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Concurrent Process Validation of the Salbutamol Tablet IP

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ABSTRACT

Background and Objective: *The primary purpose of this work is to perform a study on the concurrent validation of Salbutamol 4mg tablet that will deliver process validation approach as a quality assurance means. The process validation program will be investigated so that the plan will be designed to the character of the procedure under study. This can be performed by checking and controlling the various critical in process parameters as well as by evaluating the finish products. The secondary aim would be to ascertain documented evidence which offers a high notch of assurance that the entire procedure will reliably manufacture tablets assigning predetermined acceptance criteria and quality aspects.*
Method: *Samples from the three consecutive batches of salbutamol 4mg tablet (SL-301, SL-302 and SL-303) are collected at the different stages of the manufacturing from sifting, blending and compression as mentioned in the sampling plan for the individual processes. Each and every parameter are analysed and tested as per the specifications and all the data are recorded. The obtained result must be within the specified limit range.*
Results: *The results obtained from the evaluation of different parameters like appearance, sieve integrity, bulk and tapped density, blend uniformity and assay, content uniformity, weight variation, thickness, hardness, friability and disintegration time were found to be within specified limit range.*
Conclusion: *Process validation studies were executed for the three successive batches of salbutamol tablet. Different parameters were checked and validated as per the specification. The process validation of the salbutamol 4mg tablet shows that no any variations were observed between the batches and the process was validated.*

Keywords: *Salbutamol Sulphate, Magnesium Stearate, Sodium Starch Glycolate, Purified Talc, Colloidal Silicon Dioxide.*

INTRODUCTION

Validation in simple form can be described as documented practice which delivers the evidence that any of the process, procedure, material, equipment, action or system truly shows the estimated result.

FDA states that it is aimed with the purpose to establish documented data which ultimately delivers a high grade of assurance that the given specific procedure will reliably produce a result which tends to meet its specifications which are predetermined and also meet the quality elements.

Process validation is expressed as the practice which involves the assortment and estimation of data during the different phases of pharmaceutical activities, starting from the procedure design phase during the course of production establishing the scientific indication that a procedure is efficient of steadily manufacturing quality outcomes [1,2].

USFDA defined process validation as “the act of ascertaining documented confirmation which tends to delivers a high grade of assurance that a product will be manufactured through a specific

procedure and the product thus produce will meet all its pre-determined descriptions mentioned and quality characteristics" [3,4].

OBJECTIVES

1) To decrease dissimilarity between different batches.
2) To minimalize the possibility of defect costs and monitoring noncompliance.
3) To validate the robustness of the process.
4) To offer a high notch of assurance that the products are of quality standard.
5) To certify the uniformity of the manufacturing operations and consistency of the process.
6) To declare the presence of all obligatory quality assurance system within association.
7) To reduce the in-process and end product testing in case of fully validated procedure [5].

Strategy for Validation of Methods [5]

The various strategies for process validation of method are:

1) Preparing process flow charts and detecting the critical process variables.
2) Selecting the three sequential batches which possess same manufacturing formula and batch size.
3) Process prequalification should be performed in case of failure to encounter the prerequisite of the validation protocol on the basis of process input and output control.
4) Proper documentation should be prepared for all the validation experiment and results by maintaining a validation report.
5) Prepare a relevant process validation protocol of the specified product.
6) BMR, SOPs, finished and in process product specification along with other associated documents and batch packaging record should be maintained.
7) In other to perform the task consistently and efficiently, SOPs should be prepared.
8) Monitoring of all the respective process validation batches.
9) Accomplishment of validation protocol effectively.
10) Carrying out the in process testing during manufacturing of the product [21].

Type of Documentation in Validation [6]

The various documentations to be prepared during the validation process are:

1) Validation Master Plan (VMP)
2) Validation Protocol (VP)
3) Standard Operating Process (SOPs)
4) Validation Reports (VR) [9]

SALBUTAMOL

Salbutamol sulphate is a short-acting, selective β_2 agonist drug, prescribed in the management of respiratory diseases *i.e.* COPD and asthma. It binds to β_2 receptor present on bronchial smooth muscle and mast cell, resulting in activation of adenylcyclase which increases the formation of intracellular CAMP from ATP causing in easing of bronchial smooth muscle and also inhibits the discharge of bronchi constructing mediators from mast cell resulting in relaxation of bronchial smooth muscles [7].

MATERIALS AND MACHINERIES

All the raw materials *i.e.* salbutamol sulphate, MCCP 102, dicalcium phosphate, polyvinyl prolidone k30, magnesium stearate, purified talc and colloidal silicon dioxide were of IP grade and other chemicals used in the analysis process were of analytical grade.

