



PHARMA DEVILS

QUALITY CONTROL DEPARTMENT

GENERAL TESTING PROCEDURE

Title: Determination of Water

SOP No.:		Department:	QC	
Effective Date:		Review Date:		
Revision No.:				
Supersede SOP No.:				

1.0 OBJECTIVE:

1.1 To lay down a procedure for Determination of Water.

2.0 SCOPE:

2.1 It is applicable for the estimation of Raw material.

3.0 RESPONSIBILITY:

3.1 Analyst / Officer / Executive follow the procedure.

3.2 Head-QC are responsible for effective implementation of this SOP.

4.0 REFERENCE:

4.1 BP (Ph. Eur. Method)

5.0 DEFINITION:NA

6.0 PROCEDURE: Use Method IA unless otherwise directed

6.1 **Method I:** Semi-micro Determination of Water-The semi-micro determination of water is based upon the quantitative reaction of water with sulfur dioxide and iodine in, a suitable anhydrous medium in the presence of a base with sufficient buffering capacity.

Apparatus: The apparatus consists of a titration vessel with:

- 2 identical platinum electrodes.
- Tight inlets for introduction of solvent and titrant.
- An inlet for introduction of air via a desiccant.
- A sample inlet fitted with a stopper or, for liquids, a septum.

Inlet systems for introduction of dry nitrogen or for aspiration of solvents may also be fitted. The titration is carried out according to the instrument supplier's instructions. Care is taken throughout the determination to avoid exposure of reagents and solvents to atmospheric moisture. The end-point is determined using 2 identical indicator electrodes connected to an electrical source that



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maintains between the electrodes either a constant current (2.2.65. Voltametric titration) or a constant voltage (2.2.19. Amperometric titration). Where direct titration is used (method A), addition of titrant causes either a decrease in voltage where constant current is maintained or an increase in current where constant voltage is maintained, until the end-point is reached. Instruments with automatic end-point detection are commonly used. Instrument qualification is carried out according to established quality system procedures, for example using a suitable certified reference material (sodium aminosalicylate dihydrate for equipment qualification CRS may be used).

Standardisation: To the titration vessel, add methanol, dried if necessary, or the solvent recommended by the supplier of the titrant. Where applicable for the apparatus used, eliminate residual water from the measurement cell or carry out a pre-titration. Introduce a suitable amount of water in an appropriate form (water R or a certified reference material) and carry out the titration, stirring for the necessary time. The water equivalent is not less than 80 per cent of that indicated by the supplier. Standardise the titrant before the first use and at suitable intervals thereafter.

Unless otherwise prescribed, use Method A.

METHOD A: Introduce into the titration vessel methanol, or the solvent indicated in the monograph or recommended by the supplier of the titrant. Where applicable for the apparatus used, eliminate residual water from the measurement cell or carry out a pre-titration. Introduce the substance to be examined rapidly and carry out the titration, stirring for the necessary extraction time.

METHOD B: Introduce into the titration vessel methanol, or the solvent indicated in the monograph or recommended by the supplier of the titrant. Where applicable for the apparatus used, eliminate residual water from the measurement cell or carry out a pre-titration. Introduce the substance to be examined rapidly and in a suitable state of division. Add an accurately measured volume of the titrant, sufficient to give an excess of about 1 mL or the prescribed volume. Allow to stand protected from light for 1 min or the prescribed time, with stirring. Titrate the excess of reagent using methanol or the prescribed solvent, containing an accurately known quantity of water.



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Suitability: The accuracy of the determination with the chosen titrant must be verified for each combination of substance, titrant and solvent to be examined. The following procedure, given as an example, is suitable for samples containing 2.5-25 mg of water.

The water content of the substance to be examined is determined using the reagent/solvent system chosen. Thereafter in the same titration vessel, sequential known amounts of water, corresponding to about 50-100 per cent of the amount found in the substance to be examined, are added in an appropriate form (at least 5 additions) and the water content is determined after each addition. Calculate the percentage recovery (r) after each addition using the following expression:

$$r = 100 \frac{W_2}{W_1}$$

Where W_1 = Amount of water added, in milligrams.
 W_2 = Amount of water found, in milligrams.

Calculate the mean percentage recovery (\bar{r})

The reagent/solvent system is considered to be acceptable if \bar{r} is between 97.5 per cent and 102.5 per cent.

