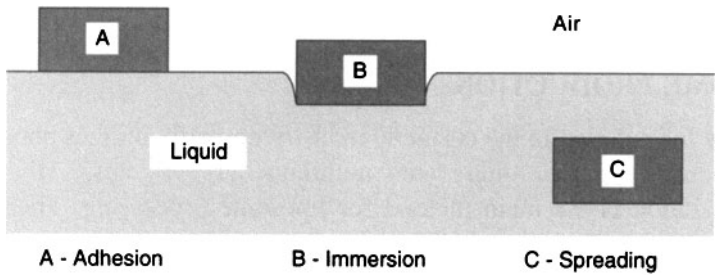


Figure 35.22. Immersion of a solid in a liquid

surface with a liquid-solid surface. This may be considered to be a three-stage process of adhesion, immersion, and spreading (Fig. 35.22). Immersion is complete when the liquid has displaced all the air and the surface of the crystal has been completely wetted by the liquid. A low surface tension results in a low contact angle (between the liquid and solid), which aids this process.

Not all powders used in cosmetics have favorable size and surface characteristics. The majority are of extremely small particle size and are highly agglomerated. The agglomerates will have a complex structure with an uneven surface and will be perforated by cavities of irregular shape. The complete wetting of such structures, involving the penetration of liquid into all the crevices and cavities together with the expulsion of air, is much more difficult. It should be noted that penetration into cavities requires a low contact angle but a high surface tension. This is in conflict with conditions for easy wetting.

Even more complex is the immersion of powders that swell in liquid to form dispersions of colloidal size, since the particles on the outside of each agglomerated mass tend to swell and adhere to each other, retarding penetration of the liquid to the still dry core.

The forces holding these agglomerates together are precisely the same as those described later in this chapter in the section on powder mixing. The obvious difference, of course, is that these agglomerates are situated in a fluid medium, the physicochemical characteristics of which may enter into the reckoning of bond strength, ease of separation, and likelihood of reagglomeration. Consequently, the theoretical treatment of particle-particle interaction in liquid media is even more complex than that for dry solids.

In cosmetic processes, the deagglomeration of solid particles in liquid media can be brought about by a variety of machines. In lipstick processing, for example, pigments are predispersed into castor oil or any other suitable liquid by preparing a coarse mixture that is then processed in a triple-roll mill, colloid mill, ball mill, or sand mill. These machines are used specifically because they can deal effectively with high solids content and high viscosities.

For less viscous formulas (e.g., the dispersion of pigments into the aqueous phase of an emulsion), a high-shear device of the rotor-stator type may be used. In this case, ensuring that the whole contents of the vessel are entrained into the shearing head by secondary stirring can shorten processing time. However, the pigments may be externally dispersed, as in the lipsticks mentioned earlier, before addition to the aqueous phase of the emulsion. Depending on the amount and type of color being used, a rotor-stator type of shearing device may increase the batch processing time. Because a ball mill utilizes only one pass to develop the color (and this may be done outside the manufacturing kettle), it is especially efficient for this method. A wetting agent should be used when dispersing pigments in this manner to aid in deagglomeration and

to minimize reagglomeration after processing. As with all deagglomeration, shear stress is critical for the particle disintegration of the agglomerate.

For soluble powders, the enormous increase in the solid-liquid interface brought about by immersion and deagglomeration ensures that the actual processor dissolution can proceed at the maximum possible rate. For insoluble powders, however, there remains the problem of maintaining a good stable dispersion. Deagglomeration is usually a reversible phenomenon, and it can usually be assumed that the opposite process, flocculation (particle accumulation), can take place simultaneously.

In the case of dry powder–powder dispersions, stabilization can be achieved by the introduction of particles of larger size to which disintegrated agglomerates can adhere. In some cases this can be applied to solid-liquid systems, for example, by preextending pigments onto talc before adding them to a liquid foundation base. In many instances all the solid particles might be too small in size for such a process. Under these circumstances, rules similar to those used in emulsion technology can be applied. Thus some or all of the following means can slow the rate of flocculation:

(1) The use of surface-active agents (sometimes as polymer coating of the powdered solid) to inhibit flocculation by steric hindrance.
(2) The manipulation of electrostatic charges on the surfaces of the powder particles.
(3) The manipulation of the viscosity of the dispersion.

Surface-active agents play a part at two stages in the process of manufacturing a stable dispersion. It has already been seen that the lowering of the solid-liquid contact angle speeds up the wetting process. In practice, the best results are often achieved not with a surfactant, which measurably lowers the surface tension of the liquid, but with what is sometimes described as a surface activator which reduces the interfacial tension between solid and liquid. These surface activators, (which are best described as "dispersing agents") can, if correctly chosen, cause an immediate improvement in the quality of the dispersion, which is manifested by an increase in the color intensity.

The rules for choosing a dispersant are similar to those used for surfactants in emulsions; part of the molecule must have affinity for the liquid medium and part for the solid. A significant difference exists, however, between emulsions in which the two phases have very different chemical affinities and dispersions of solids in which a hydrophilic solid is dispersed in water. Powders can be processed to coat their surfaces with a chemical (usually a polymer) of suitable characteristics to allow easy wetting and dispersion. Nowhere is this more clearly demonstrated than in the case of water-wettable and oil-wettable grades of titanium dioxide. In this instance, the same grade of titanium dioxide can be coated with different resins to modify the surface in such a way as

to make it wettable by either water or oil. Formulation problems resulting from flocculation are normally resolved before scale-up. Thus the addition of shear-thinning gums to nail lacquers and of colloidal thickeners to the aqueous phase of emulsions helps to slow down flocculation without materially influencing the basic flocculation process. However, reheating of liquid pigmented foundation products sometimes results in unexpected changes of hue, which are often erroneously ascribed to phase inversion. The truth is that the rate of flocculation of an intrinsically unstable dispersion has been increased because of a drop in viscosity caused by the heating process.

SUSPENSION OF SOLIDS

If a particulate solid is dispersed in a liquid in which it does not dissolve, if the suspension so formed is allowed to stand undisturbed in a vessel, and if the densities of the two components are dissimilar, some degree of flocculation will eventually take place. Where the particles are present in sufficiently low concentration to have a negligible effect on the viscosity of the suspension, the establishment in the liquid of flow patterns of sufficient turbulence can achieve resuspension. The suspension of solids in agitated tanks is frequently encountered in cosmetics processing as an aid to dissolution or as a means of obtaining a good dispersion of particles prior to a change of viscosity of the liquid medium by gelling or cooling. Although the theory concerning flow patterns in agitated tanks has already been discussed, it is necessary to reiterate that it is axial flow that is of prime importance in the movement of solid particles away from the top or bottom of a tank. At the lower viscosities a correctly sized propeller mixer at the correct angle for mixing is the best method for achieving the axial flow (Fig. 35.8(b)).

Three conditions can be recognized during the production of a suspension, namely, complete suspension, homogeneous suspension, and the formation of bottom or corner fillets [7].

Complete suspension exists when all particles are in motion and no particle remains stationary on the bottom or surface for more than a short period. Under these conditions, the whole surface of each particle is presented to the fluid, thereby ensuring the maximum area for dissolution or chemical reaction.

Homogeneous suspension exists when the particle concentration and (for a range of sizes) the size distribution are the same throughout the tank. The homogeneous suspension is always more difficult to achieve and to measure than the complete suspension. Nevertheless, homogeneous suspension is very desirable for certain types of cosmetic applications, and particularly so for continuous processing. In practice, for such processes the requirement is only

that the particle size distribution and concentration in the discharge of the homogenizer head and the vessel are the same.

Sometimes heavier particles are allowed to collect in corners or on the bottom of the vessel in relatively stagnant regions to form fillets. This may have the practical advantage of very large savings in power consumption compared with the energy that may be needed to achieve complete suspension (provided, of course, that this saving offsets the loss of the active/solids in the fillets).

In general, it may be said that a propeller at a 45° angle or turbines offer the best advantage for rapid suspension at low power consumption. If, on the other hand, radial flow agitators need to be used, these should be of relatively large shaft length-to-impeller diameter ratio, be placed close to the bottom of the tank, and have turbine blades extending to the shaft to prevent problems with central stagnant regions.

MILLING EQUIPMENT

There are many products in the cosmetics industry that require de-agglomeration and particle size reduction. Lipsticks, concealers, foundations, and mascaras are examples. They have a high solid content and are composed of pigments, fillers, and other powders dispersed in a liquid base. It is often necessary to reduce the gritty feel that these powders impart on the skin as well as to maximize the color development of the pigmented phases. By taking the portion of the formula containing the oversized and agglomerated solids, one can mill it to wet out and develop the ingredients. A pigmented phase should be milled until the shade cannot be developed further and the grit cannot be detected by touch. The method of milling will determine the required viscosity of the slurry to be processed. Colloid mills, ball mills, and three-roll mills are used extensively to deagglomerate and to produce the required feel and shade development. The colloid mill requires the lowest viscosity slurry of the three mill types mentioned and the three-roll mill requires the highest viscosity slurry.

Colloid Mills

Colloid mills are used as in-line devices. They work by hydraulic shear. The energy they produce is imparted to the product in a thin film. Colloid mills can be used to deagglomerate pigments or to disperse solids in liquid phases through recirculation. They can be used to build final viscosity in an emulsion system, as a continuous device.

The colloid mill consists of a rotor, a rapidly rotating conical member, which may be smooth, toothed, or grooved, and a similarly machined stator into which the rotor fits. Product is pumped through the mill inlet, and the fluid

mixture is forced through the small clearance [ranging from 0.004″ (0.1 mm) to 0.040″ (1.0 mm) gap size] between the rotating rotor and stator. The gap size can theoretically be set to 0.001″ (0.025 mm), but 0.004″ is typically used as a minimum to allow for tolerances due to wear in the rotor and stator. Figure 35.24 illustrates a typical design.

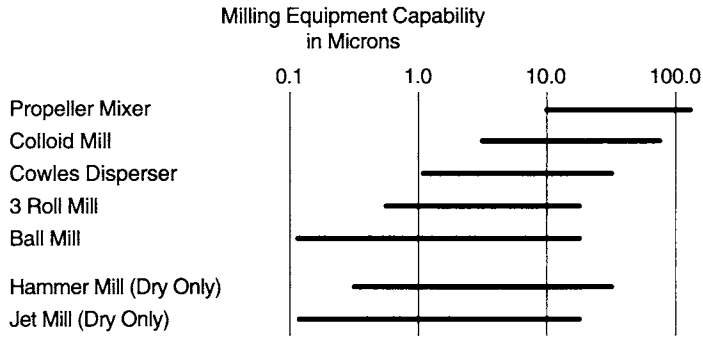


Figure 35.23. Particle size comparison for milling equipment

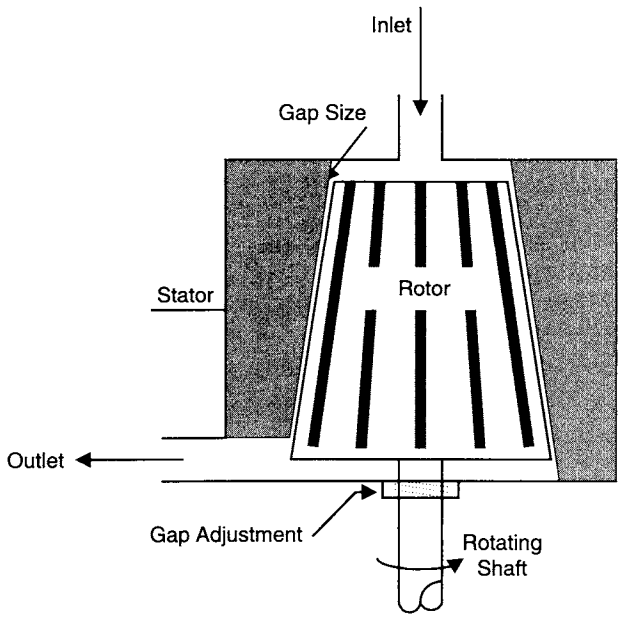


Figure 35.24. Colloid mill

There are three important process variables that affect product output: retention time, tip speed, and gap size. Each of these is a known quantity or can be measured, and each can be adjusted to give the desired result.

Retention time is the amount of time the product is exposed to the milling energy. The longer the product is in the mill, the smaller the particlet size will be. Retention time is dependent on the flow rate, rotor speed, back pressure, and gap size. The flow rate is easily measurable and should be controlled by a positive displacement pump. When rotor speed, back pressure, and gap size are kept constant, flow rate is the only variable controlling retention time. Average tip speed, the linear velocity averaged across the surface of the rotor, is the shaft speed multiplied by the average rotor circumference. Increasing the tip speed imparts more energy to reduce the particle size. Likewise, lowering the tip speed imparts less energy, which lowers particle size reduction. By varying the gap size, the product is forced through a different opening and a different void volume in the mill (see Equation 35.8).

Colloid mills are effective tools for reducing the size of particulates and dispersing agglomerates. They are usually scaleable from laboratory to production sizes if the style, retention time, tip speed, back pressure, and gap size are all kept constant.

Ball Mills

Ball mills are typically used as a side-batching or in-process device. Unlike the colloid mill, they are not normally used on the finished product, just the pigmented subphase. Ball mills are used extensively in the deagglomeration of solids (up to 60% concentration for some pigments) into a liquid medium and development of the pigment shades.

The rapid movement of grinding elements (media), which take the form of pebbles, balls, or finer sandlike particles, 1 mm or less in diameter, results in the breakdown of agglomerates. The mill style may be horizontal or vertical in which a rotor causes the grinding media to rapidly collide. The powder particles to be milled are subjected to both impact and high shear. Heat energy is produced during the milling process, so the milling chamber should be jacketed for controlled cooling. This will protect the product from reaching an unsuitable temperature. Figures 35.25 and 35.26 illustrate the design of vertical and horizontal ball mills. The annular gap or screen is used to retain the media in the mill and allow the milled product out. The milled product or phase may have to be filtered to ensure that any broken or worn media is removed.

Before a subphase can be ball-milled, the powders and pigments first must be predispersed; the quality of this predispersion may affect the quality of the finished grind. It is typical to design the process to have a ratio between in-feed

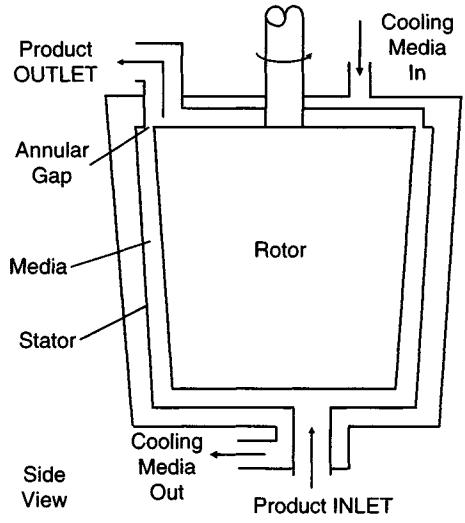


Figure 35.25. Vertical ball mill

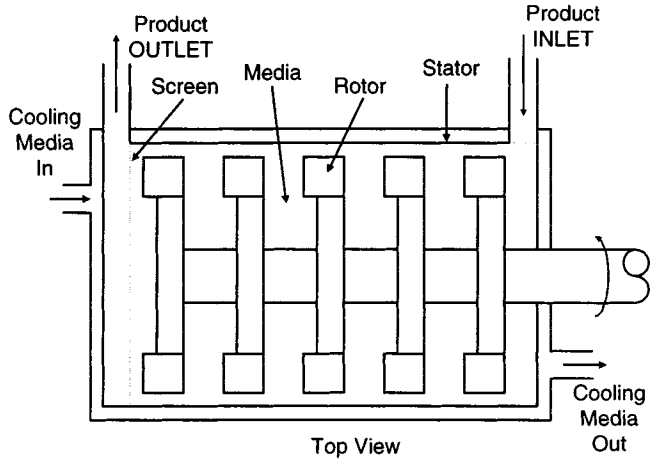


Figure 35.26. Horizontal ball mill

particle diameter to media diameter of 10 and 20 to 1. For example, if the infeed particles are between 50 and 100 microns in diameter, the milling media should be 1.0 mm in diameter [8]. If the media diameter to predispersion phase diameter is not matched, problems may occur. If the particles in the phase are too large, they will enter the ball mill and plug the screen or gap. Although

no oversized material will exit the mill, no material will be processed. If the media is too large, particles of the phase will pass between the media and not be efficiently milled. If the size of the media is too small, the power required will be higher and the particle size distribution exiting the mill will be wider than expected. Some particles will be exposed to high energy as they are processed through the mill, while some will see less as they travel a different route through the mill.

Choosing the proper media size can help control the finished distribution. There are five important process parameters that affect the milled product: retention time, rotor tip speed, media type, media size, and media loading. Each of these is a known quantity or can be measured, and each can be adjusted to give the desired result.

Retention time is the average amount of time each particle takes in the milling chamber. Generally, the longer a particle is exposed to the milling energy, the smaller the particle size will be. Retention time is a function of the void volume in the mill chamber and the volumetric flow rate of the slurry. The equations for retention time and related void volume are:

$$t = V_v/Q \quad \text{and} \quad V_v = V_c - V_m \tag{35.8}$$

Where: t = retention time in minutes
V_v = Void (available) volume of the mill in liters
V_c = Volume of the empty mill chamber, with the rotor in-place, in liters
V_m = Volume of the media in the mill in liters
Q = Volumetric flow rate of the product in liters per minute

The void volume is a function of the media loading (quantity and size used for the process). As the media loading (V_m) increases, the void volume (V_v) decreases, decreasing the retention time for constant flow. The void volume parameter (V_v) is easily controlled before processing. The flow rate is easily measurable and can be controlled by varying the speed of the product supply pump. Slower flow rates will produce higher retention time, generate an increase in the number of collisions, and yield a smaller particle size. The rotor speed controls the movement of the media, which controls the collision energy imparted to the slurry. Greater shaft speeds generate more collisions, which helps to reduce the particle size.

Choosing the proper media is crucial in getting the desired end product. Size and composition are the important factors. The media diameter must be greater than the annular gap size, otherwise media will be found in the product and normally is at least three to one media diameter to gap. Common media types used are sand, stainless steel, glass, zirconium oxide, and zirconium silicate.

The hardness (or density) of the media will determine adequate grinding versus wear on the chamber. Harder (or denser) media will reduce particles better than less dense ones. However, the interior of the mill may become pitted and wear faster. Media that is too brittle may fracture and be found in the product. The breakage pattern of the media (e.g., pulverization, crumbling, or slivers) should ensure that no long slivers or damaged media are passed through the screen and are found in the finished product. Ball mills are widely used in the cosmetics industry today. They are effective tools for grinding and reducing agglomerates. They are usually scaleable from laboratory to production sizes if the equipment style, retention time, rotor tip speed, media type, media size, and loading are kept constant.

