PROCESS VALIDATION PROTOCOL

FOR

SUGAR SPHERE

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PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

PROCESS VALIDATION PROTOCOL FOR SUGAR SPHERE

1.0 PROTOCOL APPROVAL

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2.0 OVERVIEW:

2.1 OBJECTIVE:

To validate the manufacturing process of **Sugar Sphere [Film Coated (#18#24)]** 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 **Sugar Sphere [Film Coated (#18#24)]** 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 equipment's and the process as per BMR and BPR.
Engineering	:	Maintenance of facility, equipment's 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:

2.1.1 Change or replacement in any critical piece of equipment or complete change in any equipment.

2.1.2 Changes in manufacturing process and formulation.

2.1.3 Changes in the manufacturing area and support system.

2.1.4 Three sequential batches fail to meet product specification.

2.1.5 Change in the scope of process validation parameters.

2.1.6 Change in batch size. In case of step-down batches, re-validation shall be performed up to mixing stage.

Note: In case of change in API vendor, an equivalence report will be generated.

3.0 PRODUCT INFORMATION:

Generic Name	Sugar Sphere [Film Coated (#18#24)]
License No.	…….
Product Code	…….
Description	White to off white round spherical film coated pellets
Shelf Life	48 Months
Batch Size	150.0 Kg
Storage Condition	Store in dry place, below 30^0C

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3.1 LIST OF RAW MATERIALS:

S.No.	ITEM CODE	INGREDIENTS	SPEC.	Unit formula % (w/w)	Std. Qty. For 150 Kg
1.		Sugar (Powder) #300	IHS	65.23%	97.845
2.		Maize Starch	IP/BP	14.00%	21.000
3.		PG Sugar #40#50	IP/BP	20.52%	30.780
4.		Povidone(K-30)	IP/BP	0.25%	0.375
5.		Purified Water	IP/BP	10.00%	15.000

***Do not contribute to the weight of the product as evaporate on drying during the process.**

3.2 LIST OF COATING MATERIALS:

S.No.	ITEM CODE	INGREDIENTS	SPEC.	Unit formula % (w/w)	Std. Qty. For 150 Kg
1.		HPMC E-5	USP	3.00%	4.500
2.		$ Purified Water	IP/BP	48.00%	72.000

$ Purified water to be issued 16 times of HPMC E-5

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4.0 LIST OF REFERENCE DOCUMENTS:

5.0

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

NOTE: Current revision / version of document to be referred.

6.0 RATIONALE FOR IDENTIFICATION OF CRITICAL STEPS TO BE VALIDATED:

6.1 MILLING:

Check the integrity of screen and mill the sugar (powder) through 0.5 mm screen at fast speed keeping knife in forward direction.

6.2 SIFTING:

Sift the Maize Starch by sieve 100# and Sugar powder 40#.
Collect the matter in cleaned containers, lined with poly bags. Securely seal and store in controlled conditions. weigh and record the weight.
Variables: Sieve integrity, screen integrity.

6.3 SUGAR SYRUP PREPARATION AND COATING:

Sift the PG sugar through 50#, collect the retain PG sugar for formation and fine PG sugar for sugar syrup preparation.
Take required quantity of purified water in clean SS vessel and add povidone (K-30) and then add PG sugar under continues stirring.
Filter the above solution through 100# mesh into another vessel.
Note -:PG sugar will be sifted through 50# and the fines will be used in syrup preparation. standard qty. for sugar syrup is 7.29 kg , if the fine sugar (P G Sugar) is found less than 7.29kg ,the remain qty . will be used from the sifted P G sugar (after segregation the qty. of 23.49 kg i. e to be used sugar sphere formation)
Variables: Sieve integrity.

6.4 PROCEDURE FOR SUGAR SPHERE MANUFACTURING IN SEMI AUTO: COATER MACHINE:

Carry out the setup and operation of equipment as per the respective SOP and batch manufacturing record.
Load the PG Sugar 40#50 into coating pan.
Load the Sugar Syrup into the feed vessels then start the spraying. It shall be under continuous stirring during coating process.
Keep adding mixture of Sugar (Powder) and Maize starch is added individually in **5:1** ratio quantity between in coating pan. Simultaneously keep mixing with hands.
Unload the sugar sphere and keep in Tray drier for drying.
Note: Over wetting of the cores is to be avoided as it may cause agglomeration.
Variables: Pan RPM, Peristaltic pump RPM, Atomization Air Pressure.