Calculate the regression line. The x-axis represents the cumulative water added whereas the y-axis represents the sum of the initial water content determined for the substance (M) and the cumulative water determined after each addition.

Calculate the slope (b), the intercept with the y-axis (a) and the intercept of the extrapolated calibration line with the x-axis (d) Calculate the percentage errors (e_1 and e_2) using the following expressions:

$$e_1 = 100 \frac{a - M}{M}$$

$$e_2 = 100 \frac{|d| - M}{M}$$



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a= The y-axis intercept, in milligrams of water;
d= The x-axis intercept, in milligrams of water;
M =Water content of the substance, in milligrams of water

The reagent/solvent system is considered to be acceptable if:

- $|e_1|$ and $|e_2|$ are not greater than 2.5 per cent.
- b is between 0.975 and 1.025.

6.2 Method II Determination of Water by Distillation: The apparatus (see Figure 2.2.13.-1) consists of a glass flask (A) connected by a tube CD) to a cylindrical tube (B) fitted with a graduated receiving tube (E) and reflux condenser (C). The receiving tube (E) is graduated in 0.1 mL. The source of heat is preferably an electric heater with rheostat control or an oil bath. The upper portion of the flask and the connecting tube may be insulated. Method Clean the receiving tube and the condenser of the apparatus, thoroughly rinse with water, and dry. Introduce 200 mL of toluene and about 2 mL of water into the dry flask. Distil for 2 h, then allow to cool for about 30 min and read the water volume to the nearest 0.05 mL. Place in the flask a quantity of the substance, weighed with an accuracy of 1 per cent, expected to give about 2 mL to 3 mL of water. If the substance has a pasty consistency, weigh it in a boat of metal foil. Add a few pieces of porous material and heat the flask gently for 15 min. When the toluene begins to boil, distil at the rate of about two drops per second until most of the water has distilled over, then increase the rate of distillation to about four drops per second. When the water has all distilled over, rinse the inside of the condenser tube with toluene. Continue the distillation for 5 min, remove the heat, allow the receiving tube to cool to room temperature and dislodge any droplets of water which adhere to the walls of the receiving tube. When the water and toluene have completely separated, read the volume of water and calculate the content present in the substance as milliliters per kilogram, using the formula



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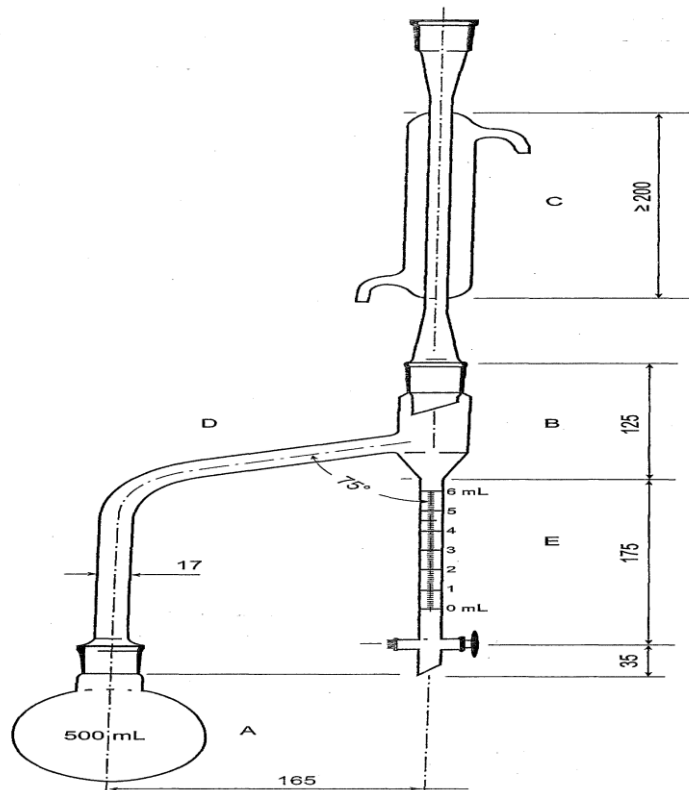
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$$\frac{1000(n_2 - n_1)}{M}$$

M

m = The mass in grams of the substance to be examined,
n₁ = The number of milliliters of water obtained in the first distillation,
n₂ = The total number of milliliters of water obtained in the 2 distillations.