Three-Roll Mills

Three-roll (roller) mills are typically used as side-batching or in-process devices. Like the ball mill, they are not normally used on the finished product, just on the pigmented subphase. Unlike the ball mill, particles are ground down to reduce their agglomerate size. Roller mills are used extensively in the dispersion of high solids content (and high viscosity) pigments into liquid media and for full development of the pigment. Typical solids content for a roller mill grind is 50 percent or higher.

The roller mill consists of three rolls each operating at different speeds and a take-off knife or doctor blade. The mill reduces particle size by using shear (adjacent rolls operating at different speeds) and mechanical pressure. The first roll (the roll nearest the operator) operates at the slowest speed, the middle roll is faster, and the third roll is the fastest. Material is transferred from roll one to roll two to roll three, where it is scraped from roll three with a knife-edge blade. In order for the material to move from one roll to the next efficiently, it is necessary for the material being ground to have some tack. Without tack, material transfers very slowly, if at all; but if the material is too tacky, it may pass through the mill too quickly.

The percent solids content of the slurry should be controlled by how well it performs on the roller mill. This needs to be developed in the laboratory. The slurry should be observed at several different points in the process, both in the laboratory and during manufacture.

Production size three-roll mills are manufactured with a slight crown (outward curve) to each roll. This is done so that as pressure is applied the rolls will flatten. The material coming off the knife blade is referred to as the tongue. If enough roll pressure is not applied, the tongue will be longer in the middle and shorter on the ends, as seen in Figure 35.27(a). If too much pressure is used, the tongue will be longer at the ends of the roll and shorter in the middle, as seen in Figure 35.27(b). With the proper pressure, the tongue

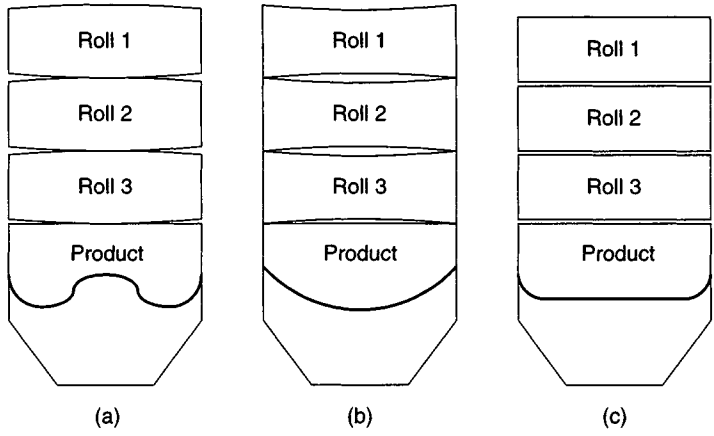


Figure 35.27. Three-roll mill pressure control

will be even all the way across the knife blade take-off plate, as seen in Figure 35.27(c).

Three-roll mill procedures are time-consuming; however, the mechanical energy imparted to the product is very effective. Due to general safety and cleaning difficulties, three-roll mills are not preferred for production. Due to the design of the feed system, particularly during the cleaning operation, items can be drawn into the gaps, called "nips," which pose a safety hazard to the operator. As the rolls are worn, minute pitting occurs. These pits can hold fine pigments and lead to contamination problems with subsequent batches. This enhances cleaning difficulties. Fortunately, based on the availability of raw materials, it is usually deagglomeration and not particle size reduction that is required, so alternate systems can be considered.

FILLING

Most cosmetic products are filled from stored bulk in machines specifically designed to handle the packaging units of a particular product. Great care must be taken in choosing and setting up these machines. The main problems concern the limitations of the machines themselves rather than the product being filled. There are at least two areas, however, where a special understanding of production filling requirements and constraints, and formula characteristics are essential for achieving efficient production. These are the molding processes (lipsticks, wax-based sticks, and alcohol-stearate gels—discussed on pages 844–846 under warm and hot fills on page

836), and compression processes (compressed eyeshadow, blushers and face powders—discussed under filling pressed powder later in the chapter).

Different products require different types of equipment to be filled effectively, which result in low cost per unit, high filling rate, low maintenance of the system, and controlled product characteristics. When selecting the proper equipment, two key questions must be answered:

1. What are the physical characteristics of the product to be filled—viscosity, flowability, temperature, shear sensitivity, potential for aeration?
2. What type of container is being filled—bottle, jar, tube, godet?

The answers to these questions along with (to a lesser degree) the speed at which the product needs to be filled will determine the type of filler that will be needed.

FILLING—LOW VISCOSITY PRODUCTS (LOTIONS, TONERS, LIQUID MAKEUPS)

Vacuum/pressure/fill-to-level equipment can take advantage of the flowability of low viscosity products to produce a very efficient fill. In vacuum/pressure equipment, the product is either pushed via a pump or gravity system or pulled via a vacuum system to the container. When the fill reaches the set height, any additional product (overfill) is directed away through a return nozzle (which is incorporated in the filling nozzle, Fig. 35.28). In these systems, the product continually flows through the nozzle, bypassing the nozzle outlet when it is not filling. Both the excess fill and the bypassed product are returned to the filling hopper. The product is then available to be reused during the filling run.

A level sensing system uses a slight air pressure flow that is delivered through a control line attached to the tip of the filling nozzle. A control sensor notes the change in back pressure once product has filled the package and reached the sensing tip of the control line. The sensor then stops the delivery of product to the filling nozzle.

Both types of filling systems fill to a set level, regardless of the container size, shape, or capacity (internal dimensions of the package). They allow a great deal of volumetric variation while delivering an aesthetic fill. This may be of critical importance for some package designs. The production of plastic packages is much better controlled dimensionally than for glass packages. The variation on a glass package volume can be as high as 10% and still be considered acceptable.

A simple timed fill can also be used with these products. For this type of operation, the product is pressurized to a filling nozzle, which is designed to open for a set period of time. These machines can be set very accurately. The

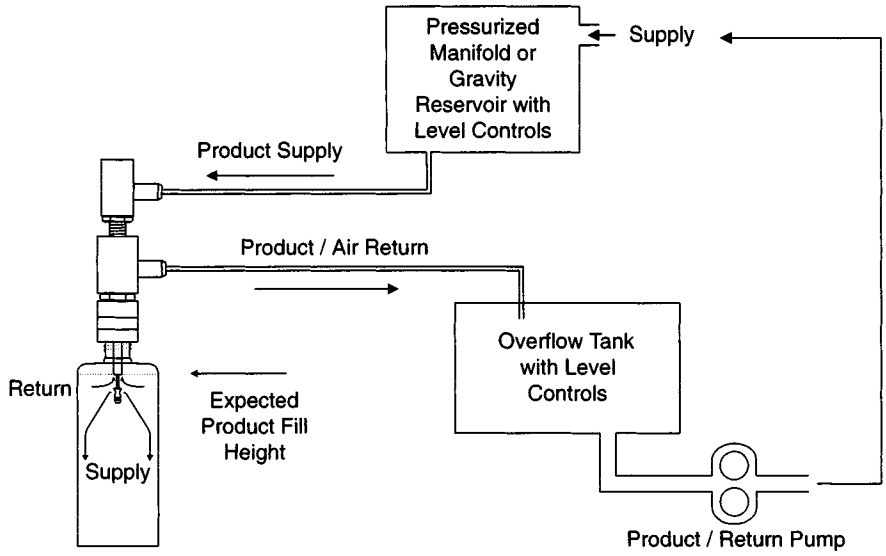


Figure 35.28. Liquid fill-to-level system

flow rate is controlled by the size of the nozzle and the supply pressure. This method is often used for very short runs of makeup products, since there is very little to dismantle for cleaning. These fillers should not use a gravity hopper since the flow rate will change as the product level changes during the fill.

Low viscosity products can aerate, foam, and striate during the handling and filling operations and affect the aesthetics of the fill by producing underfills, wet packages, poor seals, low production yields, and so forth. Shear sensitive products raise special concerns when setting up and operating the filling system. Poor setup will result in high recycle and bypass rates, which will continually add shear to the product, increase the probability of aeration and contamination, and probably produce foam in the filling hopper. By choosing an improper pump type (centrifugal versus positive displacement) and size, significant shear on the product can be the result of excessive recycle and high bypass rates. Nozzle sizing is often determined by the constraints of the package. Small nozzle size, along with high production rates, may not work well together. The rates may have to be slowed when small nozzles are used to control the flow near the top of the bottle and limit the shear on the product. These factors can limit all the production rates and all key production concerns when any new formula is produced. For efficient production and improved control, low viscosity products depend on check valves fitted into the nozzles.

FILLING—HIGH VISCOSITY PRODUCTS (CREAMS, MASCARAS, MASKS)

Products in this category will not flow readily without the assistance of an outside force. A "positive displacement" (PD) filler system is required. A PD system includes a controlled pump that works in tandem with a piston or related device, which can overcome friction and flow problems to move finished product through the filler (Fig. 35.29). With very viscous products, a pressure hopper and/or ram pump is also needed to supply nonaerated mass to the filling chamber (aerated mass will produce inconsistent fill quantities). The ram pump system contains a plate that pressurizes the supply container and minimizes aeration as the product is pumped. Pressure is often required to maintain product flow to the filling nozzle. A crowder may be designed into the hopper for this purpose. It is designed to push the mass toward the nozzle slowly while maintaining an air-free environment.

A piston or positive displacement pump is then used to dispense the product in a controlled manner. By design these fillers dispense a reproducible quantity of product for each rotation of the chamber (piston cylinder or pump head). To dispense different quantities, the piston stroke length or the number of revolutions of the pump can be adjusted. High viscosity products will typically "break off" cleanly from the nozzle tip. Special nozzles are rarely required except to control the curl, or wave, that can be developed upon completion of the fill (ice cream curl).

Beyond the use of special nozzles, high viscosity products may require special handling procedures to fill the package without voids. Bottom-up fill capabilities are often required. This also allows the minimum of residual product to remain on the nozzle tip, possibly affecting the fill of the next package. In bottom-up filling, the nozzle will dive down to the bottom of the package and rise as the level of product increases in the package. The timing between the rate of the nozzle rise and the product flow rate must be

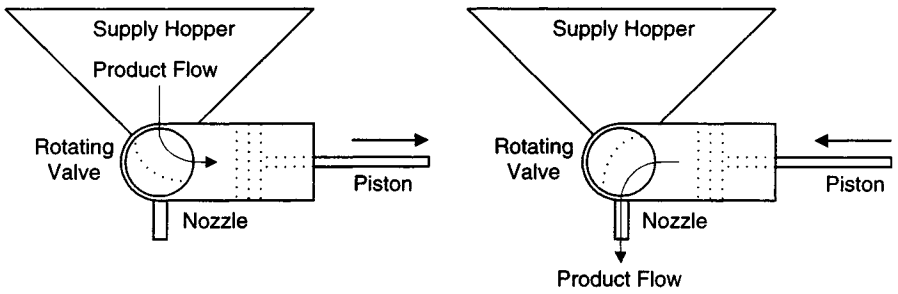


Figure 35.29. Positive displacement filler

controlled for consistent fill. Sometimes the rates may be stepped, instead of continuously controlled to ensure that product flows into all the lower corners of the package. Some difficult-to-fill packages may even require the finished package to be spun to induce the product to move into all of the top corners of the package. The packaging of viscous products in clear containers without visible voids is difficult to achieve consistently even with the current state-of-the-art controls and therefore should be avoided. The use of opaque bands on the package to hide potential areas of voids may make the filling operation appear more successful.

Some products will be packaged with a disc placed between the top of the jar and the cap. The purpose of the disc is usually to minimize the air contact with the product in the filled package. This may be due to the activity of the raw materials in the formula and to the microbiological sensitivity of the product. Other functions of the disc are to minimize a separation of the product at the surface or to prevent moisture from accumulating after a warm (above room temperature) fill. The determination of proper and acceptable disc contact are troublesome specifications for the line operator and mechanic. One hundred percent coverage is preferred. However, any overfill of the package would mean the disc no longer fits and that product will be squeezed out of the package into the threads. Significant underfill means no disc contact at all. Typical contact is between 60% and 80%. The design of the package and the filling system used will determine the actual range. It is typical to produce a bottom-up fill with the ice cream peak for improved contact. The peak is pressed down when the disc is placed, ensuring contact.

Products of low viscosity typically flow easily; they do not require the use of a PD system. PD systems are not as production-efficient (they are relatively slow) when compared with the alternate systems described earlier, which can provide higher production rates with fewer problems. However, most low viscosity products can be filled on the same equipment as high viscosity products (which is often done in the laboratory or pilot plant). Since low viscosity products typically need check valves fitted into the nozzles, this may slow the filling rate further.

FILLING—SHEAR-SENSITIVE PRODUCTS

The package will have a direct effect on the minimal shear that is added to the product during filling. Typically, a large diameter filling nozzle will produce less shear on the product during filling than a smaller size. A tube usually has a large opening by design. Therefore, the mass is rarely sheared during filling. Most bottles have a limiting neck size, but plastic is usually larger than glass for the same size cap. Jars may allow the most flexibility but can be a major problem if small promotional pieces are to be handled.

For shear-sensitive products, the pump used to supply the filler as well as whether to allow recirculation must be examined. Specially designed low-shear pumps, along with careful setup by the operator, can minimize recirculation and control the quantity of shear that may affect the finished product. The limited available adjustments on the equipment may be critical and force some shearing during filling. It may not be possible to maintain all of the "perfect" settings on the systems available to production. The low-shear pumps have special requirements that can limit their use for normal processing, for example, special seal concerns, limited flow rates, and difficulty in cleaning.

PACKAGING LINES

Fill-to-level packaging systems lend themselves very well to rotary configurations. A great deal of filling operation is performed within a short period of time. The time can be increased, with a minimal loss of productivity, by increasing the size of the line. With a rotary table, a small increase in table diameter translates to a large increase in available time for the filling process. Therefore, the flow rate can be reduced. Rotary fillers are also used to minimize floor space required for large production runs. Different filling actions can be performed in a limited space, around the rotary table, for example, bottle placement, filling, cap placement, and bottle transfer to the remaining portions of the packaging line. For large production packages, greater than 16 ounce (473 milliliter), slower lines are often needed to minimize the shear stresses on the finished mass during extended filling times. For these large packages, almost any type of filler can be used. Unlike the related smaller packages, the majority of the production time will now be used during the filling cycle, not for bottle handling, capping, and labeling. This slow speed line is often set up in a straight line along a wall to maximize the space in the room for other, higher speed, production lines (Fig. 35.30).

WARM AND HOT FILLS—CREAMS AND DISPERSIONS

A product that must be filled at an elevated temperature offers a challenging set of obstacles to overcome. The most important thing to remember is that after bulk manufacture and storage, the product must be heated before filling. This may amount to remanufacturing the product. Most products that require a warm, not hot, fill do not reprocess well and must be filled just after batching. This forces the use of a "just-in-time" operation with its associated production concerns, such as microbiological testing not being completed before filling. Possible concerns include the requirement for warm holding tanks with special agitation, the availability of packaging components, the availability of the production line, and special handling of the finished package.

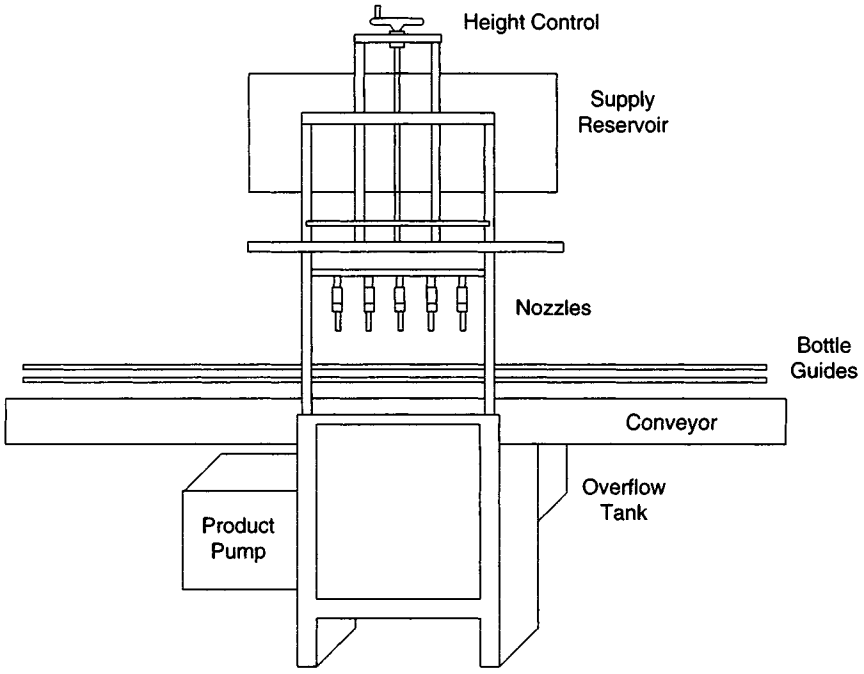


Figure 35.30. Line version of a rotary filler

Moisture is a warm and hot fill problem that is always present and depends on the formula, package, and filling area. If the product is anhydrous, the only concern is high humidity in the filling area. Moisture from the air in the package's head space may then condense on the surface of the filled package as the product slowly cools. Droplets of water can easily become locations for significant microbiological growth since it will not combine with the product. Fortunately, this rarely is a concern. If the product contains water, however, moisture can easily collect on the surface during cooling as the water leaves the product at the air interface. When filling into a tube, this is of minimal concern. The tube is squeezed in use. Any moisture will be blended with the product and sheared as it exits the orifice. When filling into a jar, a special cooling operation may be required to minimize moisture on the surface. This cooling operation is time-, temperature-, and airflow-dependent. Its purpose is to cool the filled mass and evaporate any moisture on the surface at the same time. Evaporation is necessary from both an aesthetic and a microbiological standpoint. A disc may be added to the filling process to help keep the available surface area to a minimum and cut down on the time required after filling to seal the package. However, if the amount of disc contact is insufficient, a pool

of water may still collect and be the first thing the consumer sees upon opening. A typical cooling tunnel will allow the package to cool for at least 20 minutes with 10 °C to 25 °C air flowing around and over it. Dust and dirt, as well as microbiological contamination are concerns during the entire cooling time. A standard protocol should be followed for all fills from the laboratory bench through the pilot plant and into production for consistency and uniformity.

