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Qualification of equipment: Saizoner mixer granulator and automatic coating machine (Neocota)

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ABSTRACT

Qualification is the planning, carrying out and recording of tests on equipment and systems, which will form a part of the validated process, to demonstrate that it will perform as intended. The objective is to do the performance qualification of the Saizoner Mixer Granulator (SMG) (150 L) for minimum (20%) and maximum (70%) occupancy capacities and content uniformity at different mixing intervals and of the Automatic coating machine(ACM) for minimum and maximum capacity with aqueous coating operation for 6-10 Kg Pan and 24-40 Kg Pan. The installation qualification (IQ) and operational qualification (OQ) protocols should be prepared, approved and performed as per the qualification master plan. Saizoner mixers are used for dry and wet mixing of powders of different products to prepare the tablet formulations. The machine is used in the initial stages i.e. premixing & granulation. The automatic coating system is used for automatic film coating of tablets of various shapes and sizes by batch process. The prerequisites required before starting the performance qualification of equipment is that OQ should be successfully completed, all the necessary materials, procedures and testing arrangements should be made. For the SMG samples were collected as per sampling plan at different time intervals and the collected samples analyzed for color content, content uniformity, granule appearance, amperage and water content in each sample. For the ACM, the coated tablets were checked for physical parameters such as appearance, weight variation, weight build up and thickness for different batch sizes. The equipment qualification was carried out to demonstrate the efficiency of the equipment's and ended with satisfactory results.

Keywords: Coating machine, Neocota, Saizoner mixer granulator.

INTRODUCTION

Qualification is an essential part of a pharmaceutical manufacturer's quality assurance system; it should demonstrate that facilities are suitable for their intended use and should also guarantee that the medicinal products are of an appropriate quality. Manufacturing and laboratory instruments/equipment and their supporting utilities that are used in the Good Manufacturing Practices / Good Laboratory Practices activities are to be qualified and certified for their intended purpose. Qualification of instrument / equipment is not a single, continuous process but instead results from many discrete activities. These activities have been grouped into four phases of qualification. They are: Design qualification (DQ), Installation qualification (IQ), Operational qualification (OQ) and Performance qualification (PQ).

Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified [1]. Schedule M states about the qualification of the equipment [2]. Qualification requirements of established equipment/instruments are decided on the basis of available historical data of that equipment. (e.g., usage logs, calibration records, preventive maintenance records, change controls etc.) [3]. An item of equipment is an object that is characterized by its internal technical processes. A facility is the sum of all equipment used for a common purpose [4]. The objective is to provide a method for the performance qualification of bin blender (200 L), by studying the effect of various parameters like bowl load, blending time and blender speed on mixing of available materials.

Saizoner mixers are used for dry and wet mixing of powders of different products to prepare the tablet formulations. The machine is used in the initial stages i.e. premixing & granulation [4-5]. The automatic coating system is used for automatic film coating of tablets of various shapes and sizes by batch process. Tablets are loaded in a rotating pan for rolling and mixing. The tablets are preheated by supply of filtered hot air and then coating solution is sprayed through air atomized spray guns while the drying continues. The system is designed to control all the parameters, such as inlet air temperature, tablet bed temperature, liquid spray rate, and degree of rolling and mixing etc. [6].

Regarding the "qualification of equipment," chapter 3.34 of the GMP Guideline states: "Manufacturing equipment should be designed, located and maintained to suit its intended purpose." Annex 15 to the EU GMP Guideline specifies how this requirement must be implemented [7].

Chapter 2.5.11 of Pharmaceutical Inspection Convention /Scheme (PIC/S) [4] document PI 006 therefore expressly states that the contract giver is ultimately responsible for proper implementation of the validation work: "In such cases, the responsibility lies with the contract giver to ensure that the required standards of the quality of the work which is carried out, for program control and for documentation are met [8]."

The GMP Guidelines for documentation apply in general for the layout and compilation of qualification documents which must be authorized by the head of production and quality assurance. The documentation should be retained for at least five years once the facility or equipment has been shut down. According to Annex 15, No. 2 of the EU GMP Guideline, a company's current qualification projects must be described in a validation master plan.