Apparatus for the determination of water by distillation Dimensions in millimeters

6.3 Method III: Coulometric Titration:

Principle: The coulometric titration of water is based upon the quantitative reaction of water with sulfur dioxide and iodine in an anhydrous medium in the presence of a base with sufficient buffering capacity. In contrast to the volumetric method described in general chapter 2.5.12. Water: semi-micro determination, iodine is produced electrochemically in the reaction cell by



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oxidation of iodide. The iodine produced at the anode reacts immediately with the water and the sulfur dioxide contained in the reaction cell. The quantity of water in the substance is directly proportional to the quantity of electricity (in coulombs), corresponding to electric current (in amperes) multiplied by time (in seconds), used for iodine generation up until the titration end-point. When all of the water in the reaction cell has been consumed, the end-point is reached and thus an excess of iodine appears. 1 mole of iodine corresponds to 1 mole of water, an amount of electricity of 10.71 C corresponds to 1 mg of water. Moisture is eliminated from the reaction cell by pre-titration, i.e. the electrolyte reagent is titrated to dryness before starting the sample analysis. Individual determinations can be carried out successively in the same reagent solution, under the following conditions:

- Each component of the test mixture is compatible with the other components.
- No other reactions take place.
- The volume and the water capacity of the electrolyte reagent are sufficient.

Coulometric titration is intended for the quantitative determination of small quantities of water (from 10 ug), however a working range of 100 µg to 10 mg of water is recommended for reproducibility reasons.

Accuracy and precision of the method are predominantly governed by the sample preparation and the extent to which atmospheric moisture is excluded from the system. Control of the system must be monitored by measuring the amount of baseline drift.

Apparatus: The apparatus consists of a reaction cell, electrodes and a magnetic stirrer. The reaction cell consists of a large anode compartment and a smaller cathode compartment. Depending on the design of the electrode, both compartments can be separated by a diaphragm. Each compartment contains a platinum electrode. liquid or solubilized samples are introduced through a septum, using a syringe. Alternatively, an evaporation technique may be used in which the sample is heated in an oven and the water is evaporated and carried into the cell by means of a stream of dry inert gas. The introduction of solid samples into the cell should, in general, be avoided. However, if it has to be done it is effected through a sealable port; appropriate precautions must be taken to avoid the introduction of moisture from air, such as working in a glove box in an atmosphere of dry inert gas. The analytical procedure is



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controlled by a suitable electronic device, which also displays the results. Instrument qualification is carried out according to established quality system procedures, for example using a suitable certified reference material. Sodium amino salicylatedihydrate for equipment qualification CRS may be used when proceeding by direct or liquid sample introduction, whereas amoxicillin trihydrate for performance verification CRS may be used with the evaporation technique.

Method: Fill the compartments of the reaction cell with electrolyte reagent for the micro determination of water R according to the manufacturer's instructions and perform the coulometric pretitration to a stable end-point. Introduce the prescribed quantity of the substance to be examined into the reaction cell and titrate again to a stable end-point, stirring for at least 30 s, unless otherwise indicated in the monograph. If an oven is used, the prescribed quantity of sample is introduced into the oven and heated. After evaporation of the water from the sample into the reaction cell, the titration is started. Alternatively, the evaporated moisture is immediately titrated while heating the sample in the oven to avoid loss of evaporated water already collected in the reagent solution during prolonged heating. Read the value from the instrument's output and calculate if necessary the percentage or quantity of water that is present in the substance. When appropriate to the type of sample and the sample preparation, perform a blank titration.

Verification of Accuracy: At appropriate intervals, such as at least at the beginning and the end of a series of sample titrations, introduce a defined quantity of water, in the same order of magnitude as the quantity of water in the sample, using a suitable certified reference material and perform the coulometric titration. The recovery is within the range of 97.5 per cent to 102.5 per cent for an addition of 1000 ug of H₂O and within the range of 90.0 per cent to 110.0 per cent for the addition of 100 ug of H₂O.

7.0 Annexures: NA

8.0 Distribution:

8.1 Display copy 1 : Quality Control Lab



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9.0 Abbreviation:

GTP : General Test Procedure
QC : Quality Control laboratories

10.0 Revision History:

10.1 Revision history table:

Document Number	CC Number/Date	Brief Description of Change