WARM AND HOT FILLS—GODET PRODUCTS

When a product is not filled at or around the optimum temperature, its hardness or texture may be adversely affected. This is readily noted with the change in pay-off or application when filling godets. Adverse effects can also occur when the product is not remelted to at least the minimum melting temperature. The best way to determine these temperatures (which may or may not be the same) is heating and cooling curves obtained with a differential scanning calorimeter (DSC).

A key problem for production is in trying to match the aesthetics on the filling line of the "approved" sample, which was carefully poured into the container in the laboratory. A filled product on the manufacturing line may never match the surface appearance of a laboratory poured sample. This is a particular problem when filling godets (small pans). Once the formula is ready for manufacture, a test fill should be performed on the actual filling line or a similar piece of equipment that can be scaled to the actual filling line. This is done to determine true operating parameters and to develop standards that the manufacturing facility can achieve within the expected production rate.

Once the correct filling temperature is established, there are other filling parameters that may affect surface appearance that can be set by trial and error. Some of these variables include nozzle size and outlet shape. Some nozzle types include a flared head (outward like a funnel or inward making a smaller diameter), a showerhead type (large opening with multiple holes), or a straight-through nozzle. The change in nozzle design can be used to minimize dripping and change the pour dot on the surface of the godet. The nozzle's internal diameter and flow rate determine how forcefully the product enters the container. The distance from the filling nozzle to the container affects the spreading of the product into the container. The different types of container used (steel, aluminum, tin, or plastic) all dissipate heat at different rates, which affects the spreading and cooling rate of the product and often the surface finish. The filling belt speed determines how evenly the product fills the container. Preheating of the containers, particularly metal pans, can help provide a more evenly filled product. Postheating of the filled containers may provide an aesthetically pleasing, smooth finish. However, if too much heat is applied, the texture

of the product may be altered, pearlescent pigments may migrate to the surface, or pigments may settle to the bottom. The type of conveyor used on the filling line will affect the filling operation—for example, a metal belt will hold heat, while a rubber or fabric belt will not. However, metal belts may be needed for pre- and postheating. The use of a cooling tunnel for quick cooling of the filled pieces may also affect the finished product. Too quick a set may develop an improper surface appearance or crystalline structure of the product. A good deal of trial and error is needed to establish filling parameters for a hot pour product.

WARM AND HOT FILLS—LIPSTICKS, LIP BALMS, SUPPOSITORIES

When filling into a mold (e.g., lipsticks, lip balms, suppositories), key areas of concern are the following: aeration, cooling rate, shrinkage, and finishing steps. Molds come in two basic designs—book and individual. Book molds contain several sections (leaves) that are held together to allow for filling multiple cavities. These are typically between two- and five-piece molds. The use of the mold allows for complete or partial use of the cavities by the operator. In general, there is a large amount of metal around each cavity to provide good heat transfer. Individual molds are built into a filling system. These molds (metal, plastic, or a silicone/rubber) are filled and cooled as part of an automatic system's operation. Less metal is involved, so a cooling medium is required to control the product temperature.

Most book-style molds are filled to overflow capacity. This ensures a complete fill after cooling, which may produce sinkholes. Sinkholes are a result of contraction of the solidifying product that begins at the cooled surface. The cooling of the mold may take place through a chilled liquid bath, on a chill-table or chill-tunnel, or in a refrigerator or freezer. Variations of these techniques can be duplicated from the laboratory through production. Air-cooling in the laboratory, however, cannot be duplicated in a production facility. Most godets contain very little mass, so production can simply use a longer belt to allow for a longer cooling time, when compared to the laboratory. Cooling time is more important for bullet-shaped products that may partially set quickly but finish developing their crystalline structure after a time between several minutes and 24 hours. This makes immediate handling of the just-molded stick a problem for many production designs.

Lipsticks are normally filled in a mold with the finished tip down. Lip balms are normally filled directly with the finished top up into the case. Other hot-fill products can be produced using minor variations of these two methods. Sinkholes are sometimes believed to be good for a stick product, assuming

they do not interfere with the lift mechanism. They are said to offer two outer surfaces for increased strength. Breaking strength is formula-related and differs for every shade of every product produced. To minimize aeration of the molded sticks, the mass may have a vacuum applied to it just before filling. The quantity of vacuum necessary will be formula- and temperature-dependent. Improved filling methods can also minimize aeration during fill. These methods include the use of diving nozzles, slanted molds for improved flow into the cavities, and slow flow rates to minimize swirling of the mass as it leaves the nozzle.

Finishing of the sticks is very product-specific. Most lip balms have a waxy texture that is acceptable to the consumer. Also, the finished package is rarely elevated completely before use. Therefore, a minimum of treatment is required. Lipsticks are not as simple. Since the consumer will often raise the bullet to near its full height before use, the entire appearance must be acceptable since it is continually in view. A "flaming" operation is usually performed to improve the finished appearance of the sticks. Although a flame may be used, alternate heat sources are often used (heat guns, lamps). The heat is used to melt any mold marks or other imperfection in the lipstick and to produce a smooth, shiny surface appearance. Different production techniques are available ranging from fully automated systems (that include the pouring, molding, insertion into cases, and "flaming") to 100% manual systems. The choice will be dependent on the formula, the finished package, and the production requirements.

ANTIPERSPIRANTS AND DEODORANTS

Antiperspirants (A/Ps) and deodorants are processed much like other cream and lotion emulsions using similar equipment and processing methods. High-shear mixing (homogenizer or colloid mill) is used to ensure complete dispersion of the solids, typically the actives, in the formulas. One must remember to follow governmental regulatory guidelines for the A/Ps that are regulated as over-the-counter (OTC) drug items in the United States.

Stick formulations offer a filling challenge. Like lipsticks and other hot pours, the filling operation can be more critical than the processing of raw materials into the final formula. For sticks to set properly:

(1) The mass must be hot enough so that it flows into and around the component elevator.
(2) The mass must eliminate "white spotting" caused by liquid crystallizing on the case walls.
(3) Pour marks, typically along the case wall created by hot spots where liquid is ejected from the filler nozzle, must be eliminated.

(4) The mass must set up quickly without shrinkage. A quick set is needed to prevent the suspended solids from settling and to effect a good surface appearance. Shrinkage produces a poor appearance to the consumer and can affect the package mechanism.

Thus the formulation must be held just above its drop point with sufficient mixing so that the active ingredients, usually aluminum complexes, are kept uniformly suspended while the product is filled. The drop point can be accurately determined using a DSC or by measuring the temperature at which a solid sample liquefies and "drops" out of a test apparatus. Jacketed hoppers with mixers that are capable of holding mass within ±1°C, heat traced lines and filler assemblies, preheating of the packaging component(s), and the use of cooling tunnels are normal for stick manufacture. In large-scale operations the mass is often recirculated from a jacketed mixing vessel through a customized filler manifold on a specialized filling line. A number of these filling operations and the equipment associated with them have been patented. Because of the complexity, it is advisable to utilize "make-and-fill" or semi-continuous processing for A/P and deodorant sticks. If the filling is separated from the compounding step, it is imperative that measures be taken to ensure that uniform product be delivered to the filler. The bulk can easily striate as it sets up in storage. The solid bulk must be sliced vertically for proper remelting or the entire contents of each storage container will completely melt and mix to uniformity before it is brought to filling temperature.

SCALE-UP

The cosmetics industry has been considered collateral to the fashion industry. The driving force for the product development efforts of both industries is the marketplace. The cosmetic chemist is faced with the challenge of formulating products with active ingredients, rheology, and aesthetic characteristics dictated by the marketing group. Laboratory-scale equipment is used to develop and achieve the desired product characteristics. The chemist's beaker is the place where the scaling process begins, which will culminate in production's vessels. It is common to develop a process that fits current manufacturing equipment because the time to launch a new product is almost always short and the lead-time to purchase and install new equipment is almost always long.

It is not unusual for a product that was successfully developed in the laboratory to exhibit quite different characteristics when it is transferred to production. As the product is transferred from a small, laboratory-scale apparatus to large-scale production equipment, a difference in conditions is experienced.

Even if a pilot plant is available for an intermediate scale, there is no guarantee that problems will not be encountered during manufacture of full-scale production batches. Scale-up, which is of fundamental importance to the efficient manufacture of cosmetics, is an extremely complex subject because the variables that determine the distribution of forces within a processing vessel vary considerably as its size and volume change.

Process scale-up is typically an engineering function, and this segment is written to provide information to the formulator that would not ordinarily be available. In general, the formulator develops a product without sufficient awareness of the problems that can arise during scale-up. The pilot plant is then an essential and valuable tool in choosing the equipment and processes needed for full-scale production. This is an area where a fundamental understanding of unit operations and a willingness to experiment proves most fruitful.

The items most often considered by the process team during scale-up from the laboratory bench to production are:

1. Mixing
   - Impeller dimensions and types (e.g., 1.5 pitch marine style, 316 stainless steel)
   - Impeller tip speed (e.g., RPM and diameter)
   - Impeller diameter to tank diameter (D/T ratio)
   - Turnover rate (number of batch turnovers per unit time)
   - Flow profile (based on the impeller and vessel configuration and batch loading)
2. Heat Transfer
   - Heat transfer medium
   - Heating and cooling rates
   - Maximum and minimum temperatures
3. Mass Transfer
   - Phase transfer rates

The task of the process team is to understand the characteristics controlling the process, the characteristics that must be kept constant, and those that may be allowed to vary.

One method of scale-up is to develop the product on the bench using plant (full-scale) limitations. In this method, mixing times, heating/cooling rates, and phase addition times will be held constant from the laboratory to the pilot plant and into full-scale production. The disadvantage of this method is that it will stifle creativity at the bench due to current manufacturing limitations. The existing plant becomes the model, and even the pilot plant is designed to mimic its environment and limitations.

If a cosmetic company is to prosper, it must continue to expand its technology base with new and innovative products and up-to-date production equipment. Basing all scale-up on the plant will not lead to the degree of innovation necessary to achieve vigorous corporate growth. A more progressive

approach to the scaling process makes newer technology accessible to the chemist through the pilot plant and the processing team. The formulator now has the resources of a process team not only to guide a new product from bench to production, but to suggest and institute new technology to improve the entire process. In this approach the formulating chemist and the process team together will drive the development effort forward so that the manufacturing plant can purchase and install new technology to manufacture new products.

MIXING

There are many different types of mixers used in the cosmetic industry. The marine propeller works well at viscosities below approximately 5,000 centipoise. Above this viscosity paddle-type mixing is usually required. Three rules to apply during scale-up are:

1. The same design propeller should be used in the laboratory, pilot plant, and manufacturing.
2. The mixer tip speeds (linear velocity) should be maintained within the same magnitude.
3. The batch turnover rate should remain constant.

The batch turnover rate is calculated using the pumping data supplied by the propeller manufacturer. Liters per revolution or gallons per revolution data supplied is usually based on using water as the medium. Mixer speed and the flow rate through the mixer are calculated in liters per minute or gallons per minute. As stated earlier, the mixing time required, ensuring that every part of the mixture has passed through the mixing impeller at least once, is for three times the theoretical flow rate.

The scale-up team needs to be aware that propeller mixers used in the laboratory are drastically oversized. Increasing the diameter or speed of the mixing blade will increase the horsepower requirement throughout scale-up. Increasing the blade diameter has a much greater effect on horsepower than increasing speed. To maintain scalability from the laboratory through production, a standard D/T and tip speed should be used. This will cause the most difficulty for the formulating chemist since the movement in a 1-kilogram beaker will appear to be minimal.

HIGH-SHEAR MIXING

High-shear mixing typically refers to the use of a homogenizer. There are many homogenizers on the market. As with propeller mixers, their characteristics need to be determined and understood before use. Unfortunately, the data

available through the manufacturer are often minimal and cannot be related easily to the formula under development. Data developed by the manufacturer most often were gathered using water as the working fluid. Actual data must be developed for each process and refined for each formula. To make scale-up easier, the shear developed over time must be quantified. The change in viscosity over time or particle size reduction over time data are required. The same type of problems exist with homogenizers as with propeller mixers: homogenizer speed, peripheral speed, homogenizer diameter to tank diameter (D/T ratio), turnover rate (flow per unit volume), homogenizer diameter, and flow profile. As with propeller mixers, the equipment used in the laboratory is usually oversized. In-line homogenizers allow for additional control and can make the scale-up process easier. Drop-in homogenizers are more difficult to scale up.

When scaling products that require rotor/stator homogenizers from the laboratory to production, several major criteria should be addressed. The first consideration is to keep the design of the homogenizer constant whenever possible. Second, a constant shear rate should be achieved by maintaining the peripheral (tip) speed of the rotor constant for all batch sizes. Tip speed is defined as the linear velocity of the rotor tip at a given speed and is calculated as follows:

$$T = (\pi x D)(R) \tag{35.9}$$

Where T = Rotor tip speed in meters per minute
D = Diameter of the rotor in meters
R = Rotor speed in revolutions per minute

The third consideration should be the flow rate through the homogenizer. By maintaining the batch turnover rate constant for all batch sizes, the shear rate per unit time will be maintained. This ensures that the same shear is imparted to the product over an equal time period. Additional concerns are homogenizer diameter to tank diameter (D/T ratio), turnover rate (flow per unit volume), and flow profile.

HEAT TRANSFER

When a product has been satisfactorily produced on the bench, the set of parameters used in its development must be duplicated in the production environment. Heat transfer on the bench is controlled most often by a steam table or hot plate for heating, and a water/ice bath for cooling. Agitation is provided in order to ensure the reaction mixture is homogeneous in both temperature and composition. The formulating chemist is very concerned with the batch temperature because, in order to form a proper emulsion, the waxy components

must be completely melted. Other raw materials have maximum and minimum temperature parameters, which also must be respected. During mixing of the oil and water phases, one must maintain a particular temperature and provide enough mixing to allow proper formation of the emulsion. The combination of proper temperature and adequate mixing should ensure the desired results. What is often not given proper consideration is the heat transfer rate. How fast or slow the product is heated or cooled is critical in bringing the process successfully from the bench to production. The process team is faced with the problem of duplicating the bench process in production.

A one-kilogram batch can be heated from 25 °C to 85 °C in 20 minutes. This is a 3°C per minute average rate. This rate is easy to attain in the lab but is difficult or impossible to attain in production on a 2,000-kilogram continuous stirred-tank reactor (CSTR). If this average rate must be attained in order to make satisfactory product, the process team will have a difficult time. In order to increase the heating rate, process development and production must raise the steam pressure to attain a higher kettle jacket temperature. This can lead to situations where components of the batch can be burned onto the kettle wall. Active ingredients and preservatives may be overheated, voiding their usefulness in the product. Carbomer and gum solutions may produce flakes on the kettle side, which under side-wiping conditions may result in specks or graininess in the final product. Once a batch is at a high temperature, the time at which it remains there may be critical due to volatile and heat-sensitive raw materials. Fortunately, the heating rate is seldom a scaling problem because its rate is rarely the critical processing factor.

The cooling rate is often more critical than the heating rate because of the need to allow waxes and gels to set their structure in the desired manner. If the product is a complex emulsion with an inversion temperature, attaining the proper rate of cooling through this point is absolutely critical. Because the energy-input rate due to mixing must be constant, lengthening the cooling time in production may result in a ruined emulsion due to overmixing.

The chemist normally will not use a heat transfer medium other than tap water for cooling. This can range from 10 °C to 18 °C or more depending on location and season. Ice may be added occasionally if the product must be quick-cooled. The process team must also attain the same cooling rate upon scale-up. If too fast a cooling rate is demanded, the process team may respond by providing a jacket temperature lower than normally used by the chemist in the laboratory. This may result in freezing or crystallization on the kettle surface. If the product contains many waxes, crystallization may occur prematurely and the final product may be grainy, lumpy, and not meet specifications. The reason for the variation in time versus temperature data when a product is scaled from a beaker in the laboratory to a CSTR in production

is the ratio of kettle volume to jacket surface area available for heat transfer. In any CSTR scale-up system, as one goes from a small volume to a large one, the volume of material to be heated/cooled increases as a cubic function, whereas the surface area increases as a square function. This exponential difference must be overcome in order to provide the proper heat transfer rate. As a typical illustration of this processing dilemma, a 1-kilogram cream or lotion batch may be cooled with tap water at 12 °C from 78 °C to 30 °C in approximately 16 minutes. This is a 3 °C per minute average cooling rate. For the same product in a 100-kilogram kettle, using the same temperature tap water at optimum flow rate, the average cooling rate slips to approximately 1.5 °C per minute. If we scale to a 500-kilogram kettle, this rate is even less favorable. Typical rates can be as low as 0.15 °C per minute or less, depending on jacket quality, design, and so forth. What happens during this additional cooling time as we scale from small to large? Mixing is prolonged and may not duplicate the product cooled on the bench by the chemist at a rate of 3 °C per minute. For this reason, *the chemist must strive to keep laboratory conditions similar to what is attainable in production.*

Not all products react adversely with bench-to-production variations. There are many products robust enough to withstand all but the most extreme variations. But as the science of cosmetics progresses, emulsion systems for creams and lotions, soap systems for shampoos/conditioners, and gels for body washes are becoming very sophisticated and sensitive to process variation. Thus heat transfer and heat transfer rate should always be carefully considered during formulation and scale-up.

MASS TRANSFER

In scaling up or down, phase addition times should remain constant. It is important that the rate of dilution remain constant as the batch size changes from the laboratory bench to production. This is particularly true for emulsion products during the emulsification. Maintaining this requires a conscious effort at the laboratory level. Since production often cannot transfer at rates that the chemist uses at the bench (seconds), without safety being a concern, laboratory processing must be based on actual production capabilities. Even a slow laboratory transfer may be too fast for production once the rate is scaled. One hundred grams in 30 seconds for a 1-kilogram batch is a slow-dripping addition. For a 2,000-kilogram production batch this becomes 200-kilograms in 30 seconds (with comparable agitation in the vessel). Since the mixing rate is slower, particularly for viscous systems, the dilution and related transfer rate should also be slower. Most emulsions will have a transfer phase of 10–30% of the batch. In the pilot plant and in production, this phase should transfer

in 15 to 30 minutes (silicones are a noted exception). *Laboratory operations must allow for similar addition rates.* Since the transfer phase is usually hot, partial additions over the expected time period are better than a slow addition at an uncontrolled temperature.

DRY SYSTEMS

Table 35.1 distinguishes between two types of solid-solid mixing operations: those concerned with segregating powders and those with nonsegregating or cohesive powders. The essential difference between these two categories relates to the properties of the powders themselves and, in particular, to the freedom with which individual particles have to move independently of their neighbors. Free-flowing powders exhibit many process advantages (such as easy storage, easy flow from hoppers, smooth flow into packages), but have the disadvantage that they tend to segregate unless all the constituent particles are of very similar shape, density, and size. Cohesive powder, on the other hand, lacks mobility and individual particles are bonded together and move as clumps or aggregates. Although segregation is not a problem (except, as can be seen, at very small scales of scrutiny), cohesive powders are difficult to store and do not easily flow from hoppers (bulk powder storage).

