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Review Article

Process Validation Protocol of Granules for Oral Administration

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Abstract

To ensure that the pharmaceutical product is being produced with its consistent quality standard, process validation is a very effective tool. It establishes documented evidence to ensure a high degree of assurance that specific process will consistently produce a product meeting its predetermined specifications and quality requirements. Process validation is a cGMP requirement for finished products and to standardize the method used in establishing process validation studies, a process validation protocol is developed. Based on the protocol, once the process validation is done, a complete process validation report will be prepared which will aid in preparing a complete BMR and BPR for manufacturing and packaging of pharmaceutical products.

Keywords: Process Validation; Protocol; CGMP; BMR; BPR

Introduction

Process (Prospective) validation aims to gain full understanding of the manufacturing process on the production equipment expected to be routinely used. This is achieved by establishing parameters to be used to operate within a state of control. Once the validation of process is completed, a Batch Manufacturing Record (BMR) to be finalized to use in routine manufacturing. Any variation mode to this BMR should be made in accordance with change control procedure [1-5].

Purpose

The purpose of this protocol is to cover the process validation activities for the manufacturing of Granules for oral administration. Based on the Technology Transfer set Parameters, three consecutive successful batches will be manufactured and finalized the critical process parameters for the batch manufacturing.

Scope

This protocol is applicable to validate Granules for Oral Administration under specified manufacturing conditions. This protocol shall define the responsibilities of personnel involved, equipment used, raw material details, critical process parameters, in-process control, quality attributes, acceptance criteria, change control, documentation to be carried out during Process Validation study of Granules for Oral Administration.

Product details

Product Name, Generic Name, Dosage Form, Product Category, Product Description, Label Claim, Packaging, Batch No., Mfg. Date, Exp. Date, Batch Size, Shelf Life, Product Code No.

Documentation

Check the following documents: Process Validation Protocol, Master Formulation Card, Master Packaging Card, Batch Manufacturing Record, Batch Packaging Record, Standard Test Specification, Standard Testing Procedure and Process Validation Report etc.

Validation team

The process validation team is comprised of at least one representative from all concern departments i.e. QA, QC, Production, Warehouse and Maintenance Department and the validation activity will be led by Head of Validation or Head of QA.

Responsibilities

Department	Activities	Responsibility
Quality Assurance	To prepare validation protocol.	Officer
	To ensure the activities to be followed as per the approved protocol.	
	To withdraw the samples as per sampling program.	
	To organize the training and impart the training before validation.	
	To co-ordinate the validation activity.	
	To approve the protocol.	Head, QA
Quality Control	To analyze the samples.	Analyst
	To check the results	Head, QC
Production	To review validation protocol.	Officer/Head, PR
	To ensure performance of activities as per protocol.	
	To organize the activity.	Head, PR
	To review the report.	
Maintenance	To provide required services.	Officer/Head, MN
Head, Plant	To authorized the protocol.	GM, Plant

Table 1

Training

The training on the protocol shall be imparted to all the personnel involved in the process validation activity (QA, QC, Production, Warehouse and Maintenance).

Validation methodology

- The validation will be performed on three consecutive batches of the same batch size following the established manufacturing process described in this validation protocol.
- The validation study will be carried out at extreme and optimum values within the accepted ranges of critical process parameters. All critical parameters shall be monitored and documented for reviewed.
- In process sampling will be carried out as per the sampling plan given in this protocol.
- Finished product sampling and testing will be carried out as per respective established procedure.
- During execution of the validation batches, Batch Manufacturing Record (BMR) and Batch Packaging Record (BPR) will be completed as per respective procedure.

List of equipments

Make a list of all the machine, equipment and instrument to be used during process validation activity of respective products. The list should include; equipment ID, Model Number, Manufacturer, Capacity, Material of Construction, Qualification status and the respective Operating SOP

Location of validation activity

Mention the name and address of the place where the process validation activity will be done.

Master manufacturing formula

Master Manufacturing formula includes Name of the ingredients with their compendia name, Quantity/sachet (mg), Quantity/Batch (Kg) and the category and use of each ingredient.