6.5 DRYING OF SUGAR SPHERE UNCOATED:

Air dry the sugar sphere uncoated in the tray drier for 120 minutes.
Set the temperature 40^0C - 45^0C and dry further.
Continue drying until LOD reach 1.0% to 1.5 % **Variables:** Drying time, Inlet temp**, Test Parameter:** LOD

6.6 SIFTING OF UNCOATED SUGAR SPHERE:

Sift the Sugar Sphere uncoated through #18. collect 18# retains and passing pellets separately retains pellets for discard and passed pellets for next sifting/sizing
Sift 18 # passing Sugar Sphere uncoated through #24 and collect retains and passing separately into double lined Polyethylene bag HDPE containers. Label the containers properly**.** The sugar sphere passed through 24# for discard and retain pellets on 24# mesh will be use for HPMC E-5 Coating.
Variables: Sieve integrity.

6.7 FILIM COATING STAGE:

6.7.1 PREPARATION OF COATING SOLUTION:

Take Purified water (16 times of HPMC E-5) in S.S Solution preparation tank.
Add HPMC E-5 under continuous stirring and continue the stirring until clear solution is obtained.
Filter the clear solution with 80 nylon cloth into another cleaned SS container.

6.7.2 COATING PROCESS IN FBC:

Operate the Fluid Bed Coater (FBC) as described in Standard Operating Procedure and set all parameters as per batch manufacturing record.
Loads sugar sphere uncoated into FBC.
Coat the Sugar sphere at peristaltic pump rpm of 15 to 20 and atomizing air pressure 2 – 3 Kg/cm^2 till the coating solution is completed.
Adjust the spray rate 18 rpm and inlet temperature to 40^0C - 50^0C to reach the core bed temperature 35^0C - 40^0C.
Spray the coating solution completely and after the completion of the coating solution spray, continue the drying for 10 minutes.
Remove the Sugar Sphere from FBC and unload into IPC container lined with double polyethylene bags.
Note: Over wetting of the cores is to be avoided as it may cause agglomeration.
Variables: Pan RPM, Peristaltic pump RPM, Atomization Air Pressure. **Test Parameter:** LOD

6.8 SIZING OF SUGAR SPHERE COATED:

Sift the Sugar Sphere through #18. collect 18# retains and passing pellets separately. Allow retains pellets for discard and passed pellets for next sifting/sizing
Sift 18 # passing Sugar Sphere uncoated through #24 and collect retains and passing separately into double lined Polyethylene bag HDPE containers. **Retain pellets on 24# as finish product** and passed pellets through 24# for discard.
Variables: Sieve integrity. **Test Parameter:** Description, LOD, Bulk density, Assay, pellets size

6.9 DESTRUCTION OF REJECTIONS:

Note the rejection quantity and discard the rejection as per the respective SOP.

7.0 PROCESS VALIDATION PRE-REQUISITE:

- Following shall be the pre- requisite for process validation of Sugar Sphere [Film Coated (#18#24)]

7.1 PROCESS QUALIFICATION:

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

7.2 RAW MATERIAL ACCEPTANCE:

- All the raw materials to be used in the manufacturing shall be procured from approved vendors.
- All the raw materials shall be tested as per respective specifications and approved by QC prior to use.

7.3 EQUIPMENT/INSTRUMENT QUALIFICATION:

- The manufacturing equipment and control instruments to be used for manufacturing and analysis of the product shall be qualified.
- All the instruments used in the process shall be duly calibrated as per the calibration schedule.

7.4 SUPPORT SYSTEM QUALIFICATION:

- 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.

7.5 QUALITY SYSTEM:

- Relevant SOP’s shall be in place and training shall be completed on equipment operation, manufacturing instructions and sampling.

8.0 PROCESS EQUIPMENT:

S.No.	EQUIPMENT	EQUIPMENT NUMBER
1.	Sifter	
2.	Fluid Bed Coater	
3.	Multi MILL	
4.	Semi Auto Coater 48”	
5.	Solution Preparation vessel	
6.	Solution Storage Tank	
7.	Tray Drier	
8.	Tray Drier	

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9.0 MANUFACTURING PROCEDURE FLOW CHART:

MILLING
Sugar (Powder) through 0.5 mm screen

↓

SIFTING
Maize starch #100
Sugar Powder #40

↓

SYRUP PREPARATION
Take required quantity of purified water in clean SS vessel and add Povidone (K-30) and then add sifted PG sugar under continues stirring. Filter the above solution through 100# mesh

↓

SUGAR SPHERE MANUFACTURING IN SEMI-AUTO COATER MACHINE
load PG sugar 40#50 in coating pan and load the sugar syrup into the feed vessel then start spraying.
Keep adding mixture of sugar powder and maize starch in 5:1 ratio and simultaneously keep mixing with hands.

↓

DRYING OF SUGAR SPHERE (UNCOATED)
Air drying of sugar sphere in tray drier for 120 minutes. After air dry set inlet temperature 40 to 45^{0}C till LOD reaches 1.0%-1.5%.