In a powder mass, there are forces at work that tend to make the particles bond to each other, and these are balanced by the gravitational mass of the particles that cause them to fall apart again. Although the bonding forces for a given powder are largely independent of particle size, their gravitational mass is not. Since the gravitational forces are based on the mass of the particles, particles will stick together only when they are small enough for the gravitational forces acting on them to be much smaller than the bonding forces. Powders composed primarily of such particles exhibit cohesive characteristics, and those consisting of larger particles tend to be free-flowing. To a first approximation, the division between the two types of powder is approximately 50 μm; below this particle size, powders are cohesive.

Figure 35.31 shows the particle size range of commercial grades of some powders commonly used in cosmetics production; by inference, it will be noted that they are all predominantly cohesive in nature.

The nature of the bonding forces between powder particles is of fundamental importance to many industries and is well understood [9]. The characteristics of these forces, which are essential to understand, are as follows:

- The forces operate over very short distances. Particles must be brought into very close contact to obtain maximum agglomerate strength (as in pressing).
- The forces are greatly enhanced by the presence of any liquid—particularly if it is easily capable of wetting and spreading over the particle surfaces.

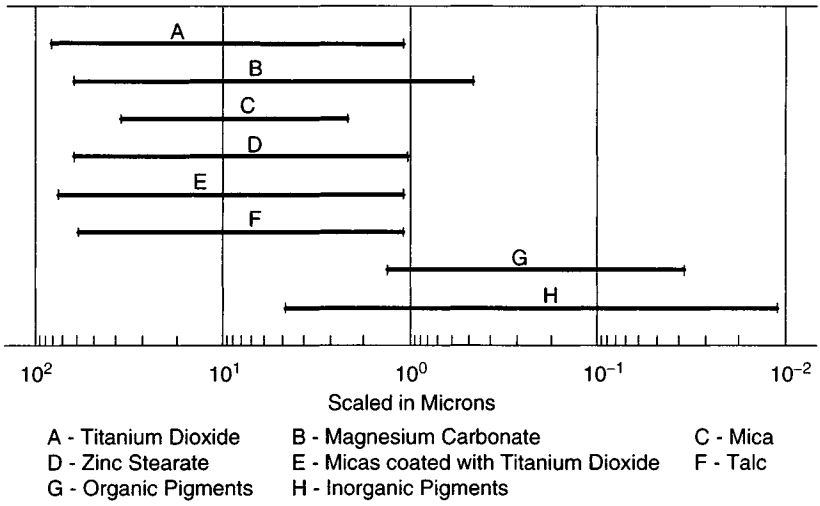


Figure 35.31. Range of particle size of some powders used in cosmetics

- The forces that create the agglomerates are very much weaker than those holding the particles themselves together. That is, it is much easier to break up agglomerates than it is to break up a primary particle.
- The probability of a small particle bonding to a larger one is much greater than that of a particles of the same size bonding to each other.
- Particle shape has as important a relationship to the bonding force as particle size since available surface may determine whether particles can get close enough to bond.

BLENDING EQUIPMENT

Powder eyeshadows, face powders, and powder blushers are commonly composed of the following types of material:

Talcs	Pigments	Liquid binder systems
Micas	Pearl agents	Preservatives

The order in which these ingredients are processed and the mixing that carries it out are specific for the type and color of the product.

The completed process is specific to, and depends largely on, the types of equipment that are used. A satisfactory powder product, when examined under high magnification, is seen to consist of small agglomerates or single particles of the pigments adhering to and covering the surface of the larger talc or mica particles. Improperly processed powders contain larger agglomerates of pigments existing as discrete entities and separate from any talc or mica

particles and unevenly coated talc or mica particles. When rubbed, for example, between finger and skin surface, such improperly processed powders change hue as these agglomerates are broken up and the smaller pigment particles are released and follow their natural tendency to coat the larger particles and the skin. This process is often referred to as the "extension" of pigments onto talc or mica. This "extension" is often intentionally performed separately and as an intermediate step in the process. This allows the overall process to flow smoothly while allowing extra processing and testing of the "extension" before use.

The processing of bulk-pigmented powder products is dominated by the need to achieve adequate "extension" on an industrial scale. Of all the devices that have been tried from time to time, none has proven more popular than the hammer mill (Fig. 35.32).

Since the premix is an additional operation and adds to the processing time, the mixer that is selected must be as efficient as possible. In the past the most widely used mixer was the "ribbon blender," which comprises a horizontal drum containing a rotating axial shaft that carries ribbon-like blades. In such a device, the premix can take between 20 and 60 minutes. Other mixers are now the standard (V-mixer and double cone), which utilize higher energy input and are quicker to achieve the same level of randomness in the finished mix. Table 35.3 summarizes the properties of some of the more conventional powder mixers. Since it is relatively easy to achieve good mixture quality (at a large scale of scrutiny) in cohesive powders, any mixing device will eventually produce a satisfactory even distribution of components. This assumes that no dead spots, where no mixing takes place, are present. The dead spots can

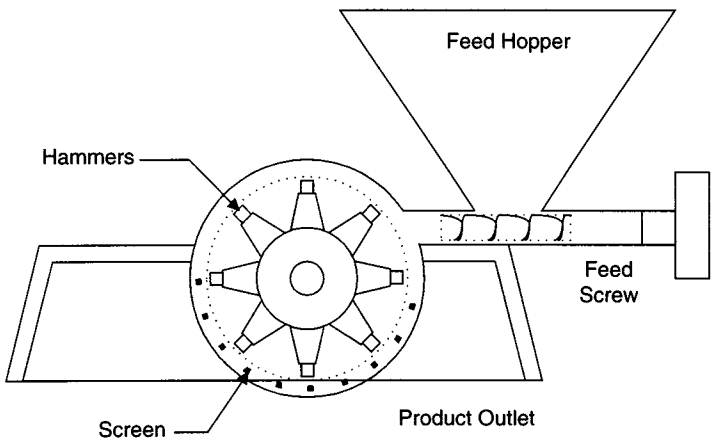


Figure 35.32. Hammer mill

Table 35.3 Conventional Powder Mixers

Type of Mixer	Batch/ Continuous	Main Mixing Mechanism*	Speed of Mixing	Process Concerns	Ease of Cleaning	Energy Consumption	Quality of Extension
Horizontal drum	B or C	Diffusive	Poor	Quality of mix	Good	Low	Poor
Löedige-type (Plough-shear)	B	Convective	Good	Dead spots at ends	Fair	Medium	Fair/Good
Ribbon Blender	B	Convective	Poor	Dead spots at ends	Fair	Low	Poor
Nauta Mixer (with cutters)	B	Convective	Good	Slow top to bottom blending	Fair	Low	Fair
V-Mixer (with cutters)	B	Diffusive	Fair	Batch size to volume of equipment	Good	Medium	Fair
Airmix	B	Convective	Good	Noisy	Poor	Low	Excellent
Double Cone or CBM** (with cutters)	B	Convective and Diffusive	Excellent	Batch loading	Good	High	Fair
Bowl Granulator (with cutters)	B	Convective and Diffusive	Excellent	Batch loading and scale-up	Good	High	Excellent
Extruder	C	Diffusive	Poor	Formulate to the equipment	Fair	High	Fair
Fluidized Bed	B	Convective and Diffusive	Good	Formulate to the equipment	Fair	High	Poor

B (Batch)—Discrete processing of ingredients
C (Continuous)—Continuous processing of ingredients
*All mixing mechanisms include bulk flow
Cohesive Mixing: natural or forced combining of particles during blending
Distributive Mixing: controlled or uniform diffusion of particles during blending
**CBM—Containerized batch mixing

be "controlled," typically through manual scraping by the operator during processing, if required.

It is typical to add the binder as a liquid after the preliminary mixing stage. Solid waxes may be included in the binder if they are added at a sufficiently elevated temperature to ensure complete liquefaction. The binder may be poured or sprayed through a suitable orifice in the mixer. It is preferred to spray the binder into the mixer cavity as an aerosol through a venturi or similar orifice/nozzle device. This procedure helps to distribute the liquid more evenly and avoids the formation of wet, lumpy areas in the powder body. Detrimental heat can develop during the manufacture of these high solids formulations. Many times liquid binder sequences (oils, fragrances, preservatives, actives, etc.) are added that must be well mixed to avoid spotting. If they are heat-sensitive or volatile, allowing the blending or milling operation to overheat these components may damage the integrity of the batch.

The separation of large agglomerates that takes place subsequently in the milling step that normally follows the binder addition ensures the completion of the wetting process provided only that the binder is correctly chosen. Should the binder still appear to be unevenly distributed after the passage of the powder through the mill, the product can often be rescued by passing it through a fine-mesh sieve as much as possible. (Additional milling has its own concerns, which are discussed in later sections). The addition of the binder through high-pressure nozzles improves the fineness of the spray. However, some blending vessels cannot handle the higher pressures, usually 100–900 psig (6–60 bar). In general, the finer the liquid addition, the more control of the finished batch is available. An alternate design to the high-pressure spray concept uses cutters to improve the distribution of the liquid and may not require an additional milling step. The cutters provide the additional energy to disperse the binder as smaller droplets in a uniform fashion.

Batch loading will determine the effectiveness of the mix in any particular vessel. Overloading the processing capacity of a vessel lowers the quality of the mix and possibly increase the temperature during processing. Undersizing the capacity will limit production and affect the quality of the liquid binder distribution. *All scale-up should ensure proper and consistent batch loading throughout—bench, pilot, and production.* For CBM and related higher energy systems, the loading is between 5 and 8 kilograms per cubic foot (28.3 liters) of vessel contents. Acceptable products can be produced within these ranges. For bowl granulation, the loading is less than 20% of capacity and cannot be varied from one vessel size to another.

The use of the liquid binder to assist in the development of color is a technique to be used only under special circumstances. The liquid binder will assist the high-shear equipment to disperse the pigments onto the chosen substrate.

However, the pigments will be much more high-temperature sensitive to color shifting after the liquid has been added. Therefore, each lot of the chosen colors will be extended out differently. Extending the pigments and then properly distributing the binder as separate steps can minimize this effect. A special case to be considered deals with organic pigments. These will darken significantly with heat. Some processes are designed to include this effect. However, a slight hydrogen sulfide odor may be noted when this takes place. Also, the color is not a more intense version of the original shade, but a less vibrant, dirtier, and deeper version. To match the shades produced in the laboratory, all development and production must use the same method of extending the pigments.

Pearling agents, especially the titanium-coated micas, present a special problem. Many of these brittle materials, which depend on their size to achieve the desired effect, are prone to disintegration in the hammer mill. For this reason, they usually have to be mixed into the bulk after its passage through the mill, necessitating an additional mixing operation. The pearls are normally added after the binder has been uniformly distributed throughout the batch. Again, this is an effort to minimize the work energy applied to the pearls. Some pearl coatings can handle the additional oils normally associated with the binder. In those cases, the pearls may be added before the binder. The lower energy of the "cutters" (noted in Table 35.3), compared with that of the hammer mill, can be used to disperse the binder with "minimal" effect on the pearls. The pearl may be added in to the bulk in the same device used to perform the preliminary coarse mixing, providing the device has been cleaned. It may sometimes be necessary to pass the bulk finally through a sieve or coarse screen to break up agglomerates of pearl and to ensure its even distribution. Some formulations use pearls that are processed through the hammer mill to develop a particular feel. Less expensive materials should always be evaluated, if this is required for a successful product, rather than purchase specialty-sized particles designed to impart appearance effects that are then resized to meet physical and not visual aesthetics. Minimum energy should be applied to pearls to maximize their benefit to the product while minimizing the cost of the product.

SHEARING EQUIPMENT

The hammer mill was designed as a comminution or particle size reduction machine. It consists of a fast-rotating shaft fitted with freely swinging hammers mounted in a cage that is equipped with a breaker plate against which the feed is disintegrated, chiefly by impact from the hammers. The very high speed at which the hammers move (60–80 m s^{-1}) increases the chance of a hammer

making contact with each particle and with particles making contact with particles. The dwell-time of particles within the chamber is controlled by the placement of different size screens over the exit.

Hammer mills are very efficient in the comminution of brittle particles in the range of 1,500–50 micron but below this size their efficiency (the probability of direct impact) falls off rapidly. This is fortunate, since it means that small particle size cosmetic talcs and micas (not pearls or pearl extensions) can be passed through without being substantially altered. At the same time, however, the very high rotational speed of the hammers and the airflow within the chamber ensure that there are enough weak secondary impacts (particle-wall and particle-particle) to break the much weaker pigment agglomerates—which may be up to 500 micron in diameter. The primary particle size for most pigments is 0.1 micron in diameter. The disintegrated agglomerate fractions then stabilize by becoming coated onto larger talc or mica particles and should not be further changed by subsequent passes through the mill. The tip speed of the mill should be controlled to ensure that its energy level is higher than that developed during subsequent processing.

Nevertheless, the hammer mill, in its role as an extender of pigments onto talc or other substrates, has certain disadvantages. For example, most of the extremely high energy that it makes available is wasted and is largely dissipated in heating the powder. From the viewpoint of energy consumption, a hammer mill is very inefficient. The feed-rate and therefore the processing time for all but the smallest batch sizes of powder is very slow. The screen size is adjustable, but one does not set the screen at the size particle that is needed. The finest screen is normally 0.010″ (0.254 mm) wide slits approximately 0.5 inches (12.7 mm) long in a herringbone pattern. An attempt to speed up the process by the substitution of exit screens of larger diameter opening reduces the residence time in the mill. On the other hand, increasing the residence time of powder within the grinding chamber by decreasing this opening size can cause the screen to become blocked with compacted and bridged powder, resulting in overheating and damage to both the machine and the product. The design of the hammer mill allows a high volume of air to pass through it during the milling operation. This airflow can assist in minimizing a temperature rise during processing, but it cannot eliminate it. The airflow will also cause a fraction, usually less than 2% of what is being milled, to be lost as fines (small particles that are easily carried through the air handling system). If the process is not properly adjusted, the losses can be as high as 30%. If such a high level of milling is required for the process, an alternate high-shear device should be examined, like the jet mill, turbine mill, or classifier.

Perhaps the biggest disadvantage is that the hammer mill is a noisy, continuous processing device being used for batch processing. Since it is a continuous

processing device, it must be fed with a powder mixture, which has already been effectively mixed; otherwise, the color of the exiting product will change as each section of unmixed bulk passes through.

The hammer mill has a design flaw that must be remembered. Some powders can drop vertically through the unit without being affected by the rotating hammers. It is typical when milling pigments to pass the batch through the hammer mill at least two times to increase the probability that all particles are hit and extended at least once.

ALTERNATIVES TO THE HAMMER MILL

The drawbacks to the hammer mill, as used for powder extension, have led to a search for other machines, which can fulfill this function more satisfactorily. The ideal equipment would probably have the following properties:

- It would be capable of breaking up weak particles in the size range 0.5–50 μm without damaging talc or mica particles of similar diameter.
- It would be a low-energy device, consuming little power without heating the powder mixture excessively.
- It would be both a batch and a continuous processing device capable of mixing and extending in one operation.
- It would have rapid processing times of less than 10 minutes for 100 kilograms.
- It would not cause aeration of the powder (since this causes problems in later processing).
- Its efficiency would not vary with the cohesiveness of the powder—it would not be affected by poor flow characteristics of the raw materials.
- It would be quiet, clean in operation, and easy to clean.

Other comminution devices have been shown to produce extension. Pin mills (inefficient when compared with a hammer mill) and fluid energy or jet mills (too efficient at particle size reduction when compared with a hammer mill) are two examples. No alternative seems to work as efficiently as the hammer mill at spreading the pigment onto the talc or mica.

In recent years, however, the development of high-speed powder mixers, which are also capable of producing some degree of extension, has brought the industry closer to the ideal. Two types in particular are worthy of mention. The first of these is best described as the horizontal vortex mixer. As an alternate high-speed mixer, it is often referred to as a plough-shear device because of the unusual shape of the mixing paddles, which rotate on an axial shaft in a cylindrical-like horizontal mixing chamber (similar to a ribbon blender). These paddles cause the powder from all parts of the chamber to be thrown about in such a way that it all passes rapidly through a zone occupied by a series of rapidly revolving blades off a separate shaft referred to as a "chopper." The

chopper is largely responsible for the powder extension and may be switched on or off independently of the main axial drive.

The second type is a high-speed modified bowl granulator. It has a propeller or anchor shaped blade of "good aerodynamic" design that rotates very rapidly in the dished base of the mixing bowl. This design mixer has a separate "chopper" shaft to increase the available energy to extend the pigments. Mixing and dispersion occur at the point of collision of the powder particles (in the upper part of the mixing bowl) by particle-particle and chopper-particle collisions. The flow pattern in modified bowl granulation vessels must be properly scaled from the laboratory through the pilot plant and into production. Specific batch sizes, with less than 20% powder loading, are required to maintain the proper flow characteristics. The tip speeds are usually matched for all of the process sizes being utilized. This will help to control the time factors in scale-up. Often special designs are required to ensure scale-up, including upgraded motor controls and blade speed operating ranges.

Both types of mixer have been used as partial or complete replacements for the traditional blender–hammer mill combination. Variations of these mixers have also been used in the solids-liquids processing area.

LOOSE POWDERS

Loose powder production uses similar equipment and follows a process similar to that of pressed powders. The blending operation is relatively simple with little high-shear energy needed—except for some preservatives, a little color, and the addition of oil or fragrance. The requirements for chemical uniformity are lower (from a specifications standpoint) for a loose powder than for a pressed powder. The loose powder is usually examined as a gross or large quantity powder. The pressed powder (cake or tablet) is usually examined based on the actives or the pick-up from a brush or sponge.

Particle size distribution and the associated handling concerns, are usually more critical with a loose powder than with a pressed powder. Inhalation concerns will often require the formula and process to be very specific and therefore limit the formulator's flexibility. Oils and waxes may be added to the formula to intentionally agglomerate the finer particles due to limited availability of raw materials with the preferred (safer) particle size distribution. This addition may be performed as a side phase and is then combined with the main batch as a previously processed ingredient.

The packages for loose powders are larger than those of pressed powders. Therefore, larger batch sizes are normally produced for loose powders. Loose powders may contain a small pigment phase that requires milling, but most do not. Even high levels of fragrance usually do not require a great deal

of milling since if the mass is too wet, it will agglomerate and no longer be loose. Without the need for higher energy during processing, less efficient mixing systems can be used by production. The batching times for these large, loose powder batches may be longer than those for a similar formula pressed powder.

