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QUALIFICATION OF EQUIPMENT: SAIZONER MIXER GRANULATOR, COMPRESSION MACHINE AND COATING PAN

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ABSTRACT:

Qualification is the action of proving that any equipment works correctly and leads to expected results. The main objective of the present study was to perform the performance qualification of critical tablet manufacturing equipments like Saizoner Mixer Granulator, Compression machine and Coating pan. Saizoner mixers are used for dry and wet mixing of powders. The performance qualification protocols were prepared, approved and studies were performed as per the approved protocols. The performance qualification of Saizoner Mixer Granulator, samples were collected from the bowl with maximum working capacity and then the samples were analyzed for content uniformity, granule appearance and amperage. The performance qualification of compression machine, core tablets of smallest size were compressed and checked for their parameters such as appearance, average weight, hardness, friability, disintegration time, thickness and content uniformity. The performance qualification of coating pan, the coated tablets was checked for their physical parameters such as appearance, weight variation, dimensions and thickness for different tablet sizes and shapes. The results of all performance qualification works were satisfactory and demonstrated the efficiency of the equipments for their intended use.

Keywords: Equipment qualification, Saizoner mixer granulator, Compression machine and Coating pan.

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INTRODUCTION

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 specified¹. Schedule M states about the qualification of the equipment². 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 quality³. 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 implemented⁴.

Chapter 2.5.11 of Pharmaceutical Inspection Convention /Scheme (PIC/S)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 met⁵. 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's delivered, it may be necessary to make sure that the user requirements are complied with at the manufacturer's premises (Factory Acceptance Test, FAT)⁶.

The objective of the present study was to perform the performance qualification of critical tablet manufacturing equipment like Saizoner Mixer Granulator, Compression machine and Coating pan. The saizoner mixer granulator is a high shear powder mixer having mixing and wet massing facility for powders within the same equipment. The compression machine is used to produce core tablets of various sizes and shapes. The coating pan is used to coat tablets of various shapes and sizes by batch process. 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), Lactose (IP), Starch (IP) & Purified water (USP). Compression machine (Cadmach Machinery Co Pvt. Ltd., 37 stations double rotary "B" tooling). Automatic coating machine (Neomachine Mfg. Co. Pvt. Ltd, model: Neocota 40 D) core tablets.

Performance Qualification of Saizoner mixer granulator

Saizoner mixer granulator is a vertically designed bowl having a high shear mixer blade, a chopper blade and pneumatic discharge port for automatic discharge of the material inside the mixer and ammeter for determining the end point of granulation. The mixing blades can be operated at slow speed (50 rpm) and fast speed (100 rpm) depending on the requirement of the process. The chopper blades can be operated at slow speed (1750 rpm) and fast speed (3500 rpm) depending upon the requirement of the process. The lid has two opening, one for addition of binding solution to the contents inside the bowl and the other for air exhaust sleeve.

Table 1: Quantity of ingredients for Batch size

S.NO	Ingredients	Quantity per batch (KG)
Dry mix		
1.	Active ingredient- A	77.00
2.	Active ingredient- B	20.91
3.	Starch	51.00
4.	Lactose	131.09
Binder Paste		
5.	Starch	20.00
6.	Purified water	130.00

DRY MIXING

Active ingredient-A, Active ingredient -B, Starch and Lactose were sifted through 40 mesh and loaded into rapid mixer granulator. The materials were mixed for 30 minutes with impeller at slow speed and chopper off. The samples were collected in triplicate each equivalent to three times of the weight of unit dose using appropriate unit dose sampler from different locations as shown in Fig. 1 and analyzed for the contents of active ingredients A and B. Similarly two more trials were performed.

Acceptance Criteria

Table 2: Process parameters and Specifications

Parameter	Specification	
	Active ingredient-A	Active ingredient -B
Assay	90-110%	90-110%
Mixing time	30-35 minutes.	30-35 minutes.

