PROCESS VALIDATION PROTOCOL FOR DUTASTERIDE PELLETS (0.5%) FILM COATED

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TABLE OF CONTENTS

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1.0 PROTOCOL APPROVAL:

PREPARED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE

REVIEWED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE

APPROVED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE

AUTHORIZED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE

PROCESS VALIDATION PROTOCOL FOR DUTASTERIDE PELLETS (0.5%) FILM COATED

2.0 OVERVIEW:

2.1 OBJECTIVE:

To validate the manufacturing process of **Dutasteride Pellets (0.5%) Film Coated** as per the Batch Manufacturing Record & Batch packing record to establish documentary evidence that the process will consistently produce the product, meeting its predetermined specifications & quality attributes by examining three consecutive batches.

2.2 SCOPE:

This protocol is applicable to the three batches of **Dutasteride Pellets (0.5%) Film Coated** manufactured in tablet section to be taken for conducting validation study.

2.3 RESPONSIBILITY:

Following functional groups shall be responsible for conducting validation study.

Production	:	Operating of equipments and the process as per BMR and BPR.
Engineering	:	Maintenance of facility, equipments and utilities as per the Batch requirement.
Quality Control	:	Testing of In-process and finished product samples as per the specifications in Protocol.
Quality Assurance	:	Monitoring the key quality parameters, sampling at various Processing stages as per protocol. Collection of reports from QC, processing data from production, compilation, review and approval the protocol and report.

2.4 RE-VALIDATION CRITERIA:

Revalidation on three consecutive batches shall be carried out, if there are:

2.4.1 Changes in the Raw material(s), if there is change in vendor (API).

2.4.2 Change or replacement in any critical part of equipment or complete change in any equipment.

2.4.3 Changes in manufacturing process or other changes that could affect product quality.

2.4.4 Changes in the manufacturing area and support system.

2.4.5 Three sequential batches that fail to meet product & process specification.

2.4.6 Change in the process validation parameters.

2.4.7 Change in batch size.

3.0 PRODUCT INFORMATION:

Product Name	**Dutasteride Pellets (0.5%) film Coated**
Product Code	
Manufacturing License No.	
Description	White to off white round spherical film coated pellets.
Label Claim	**Each 100 mg pellets contains:** Dutasteride 0.5 mg
Shelf Life	24 Months
Batch Size	5.0 kg
Storage Condition	Store in a dry place, below 30ºC

3.1 LIST OF RAW MATERIALS:

S.No.	ITEM CODE	INGREDIENTS	SPEC.	Unit formula % (w/w)	STD. QTY./ 5.0 (kg)
1.		*Dutasteride	IP/BP	0.50	0.030
2.		Sugar Sphere (#18/24)	BP	96.50	4.825
3.		HPMC E-5	IP/BP	2.0	0.100
4.		Polyethylene Glycol 6000	USP	1.0	0.050
5.		**Isopropyl Alcohol	IP/BP	66.00 (w/v)	3.300
6.		Dichloromethane (Methylene chloride)	IP/BP	27.00 (w/v)	1.350
7.		*Purified Water	IP/BP	7.0 (w/v)	0.350
***Dutasteride to be dispensed based on 100% assay value as such basis. Overages to be added 20% to compensate loss during manufacturing process.**					
****The solvents (IPA, dichloromethane & purified water) evaporate during manufacturing process. Hence, weight not added.**					

4.0 LIST OF REFERENCE DOCUMENTS:

S.No.	DOCUMENT NAME	DOCUMENT No.
1	Master Formula Record	
2	Batch Manufacturing Record	
3	Finished Product Specification	

NOTE: Current revision / version of document to be referred

5.0 RATIONALE FOR IDENTIFICATION OF CRITICAL STEPS TO BE VALIDATED:

5.1 PREPARATION OF DRUG SOLUTION:

5.1.1 Take IPA and Methylene Chloride solvents in solution preparation vessel and mix under continuous stirring.

5.1.2 Take some quantity of mixed solvents from step 5.1.1 in another SS vessel, add PEG 6000 and Dutasteride under continuous stirring. Continue stirring to get uniform lump free suspension.

5.1.3 In a separate SS vessel, take purified water and add HPMC E-5 under continuous stirring. Then Add remaining quantity of step 5.1.1 solvents, under continuous stirring.