FILLING LOOSE POWDERS

Filling of loose powders is dependent on the flow characteristics of the powder and the package being filled. An auger screw is used to assist flow of the powder at a controlled rate. These are used for powders that are slightly moist and may agglomerate or compact freely upon storage. They are also used to induce the product to flow into unusual containers—like filling tubes and narrow-necked bottles. An auger filler consists of a moving screw that will deliver a set quantity of powder based on a predetermined number of revolutions. Variations of this design can be similar to a positive displacement pump or high viscosity cream filler.

Rotary volumetric fillers are used to fill powders at high production rates. These systems are designed to enable the powder to freely flow into moving chambers that control the weight and volume of powder to be filled. The chambers are designed to completely release the correctly set quantity of product into the package (usually boxes or bags) just prior to sealing the package. Automatic dishwashing detergents, powdered batch products, and cereals are packaged this way. Due to variations in bulk density that may be enhanced through shipping, these packages are completely opaque and are typically labeled "Note that settling may occur during shipping and storage." The volumetric filling system design can tightly control fill variation of the package assuming the variation of powder to be minimal.

FILLING PRESSED POWDERS

Several different systems are used to produce pressed powders. However, they all have certain components in common. The powder must be presented to the filler. The appropriate cavity is filled and the cavity is placed under pressure. The pressed unit is collected, tested, and placed in a package for shipping.

In presenting the powder to the filler, it must be uniformly presented to each pan. This may require "fluffing" just prior to filling. This fluffing may be as simple as rolling the drums of powder before use to evenly aerate the mass. It may be as formal as a container with a mixing blade designed to aerate the powder as it travels to the filler. It may be an air conveyor system that aerates the powder as it is moved. Aeration is not a preferred action, since the air must be pressed out of the powder in the next step. However, the change in

density after storage may be necessary to achieve uniform production at the press over multiple shifts.

The standard cosmetic powder presses are either waffle-style (hinged at the side) or vertical presses (no hinge). Both presses can produce acceptable tablets within the pressure range of 100–1,000 psig (6–70 bar). It is important to remember that the pressure across a single pan is not the same pressure across several pans unless the total surface area remains constant. The vertical press is available as a single pan press, usually part of a rotary table to increase production rate or as part of a multiple die/pan design. A laboratory press is typically a single pan press. Variations in tablet press quality may be due to flexing of the structure, cycle rate, internal pressure measurement, pan variability, and fill variability. Formulation will affect very few of these variables. However, it is important for the formulator to understand the variability of the press during formulation. If the pressing pressure range for an acceptable tablet is too small due to the acceptance of other characteristics (pay-off, coverage/sheerness, packing density/durometer, size and shape of pan, type of applicator, etc.), good production runs will not be the norm. A small variation in the pressing pressure should not produce a significant change in the aesthetics. The formula may not need to be adjusted, but an acceptable pressure range may be required.

Some variations in the consumer's perception of quality of the finished product may depend on the following press factors: weave of cloth, multiple press, dwell time, molds/dies, pan material, and pan shape and depth. The weave of the cloth [threads per inch (or millimeter) and the size (diameter) of the threads] is used to produce a consistent texture across the finished pan. The cloth also allows for the release of air from the mass. If the mass contains too much air for the cloth to vent, the pressed piece may immediately crumble once the pressure is removed or it may bow as the air bubbles in the powder are released from being under pressure. If the pressing cloth is too fine for the air to release, a second press may be necessary. In normal operation, the pressing cloth is changed and the press is operated a second time. Some automated machines can perform these two pressings at different pressures to best control the density of the powder throughout the pan—start low, finish high. The dwell time, the time the press maintains pressure, can sometimes produce a different product feel. Any increase in dwell time decreases production capacity. The design of the mold and die will determine the net pressure available for each pan and therefore the capacity limitations. Different pan materials hold and dispel static charge differently. Most pans are steel or aluminum if water is involved. Some pans are plastic. The handling characteristics are very different. Pan shape and depth will affect the flow of the powder prior to and during the pressing operation. Sharp corners make for easy breakage. Round pans handle high pressures more evenly across the entire surface.

Pharmaceutical tablet and soap pressing are to be examined separately. Tablet presses are designed for near-continuous operation and can be used to generate over 10,000 psig (667 bar). They can produce over 10,000 tablets a minute, using dual station operation that are not pressed into a pan. Soap pressing may be performed at very low pressures, which are formula- and package-dependent. The slurry of bar soap is injected (sometimes using an extruder) into a mold, minimizing uncontrolled air and the bar is shaped. The soap bars are then dried and packaged. Molds are typically brass or sometimes stainless steel. There are occasional uses in cosmetics, like bath and toilet bowl additives, that have smaller production requirements. The key part for both of these presses is the control of the process from raw materials through the exit from the press.

POWDER SCALE-UP—BATCH

Scale-up of powders is dependent on controlling many processing parameters. These include the following, which must be measured and controlled from the laboratory bench, through the pilot plant, and throughout production.

- the batch loading by volume and/or by weight [maintained] —which affects the flow patterns in the compounding vessel
- the shear being imparted on the powders and powder dispersions (typically measured as tip speed) [maintained]—which affect the color and color development of the raw materials
- the process time [scaled or maintained]—which affects the overall production capacity
- the batching temperatures [maintained]—improper processing can produce temperature elevations of over 40 °C from the normal batching temperature
- the batching procedure [scaled or maintained]—due to the use of high-shear, detailed procedures will maintain the quantity of shear consistently through all production
- the sequencing of the phases [maintained]—changes in sequence will affect the color or intensity and consumer characteristics ("feel") of the finished product
- the raw materials [maintained or at least controlled]—examples: (1) variations in dye strengths, in different lots of pigments, change the finished shades and require color adjustments; (2) changes in particle size distributions will change the appearance of larger particle pearls; (3) changes in the source may shift the color range from Red with Yellow to Red with Blue.

Batch loading the quantity of powder to be produced in a given vessel configuration is a particular problem for all new formulas. If a new shade is being made of an existing product, a history through production has already been developed. A new product may be less dense, more cohesive, more brittle; contain a higher pigment load, a higher binder level, a higher pearl level; be

more temperature-sensitive and harder to press than a current formula. All of these variables can affect the batch loading. If the loading is too high, the process will usually create a higher intermediate temperature. The spraying characteristics (spray pattern and particle size distribution) of the binder will also be affected if a constant addition time is maintained, since the flow rate will be changing. If the batch is being milled in situ, using a bowl granulator, for instance, loading can significantly affect the color development. Unfortunately, multiple laboratory, pilot, and production batches may be required to determine and fine-tune the proper loading.

Process time in scale-up has some additional flexibility with powders that is not always available in liquid systems. Since heating and cooling are not usually taking place during the mixing or shearing operation, the actual time necessary is less critical. However, the steps should be performed in a very consistent manner with times that can be duplicated. If the scale-up time from the laboratory to the pilot plant for one product is 1 to 10, it should be maintained for all products that use the same equipment system. If it is not, some process variable is not being controlled and could return as a major problem for production.

The development of accurate and detailed procedures is key to proper color development and shade-matching of products. The protocols used to evaluate finished mass, products, and, where necessary, sequences must be as controlled as is the equipment being used. Evaluation of aesthetics can be difficult to translate to an intermediate process test. Standard measurements of rotational speed, temperature, and time may be all that is available and may be sufficient. In addition, motor current draw, on a high- or low- shear drive, may be used to indicate that a spray addition was uneven or that a batching scale is out of calibration.

Production may schedule a series of batches of loose powders based on fragrance intensities. They may schedule a series of batches of pressed powders based on color intensities. These scheduling differences can help production department to minimize the effects of a poorly cleaned system. Some of the newer equipment designs allow "clean-in-place" (CIP) operation. [CIP is an automated system for cleaning equipment the exact same way every time. It is used when a system is designed and tested to ensure that proper controls make the system clean every time]. Most of the older equipment, notably the ribbon blender, cannot be CIP due to the design limitations of its sealing systems. Cleaning of a ribbon blender can be a slow, tedious process and is rarely 100% effective. Powder systems with low water level (activity) are rarely a microbiological problem. However, the use of preservatives is included in all formulas due to the package design and the methods of use by the consumer. Even if the equipment has not been completely cleaned before the next batch,

it must be sanitized. This may produce "clean" dirt, but the finished product will not be a site for potential microbial growth while the consumer uses the product. The newer systems that allow CIP usually allow SIP (sanitization-in-place), preferably with steam.

WET CONTINUOUS PROCESS

The objective of building a continuous process, as compared with the batch processes discussed earlier, for an emulsion, liquid/liquid, or liquid/solid cosmetic product is high-volume production. It may also be desired for just-in-time manufacture or to make a special product where intense energy is required to form a viscous product such as a hair styling gel. Examples of the most common cosmetic products made via this method include hydro-alcoholics, creams, lotions, shampoos, hair conditioners, hair dye developers, and hair styling gels. Color cosmetics, such as liquid or cream makeups, may also be made by continuous processes, provided color correction is not required.

Formula composition is stoichiometrically maintained, usually by means of a series of piston pumps, connected by a common shaft and variable speed motor. Piston pumps are generally used to allow for higher pressures and accurate delivery. Each phase in the formula requires a separate pump to control its composition in the total formula. Each pump is calibrated for weight delivery by adjusting its stroke length at a constant drive motor speed. This will lock that ingredient or phase into the proper formulation. Production rate is then increased or decreased by speeding up or slowing down the drive motor. Pumps employed may be of several designs, depending on the application. Sanitary pulsation dampeners may be employed downstream to smooth out flow but often are not necessary. Other components of the process may include some or all of the following items:

- a static mixer for premixing some or all of the formulation constituents
- a dynamic mixer to provide additional mixing energy to set the emulsion or dispersion
- a scraped wall, plate-and-frame, or tubular heat exchanger to cool the product if required

The final components in the system prior to storage or filling are usually pH or conductivity and viscosity in-line measuring equipment used to monitor quality. They will usually control adjusted pump delivery to maintain the finished product specifications or alarm to shut the system down. The complete process may be free-standing and require considerable space or mounted on portable skids and rolled up to a production filling line for just-in-time manufacture, depending on the design, size, and application.

EMULSION PRODUCTS REQUIRING COOLING

Experience has shown that for lotions, creams, and so forth, it is usually possible to form a crude emulsion by metering the oil and water phases and gum phase first into a static mixer (Fig. 35.33). The crude emulsion is then finished either in a dynamic in-line mixer or a scraped-wall heat exchanger where other temperature-sensitive colors, fragrances, and actives are injected just before the heat exchanger inlet. This minimizes exposure to heat to a few seconds during the rapid cooling process. Injected ingredients should be added into the center line of the pipe at a velocity equal to the mass velocity of the formula passing that point to minimize concentration pockets in the stream. The advantage of the scraped-wall heat exchanger is that it can be used as a final mixing element by controlling its internal shaft speed (mutator) during very rapid cooling to set product rheology prior to storage or filling. Cooling capacity and rate is very high in these units, being four to five times more efficient and substantially more rapid than cooling in a continuous stirred tank reactor. Some products, however, cannot tolerate the turbulence and cooling rate produced in these units. Plate and frame or tubular heat exchangers may be employed whenever cooling rate is less critical, product viscosities are low, and mixing energy during cooling is detrimental to product rheology.

There are two things to keep in mind when it is desired to convert an existing batch-made product on a continuous flow process. First, the continuously made

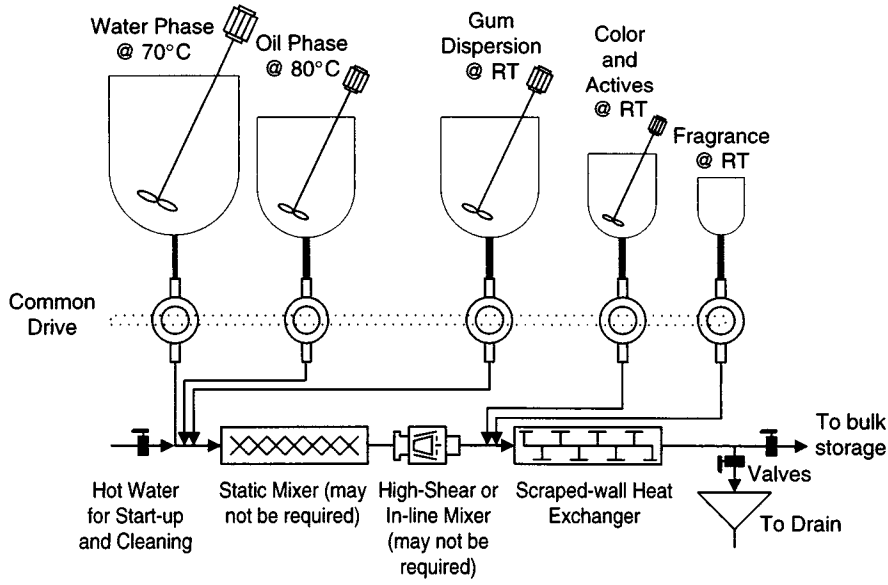


Figure 35.33. Simple continuous process liquids system

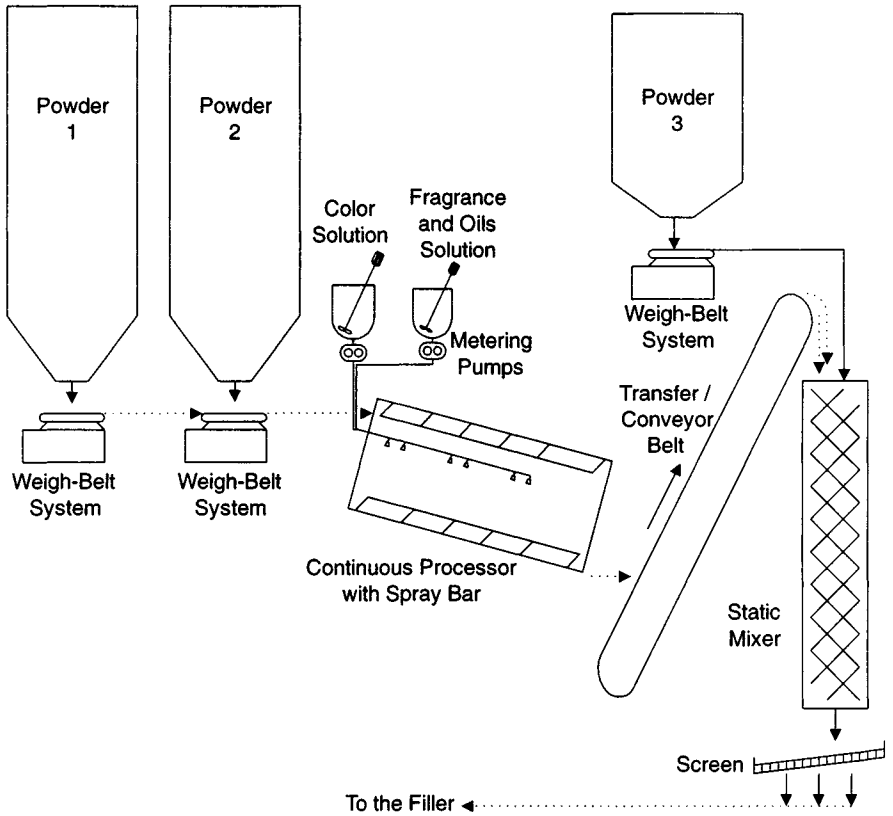


Figure 35.34. Simple continuous powder system

emulsion will have a smaller mean average particle size and a much narrower particle size distribution compared with the batch-made product. This may change product rheology and affect aspects such as rub-in and feel on the skin. This occurs because every particle of the continuously made product is exposed to much more uniform intense mixing than is possible in batch-made product. Experience has shown, however, that through careful tuning of the continuous process, the rheological properties can be brought close enough to those made by batch process so that the consumer cannot detect a significant difference. Second, one should be aware that continuously made product, particularly lotions, may have a much lower initial viscosity, perhaps as low as 20% of that compared with initial batch-made product. This is due to the intense mixing energy imparted in either the in-line mixer or the scraped-wall heat exchanger. However, the rate of viscosity build may be much faster achieving the same value as the initial batch viscosity within the first two

or three hours. This may require that the product be stored for several hours prior to filling to prevent premature shut-off of the filling nozzles, producing uneven fills due to rapid viscosity change. Normally the product equilibrium viscosity should reach the same value as that of batch-made product within a few days, if total and finishing work energy in the heat exchanger (mutator shaft speed and velocity of product) have been controlled.

EMULSION HAIR CONDITIONERS

Emulsion hair conditioners may require much more sensitive temperature control during the process prior to filling or storage than most other products. A typical arrangement for this type of product would require the following in sequence:

- heated oil phase
- heated water phase
- metering pumps for the above
- static mixer
- plate and frame heat exchanger—a simple design that is easy to maintain with excess area to control the exit temperature of the crude emulsion to within ±0.5°C of a predetermined intermediate temperature
- dynamic mixer (rotor/stator)—used to set the product rheology at that temperature
- another plate and frame heat exchanger—cool the product prior to storage or filling
- back-pressure valve—to control the residence time in the dynamic mixer
- in-line pH and viscosity instrumentation—used to monitor product quality, adjust phases, or note alarm conditions and shut the system down

Use of a scraped-wall heat exchange is unlikely to work in this application due to destruction of the product viscosity at lower temperatures. Experimental work is required to determine the correct temperature of feed to the dynamic mixer combined with the correct rotor/stator configuration, rotor speed, back-pressure, and product flow rate, to obtain desired results prior to scale-up.

HAIR GELS

Hair gels are generally processed cold. They consist of a water phase containing polymers and styling agents and a solvent phase containing neutralizer, colorants, and other desired ingredients. These phases are generally metered together at room temperature into a static mixer to form a crude gel followed by a dynamic mixer to complete the gel structure. The finished gel then passes through in-line pH and viscosity instrumentation prior to filling or storage. Instrumentation can be provided to adjust the neutralizer phase pump based on pH feedback and viscosity.

SCALE-UP OF CONTINUOUS SYSTEMS

A pilot system producing 0.5–3 kilograms per minute of product containing all of the main components envisioned for the full-scale production system is recommended to work out the process. This size of system lends itself well to the use of small commercial equipment. It can also demonstrate product characteristics and stability, determine operating parameters, and develop data for control of the process and the sizing of full-scale production equipment. In addition, it makes pilot runs of 30 minutes to two or more hours reasonable to handle.