The first stage of a qualification should be the (DQ). Conformance of the design with the GMP requirements should be demonstrated and documented. Before the facility is delivered, it may be necessary to make sure that the user requirements are complied with at the manufacturer's premises (Factory Acceptance Test, FAT) [9].

The correct implementation of the aforementioned requirements when assembling/setting up the facility is documented in the IQ. It serves as a check of the documents that were required for the DQ. The OQ provides evidence that the facility is functioning on the basis of established parameters and within defined limits whereas PQ is performance testing of the facility with all production materials subsequently processed during routine operation.

All qualification phases must be implemented on the basis of qualification protocols that have been approved beforehand.

MATERIALS AND METHODS

Materials

Saizoner mixer granulator (Sainath boilers & pneumatics, model: SAI-150 as in figure 1), Lactose (IP), MCC (IP), PVP K-30, Ponceau 4R supra (IHS), Purified water (USP) & Magnesium stearate (IP). Automatic coating machine (Neomachine Mfg. Co. Pvt. Ltd, model: Neocota 40 D as in figure 2), core tablets, Opadry white YS-1-7059 and purified water.

Figure 1: Saizoner mixer granulator.

Figure 2: Automatic coating machine (neocota 40 D)

SAIZONER MIXER GRANULATOR:

METHODOLOGY FOR PERFORMANCE QUALIFICATION: To provide a method for the performance qualification of SMG 150 L, by studying the effect of following parameters on mixing of available material.

- Bowl load
- Dry mixing time

- Impeller speed

To verify granulation end point with the help of impeller and chopper ammeters.

PROCEDURE (DRY MIXING):

BATCH SIZE: 12.0 KG & 42.0 KG
The batch formula for batch size of 12.0 Kg and 42.0 Kg was taken as shown in Table 1.

Table 1: Batch formula for Batch size of 12.0 Kg & 42.0 Kg

S.No.	Material name	%w/w	Quantity for minimum batch (in kg)	Quantity for maximum batch(in kg)
1	Lactose	50	6	21
2	MCC	44.5	5.34	18.69
3	PVP K-30	5	0.6	2.1
4	Ponceau 4 R supra	0.5	0.06	0.21
5	Purified water	QS	QS	QS
	Total	100	12	42

Cleaned the equipment as per the cleaning procedure and recorded the cleaning details. The line clearance was taken before starting the process.

Sifted Ponceau 4R supra and together lactose & microcrystalline cellulose through vibratory sifter, using SS sieve ASTM # 40 and collected in a double polythene lined HDPE / SS container and labeled accordingly.

Added Lactose, Microcrystalline cellulose and Ponceau 4R supra (sifted through 40#) into Saizoner Mixer Granulator and mixed the material for a period of 15 minutes.

The samples were collected as per sampling plan at different time intervals of 5, 10 and 15 minutes as in figure 3. The samples were Collected in triplicate each equivalent to three times to the weight of unit dose using appropriate unit dose sampler from different locations as per unit dose sampling procedure and transferred in to individual labeled glass vials.

Figure 3: Side view of sampling locations drawing for mixer/drier bowl

Sampling Points:

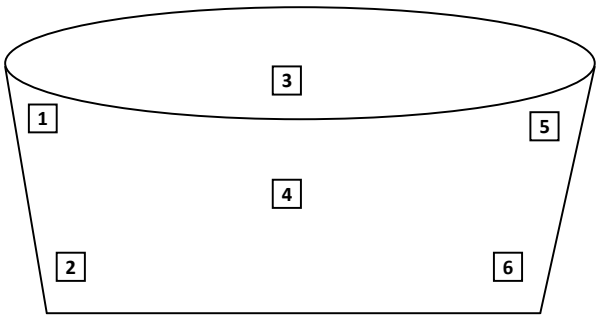

Figure: Locations 1- Top Left; 2- Bottom Left; 3- Top Centre; 4-Bottom Centre; 5-Top Right; 6- Bottom Right

The Collected Samples were submitted to Analytical development Department for analysis of color content in each sample. The method used here describes a procedure to quantify Ponceau 4R supra in the blend sample. Ponceau 4R supra was determined by visible spectrophotometer at 506 nm using external standard method

The results of performance qualification were recorded in result data sheets.