5.1.4 Mix the solutions of step 5.1.2 & step 5.1.3 and mixing under stirrer for 30 minutes to get uniform solution.

5.1.5 Filter the suspension through 100 # filter cloth. Label the container and close the lid of the vessel till its use (Use coating solution on same day).

5.2 COATING PROCESS (FILM COATING):

5.2.1 Transfer the sugar sphere pellets from Material storage area to the coating area.

5.2.2 Set the initial parameters as per the table.

PARAMETERS	STANDARD
Inlet Air Temperature	50° - 60°C
Peristaltic Pump RPM	1 - 2
Atomizing Air Pressure	1 - 2 kg/cm^2
Pan RPM	40 - 48 RPM
Number of spray guns	01 nos.
Nozzle size	1.0 mm
Angle between spray gun and pellets bed (initial)	Perpendicular
Spray gun distance from bed (initial)	6 – 10 inches

5.2.3 Load the Sugar Sphere pellets into the coating pan and start the pan to roll on slow speed.

5.2.4 Load the film coating suspension/ solution into the feed vessels then start the spraying. Coating suspension shall be under continuous stirring during coating process.

Note: Over wetting of the cores is to be avoided as it may cause agglomeration.

5.2.5 After completion of spraying, dry the coated pellets under rolling using hot air blower at set parameters for 10 minutes. Further allow coated pellets to cool by inching the pan for 10 minutes with inlet and exhaust ON

5.2.6 Unload the film coated pellets in IPC's having double polybags, tie individual bags and affix the status label.

5.2.7 Check and record the physical parameters of coated pellets

Test parameters: Description and Assay of dutasteride.

5.3 SIFTING OF DRUG COATED PELLETS:

Sift the Film Coated Pellets through #18 and collect 18# retains and passing separately. Discard the retained pellets on #18. Collect the passing pellets through #18 in HDPE container lined with double polyethylene bags for the further sifting through #24.

Take the previously passed Film Coated Pellets and sift through #24 and collect retains and passing pellets separately. Discard the passing pellets through #24. Finally pack the retained pellets ton #24 in HDPE container lined with double polyethylene bags as finish product.

Test Parameter: Sieve integrity before and after sifting

6.0 PROCESS VALIDATION PRE-REQUISITE:

Following shall be the pre- requisite for process validation of Dutasteride Pellets (0.5%) Film Coated.

6.1 PROCESS QUALIFICATION:

6.2.1 All the key process variables are to be identified and their operating ranges to be established.

6.2 RAW MATERIAL ACCEPTANCE:

6.2.1 All the raw materials to be used in the manufacturing shall be procured from approved vendors.

6.2.1 All the raw materials shall be tested as per respective specifications and approved by QC prior to use.

6.3 PACKING MATERIAL ACCEPTANCE:

6.3.1 All the primary packing materials and printed packing materials to be used in the manufacturing shall be procured from approved vendors.

6.3.2 All the packing materials shall be tested as per respective specification and approved by QC prior to use.

6.4 EQUIPMENT/INSTRUMENT QUALIFICATION:

6.4.1 The manufacturing equipment and control instruments to be used for manufacturing and analysis of the product shall be qualified.

6.4.2 All the instruments used in the process shall be duly calibrated as per the calibration schedule.

6.5 SUPPORT SYSTEM QUALIFICATION:

6.5.1 The support system, i.e. HVAC & Water system shall be qualified. The environmental conditions should meet the pre defined acceptance criteria prior to conducting the process validation study.