The pilot system should be designed with maximum flexibility built into each component of the process to allow collection of scale-up data over the entire operating range. This would include such things as variable speed drives on phase pumps, dynamic mixers, and scraped-wall heat exchangers. Sufficient instrumentation should also be provided to allow accurate recording of temperature, pressures, and speeds of dynamic equipment during experimental runs so that material and energy balances can be calculated for each component. Some scale-up rules of thumb to keep in mind are based on the production size and design as follows:

- pipelines should be sized for equal velocities and pressure drop
- static mixers should be of the same style and contain the same number of elements
- dynamic in-line mixers should have the same rotor/stator design, number of stages, variable speed drives, and rotor tip speeds where possible
- scraped-wall, plate and frame, or tubular heat exchangers should be connected for overall countercurrent heat transfer for maximum efficiency and sized to match developmental parameters—equal velocity throughput, residence time, rotator shaft tip speed where applicable, and overall heat transfer coefficient

PRODUCTION DESIGN CONSIDERATIONS

If heated phases are required in the process, it is necessary to trace, insulate, and control the temperature of pipelines from the bottom of the heated phase tanks to and including the metering pumps and the return lines to the top of the phase tanks for weight calibration purposes. Tandem phase tanks may be required for water and oil phases, since materials must be melted or dissolved. One phase tank is thus "on-line" while the other is being prepared. In some cases it may also be necessary to control the temperature of phase lines on the pump discharge leading to the point where the initial emulsion or dispersion is formed in order to prevent "salting out" or solidification in lines. The need for this must be determined in the pilot plant. If the product requires "aging" to ensure conformity to specifications, bulk storage of mass may be required.

Weight calibration of each phase must be established at constant drive motor speed set at the actual flow conditions and line pressure expected during production. If the calibration is not performed at constant drive motor speed, the composition will not be correct during production. This requires installation of an adjustable valve in each recycle/calibration line to pressurize the pumps and recycle lines to ensure accurate calibration. Each recycle line should also have a check valve at the kettle return discharge point to keep the line full for weight accuracy. Suitable controls and instrumentation are required to allow flow to process or to recycle for each phase independently, and to divert all phases to recycle or process simultaneously.

Once the stroke positions are set properly for each phase pump, calibration is complete. Startup is accomplished by first adjusting the drive motor to the selected speed and allowing the system to run in recycle mode under production line pressure conditions. Each phase process line is then primed to its injection point. Next, if heated phases and product cooling are required, the process portion of the system is made ready for product manufacture by passing hot water through the in-line mixers and heat exchangers (Fig. 35.33). This is necessary to bring the pipeline, mixers, and heat exchange equipment up to equilibrium conditions.

Production begins by switching all pumps to process mode and simultaneously cutting off the hot water flow. Product exiting the heat exchangers is diverted to drain or rework for a few seconds before allowing it to pass through the quality control in-line measuring equipment and into the storage or filling lines. The system is shut down in reverse order as it was started up. The pumps are diverted into the recycle position, and hot water is flushed through the pipeline, mixers, and heat exchangers and routed to the drain. This cleans the system in preparation for sanitization and the next run. Supply and recycle lines from and to the heated phases and ingredient tanks are blown back to the tanks with air pressure and are cleaned and sanitized as required.

DRY CONTINUOUS PROCESSING

Continuous production of powder products requires flexibility in the formula and large volumes for filling. Typical examples are powder water softeners, automatic dishwasher detergents, and bath products. In general, these products all share a few characteristics—they do not foam a great deal, they do not contain a large quantity of oils, the powders are the active ingredients, and all raw materials flow well (Fig. 35.34).

The powder formula must be flexible to allow for a larger variation due to the different processing controls used in a continuous process. Typically the raw materials are stored in bulk. Bulk storage expands the range of temperature

and humidity to which the powders are exposed by comparison to laboratory storage conditions. The ingredients for the formula are metered automatically or subphased as large batches to be used continuously. Therefore, only gross adjustments (color or fragrance level) can be made under controlled circumstances. Exact shades can rarely be reproduced. Even with modern process controls, the mixing systems will have normal variations. Without continuous in-line testing, finished product samples are grouped together for a general analysis.

BULK POWDER STORAGE

The two factors that have an important effect on stored cosmetic powders are moisture and pressure. It is not always appreciated that a small increase in relative humidity can give rise to sufficient moisture in stored powder to change the main mechanism of particle-particle bonding, which will increase the bond strength of agglomerates by a factor of two or more. Such an increase in cohesiveness can make the handling and flow problems already inherent in cosmetic powders perceptibly worse and can change the processing characteristics of (for instance) an eyeshadow to the point where all the pressing machine settings may have to be altered to compensate.

In the same way, powder bulk that has been stored in vertical containers exhibits increasingly difficult flow characteristics as the container gradually empties. The lower layers, having been compressed by the weight of powder above them, become increasingly cohesive as the bottom is approached. If oil or moisture has been added to the powder, they may migrate toward the bottom of the container and produce a significant product change between the top and the bottom. For this reason it is sometimes better to store powder in a large number of small, well-sealed containers than in loosely covered large bins. Each container should be mixed before removing any of its contents.

If the variability of the powders being stored is known, or at least controlled, the flow characteristics within a container can be adjusted through the design of the container. The most efficient design would have the first particle that was dropped in to be the first particle that comes out (FIFO). Most simple silo designs do not function that well. Powders tend to settle toward the edges as fines while only a center core of material leaves the silo. This is termed "funnel flow." Modifications to an existing silo are always cumbersome at best. Therefore vibrators or sometimes air jets are added to enhance the flow of material.

Design improvements have lead toward an almost FIFO design called mass flow. Several variations have been designed, but they all require specific knowledge of the powders being stored, such as particle size distribution,

particle shape, density, angle of repose, and so forth. The angles of the sidewalls are designed to ensure that the particles cannot sit and accumulate. Any change in the powder being handled may require a new silo (Fig. 35.35).

Mass flow versus funnel flow, as pictured in Figure 35.35, shows the general physical difference of the two hopper/silo designs. The volumes and the outlet diameters are the same for the two hoppers. The funnel flow design allows flow through a center core with finer particles gravitating toward the walls of the vessel. This produces a change in particle size distribution as the level in the hopper changes. The mass flow hopper, by design, allows the lowest material to leave first while the top material leaves last. There is virtually no mixing or separation of the horizontal layers. As noted in Figure 35.35, the mass flow hopper is taller and narrower than the funnel flow design. Alternate designs can be used to improve the flow characteristics of the silo; these designs modify the flow with internal changes, typically baffle plates. These alternate designs do not allow for complete cleaning without special attachments and will have some particle size distribution changes during use.

Industrial bulk containers in an assortment of sizes, shapes, and materials of construction are commonly used to store large volumes of powder. They can range in design from a large bag to a skid-mounted silo. Since they hold less material than a "normal" silo, segregation due to particle size is less. These containers are normally filled at the supplier and emptied at the cosmetics manufacturing facility. Therefore, there is no concern that the first material received by the manufacturing facility will be the last out during use, as in the case in a poorly designed silo. The key concern for the cosmetics and drug industries is contamination. Special bags have been designed to minimize sifting, which is the loss of powder at the seams of the bag. Sometimes

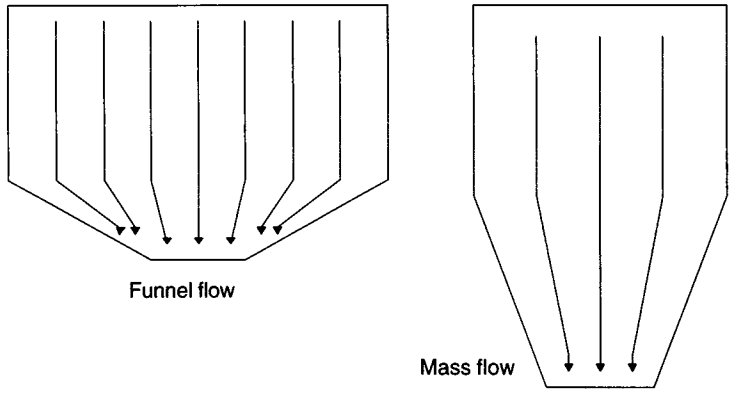


Figure 35.35. Hopper flow of powders

special one-piece liners are inserted into the bag to minimize sifting. The cost of liners can be a problem. Single-use liners can be very expensive but can be maintained microbiologically clean until use. Multiple-use liners may control sifting. It is assumed that if powder can come out, moisture and microbiological contamination can enter. Multiple-use liners may control sifting but require cleaning and sanitization between uses.

Once the bulk container has been filled with powder, a transfer system is used to move the powders through the process. The typical conveyor systems fall into three main categories. The first design is pneumatic. An air blower is used to fluidize and then move the powders through special tubing. If the line sizes are not well matched to the flow rates, some segregation of particles may take place. The second design is mechanical with product-to-product contact. A screw conveyor is a classic example of this technique; another is a chain within a tube or housing. The screw is used to move the powder at a very controlled rate. By design, the distance between supply and deposit cannot be large. Since the movement of the screw or chain physically pushes or pulls the powder, degradation and compaction of the powder may take place. The third design is mechanical without product-to-product contact. Examples are bucket and belt conveyors, which move the powder in discrete increments with little detriment. Atmospheric conditions must be controlled, particularly if moisture is a concern; transfer operations are usually open to the air, and microbial growth is always a finished product concern.

All powder conveying systems are subject to potential dust explosions when dust levels reach a critical point. The combustible material is usually an organic dust—sulfur, starch, wood, flour, sugar, carbon, rubber, and some plastics are examples. When the dust reaches sufficient concentration and its powder minimum ignition energy is reached, an explosion may take place if an ignition source is available. Special design changes may be required and are dependant on the raw material being examined, the process, and the environment. Some possible control methods include the following:

- change the particle size distribution from the supplier to minimize finer particles
- change the conveying system to minimize particle degradation
- the addition of a liquid spray to the dust atmosphere to agglomerate the fines, cool the powder to lower the ignition energy, minimize static buildup, and lower the oxygen level in the atmosphere
- increase the level of fines in the controlled environment to lower the oxygen level in the atmosphere to a point where an explosion cannot occur

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CHAPTER 36
Packaging

INTRODUCTION

The packaging of cosmetics and toiletries is in principle no different from the packaging of any other product. The package is intended to contain the product in fresh and usable condition and to act as a protective device and sometimes as a dispensing device. The package must identify the characteristics of the contained product and differentiate it from related or competitive products. In recent years regulatory agencies have required that container labeling also include pertinent information and that this information must conform to a prescribed language in the case of over-the-counter (OTC) drugs. It is apparent that control over package appearance is not a matter for the formulator, with the exception that the package must not interact with the product.

In the absence of other directions, formulators routinely store newly developed compositions in essentially unreactive, easily sealed glass containers. The selection of packaging (and shipping) containers is the responsibility of packaging engineers with special skills for securing suitable packaging components. The cosmetic industry uses packaging materials that range from glass to plastic and from paper to paperboard. As an industry it must possess the ability to design, develop, and integrate these packaging elements with equipment to transmute them into viable containers.

The packaging industry is defined as the many companies engaged in the plastic, paper, board, metal, and glass production, which create components that allow synergistic packaging combinations. The purpose of this chapter is to provide the reader, who may be primarily concerned with formulation, with an overview of pertinent information and a demonstration that the creation of a properly engineered package is a highly developed specialty. Packaging today is a substantial discipline; it ensures the safe delivery of the product to the ultimate consumer in sound condition at a minimum cost. Packaging sells what it protects and protects what it sells.

PACKAGE DEVELOPMENT AND DESIGN

The package must contain, protect, identify, and sell the product. The package is the tip of the spear composed of marketing, advertising, and sales. The package is often remembered only by color, shape, or some identifying icon. The aims of package development are increased sales and profits through proper design. Packaging must be considered as early as possible in the development of any new product to allow time to ensure that the package and the product are compatible. The average shopper in a supermarket, mall, or department store is exposed to some 30,000 products but spends less than a sixth of a second in making a decision. Design factors should ensure that the package is suitable for the product and, if possible, should elicit an emotional response or psychological reaction from the consumer. Finally, in the development of the package, environmental factors should be considered to permit either recycling or reprocessing.

TECHNICAL ASPECTS OF DESIGN

The technical aspects of packaging design are extremely diverse and too involved for any detailed discussion in this text. When a package is received that has a wet display carton or outer box, it is understood that the package is flawed. The most important consideration remains product protection. For example, despite their presumed inertness, glass containers may be inappropriate packaging components for fluoride-containing oral care products. Even under the best circumstances, loss of fluoride with accompanying decrease in efficacy in glass containers is unavoidable. Simple polyethylene containers may absorb hydrophobic cosmetic components including preservatives, and combinations in which a packaging component may preferentially absorb a product component should be carefully avoided. This means that the unit must not only be tested but also that design requirements such as thin necks, deep cut surfaces, unstable bases, and highly stressed areas must be eliminated during the design process.

The package must not only be attractive to the consumer but also allow the package to be filled, distributed, displayed, and used with ease. There is nothing more infuriating to the consumer than a container that refuses to open, tears easily, has no reclosing feature, and a host of other consumer problems when the package is poorly designed or implemented. Sometimes the package not only holds the product but also is used as the appliance to place the product on a specific area of the body. Such is the case with applications that are used for antiperspirant and any other products that are applied directly to a body surface. In the field of antiperspirants innovative applicator designs have

been created. For example, these products can be purchased in a variety of forms: hand-operated pumps, pressurized packages, roll-ons, and sticks. Other products such as toothpastes are presented in multipart containers. The action of the pump allows the two dissimilar—possibly reactive—components to mix at the time of use. This dual-chambered pump can provide the consumers with a specificed product without any of the problems resulting from mixing the materials before they are blended. Multipart containers are also available for use in hair coloring and skin products. Designs of specialty packages for makeups (roll-on or brush-dispensed lipstick, mascaras, and the like) appeared on the market and were then quickly replaced by improved or simplified designs. This important area of package design is expected to grow as more products are developed, especially those in which two materials are mixed for the sake of utility or dispensed in an attractive multicolored pattern. In the flexible area, a pouch has been developed that houses two dissimilar materials. Upon application of pressure, the seal separating the materials is ruptured, the materials are mixed, and the contents are then dispensed for use.

It is an axiom of design that the package represents the brand or company. The package must project an image that allows the consumer to identify the product. Furthermore, the package must provide for its being turned into an image on the television or internet monitor. The package must stand on its own without the support of sales assistance. The lack of human sales personnel pervades all areas of the retail trade and will continue to accelerate in the future. Therefore, the package must clearly advise the consumer about its contents, must stack easily on the shelf, and must give the retailer the maximum profit per linear unit of shelf space. The trilogy of good product, good advertising, and good packaging is more significant today than ever before.

TECHNOLOGY OF PLASTIC PACKAGING

The following discussion assumes that the compounding scientist is not responsible for creating or designing the package intended for marketing. On the other hand, those who generate such package designs must be fully aware of the intricacies of the given formulation. Formulators, too, must have insight into the capabilities of miscellaneous package components. Thus the discussion is designed to establish close rapport between the formulating chemist and the packaging expert. To ensure prompt delivery of a new product, the early interaction of the formulation and packaging groups is required.

Early cooperation between the specialists should eliminate many of the problems that may interfere with timely product delivery. One example illustrates the need for collaboration. Typically formulators study their newly developed products in glass containers, although they know product

introduction is planned for several sizes of plastic bottles. A glass package can be expected to contain the product in virginal state, but permeation of a product component into and through a plastic package should be expected during storage. Any loss of a component may or may not be critical, but the magnitude of the loss depends on the ratio of the container's content to its surface area.

Thus more bothersome sorption or permeation should be expected to occur in small plastic packages than in larger ones. In the case of sample packages, it may become necessary to seek alternate components to ensure that product integrity is maintained until the unit is used by the consumer. The described size (or shape) effect on stability becomes more critical if the plastic container should absorb a key component of a finished formula. A hydrophobic polyolefin package may absorb a preservative component that may not make the product unusable but may make it microbiologically unsafe. As a rule, problems of this type can be avoided if packaging and product development begin their cooperation early. It is particularly important that the "final" package (in various sizes) be available early for definitive product stability testing.

PLASTIC BOTTLES

The replacement of glass with plastic in many consumer products has been matched by the cosmetic industry. In the future, it is anticipated that the lightness and ease of use of plastic containers will increase. There are two groups of plastics that are used: thermoplastic and thermosetting resins. Thermoplastics can be extruded at their melt temperatures and then blow-molded or injection-molded. After cooling, thermoplastic remnants can be remelted and reused. Thermosetting resins, by contrast, are molded by using an irreversible chemical reaction. The resultant polymer tends to be rigid, hard, insoluble, and unaffected by heat up to the decomposition temperature.

As noted already, one of the advantages of plastic packaging is lightness, by comparison to the heavy glass packaging used in the past. In addition, the fragility of glass may cause delays in the filling operation and can be a problem in shipping and in the hands of the consumer. Finally, advances in technology have made decoration of plastic containers easier than that of glass units.

The principal steps for creating a plastic cosmetic package involve two operations, synthesis of the polymeric plastic, which then in the second step is molded into diverse shapes. Most thermosetting resins are synthesized in the mold by compression molding, as described briefly in the following section.

THERMOPLASTIC RESINS

Polyethylene (PE)

Polyethylene is the most widely used and most familiar of all the polyolefins. The different densities of PE result from the method of synthesis. High-density

PE results from polymerization of ethylene in the presence of metallic catalysts; the degree of branching of the chain molecules is low, and the chains approach each other closely. The lower-density PEs are created by different catalysts and exhibit different degrees of chain branching. Low-density PE is particularly useful for film. High-density PE can easily be identified by the rigid, parchment-like feel when it is in film form.

Polypropylene (PP)

Polypropylene, the next most commonly used polymer, is a cousin of polyethylene. The resin is a result of linking propylene molecules, sometimes with the addition of ethylene. PP is used for thermoforming, blow-molding, and film-making. Some of these films are used as carton overwraps. PP bottles are not glass clear, but when the product contacts the inside, better clarity occurs. The reason to choose PP is to make use of its resistance to temperatures or to aggressive chemicals that might stress-crack other plastic containers such as high-density polyethylene.

As a group, polyolefins show high oxygen permeability but low water vapor transmission. PP protects products better than PE, but both types of resins exhibit excellent chemical resistance.

Polycarbonates

Polycarbonates are formed from the reaction of bisphenol A and phosgene. These tough polymers are transparent but allow high water vapor permeation.

Polyesters

Polyesters comprise a large group of polymers used for packaging. Some typical representatives are the esters of various isomers of phthalic acid with ethylene or butylene glycols. The most useful of these is poly(butylene terephthalate), one of the oldest polyester resins processed by injection or blow-molding. These polymers are transparent and remain flexible at low temperatures normally encountered by cosmetic products. Polyesters as a group exhibit relatively low water vapor transmission and oxygen permeability.