GRANULATION

20 kg of starch was dispersed in 20 kg of purified water to prepare slurry. The slurry was added to 110kg of boiling water and stirred continuously to form a paste. The paste was added to the mixed powder with the impeller at slow speed. The mixing was continued until the granules of required size were formed. The total granulation time and the ampere readings were recorded. Samples were collected in triplicate each equivalent to three times of the weight of unit dose using appropriate unit dose sampler from different locations as per sampling procedure and the moisture content of the granules were determined at 105°C for 10 minutes. Similarly two more trials were performed.

Acceptance Criteria

Table 3: Process parameters and Specifications

Parameter	Specification
Granulation time	15-20 minutes
Ampere reading	40±2 amps
Moisture content of wet granules	10±2% w/w

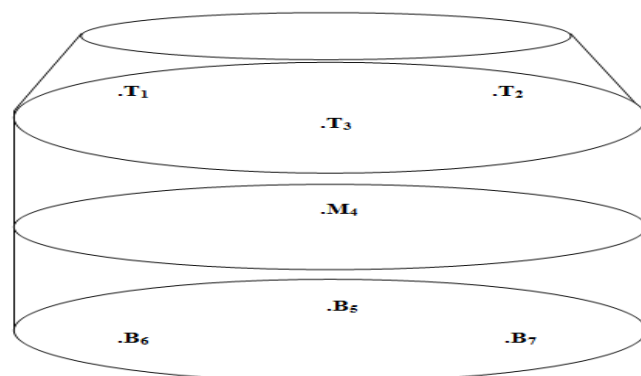


Fig. 1: Sampling location for dry mixing and granulation
Performance Qualification of Compression Machine:

The compression machine was fitted 5.0 mm circular, deep concave upper and lower punches and dies. The lubricated granules were loaded in both hoppers and compression cycle was started by operating the machine at 24 rpm and physical parameters were recorded every one hour till the end of the cycle.

Acceptance Criteria

Table 4: Process parameters and Specifications

Parameter	Specification
Average weight	48 to 52mg
Weight per tablet	45 to 55mg
Thickness	2.3 to 2.5mm
Hardness	1 to 3 kg/cm ²
Friability	NMT 1%/w/w
Disintegration time	NMT 5 minutes

Performance Qualification of Coating pan:

Opadry white (3kg) was dispersed in purified water (50 kg) with continuous stirring. The coating suspension was stirred for 45 minutes and strained through #60 and collected in a SS vessel.

The dedusted tablets were loaded into coating pan and coated with the following parameters:

Table 5: Process parameters and Specifications

Parameter	Specification
Inlet temperature	60±5°C
Bed temperature	40±5°C
No. of guns	3
Spray rate	120gm/min
Exhaust temperature	40±5°C
Air pressure	3 to 6 kg/cm ²

Samples were removed at the end of the coating process in triplicate as per the sampling plan (Fig. 2) and analysed for physical parameters.

Acceptance Criteria

Table 6: Process parameters and Specifications

Parameter	Specification
Average weight	1350mg ±2%
Average thickness	6.3 to 6.7 mm
Average length	17.2 to 17.6 mm
Average width	10.2 to 10.6 mm
Appearance of the tablets	Smooth

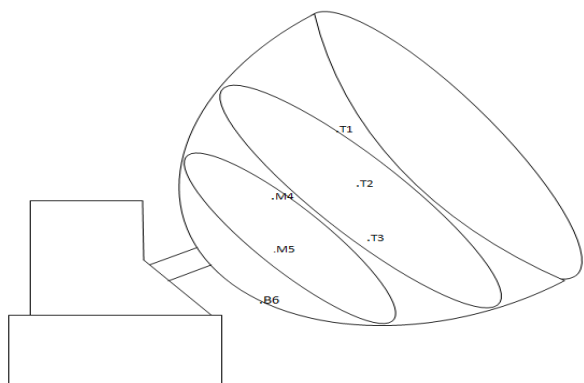


Fig 2: Sampling location for coating pan

RESULTS AND DISCUSSION

Saizoner Mixer Granulator

The mixing efficiency of the Saizoner mixer granulator was evaluated by determining the content uniformity of the active ingredients in samples collected from different locations using spectrophotometrically. The percentage of active ingredients A and B in trials 1, 2 and 3 were shown in Table 7. The results were within limits.