6.6 QUALITY SYSTEM:

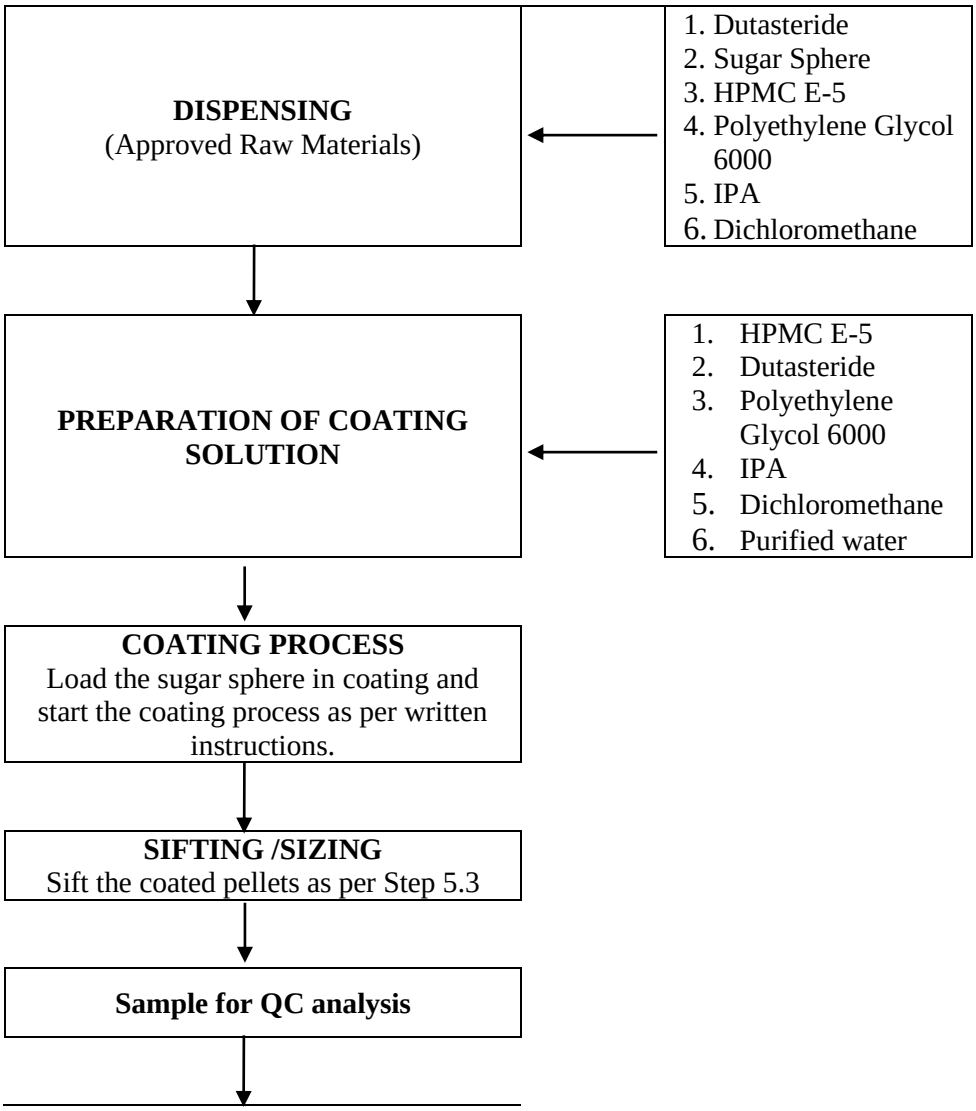
6.6.1 Relevant SOPs shall be in place and training shall be completed on equipment operation, manufacturing instructions and sampling.

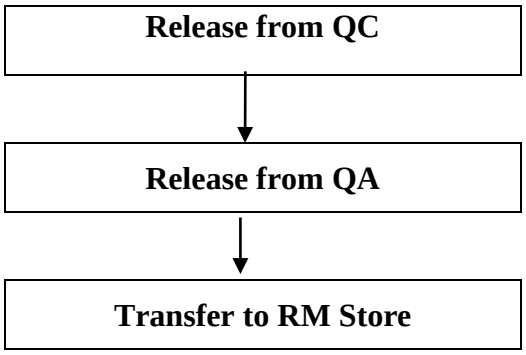
7.0 PROCESS EQUIPMENT:

S.No.	EQUIPMENT	EQUIPMENT NUMBER
1.	Sifter	
2.	Coating pan (18 inch)	
3.	Solution Preparation Vessel	