Identification of critical process variables parameter

Probable causes that may affect final products

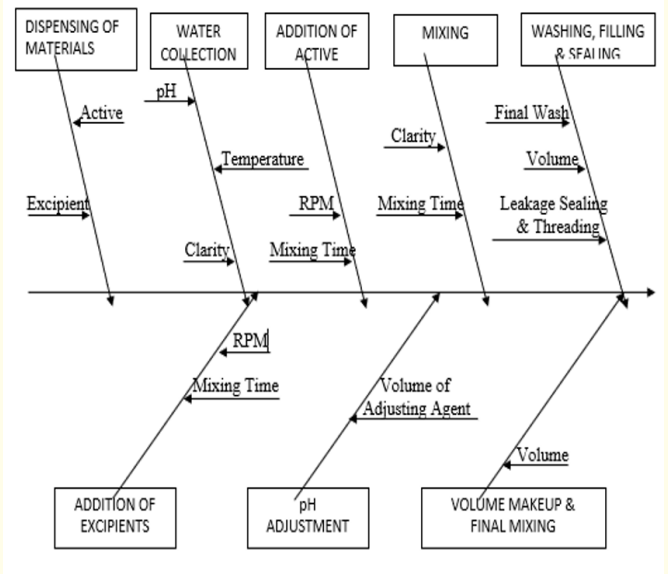


Figure 1: Probable Causes.

Critical process parameter

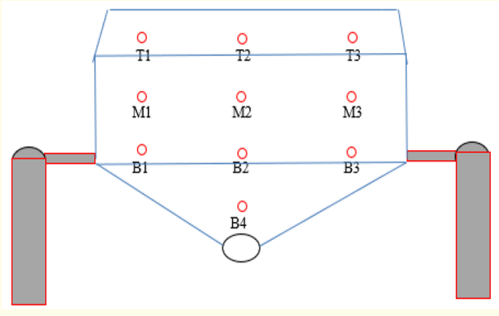
Stage: Manufacturing	Process Parameter
	Manufacturing Area Temperature
	Manufacturing Area RH
	Ampere Load
	Total Drying Time
	Moisture Content (By KFT)
Stage: Blending	Mixing Time
	Bulk Density (Tapped)
	Sieve Analysis (Fines)
	Weight of the Granules
Stage: Filling and Sealing	Filling Area Temperature
	Filling Area RH
	Sealing Temperature (Bottom Sealer)
	Sealing Temperature (Vertical Sealer)
	Sealing Temperature (Top Sealer)
	Machine Speed
	Auger Speed
	Auger Count
	Leak Test
	Quality of Batch Printing
	Packaging Area temperature
	Packaging Area RH

Table 2

Sampling, test parameters and acceptance criteria

Sampling plan and sampling location

Wear nose mask and surgical hand gloves before Sampling. Take out 75g sample as shown in the table from Top, Middle and Bottom of the blender, in a clean polyethylene bag. Label the samples with Product Name, Batch No., Stage, Area, Time and Date. Send the samples to QC for analysis. Ensure that no further mixing is done in QC.



o **Sampling Points**

T1: Top 1, T2: Top 2, T3: Top 3, M1: Middle 1, M2: Middle 2, M3: Middle 3, B1: Bottom 1, B2: Bottom 2, B3: Bottom 3, B4: Bottom 4

Figure 2: Octagonal Blender.

Stage: Granulatation					
Drying					
Sl.	**Sampling Location**	**Sampling Points**	**Frequency**	**Sampled Quantity**	**Test To Be Carried Out**
1.	FBD Bowl	After drying from Top, Middle and Bottom layer of FBD Bowl.	One sample from each Tray (Top, Middle and Bottom)	1 g X 6	Moisture Content
Drying					
1.	Tray Dryer	After drying from Top, Middle and Bottom layers.	One sample from each Tray (Top two, Middle two and Bottom Two).	1 g X 6	Moisture Content
Blending					
1.	Octagonal Blender	After drying from Top (T1, T2 and T3), Middle (M1, M2 and M3) and Bottom Trays (B1, B2, B3 and B4).	10 samples each after 05 minutes, 08 , minutes and 10 minutes	1 g X 10 (Triplicate)	Assay of individual sample.
		Composite Sample.	After completion of mixing.	60 g	Bulk analysis as per specifications, bulk density and sieve analysis.
Stage: Filling/Sealing And Packaging					

1.	Sachet Filling and Sealing Machine	During sachet filling and sealing operation (Auger speed 900-1000 rpm, Auger count 2000-2500 No.)	At Machine Speed 60 Sachet/Min and Sealing Temp. (Bottom) 135^{0}C, Sealing Temp. (Vertical) 150^{0}C, Sealing Temp. (Top) 175^{0}C.	5 15 sachets	Appearance, Physical Verification, Leak test, Average Fill and Fill Variation.
			At Machine Speed 70 Sachet/Min and Sealing Temp. (Bottom) 135^{0}C, Sealing Temp. (Vertical) 150^{0}C, Sealing Temp. (Top) 175^{0}C.	15 sachets	
			At Machine Speed 80 Sachet/Min and Sealing Temp. (Bottom) 135^{0}C, Sealing Temp. (Vertical) 150^{0}C, Sealing Temp. (Top) 175^{0}C.	15 sachets	
			Initial, Middle and End at Optimum speed and sealing Temperature and Full, Half and Low Hopper.	15 sachets each	Appearance, Average Mass, Uniformity of Mass, Quality of Batch Printing, Leak Test and Assay.
2.	Packing Room	From Packing Belt	As per SOP	21 sachets	Complete analysis as per specification.