Table 7: Uniformity of drug content in various trails with different locations

SAMPL E	TRIAL 1		TRIAL 2		TRIAL 3	
	Active ingredien t A (%w/w)	Active ingredien t B (%w/w)	Active ingredien t A (%w/w)	Active ingredien t B (%w/w)	Active ingredien t A (%w/w)	Active ingredie nt B (%w/w)
T ₁	100.08	101.20	99.28	98.80	98.81	102.41
T ₂	101.47	103.57	98.36	98.80	98.72	101.20
T ₃	101.83	104.76	98.53	101.20	98.17	103.61
M ₄	100.37	102.40	101.47	101.20	101.10	102.41
B ₅	98.17	100.08	98.72	98.70	98.90	101.20
B ₆	102.19	103.57	99.63	98.80	98.17	101.20
B ₇	98.90	103.57	98.90	99.49	102.65	100.63
MEAN	100.42	102.74	99.27	99.40	99.50	101.81
%RSD	1.52	1.58	1.07	1.18	1.72	1.02

The percentage moisture content of the granules was determined using a calibrated Halogen moisture analyzer at 105°C for 10 minutes and were found to be within limits. The results were presented in the Table 8.

Table 8: Moisture content in various trails with different locations

SAMPLE	MOISTURE CONTENT (%W/W)		
	TRIAL 1	TRIAL 2	TRIAL 3
T ₁	9.05	10.05	8.82
T ₂	9.80	9.63	10.88
T ₃	8.38	9.71	9.63
M ₄	9.61	8.93	9.90
B ₅	10.09	10.68	10.61
B ₆	9.87	9.05	9.83
B ₇	9.63	9.62	9.53
MEAN	9.49	9.67	9.89
%RSD	1.56	1.68	1.72

COMPRESSION MACHINE

Samples of compressed tablets were evaluated for average tablet weight, thickness, hardness, disintegration time, friability, content uniformity, capping, lamination, chipping, sticking and picking. Samples were collected every 15 minutes throughout the entire compression cycle for the determination of average weight.

The average weight of the tablets determined during the trials 1, 2 and 3 were 50.5, 50.8 and 50.9 mg respectively. The average thickness of the tablets determined during the trials 1, 2 and 3 were 2.43, 2.46

and 2.46 mm. The average hardness of the tablets determined during the trials 1, 2 and 3 were 1.44, 1.45 and 1.33 kg/cm² respectively. The average percentage friability of the tablets determined during the trials 1, 2 and 3 were 0.24, 0.22 and 0.23 percentages respectively. The average disintegration time of the tablets determined during the trials 1, 2 and 3 were 22, 23 and 24 seconds respectively. The content uniformity of the tablets determined during the trials 1, 2 and 3 were 4.88, 4.86 and 4.85 mg respectively. The results were within the limits and these were presented in the Table 9 to 14.

Table 9: Weight of various trails of Compressed Tablets (mg)

TRIAL 1		TRIAL 2		TRIAL 3	
RHS	LHS	RHS	LHS	RHS	LHS
0.50	0.50	0.49	0.50	0.49	0.49
0.50	0.50	0.50	0.50	0.49	0.49
0.49	0.49	0.49	0.49	0.49	0.50
0.50	0.50	0.51	0.50	0.50	0.50
0.49	0.49	0.49	0.49	0.50	0.49
0.50	0.50	0.50	0.50	0.50	0.49
0.50	0.49	0.51	0.49	0.50	0.49
0.49	0.50	0.49	0.50	0.51	0.50
0.49	0.51	0.50	0.51	0.51	0.50
0.50	0.49	0.50	0.49	0.50	0.50
0.50	0.50	0.51	0.50	0.50	0.50
0.50	0.49	0.50	0.49	0.49	0.49
0.50	0.50	0.51	0.50	0.49	0.51
0.50	0.51	0.51	0.51	0.50	0.51
0.49	0.49	0.50	0.49	0.49	0.49
Mean	50.5	50.8		50.9	
SD	0.01	0.01		0.01	