The above procedure with different batch sizes (12 Kg and 42 Kg) was followed so as to get minimum and maximum occupancy levels in the Saizoner Mixer Granulator.

ACCEPTANCE CRITERIA [10]:

- Color content (assay) of all samples should be in between 90 - 110 %
- The average of assay results at each interval should be in between 95 -105 %
- Content uniformity of six samples RSD should not be more than 5%

PROCEDURE (WET MIXING):

Poly Vinyl Pyrrolidone (PVP) was added in sufficient quantity of purified water and dissolved completely.

PVP binder solution was added to the granulator and granulated at slow speed till the required consistent granules were formed.

The additional water quantity added for granulation was recorded.

The above procedure was followed with different batch sizes so as to get minimum and maximum occupancy levels in the Saizoner Mixer Granulator.

ACCEPTANCE CRITERIA:

- SMG should be capable of producing desired granules.
- Amperage reading should be proportionate to the load.
- Functioning of SMG should be in normal, safe and secure condition.

CRITICAL PROCESS CONTROL VARIABLES: Critical process control variables of dry mixing and wet mixing operations are load size, mixing time and impeller speed, chopper speed, granulation time respectively. The measured parameters for dry and wet mixing are content uniformity and granule appearance, amperage & water content/ LOD respectively.

AUTOMATIC COATING MACHINE:

PREPARATION OF COATING SOLUTION

The required quantity of the coating suspension was prepared for different batches with different quantities of Opadry white and water.

Opadry white was added in purified water with continuous stirring. The coating solution was stirred for 45 minutes to get a smooth suspension and then it was passed through #60 and collected in a SS vessel.

Weights of ingredients for different batch sizes are specified in Table 2 and Table 3.

Table 2: Quantity of ingredients for 18 kg and 30 kg batch

S.No.	Ingredient	Net weight for 18 kg batch	Net weight for 30 kg batch
1.	Core tablets (Kg)	18.00	30.00
2.	Opadry white YS-1-7059 (g)	10.60	780.00
3.	Purified water (Kg)	1.975	7.800

Table 3: Weights of ingredients for 10 kg and 6 kg batch

S.No.	Ingredient name	Net weight for 10kg batch	Net weight for 6kg batch
1.	Core tablets (Kg)	10.00	6.00
2.	HPMC (g)	260.00	156.00
3.	Propylene glycol (g)	26.00	15.60
4.	Talc (g)	2.60	1.56
5.	Purified water (kg)	2.300	1.39

COATING OPERATION:
The equipment was cleaned as per the cleaning procedure and recorded the cleaning details. Line clearance was taken before starting the process.

The tablets were loaded into coating pan and pre heated the tablets to 50°C before coating till no further loss in tablet weight.

The spray guns were fixed on stand and atomized air supply was started, hot air blower and exhaust system and the coating parameters were set as shown in Table 4.

Table 4: Process parameters and Specifications

Parameter	Specification
Atomizing air pressure	2.0 – 4.0 kg/ cm^2
Spray rate	50-130 g/min
Temperature of inlet air	60±5 °C
Distance between spray guns and tablet bed	Suitable distance
Bed Temperature	45±5 °C
Nozzle size	1.0 mm
No of guns	2
Pan RPM	2-5
Distance between guns	10-12 cm

The rotating pan was started at suitable RPM and started spraying the coating suspension after attaining the bed temperature. The coating operation was continued till weight gain was 2.0±0.25 % of the average weight of core tablets. After completion of spraying, the pan speed was reduced to 1-2 rpm and dried at 40°C for 15 – 20 minutes.

The tablets were collected and checked for physical parameters such as average weight, thickness and weight built-up.

The above procedure was followed for all four lots.