Table 3

Specifications

Bulk specification

Bulk specification should include description, identification, solubility in water, pH, moisture content and assay of granules.

Finished product specification

Bulk specification should include description, identification, average mass, uniformity of mass, solubility in water, pH, moisture content, assay and microbial limit test of granules.

Operation

Dispensing details

Operation/Parameter	Std. Specification
Room Cleaning	Should be clean
Equipment Cleaning	Should be clean
Utensils Cleaning	Should be clean
Equipment Calibration	Should be calibrated
Temperature	Not more than 25^{0}C
Humidity	Not more than 60%
Material Dispensing	Should complies to BOM

Table 4

Bill of materials (Bom)

All the ingredients should be dispensed as per approved Bill of Materials. Care should be taken to ensure that right materials are being dispensed in right quantity.

Sifting details

Operation/Parameter	Std. Specification
Room Cleaning	Should be clean
Equipment Cleaning	Should be clean
Equipment Calibration	Should be calibrated
Sifting Area Temperature	Not more than 25^{0}C
Sifting Area Humidity	Not more than 50%
Frequency of Recording	Initial and every one hour interval
Sieve Used	Sieve Size and Sieve Integrity

Table 5

Granulation details

Pre-check For Granulation and Conditioning	
Operation/Parameter	**Std. Specification**
Room Cleaning	Should be clean
Equipment Cleaning	Should be clean
Equipment Calibration	Should be calibrated
Area Temperature	Not more than 25^{0}C
Area Humidity	Not more than 60%
Frequency of Recording	Initial and every one hour interval

Table 6

Stepwise batch manufacturing operation

Sl. No.	Step Instruction	Std. Specification/ Parameter	
Stage I: Granulation			
Step-1	Sieving	Sieve Used	
		Sieve Integrity	Before
			After
Step-2	Solvent	PW Quantity	
Step-3	Dry mixing	Impeller Speed	
		Mixing Time	
Step-4	Wet Mixing	Impeller Speed	
		Chopper Speed	
		Solvent Quantity	
		Mixing Time	
		Amperage	
Step-5	Drying in FBD	Inlet Temperature	
		Outlet Temperature	
		Total Drying Time	
Step-6	Sizing	Screen Used	
		Sieve Integrity	Before
			After
Step-7	Send the sample to QC for determination of moisture content.	Moisture Content	
Stage II: Blending			
Step-8	During the granules with Blender Machine	Blender Speed	
		Blending Time	
Step-9	Send the sample to QC for determination of moisture content.	Assay and blend uniformity	
Stage IV: Packaging (Sachet Filling, Sealing and Packaging)			
Step-10	Packaging (Sachet Filling, Sealing and Packaging) at Lower speed, higher speed and optimum speed with full, medium and low hopper	Filling Area Temperature	
		Filling Area RH	
		Average Net Weight	
		Machine Speed	
		Auger Speed	
		Auger Count	
		Sachet Sealing Temperature [Bottom]	
		Sachet Sealing Temperature [Vertical]	
		Sachet Sealing Temperature [Top]	
		Leak Test	
		Quality Of Batch Printing	
		Packing Area Temperature	
		Packing Area RH	

Table 7

Yield reconciliation

Calculate the yield as per BMR and BPR and find out the maximum and minimum range.

Operation / Parameters	Purpose
After Blending	For Information only
After Filling	For Information only

Table 8

Stability

Carry out the normal room temperature and accelerated temperature stability studies as per the stability protocol. This stability shall be concurrent stability.

Summary

Summary report and conclusion shall be prepared and approved based on the acceptance criteria and the data collected during Process Validation studies and all the results shall be verified against acceptance criteria.

Discrepancy and corrective action

Report any discrepancy observed in the process or test result beyond the standard specification and mention what corrective and preventive action is taken against the discrepancy.

Approval

Based on the results reported and summary in the validation reports, approve the process validation report as preliminary and final approval. Approval section should include; prepared by, checked by, verified by, approved by and authorized by signature with date.

Conclusion

If validation is not done, product quality may vary from batch to batch of manufacturing. To avoid this limitation, process validation activity poses a significant role in establishing documented evidence to ensure consistent quality product meeting its controlled specification. The outcome of this paper is to focus the importance and stepwise procedure for conducting process validation through an approved validation protocol.

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