Table 10: Thickness of various trails of Compressed Tablets (mm)

TRIAL 1		TRIAL 2		TRIAL 3	
RHS	LHS	RHS	LHS	RHS	LHS
2.42	2.46	2.45	2.47	2.41	2.46
2.46	2.41	2.43	2.50	2.46	2.46
2.43	2.43	2.41	2.55	2.39	2.49
2.48	2.49	2.45	2.53	2.40	2.43
2.42	2.45	2.39	2.50	2.38	2.40
2.39	2.39	2.42	2.53	2.40	2.50
2.36	2.37	2.46	2.49	2.51	2.55
2.41	2.38	2.51	2.47	2.50	2.48
2.39	2.42	2.46	2.43	2.53	2.50
2.38	2.46	2.43	2.51	2.48	2.48
2.42	2.43	2.39	2.47	2.55	2.50
2.46	2.49	2.43	2.49	2.47	2.50
2.42	2.41	2.43	2.43	2.47	2.48
2.45	2.37	2.41	2.50	2.47	2.43
2.44	2.42	2.42	2.46	2.46	2.41
Mean	2.42	2.46		2.45	
SD	0.04	0.04		0.04	

Table 11: Hardness of various trails of Compressed Tablets (kg/cm²)

TRIAL 1		TRIAL 2		TRIAL 3	
RHS	LHS	RHS	LHS	RHS	LHS
1.43	1.39	1.42	1.36	1.31	1.62
1.41	1.36	1.37	1.38	1.28	1.49
1.38	1.52	1.46	1.60	1.22	1.41
1.46	1.50	1.49	1.53	1.41	1.37
1.52	1.43	1.38	1.42	1.49	1.47
1.39	1.42	1.52	1.37	1.41	1.53
1.36	1.51	1.39	1.46	1.32	1.44
1.42	1.49	1.46	1.41	1.48	1.48
1.50	1.53	1.41	1.49	1.43	1.27
1.43	1.50	1.43	1.37	1.19	1.13
1.48	1.38	1.48	1.52	1.13	1.21
1.36	1.42	1.39	1.46	1.28	1.13
1.33	1.46	1.42	1.38	1.21	1.20
1.52	1.43	1.43	1.43	1.51	1.38
1.50	1.45	1.39	1.49	1.37	1.52
Mean	1.44	1.45		1.33	
SD	0.06	0.06		0.13	

Table 12: Friability of various trails of Compressed Tablets (%w/w)

TRIAL 1		TRIAL 2		TRIAL 3	
RHS	LHS	RHS	LHS	RHS	LHS
0.34	0.36	0.29	0.23	0.26	0.15
0.19	0.23	0.20	0.22	0.17	0.17
0.24	0.19	0.28	0.27	0.27	0.19
0.31	0.20	0.20	0.21	0.17	0.42
0.23	0.23	0.20	0.27	0.21	0.21
0.20	0.14	0.26	0.23	0.15	0.56
0.20	0.19	0.24	0.28	0.19	0.21
0.21	0.22	0.23	0.17	0.23	0.22
0.33	0.30	0.24	0.18	0.23	0.13
0.28	0.23	0.28	0.19	0.19	0.31
0.19	0.28	0.29	0.22	0.25	0.21
0.28	0.19	0.20	0.15	0.30	0.17
0.40	0.15	0.18	0.18	0.26	0.23
0.18	0.27	0.19	0.20	0.30	0.11
0.29	0.22	0.22	0.19	0.19	0.39
Mean	0.23	0.22		0.23	
SD	0.06	0.04		0.09	

Table 13: Disintegration time of various trails of Compressed Tablets (Sec.)