↓

SIFTING/SIZING
Sizing of pellets through #18#24

↓

FILM COATING IN FBC
Operate the FBC as per respective SOP and set the parameters as per batch manufacturing record.
After the completion of the coating solution spray, continue the dry for 10 minutes

Sample for QC Analysis

Release from QC → **Packing:** HDPE container with dual polyethylene bags → Transfer to store Department

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9.1 CRITICAL PROCESS VARIABLES BE MONITERED DURING PROCESSING:

S.No.	PROCESS	PARAMETER	SPECIFICATION
1.	SUGAR SPHERE MANUFACTURING IN SEMI-AUTO COATER MACHINE	Coating pan RPM	1-15. RPM
		LOD	1.0%-1.5%
		Peristaltic pump RPM	5-15 RPM
		Atomization air pressure	0.5-1.0 kg/cm^2
2.	DRYING IN TRAY DRIER	Inlet temperature	40-45^{0}C
3.	COATING IN FBC	Inlet temperature	40-50^{0}C
		Bed temperature	35-40^{0}C
		Peristaltic pump RPM	15-20 RPM
		Atomization air pressure	2.0-2.5 kg/cm^2

10.0 VALIDATION SAMPLING PLAN:

UNIT OPERATION	SAMPLING POINT	SAMPLE QUANTITY	SAMPLE CODE	CONTROLLED PARAMETER	MEASURED RESPONSE
	Sampling from FBC Samples shall be drawn from 5 locations after complete of coating.	10g each from each sampling location	• **1**-Top Left • **2**-Top Right • **3**-Bottom Left • **4**- Bottom Right • **5**- Middle center	• Inlet Temp. • Spray Rate • Product Temp.	• Description • LOD • Assay
	Collect composite sample from Top, Middle and Bottom layers from the Intermediate Process Containers	150 g	**FPS**	• Inlet Temp. • Spray Rate • Peristaltic pump RPM • Product Temp.	• As per finish product specification

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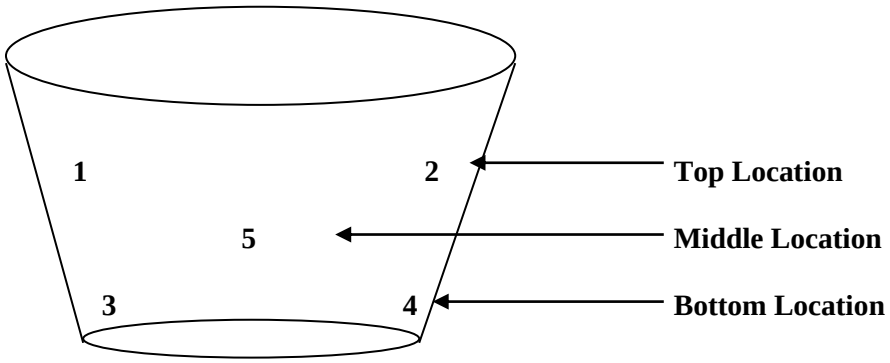
10.1 SAMPLING LOCATIONS FOR FLUID BED COATER:

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

- **1 -** Top Left
- **2** - Top Right
- **3 -** Bottom Left
- **4-** Bottom Right
- **5** -Middle Centre



11.0 VALIDATION ACCEPTANCE CRITERIA:

The Process of **Sugar Sphere [Film Coated (#18#24)]** stands validated if various critical steps meet the following acceptance criteria:

STAGE	PARAMETER	ACCEPTANCE CRITERIA
After coating	**Description**	White to off white pellets
	Identification	
	By TLC	The principle spot in the chromatogram obtained with the test solution is similar in the position, color and size to the principle spot in the chromatogram obtained with reference solution
	By Chemically	A dark-blue color is produced, which disappears on heating
	By Chemically	An orange precipitate is formed immediately.
	Solution S	Filter under vacuum to obtain a clear solution
	Pellet size	NLT 90% is passed through 18# NLT 90% is retained on 24#
	LOD	NMT 5.0%
	Sulphated Ash	NMT 0.2%
	Bulk density	0.55%-0.80%
	Heavy metals	NMT 5 ppm
	Assay	NMT 92% of sucrose, calculated on the dried basis.
	MICROBIAL LIMITS: 1. TAMC 2. TYMC **Pathogens** 1.E. Coli 2.Salmonellae	 NMT 500 cfu NMT 50 cfu Absent/gm Absent/10 gm

12.0 YIELD VERIFICATION:

S.No.	Stage	Yield % Acceptance Criteria
1.	Coating	NLT 95.0 %

13.0 CONCLUSION:

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

14.0 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

15.0 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