ACCEPTANCE CRITERIA:
The coated tablets should comply as per the given specification

RESULTS AND DISCUSSION

SAIZONER MIXER GRANULTOR
The results of content uniformity of color (%) in collected samples from batch of 12 kg and 42 kg are depicted in Table 5.

Table 5: Content uniformity of color (%) in collected samples

	CONTENT UNIFORMITY OF COLOR IN %					
	For batch size 12kg			For batch size 42kg		
	After 5 minutes	After 10 minutes	After 15 minutes	After 5 minutes	After 10 minutes	After 15 minutes
Mean	106.5	107.9	103.3	109.6	109.7	109.9
RSD	6.51	5.63	6.71	1.38	2.87	2.33

For the batch of 12 kg, the color content (% assay) of some samples were found to be out of limits (90-110%).The mean of assay results for 5 min and 10 min of mixing were found to be out of limits (95-105%) and the RSD values for content uniformity of six samples were found to be out of limits (NMT 5%).

The reason for these results was found to be inadequate sampling due to small batch size of 12 Kg .Hence to verify the performance of SMG the minimum occupancy capacity was fixed as more than 30% of SMG capacity and dry mixing time was recommended for 10 min.

For the batch of 42 kg the color content (% assay) of all samples were found to be within limits (90-110%).The mean of assay results for 5 min ,10 min and 15 min of mixing were found to be within limits (95-105%) and the

RSD values for content uniformity of six samples were found to be within limits (NMT 5%).Thus to verify the performance of SMG the maximum occupancy capacity was fixed as 70% of SMG capacity and dry mixing time was recommended for 10 min.

From the results of granulation i.e., wet mixing for 12 kg and 42 kg batch it was concluded that SMG can produce desired granules and the amperage reading was found to be proportional to the load with LOD of granules of 24.42 % and 24.60 % respectively. The Qualification was completed for wet mixing & it was released for use.

AUTOMATIC COATING MACHINE

The results of tablets physical parameters were recorded and shown in Table 6.

Table 6: Specified physical parameters of tablets

S.No	Parameter	Specification (For 6 Kg, 10 Kg ,18 kg and 30 Kg batch size)
1.	Description	Grey colored, modified diamond shaped, biconvex, beveled edge film coated tablets debossed with "A" on one side and "101" on other side.
2.	Average tablet mass	612 mg ±3 % (593.64-630.36)
3.	Mass of 20 tablets	12.240 g ±3%(11.873 – 12.607)
4.	Thickness	5.80 ± 0.30 mm (5.50 to 6.10 mm)
5.	Weight build up	1.75 -2.25 % w/w

The results of weight variation and thickness were recorded in Table 7.

Table 7: Result of weight variation and thickness of tablets

S.No. (tablets)	For different Batch sizes (kg)							
	Weight variation of 20 tablets				Thickness (mm) of 20 tablets			
	6 kg	10 kg	18 kg	30 kg	6 kg	10 kg	18 kg	30 kg
min.	596.9	601.5	598.3	598.1	5.67	5.68	5.63	5.62
Max.	621.4	625.9	620.8	620.8	5.76	5.86	5.75	5.75
Total mass (g)	12.180	12.230	12.202	12.214	12.180	12.230	12.202	12.180
Average weight (mg)					Weight build up (%)			
	608.69	611.50	610.10	610.745	2.17	2.05	2.08	2.09

All the parameters were found to be within the acceptance limits mentioned in Table 6. The automatic coating machine was qualified for the batch size of 6.0Kg, 10 Kg, 18 Kg and 30 Kg.
Thus the Performance Qualification was completed and it was released for use.

CONCLUSION

Qualification is an essential part of a pharmaceutical manufacturer's quality assurance system. The performance qualification of SMG (150 L) was done for minimum (20%) and maximum (70%) occupancy capacities and content uniformity at different mixing intervals. The performance qualification of the Automatic coating machine for minimum and maximum capacity with aqueous coating operation for 6-10 Kg Pan and 24-40 Kg Pan was done. For both the pan sizes, the physical parameters such as weight variation, thickness and weight built up % were as per the specifications and thus SMG (150 L) and Automatic coating machine were successfully qualified.

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