TRIAL 1		TRIAL 2		TRIAL 3	
RHS	LHS	RHS	LHS	RHS	LHS
21	25	25	23	27	22
26	22	21	23	22	27
25	20	25	27	20	28
17	19	21	25	21	20
18	25	20	26	25	22
19	23	18	17	24	21
20	22	21	21	23	26
21	19	18	20	24	25
23	27	27	22	23	19
22	25	23	27	20	26
20	26	20	24	22	25
17	18	19	26	20	26
21	23	23	25	21	25
24	22	20	22	24	23
20	23	26	21	21	24
Mean	21	23		23	
SD	2.82	2.85		2.49	

Table 14: Content of uniformity of various trails of Compressed Tablets (mg)

TRIAL 1		TRIAL 2		TRIAL 3	
RHS	LHS	RHS	LHS	RHS	LHS
4.59	4.65	4.86	4.93	4.78	5.16
4.63	4.93	4.72	4.76	4.69	4.96
4.79	4.79	4.93	4.62	4.83	4.87
5.06	4.84	4.65	4.58	4.91	4.76
4.83	4.63	4.97	4.63	4.72	4.53
4.91	4.58	5.03	4.79	4.53	4.69
4.72	5.19	5.16	5.18	5.08	4.82
5.08	5.08	4.82	5.03	5.02	4.73
5.13	4.86	4.75	4.97	4.63	4.97
5.01	5.13	4.91	4.82	4.57	4.73
Mean	4.87	4.86		4.80	
SD	0.19	0.16		0.17	

COATING PAN

The average weight after coating during all the three trials was 1349.9, 1350.6 and 1351.6 mg respectively. The average thickness and dimensions after coating were also calculated. The results were presented in the Table 15 and 16.

Table 15: Weight of various trails of Coated Tablets (mg)

SAMPLE	TRIAL 1	TRIAL 2	TRIAL 3
S1	1342.1	1352.6	1353.6
S2	1351.7	1354.2	1354.8
S3	1352.7	1346.9	1351.9
S4	1356.8	1345.2	1344.8
S5	1347.6	1349.8	1351.8
S6	1348.4	1354.7	1352.9
Mean	1349.9	1350.6	1351.6
SD	5.04	3.93	3.53

Table 16: Thickness of various trails of Coated Tablets (mm)

SAMPLE	TRIAL 1	TRIAL 2	TRIAL 3
S1	6.58	6.58	6.64
S2	6.58	6.54	6.62
S3	6.59	6.56	6.63
S4	6.59	6.54	6.63
S5	6.59	6.59	6.64
S6	6.61	6.60	6.63
Mean	6.59	6.57	6.63
SD	0.01	0.03	0.01

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Table 17: Dimension of various trails of Coated Tablets (mm)

SAMPL E	TRIAL 1		TRIAL 2		TRIAL 3	
	LENGT H	WIDT H	LENGT H	WIDT H	LENGT H	WIDT H
S1	17.42	10.39	17.43	10.38	17.38	10.37
S2	17.42	10.42	17.41	10.38	17.39	10.39
S3	17.43	10.40	17.41	10.40	17.38	10.38
S4	17.43	10.39	17.42	10.39	17.40	10.38
S5	17.43	10.39	17.43	10.42	17.40	10.40
S6	17.42	10.41	17.42	10.41	17.39	10.40
Mean	17.43	10.40	17.42	10.40	17.39	10.39
SD	0.01	0.01	0.01	0.02	0.01	0.01

CONCLUSION

The present study was done on the performance qualification of some of the equipment designed for the manufacture of tablets namely Saizoner mixer granulator, Compression machine and Coating pan. The performance qualification trials demonstrated that the tablet manufacturing equipment performed consistently under a given set of conditions. The Saizoner mixer granulator was evaluated for its intended use of mixing of active ingredients with excipients and wet granulation of powder mixture. The content of the active ingredients in the powder mixture was within the specified limits. The appearance of granules and results of moisture content analysis were found to be satisfactory. The compression machine was evaluated for its intended use of compression of granules into tablets. The average weight, thickness, hardness, disintegration time, friability and content uniformity of tablets were within the specified limits. The coating pan was evaluated for its intended use of coating of core tablets of various shapes and sizes. The average weight, thickness and dimensions of tablets were within the specified limits. Reviewing the entire data generated during qualification, it can be concluded that the equipment studied are suitable for which they are used.

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