Polyamides

Polyamides are commonly derived from dicarboxylic acids and diamines, as exemplified by nylons. These resins can be injection-molded or extruded to produce sheets.

Polystyrene

Polystyrene is a rigid transparent material with excellent flow characteristics that permit the formation of intricate shapes, formed principally by injection molding. It is widely used for jars, bottles, lipsticks, and mascara cases. The brittleness of the polymer can be modified by mixing it with synthetic rubber to

form other varieties of polystyrene. This material is widely used for packaging components wherever solvent attack is not a problem. Expanded polystyrene is used for protecting fragile products by supporting them through a close-fitting formed unit. Polystyrene exhibits high water vapor transmission.

Polyvinyl Chloride (PVC)

Polyvinyl chloride is one of the most commonly used plastics. The polymer can vary from transparent to opaque. In the unplasticized state, the product is rigid and chiefly used for bottles. When plasticized, it becomes flexible and is used in sheet form either by itself or reinforced with PE to form a blister. PVC exhibits high water vapor transmission and only modest resistance to oxygen permeation.

Thermoplastic resins include many other types usually manufactured by vinyl (co)-polymerization. Of particular interest are copolymers of acrylonitrile and various acrylic acid esters. Readers requiring further details should consult References 1 and 2.

THERMOSETTING RESINS

Aminoplastics

The generic term is used for plastics produced by reacting formaldehyde with amines, commonly urea or melamine. These materials are gradually being replaced by thermoplastic resins. These thermosetting resins are widely used in applications such as presentation cases, caps, and closures.

Phenolics (PF)

Phenolics are related to aminoplastics in that they are formed by a reaction between formaldehyde and phenol. Their general characteristics are similar, but the products commonly are brown or black.

PLASTIC TECHNOLOGY

There are five methods for converting plastic resin into packaging components:

1. Injection Molding. This is used in thermoplastic conversions. The molten resin is injected into a mold and allowed to cool. The mold is opened, the component is removed, and the cycle is repeated. This type of molding is used for caps, closures, fittings, trays, and boxes.

2. Extrusion Blow-Molding. In this process, a parison (tube) of molten plastic is extruded from a die; the tube is cut to length while still hot and amorphous and transferred to a mold. Compressed air is then applied through the tube, forcing it to conform to the mold. The mold is opened, the component is removed, and the cycle is repeated. Extrusion blow-molding is the main source of jars and bottles.

3. Compression Molding. Its principal use produces packages from thermosetting resin. The resin and a catalyst are placed in a mold and put under high pressure. The mold is heated by induction, electricity, or steam until the reaction is complete (several seconds). The mold is then opened and the unit removed. This is a major method for producing caps and closures of thermosetting materials.
4. Thermoforming. This is used for blister packaging. A sheet of material is placed over a female mold and heated. When the material is soft, (vacuum) suction is applied, and the material moves down into the mold. The heat is then switched off, the vacuum is released, and the component is removed from the mold. This method is used for trays and point-of-sale displays. This is also the method used to produce thermoformed blisters on horizontal form and fill blister machines.
5. Injection Blow-Molding. This is a combination of injection and extrusion blow-molding. It is used for bottles where tight neck tolerance is required. The parison, including the neck finish of the bottle, is first made in an injection mold. This "preform," which includes the neck and "finish" of the bottle, is then transferred to another machine or plant in which it is reheated and then completed by blowing into a mold on a blow-molding machine.

As plastic moves inexorably into areas previously dominated by glass, it must be understood that compatibility tests must be performed. Some thermoplastics are permeable to oxygen, water vapor, and other gases. To ensure that the product can be held for the time frame required, shelf life and permeability tests are required.

COLLAPSIBLE TUBES

The collapsible tube is a remarkable package that can hold many products. The industry today is divided, as Caesar divided Gaul, into three types: coextruded plastic tubes, aluminum tubes, and high-barrier laminate tubes. All tubes are presented to the filler with the cap in place and the tail of the tube open.

Aluminum tubes are produced by having a slug of metal fed into a horizontal machine. The ram of the machine forces the metal slug into a tool with both male and female molds set up to produce the tube. After working the metal and essential hardening, the tube is annealed to soften the aluminum. The annealed tube is cooled, and a product resistant lining, for example, epoxy phenolic or acrylic lacquer, is applied to the interior to prevent the product from attacking the tube. The tube is then printed in dry offset by inserting the tube onto a mandrel and then rolling it past the printing blanket.

Plastic tubes are made of polyethylene (high or low density). The selection of the proper plastic for the tube is critical in the performance of the tube. The tube is produced by extruding a thin-walled cylinder, which is then drawn over a chilled internal mandrel that allows the tube to shrink to the proper diameter

when removed. This is the "sleeve" and is not yet a tube. Printing is done in dry offset using the same type of printing press used for aluminum tubes. UV-cured inks and thermal inks are used to decorate the tube. Tubes produced for the cosmetic industry can be hot-stamped with foil or silk-screened. After the ink is cured, the sleeves are coated with a high-gloss oxygen barrier coating. Other coatings such as amine-cured epoxy coatings are available to reduce the coefficient of friction and to reduce tube permeability. In the last step, the head of the tube is added by the use of injection molding. It is necessary to use similar grades of polyethylene for the head and for the tube body. A polypropylene tube can be fitted only with a polypropylene head. With the head now in place, the unit is capped and shipped for use.

Laminated tubes were developed relatively recently. This tube is a lamination of materials such as plastic, film, foil, and paper and is far superior to the plastic tube. This tube can be built to possess specific characteristics determined by the constituent materials. Furthermore, some of these materials can be extrusion laminated, giving the final tube a multiplicity of protective and keeping qualities. The seaming process takes the flat wet web and turns it into a cylinder. After the seam is made, the tube is cut to length. The head of plastic is added to the tube and bonded by means of radio frequency heating. An example of this type of tube construction (from outside in) would be low-density polyethylene/ink/white polyethylene/paper/low density polyethylene/adhesive/foil/low-density polyethylene. The printing on the tube is locked between the outer layer and the white polyethylene layer. The printing is executed by rotogravure when the material is in roll form. This allows for superb graphics.

FLEXIBLE PACKAGING

The cosmetic industry uses flexible packaging to provide samples in sachet (pouch) form for such products as facial cleansers, sunscreens, creams, lotions, and mouthwashes in small sample and sales units. The materials for these flat sachets or thermoformed specimens are made of flexible materials. These materials, which are combinations of film, foil, metallized films, and paper, can be produced at average speeds of approximately 150 units per minute. The sachet (pouch) is a four-sided sealed unit. The typical pouch that might hold an alcohol-based fragrance could be made up of polyester/ink/adhesive/metallized polypropylene and a special sealant such as ethylene/acrylic acid. The use of aluminum foil has decreased over the past several years because of the strong growth of metallized and siliconized materials. Aluminum foil suffers from dead fold characteristics, which can sometimes allow leaching of product through the seals. Metallized polypropylene is not subject to this

type of problem and is being employed to replace aluminum foil. It should be remembered that aluminum foil—as the 1100 or 3003 alloy—is the single best material for preventing either moisture loss or oxygen penetration. Basic materials used for laminations are polyester, polyamide, polypropylene, and polyethylene.

The flexible packaging industry also has ability to take resins such as high- or low-density polyethylene and to melt them in extruders, which allows them to be used in place of adhesives. These coextruded films have essentially been merged chemically and therefore have overcome the normal permeation characteristics of their components to form new synergistic materials. The films are printed either in flexography or rotogravure, which is almost always between the surface layer and the next lower layer of the substrate. This provides protection to the print and prevents scuffing or surface attacks on the graphic elements.

GLASS

As noted in the previous section under plastics, glass is being rapidly replaced in the health and beauty aid areas of the cosmetic business. With all of its, defects, glass is a wonderful and long-used product. Glass is chemically inert and will not contaminate any material packaged. In addition, it has the imprimatur of the U.S. Food and Drug Administration (FDA) for packaging a wide range of products. With a properly designed closure or cap, glass is a 100% barrier material and provides an excellent means for displaying the product at the point of sale. Finally, glass can be molded into very attractive designs, giving the product excellent brand image and reinforcing the quality perception of the product.

Glass is manufactured in many different formulations, but most common is soda-lime glass composed of silica (sand or quartz), calcium carbonate, sodium carbonate, and aluminum oxide. Trace elements can be used to add color to glass, with green and amber being most available. A very significant raw material in the making of glass is an energy source, since glass manufacture demands high temperatures.

GLASS TECHNOLOGY

The technology of glass is thousands of years old, but modern methods have made it a fully automatic process. Molten glass is made in furnaces in a continuous process in which a mix of fresh raw materials matches the amount of glass drawn off. Furnaces run continuously at temperatures of 1500 °C for many years. The molten glass is fed into conversion machines for forming

where containers are made. The molten glass is then converted into bottles using a variety of processes in molds with the aid of air pressure. These processes do not impact the relationship of the container to its contents. In contrast to plastics, glass contains no solvent extractable.

PAPER AND PRINTING

PAPER

Every cosmetic and health and beauty aid uses paper or paperboard in various forms. An almost infinite number of grades of paper and paperboard is available for use in labels, composite lids, leaflets, printed cartons, wraps, and corrugated boxes. The technology of papermaking has essentially no impact on cosmetic formulation.

PRINTING AND GRAPHICS TECHNOLOGY

All packaging components must be printed to identify and decorate them. The choice of the printing method is based on the material and the number of units to be decorated. The various methods of printing are briefly mentioned. It should be noted that the previous technologies for the production of plates and for the revision of artwork have been replaced by computer-driven processes. Like so many other aspects of packaging, the processes used for labeling, decorating, and printing of packaging components in the cosmetic industry have no impact on the quality or stability of the product.

Letterpress

Letterpress is an above-the-surface, very old method of printing. The raised surface (plate) is inked and the ink is then transferred to the material (substrate). The main use for letterpress today is the printing of folding cartons or labels.

Flexography

Flexography uses plastic plates as the raised surface rather than the metal plates used in letterpress. Flexography is used for the printing of flexible materials such as polyethylene and polypropylene labels, overwraps, and laminates. Almost 90% of flexible packaging materials are printed by flexography.

Lithography

Lithography is a surface method of printing, with the plate presenting both hydrophilic and hydrophobic areas as a result of having been treated to accept or reject the ink. The inked areas are then transferred to an offset blanket, one color at a time, and from there to the substrate. The main use for lithographic

printing is for folding cartons, metal cans, labels, brochures, and catalogue sheets.

Rotogravure

Rotogravure is an engraved or intaglio method of printing, with the printing cell engraved or under the surface of the cylinder. The engraved cylinder deposits only one color, so that a multiple number of cylinders is required. This extremely accurate printing method meets the most precise color requirements.

If printing is exposed, spillage of cosmetic product during filling or in the hands of the consumer may cause bleeding or undesirable discoloration. It is important to ascertain that decorated or printed surfaces remain unaffected by product contact. As was mentioned in the discussion of flexible packaging, printing in modern practice is between the surface layer and the next lower layer to reduce potential problems because of product contact.

CLOSURES

A closure seals the egress of product from glass, plastic, or metal containers and is required for cans, bottles, and vials. The closure is designed to seal the container to ensure that neither the product nor any of the essentials of the product escape. The closure provides a barrier against gases, water vapor, and other environmental contaminants. Materials for closures are manufactured from plastic, metal, or glass. Metal closures are made of either aluminum or tin-free steel.

Screw caps are the most commonly used devices to seal bottles, jars, and tubes. Screw caps are provided with threads that engage the threads on the container. The cap must provide a positive seal by tightly contacting the top of the container or tube. A variety of resilient materials are used to form a compression point between the closure and the sides (lands) of the package. Screw caps are generally provided with a soft wad or foam liner that in turn is coated with wax, vinyl, or other material that contacts the product and creates the tight seal to the container.

Other types of closures exist that are specifically designed for a particular product and use. In fact, contemporary package and closure are determined by the demands of the consumer. The requirement of ease of access to the product along with the legal mandates of government have increased demands on the packager. Many packages today deliver their products through closure devices that include valves, pumps, and multipart chambers.

In addition to the plastic closure, the wad formerly available in various grades of paper with wax, vinyl, and other coatings has been largely replaced and augmented by the new plastic "Polly" liners. This foam liner is a foamed

polyethylene between two layers of polyethylene. This has great compressibility and therefore sealing quality. In addition to this type of workhorse structure, liner material can be combined with aluminum foil, Saran®, and other barrier materials. One of the new liner structures combines an inner oxygen scavenger with the liner facing the product. This closure and the liner prevent oxygen penetrations through the closure, while the inner scavenger removes residual oxygen.

The simple act of opening the majority of containers requires the ability to unscrew the closure without excessive force. In normal filling operations closures are applied with a certain torque to ensure reliable sealing of the package. If the cap liner should swell or interact with the contents and/or the container, the torque required to remove the closure may be increased. It is therefore common practice to control the application torque and to make certain that this torque does not change during product storage.

The choice of closure must be aimed at the market served. Childproof closures are intended to prevent children under the age of five from opening the package. This is accomplished by establishing a set of steps that are beyond the child's motor skills development. These childproof resistant closures can also pose difficulties to elderly people.

For convenience, closures can be divided into several groups. All closures are, of course, containment closures, but not all closures are produced exclusively for containment. Closures exist today that not only contain but also provide a special function such as the flip top, fixed spout, plug orifice, and many other types of application closures. Application closures can contain droppers, daubers, rods, spray tops, and dispensers. Fitment closures, finally, are those that contain valves or other regulating devices that meter the material flowing through the closure. Some specialized closures are more aesthetic than practical. They range from molded glass stoppers to stoppers that incorporate a figure or an animal.

PACKAGE TESTING

Testing is required to determine whether the material chosen has the chemical, mechanical, and physical qualities to provide the packager with a finished unit that will contain the product without change for the period of time before use by the consumer. The testing methods used in the packaging industry on materials and finished packages include mechanical testing such as tests for tensile strength; impact and flex tests; and tests for compression to study the use of paper, paperboard, and flexible materials. Physical properties are designed to test for water absorption, moisture vapor transmission, aging of material, thermal conductivity, and flammability. Chemical properties tests determine

resistance of the package to the product. Standards for these tests have been established by the American Society for Testing and Materials (ASTM), the British Standards Institute, and the Deutsches Institut für Normung.

PERMEATION TESTING

There are two ways that gases or water vapor can enter or leave a package; one is leakage, the passage of gas or vapor through defects in the unit such as cracks, pinholes, microscopic apertures between the closure and the bottle; the other is diffusion of gas or water vapor through the material of the container, the wall of the bottle, and so forth. It is extremely important that permeation through the container be determined. Almost all vendors of packaging materials have already performed flat tests (in which flat sheets of material are tested), but if the same material is molded into a container it must be tested.

Gas permeability coefficients are usually reported for use in the packaging industry along with temperature and humidity. As a rule, standards document the rate at which gas will pass through a piece of packaging material during a 24-hour cycle. The standard thickness of the material is one mil (25.4 μm) and a surface area of 100 in^2 (0.065 m^2) through which a volume of gas (in ml) will pass during a 24-hour period. The usual conditions are 1 atm. pressure, 77 °F, and 50% RH. Permeability coefficients of water vapor are reported similarly as mil. (100 $in.^2$) at 95% RH and 36 °C. The usual test period is a minimum of 30 days. Initially, there is a buildup of gas, which begins to permeate and then diffuse through the material. Eventually, a steady state of permeation rate develops, which is the maximum possible rate for that sample. The more rapidly a gas passes through the material, the shorter the product's shelf life. It is necessary that a steady state rate be established so that a conservative estimate can be made; it is almost always better in these cases to be conservative.

A particularly simple way of measuring transmission rates is to package a liquid product and then monitor its weight (loss) over a period of time. For testing, a material can be sealed over a cup filled with desiccant, which is then weighed continuously over several weeks. Instrumentation is available for determining oxygen or carbon dioxide penetration. In addition, water vapor transmission can also be tested instrumentally. It must always be remembered that testing must be of the completed package, since the material that is folded or "blown into shape" does not function the same as does a flat sample.

Gas chromatography is used to determine whether organic vapors, such as solvents, flavors, or fragrances, are migrating through the package or closure. This requires that the complete package be inserted into a suitable test cell. Results alert the packager as to whether the unit is leaking. Gas chromatography can also be used for measuring water vapor, oxygen, carbon dioxide,

and nitrogen transmission rates. For products requiring the use of filled units that are moved from one installation to another before final packaging, helium leak detectors can be used to determine any leakage and to prevent the use of material that has possibly been contaminated.

Test protocols and equipment are designed and published by ASTM to determine the package response to impact, vibration, and changes in the environment. The significance of any of these tests should not be underestimated since all the work in creating the package can be destroyed by poor and adverse shipping conditions. The packaged product must withstand shipping. To test product fragility, the product is subjected to a battery of standard ASTM tests. These tests have become the North American standards for all shipping containers; it is noted that depends on the ASTM tests for approval. The tests include exposure to vibration, frequent shock, and horizontal and vertical impact. Product distributors may at times also use additional shipping tests.

The ASTM has become the overall authority for package testing and standard shipping tests. For test information and procedures, ASTM should be contacted at 100 Barr Harbor Drive, West Conshohocken, PA, 19428-2959, U.S.A.

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CHAPTER 37
Stability

INTRODUCTION

Formulators of cosmetics routinely examine product stability using various procedures. It is rarely possible to predict the long-term stability of any product, even after repeated examinations of the product during and after exposure to artificially created stress conditions. Heating, freezing, and centrifugation are typical stress conditions used by compounders in the hope that product performance and appearance are not adversely affected during the projected shelf life of the composition. Estimations of shelf life based on chemical analyses and physical criteria are conducted with much care in the drug industry, and expiration dating is routinely practiced. In the cosmetic industry, such rules are not as rigidly formalized; shelf life projections are based instead on the formulators' assessment of stability data. This judgment is most likely modified by the activities of quality assurance, pilot plant, and manufacturing personnel who must deal with much larger batches and reproducibility.

It is axiomatic that any formulated product undergoes changes due to aging and packaging. The criteria of concern in the case of cosmetics are cosmetic elegance, consumer acceptance, and utility; the answer sought is how long after manufacture can the product be sold on the open market. In the case of drugs—and this includes over-the-counter (OTC) drugs—stability is an absolute criterion. A stable drug product can be expected to remain within established specifications and to deliver the active (drug) at an effective level. During the period of storage, neither identity nor quality is allowed to change. Cosmetic elegance or appearance are not the primary concerns of a pharmaceutical stability program. Such features are subordinate to the functionality of the drug product while it approaches its expiration date.