8.0 MANUFACTURING & PACKING PROCEDURE:

8.1 PROCESS FLOW CHART:





8.2 CRITICAL PROCESS PARAMETERS TO BE MONITERED DURING PROCESSING:

S.No.	STAGE	PARAMETER	SPECIFICATION
1.	Coating process	Inlet Air Temperature	50° - 60°C
		Peristaltic Pump RPM	1 - 2
		Atomizing Air Pressure	1 - 2 kg/cm^2
		Pan RPM	40 - 48 RPM
		Number of spray guns	01 nos.
		Nozzle size	1.0 mm
		Angle between spray gun and pellets bed (initial)	Perpendicular
		Spray gun distance from bed (initial)	6 – 10 inches
		LOD	NMT 3.0%
		Assay	90% to 110% RSD (NMT 2.0%)
2.	Packing	**Description**	White to off white spherical pellets.
		Identification (HPLC)	The retention time of the principal peak in the chromatogram obtained with assay preparation corresponds to that in the chromatogram obtained with the standard preparation as obtained in the assay.
		Moisture content	NMT 3.0%
		Residual solvent by GC: Isopropyl Alcohol	NMT: 5000 ppm
		Dissolution	NLT 75% in 60 minutes
		Assay	90.0% to 110.0%
		Particle size	NLT 90% passing through 18 mesh.
			NLT 90% retained on 24 mesh.
		MICROBIAL LIMITS	
		1. Total aerobic microbial count	NMT 1000 cfu/g.
		2. Total combined yeasts/ mold count	NMT 100 cfu/g.
		Escherichia coli	Should be Absent/g.
		Salmonella	Should be Absent/10g.

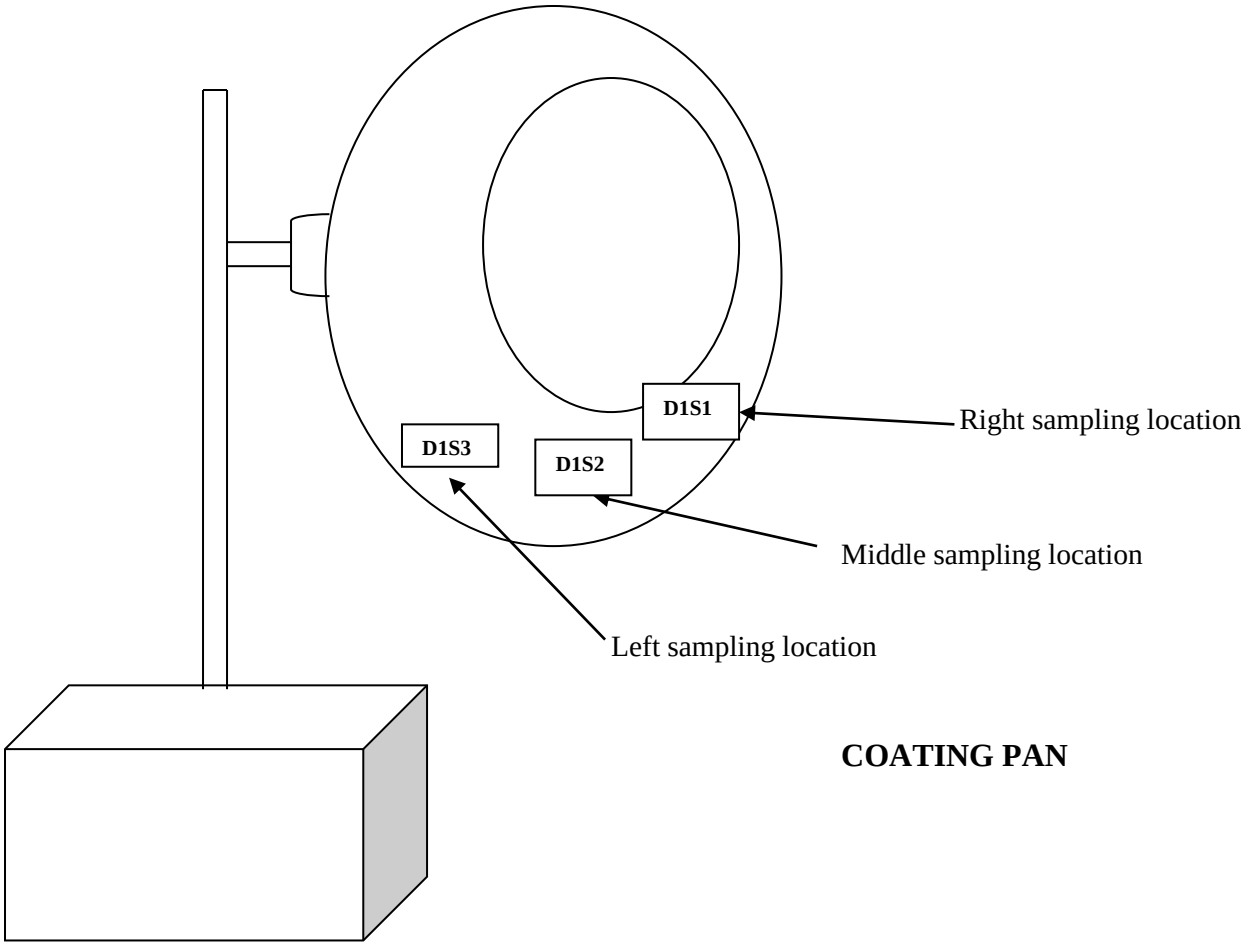
9.0 VALIDATION SAMPLING PLAN:

UNIT OPERATION	SAMPLING POINT	SAMPLE QUANTITY	SAMPLE CODE	CONTROLLED PARAMETER	MEASURED RESPONSE
Coated Pellets	Sample shall be drawn from coating pan after completion coating process from 3 locations.	5 g each from each sampling location	• D_1S_1- Right • D_1S_2- Middle • D_1S_3- Left	• Inlet Temp. • Drying Time • Pan RMP • Peristaltic Pump RPM	• Description • Assay (RSD)
Sifting	Collect composite sample from Top, Middle and Bottom layers from the Intermediate Process Containers	20 g	• DC	• Mesh size	• As per finished specification

9.1 SAMPLING LOCATIONS FOR COATING PAN:

After completion of coating for the defined period of time, the samples shall be collected from different locations as shown in diagram.

D_1S_1- Right
D_1S_2-Middle
D_1S_3- Left



COATING PAN

10.0 VALIDATION ACCEPTANCE CRITERIA:

The Process of **Dutasteride Pellets (0.5%) Film Coated** stands validated if various critical steps meet the following acceptance criteria:

STAGE	PARAMETER	ACCEPTANCE CRITERIA
Coating	Description	White to off white coloured spherical pellets.
	Assay	90.0% to 110.0%
	RSD	NMT 2.0%
Packing	Description	White to off white coloured spherical pellets.
	Identity (HPLC)	The retention time of the principal peak in the chromatogram obtained with assay preparation corresponds to that in the chromatogram obtained with the standard preparation, as obtained in the assay.
	Moisture content	NMT 3.0% w/w
	Residual solvent By GC Isopropyl Alcohol	NMT: 5000 ppm
	Dissolution	Not less than 75% in 60 minutes
	Assay by HPLC	Not less than 90.0% and Not more than 110% of the label claim of **Dutasteride**
	Particle size	NLT 90% passing through 18 mesh NLT 90% retained on 30 mesh
	Microbial enumeration tests and tests for specified microorganisms	
	Total aerobic microbial count (TAMC)	Not more than 1000 cfu/gm
	Total combined yeasts / mould count (TYMC)	Not more than 100 cfu/gm
	Pathogen Escherichia coli Salmonella	Shall be Absent/g Shall be Absent/10g

11.0 YIELD VERIFICATION:

S.No.	Stage	Yield % Acceptance Criteria
1	Packing	Observed The Yield

12.0 CONCLUSION:

Statement made for in this protocol on acceptability of manufacturing process meeting the objective of protocol.

13.0 REPORT:

Process validation report shall cover the following:

- Summary Plan of Study
- Acceptance Criteria
- Results, Discussion and Conclusion

The following attachment shall be referred to in the Process validation report:

- Validation Samples Report
- Analysis Reports
- Batch Manufacturing Record / Batch Packing Record
- Finished Product Analysis Report
- Process Deviation report.

14.0 ABBREVIATIONS:

ABBREVIATED FORM	EXTENDED FORM	ABBREVIATED FORM	EXTENDED FORM
PVP	Process Validation Protocol	BMR	Batch Manufacturing Record
HDPE	High density polyethylene	MCC	Microcrystalline cellulose
HCL	Hydrochloride	mm	Millimeter
Ltrs.	Liters	HVAC	Heating Ventilation and Air Conditioning.
MFR	Master Formula Record	“	Inches
QC	Quality control	Mins.	Minutes
API	Active Pharmaceutical Ingredient	#	Mesh
&	And	IHS	In House Specification
No.	Number	w/w	Weight by weight
Kg	Kilogram	SOP	Standard operating procedure
BP	British Pharmacopoeias	B.D & T.D	Bulk density & Tap density
mg	Milligram	ID	Identification
Eq.	Equivalent	LOD	Loss on drying
MPR	Master Packing Record	UOM	Unit of Measurement