Cosmetic products may exhibit instability due to chemical changes of the constituents or the presence of undesirable microbiota. Products exhibiting these types of defects are not acceptable and should be categorically rejected. Such products require reformulation before they can be marketed. Signs of

emulsion instability due to physical changes may still be acceptable as long as the degree of deterioration does not interfere with customer satisfaction.

Some general procedures for the assessment of stability of cosmetics can be found in IFSCC Monograph #2 [1]. This pamphlet deals with the objectives of stability testing that includes among other practical procedures for determining content stability and container compatibility. This is followed by test approaches at elevated temperatures and humidities, cycling tests (including freeze/thaw), light testing, and finally mechanical testing for demixing of solids, emulsions, and foams. Formulators can avoid trouble during stability testing by selecting ingredients that on the basis of chemistry and preformulation data should not undergo changes that may lead to instability in the product. In principle, compounders should make a concerted effort to build in stability before the first prototype is prepared.

Real-time testing of cosmetics or drugs usually delays market entry and is not acceptable to market-driven companies. Instead, such companies rely on ingeniously devised stress tests to permit a shelf life prediction. This type of program has been practiced for many years and has served the industry well. Approaches to make shelf life predictions practical will be discussed below. In addition, some more insidious and less overt stability concerns will be noted.

As will be explained later, predictive shelf life testing is an almost impossible task. During development the formulator uses all types of devices and procedures to coax the emulsified globules of the internal phase to remain separate from neighboring globules and to ignore the law of gravity by remaining stationary within the product. Clearly the laws of physics do not condone these attempts of formulators. Macroemulsions are not stable and must obey the laws of thermodynamics. Formulators can only strive to slow down the rate at which instability of an emulsion takes place and must confine their activities to the product's shelf life, that is, the usually brief period during which the product remains saleable.

Formulators intending to project an emulsion's shelf life are well advised to examine the factors that account for the ability of a system to form an emulsion. For example, if an emulsion or suspension cannot be created without the presence of a viscosity-imparting cellulosic, the stability program should include an examination of all the factors that may alter the stability of the cellulosic. Chemical depolymerization, possible cross-linking, and viscosity changes as a result of agitation or modest temperature variations should all be considered before a stability program is launched. Even in the absence of microorganisms, the formulator might want to confirm that cellulases, commonly found in paper packaging materials, are kept out of the emulsion. Recognition of the instability of the cellulosic thickener can avoid the costly mistake of initiating a complex—and by necessity doomed—stability program on an emulsion. Another example is

more directly related to the survival of an emulsified particle, which may be surrounded by a tough resilient film, as explained in Chapter 10. If this should be the primary stabilizer, all heating and cooling conditions that destroy this film at temperatures encountered under any imposed stress conditions but not in normal storage will needlessly destroy the formulation.

Thus the selection of a stability test protocol is not simply determined by executive or governmental fiat but should be based on a rational assessment of what holds the emulsion together. In the case of emulsified products, physical instability is signalled to the observer by separation, viscosity changes, or the appearance of large globules of the internal phase. These three phenomena are not independent of each other. Stokes's equation controls separation (rising or creaming of oil or settling of a phase of high specific gravity). In many cases, the separation is caused by a drop in viscosity and is followed by some globule coalescence to create large particles.

Stability requirements for cosmetic emulsions in general include appearance (separation and color changes), odor, viscosity (dispensability), preservation, chemical changes (pH, hydrolysis, etc.), and light stability.

Other concerns include packaging, weight change, and robustness during manufacture and filling.

PREDICTIVE COSMETIC STABILITY TESTING OF EMULSIONS

The long-term stability of macroemulsions in cosmetics is essential for successful marketing of all types of creams and lotions. The distinction between macroemulsions and microemulsion is of fundamental importance to stability. The former are subject to physical phenomena that might identify them as unstable in the range of temperatures encountered during storage and use. The latter, which include clear (transparent) and opalescent preparations, are thermodynamically stable. Their composition is carefully adjusted to create a clear product within the range of contemplated temperatures without complicated processing. Spontaneous formation is a hallmark of microemulsions and depends critically on micellization.

Microemulsions may become cloudy or even opaque under a variety of extreme temperature conditions but regain their original clarity spontaneously at more normal temperatures. The ability of microemulsions to return to their original appearance reduces the need for some physical testing.

Cosmetic stability testing classically was not concerned with the assays of any pharmacologically active constituent. Instead, the primary concerns were the physical appearance and the product's use characteristics. Discussion of cosmetic product stability dealt primarily with the phenomenon of emulsion

stability. The thermodynamics of emulsions indicate that they are unstable and tend to separate into an aqueous layer and an oily layer [2]. Thus excessive stress by high heat or excessive mechanical force can quickly destroy emulsions, although they may survive less stressful conditions, allowing for an acceptable shelf life.

TEMPERATURE

The time-honored procedure is to place a newly formed emulsion at an elevated temperature for a period of time during which the product is examined critically for evidence of separation. As a rule of thumb, it is assumed that three months' storage at a modestly elevated temperature (between about 37 °C and 45 °C) with no evidence of separation should guarantee stability of the product at room temperature (25 °C to 30 °C) for about one year. This is probably not a valid approach since it is based on the principles of the Arrhenius equation [1,2]. This powerful tool, based on activation energy, works admirably whenever the reaction at elevated temperature is identical to that taking place at the lower temperature. Such conditions do not exist in emulsions because temperature-caused changes in melting points of components, solubility of emulsifiers, and distribution coefficients may all affect an emulsion's stability. The viscosity of emulsions controlled by the dispersed phase or by added gums and their hydration also do not conform to the postulates of the Arrhenius equation, as pointed out by Zografi [3]. This alert should not be construed as a warrant against elevated temperature testing because cosmetic products may encounter warm environments during storage. It is a warning, however, to limit such testing to temperatures that are reasonable, that is, close to those normally encountered. It is unsound to base shelf life predictions of emulsions on the results of "high" temperature testing. Zografi concludes that "there is no clear cut basis for expecting that accelerated studies allow extrapolation to normal storage conditions and quantitative expiration testing." The reasoning behind this concept also requires that extreme stress conditions should be avoided during formulation programs because instability is almost ensured and results in the abandonment of compositions with considerable merit. Therefore storage temperature close to transition points—as defined by Eccleston [4]—or the phase inversion temperature—discussed in Chapter 10—should be avoided during stability testing.

RHEOLOGY

Another favorite tool of formulators relies on an examination of rheological changes. Structural viscosity in pourable or semisolid cosmetic emulsions is commonly due to the interaction of particles. The rheology pattern of such

cosmetic emulsions is viscoelastic, and single point measurements are not very useful. The more complex modern instruments measure shear stress as a function of shear rate and can be expected to demonstrate classic hysteresis (Chapter 11). Unfortunately, the first rheogram on a sample may modify the nature of the second or subsequent rheogram. Thus any sample once agitated may no longer be useful for further testing. Shear-thinning and thixotropy determine the time at which meaningful rheological data can be obtained. Nevertheless, viscoelastic data—properly obtained—are a powerful tool for ascertaining the utility of cosmetic emulsions or suspensions. For example, viscosity changes of a toothpaste during a three- to six-month period at ambient conditions can help to eliminate those compositions that may not be acceptable to the consumer. Again, rheology studies of sample stored at excessively high temperature can be misleading.

The rationale for and the principles of rheological assessment were discussed in Chapter 11, with special emphasis on rotational rheometry; the most commonly found and useful instruments include the Stormer, Haake, MacMichael, Brookfield, and cone and plate viscometers. In addition, some more viscous cosmetic products require the use of cone or needle penetrometers. Some aspects of these instruments were described by Schott [5].

PARTICLE SIZE

The particle size measurement of the disperse phase in an emulsion requires careful interpretation. Ideally, particles should be examined without the need for complicated dilution procedures. If the average particle size remains invariant under normal storage conditions, the formulator may assume that particle coalescence in the emulsion does not present a problem; however, this does not preclude that other types of instability may not play a role in product stability. A continuous increase in particle size should result in emulsion instability unless the preparation is very viscous. Particle size increase of the disperse oil phase in so-called multiphase emulsions may not be a prelude to instability. Such emulsions include crystalline gel phases, as explained by Eccleston [6] (on the basis of studies by Junginger in the Netherlands). The oil droplets are essentially immobilized in the structured continuous aqueous phase and are not subject to coalescense or flocculation. In this type of emulsion, repulsive forces exist between the bilayers of surfactant and amphiphile, separated by relatively thick layers of water that prevent the close approach of oil globules to each other. An emulsion of this type commonly exists in cosmetic creams; its instability results from destruction of the gel network by agitation or by excessive heat.

A still more complicated problem involving particle size (changes) in o/w emulsions comprising solids may exist in many liquid makeup preparations.

As explained by Friberg et al., finely divided solids stabilize o/w emulsions by adsorption to the surface of the oil globule [7]. The exact placement of the solid depends on the contact angles to the water or oil phases and on the degree of wetting due to the presence of adsorbed surfactant. Any temperature-dependent alteration in the bonding of the solid to the wetting agent can alter the stability of the system. The solid may actually become submerged in the emulsified oil droplet or be totally desorbed from the oil globule. In practice, any instability is accompanied by particle size changes of the suspended (makeup) solid or the oil globule.

Particle size measurements can be a formidable task, and formulators have made efforts to find other means for making these types of measurements. A good summary is included in Allen's book [8]. The combination of sedimentation field-flow fractionation and photon correlation spectroscopy can provide particle size distribution data (Jianmin, L., et al., *Pharm. Res. 10*, 535–541, 1991). Measurement of dielectric constant (Reddy and Dorle, *Cosmet. Toiletries 99*, X, 67–72, 1984) and conductivity (Bury, M., et al., *Int. J. Pharm., 124*, 193–195, 1995) reportedly correlate with particle size changes.

The important conclusion from this discussion is the need for formulators to fully understand the nature of the emulsion's stabilizing system. A meaningful stability protocol can then be devised to ascertain the conditions leading to instability. Such a protocol must take into account the likely storage conditions and the unique stabilizing system devised by the formulator.

TEST PROTOCOLS FOR EMULSIONS

In the 1980s a round-robin assessment of emulsion stability of three products was conducted in nine European laboratories. The test conditions included all of the following:

Test Condition	Time of Assessment
−20 °C	24 hours (after thawing)
−5 °C	1 week (after thawing)
Room temp. (dark)	1, 2, 3, and 4 months
40 °C	3 days; 1, 2, 3, 4 weeks; 2, 3 months
45 °C	3 days; 1, 2, 3, 4 weeks; 2, 3 months
50 °C	1, 3 days; 1 week

Regardless of the outcome of the study, such a protocol should not be rigidly imposed on the compounder. Test times and stress conditions suggested in Reference 1 are less rigid and allow modifications warranted by the nature of the product. More recently, guidelines developed by the FDA and the ICH can be used with more confidence. Details of these guidelines can be found in Chapters 16 and 17 of Reference 9. The protocols employ more

moderate elevated temperatures and include additional recommendations for testing procedures.

The recently developed guidelines emphasize the need for flexible test conditions to include the environmental situations likely to be encountered by the product. This was the thrust of the presentation of Zografi before the meeting of the Society of Cosmetic Chemists in 1981 [3]. The salient features are repeated below for emphasis.

- High speed centrifugation is not a very useful tool. It tends to distort the shape of the suspended internal phase droplets and forces merging of droplets under totally artificial conditions. Centrifugation at 2–3 g is particularly well suited for pigment suspensions and may help to establish the suitability of emulsion products.
- Temperatures higher than those recommended for product storage in Table 37.1 may create conditions of overkill. Such testing is not predictive and may result in the abandonment of perfectly acceptable emulsions.
- Rheology can measure subtle changes in viscosity and must be critically reviewed. The most useful modes are studies at low shear.
- The most useful stability indicating test is gentle shaking, perhaps at moderately elevated temperatures. The steady rocking motion enhances the kinetic energy of collisions of droplets resulting in coalescence, especially since the low agitation during shaking also reduces the viscosity of the system. Even if the emulsion should survive the shaking, it may not recover its original viscosity (measured at low shear), or the particle size distribution may have been altered. This test resembles the so-called "shipping test" but is conducted in a much more controlled environment.

Table 37.1 Summary of Currently Accepted Guidelines for Accelerated Stability Testing

Condition	Time of Assessment
25 °C ± 2 °C	One year
30 °C ± 2 °C	One year (equivalent to room temperature)
40 °C ± 2 °C	Six months
Freeze/thaw	Cycle repeatedly between 4 °C and 40 °C or 45 °C
Light Testing	
Fluorescent	One to two weeks (or longer)
Xenon	One to two weeks
Ultraviolet	One to two weeks
Daylight	One year
Other Testing	
Shaking	One week at 30 °C or 40 °C
Centrifugation	One or two hours.

- Elevated temperature testing based on ICH guidelines should be at 40 °C ± 2 °C for six months. The container(s) used for test storage should be identical to the container(s) planned for marketing. The FDA guidelines also consider storage at 45 °C ± 2 °C as useful.
- Stability is defined as the capacity of a drug product to remain within specifications established to ensure identity, strength, quality, and purity. Cosmetic elegance is not a primary stability criterion for drugs.
- Drug emulsions should be examined for appearance, color, odor, pH, viscosity, and "active"-strength. Product should also be stored on the side or upside-down. Heating/cooling cycles are normally conducted between 4 °C and 45 °C.
- The ICH and FDA guidelines agree on the maintenance of 95% drug potency and require that (drug) degradation products be detected, isolated, and identified. The reaction kinetics accounting for degradation need be established. Product sampling for any purpose should include the top, middle, and bottom portions of the specimen.
- The ICH guideline recognize the existence of climatic zones, and stress conditions may be varied to account for these differences.

The results of these stability studies should be evaluated via a valid statistical model on several batches. Up to this point the discussion of stability was limited to the critical assessment of emulsions. Cosmetic emulsions and suspensions may also include various drugs (OTC products) or constituents intended to benefit the skin. Stability requirements for such ingredients are briefly described below.

THE STABILITY OF ACTIVES IN COSMETICS

Even in the absence of active constituents, changes observed during routine storage may dictate the need for additional studies. Discoloration and pH changes are indications of reactions signaling instability. Changes in drug particle size distribution are probably not acceptable.

The testing of drug constituents via the Arrhenius equation [1,2] requires storage at two temperatures at which chemical decomposition may occur. The wider the separation between these temperatures, the more reliable the analysis. The tendency of emulsions to separate at elevated temperatures may have effects on drug solubility and can alter reaction rates. It is extremely complicated to ascertain a drug substance's stability under these circumstances. Formulators may prefer to depend on the results of preformulation studies to identify incompatibilities and instabilities. Ultimately, chemical studies of actives in the finished product are required. Proper use of decomposition rate changes requires that measurable drug loss or deterioration be observed at two elevated temperatures. The practical use of the Arrhenius equation in drug and personal products is described in numerous pharmaceutical textbooks

(which should be consulted). It has recently become common practice to include various types of ingredients, for example, vitamins or plant extracts, in cosmetic preparations. Ethical considerations may require assays for the presence of such substances at effective levels and absence of degradation during storage. Formulators should always insist on *stability indicating* assays. For example, analyses for zinc ion during storage of a zinc pyrithione—containing product do not indicate that this antidandruff drug is stable in the product.

In practice, the results of a classic Arrhenius drug stability study are extrapolated to an (expiration) time at room temperature. As a general rule, 95% of the active should be present at the computed expiration date.

CHEMICAL INSTABILITY OF COSMETIC INGREDIENTS

In addition to the instability of emulsions and the decomposition of drug substances, the compounder must guard against other chemical phenomena. Many cosmetic ingredients are subject to all types of decomposition reactions.

TRANSESTERIFICATION

Transesterification reactions rarely cause problems during formulation programs but can become extremely troublesome during stability studies. A typical case may be the reactions between moisturizers, for example, sorbitol or glycerin, and the commonly used hydroxybenzoates. In media high in humectants, the parabens may undergo transesterification to, for example, glyceryl hydroxybenzoate. Other esters, including those used as skin emollients or surfactants, are also subject to transesterification, especially at pHs near 7. If this should be a continuous reaction, a carefully studied preservative system may not persist to protect the product against inadvertent contamination. It is advisable therefore to examine preservative activity and chemistry not only in the freshly prepared product but also after extended storage. A typical example of transesterification of parabens was recently described by A. Hensel et al., *J. Pharm. Sci.*, 1995, 84, 115–118.

SOLUBILIZATION

The solubilization of preservatives by surfactants is known to affect antimicrobial activity. This phenomenon was first described about 50 years ago and has been explained on many occasions as a solubilization phenomenon during cosmetic and drug formulation (Chapter 14).

The sequestration of a drug into a surfactant micelle can have the benefit of stabilizing the drug against hydrolytic attack. It is critically important that formulators familiarize themselves with the effects of surfactants on drug

availability and drug stability. As a general rule, a drug constituent subject to hydrolysis may be stabilized by micellization. By contrast, micellization in other cases may enhance decomposition reactions. This phenomenon, called micellar catalysis, is the subject of several publications [10]. Another aspect of drug micellization is drug availability or skin permeation. The size of micellized drugs can play an important role in topical drug therapy.

OXIDATION

The most prevalent attack on product integrity is due to oxidation, especially in the presence of light. The basic chemistry of oxidation and the formation of reactive oxygen species was reviewed in Chapter 12. The attack of oxygen on cosmetic components is not confined to unsaturated substances. In fact, the most insidious attack is peroxidation of polyoxyethylene ethers. Formulators can normally protect a formulated product by avoiding UV light, metal contamination, or access to oxygen. These measures do not ensure stability once a product has been applied to an exposed skin surface. In fact, some sensitizers may be formed by light exposure on the skin. For example, a compound like laureth-5 or -6 is subject to chain shortening and production of the formic acid ester of laureth-4 or -5 due to oxidation [11]. Compounders have limited control over the combination of products applied simultaneously to the skin and the in-use exposure to UV light. The true impact on hypersensitivity responses to this phenomenon cannot be assessed by in vitro testing but probably must rely on open patch testing. The important message to formulators is the fact that stability during careful in vitro testing does not guarantee chemical stability during actual use. One can argue that these phenomena should not be part of a true stability protocol. On the other hand, one may ask whether a formulator should avoid the use of cosmetic ingredients that may form undesirable species on the skin during use. For additional background readers might wish to review D.E. Moore's contribution to H. Tønnesen's book [12].

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Note: boldface numbers indicate illustration *(t)* indicates tabular information.

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