The different machineries and equipment used were powder sifter (30 inches), rapid mixing granulator (60kg), fluidized bed dryer (60kg), double cone blender (150kg),

rotatory compression machine (27 station), hardness tester, high performance liquid chromatography (HPLC), disintegration apparatus, friability test apparatus, electronic balance (120gm), Vernier caliper (12 inches), strip packaging machine, cartoon strapping machine and batch coding machine.

METHODS

1) **Pre-dispensing Checks**
   Dispensing area should be checked before the raw materials are dispatched.

2) **Raw Material Dispensing**
   The quantity of the raw material should be measured properly and proper checking should be made during the time of dispensing of raw materials.

3) **Verification of Raw Materials**
   Tag of stores should be placed on each raw material in which name of product, Batch No., Material's name, Quantity against Raw Material Requisition Sheet and A.R. No, Mfg. date & Exp. Date of Raw Materials should be mentioned and should verify according to the BMR. All the tags should be then attached to the BMR.

4) **Shifting**
   Sifting area should be cleaned thoroughly before the process is carried out in order to confirm the area is free from previous product and for this line clearance should be done. Get the line clearance and then carry out the sifting.
   MCCP 102…… 2.800 kg
   Di calcium phosphate……. 74.616 kg
   Polyvinyl pyrolidone K30… 1.800 kg
   Sift all the above mentioned materials through sifter of #60 mesh.

5) **Dry Mixing**
   Transfer the sifted materials from step 3 into RMG and then blend them for 30 minutes.

6) **Preparation of Granulating Solution**
   R.O. water…… 16.00 kg
   Salbutamol sulphate …… 1.986 kg
   Dissolve salbutamol sulphate in sufficient quantity of R.O. water and make a solution.

7) **Granulation**
   Add the granulating solution prepared in step 6 with the mixture of step 5 to form the granules. Continue mixing for 3 minutes to prepare the wet granules.

8) **Drying**
   Semis dry the wet granules under predetermined air flow at 55ºC for 15 minutes. And supply the air dried granules in the fluidized bed dryer and dry it at 55ºC for 35 minutes.

9) **Dry Screening**
   Dried granules should be sifted through a sifter of mesh size 18 and then transfer the dried granules in double polythene lined drums.
   Note: Moisture content should be 1.75%.

10) **Lubrication**
    Sodium starch glycolate…… 2.000 kg
    Magnesium Stearate…….. 0.800kg
    Purified Talc……. 1.200 kg
    Colloidal silicon dioxide….. 0.400 kg
    - All the above mentioned materials should be sifted through 60# mesh and should be collected in a poly bag
    - Shift the granules from step 9 and powder from step 10 into DCB and blend for 15 minutes in clockwise direction and then 15 minutes in anticlockwise direction. Now blend the mixture of the Double cone blender for 10 minutes.
    - Gather the lubricated granules in drum lined with double polythene

and record the weight of lubricated granules.

- Send the collected samples of granules for the IPQC testing with proper identification no., batch no., sample name and all the information required and mentioned in the BMR.
- After the IPQC testing, only after the approval from Quality Assurance department, the granules are released for the compression process. Transfer the granules into the compression area for compression process.
- Indicate the date of release in BMR and intermediate Release no.

(Place the Release Slip of granules from quality assurance for compression to BMR)

11) **Tablet Compression**

Before initiating the compression line clearance of area for compression is done from Quality Assurance department. Rotary Tablet Compression Machine with 6.0mm dies and 6.0mm round concave punches with emboss on lower punch is made ready for the compression. Sequential in process check is carried out as per in process specification of compressed tablets and the data is recorded in the BMR. All the compressed tablets are then collected and stored in drum lined with double polythene.

12) **Strip Packaging**

The packaging of the compressed tablet is to be done as per the batch packing record. In this stage, three batches *i.e.* SL-301, SL-302 and SL-303 shall be considered for validation. The packing results of all the batches lies within the acceptance criteria.

EVALUATION PARAMETERS

Weight variation

Form each batch, twenty tablets were randomly selected and weighed individually. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in table no. 11.

Hardness

The hardness of 10 randomly selected tablets from each batch was determined by using hardness tester. The average hardness and standard deviation was determined. The results for hardness are shown in table no. 13.

Thickness

The thickness of 20 randomly selected tablets from each batch was determined using Vernier caliper. The result is shown in table no. 12.

Friability

Twenty tablets were randomly selected from each batch and weighed. Friability test was carried out using friability testing apparatus. The friability testing apparatus was rotated at 100rpm. The percentage friability was measured using formula,

$$\% \text{ friability} = \frac{\text{Initial Weight} - \text{Final Weight} * 100\%}{\text{Initial Weight}}$$

The results for percentage friability are shown in table no. 15.

Assay

Salbutamol sulphate tablet was estimated by using HPLC as per Indian Pharmacopoeia method.

Test Solution: Add 50ml of water to one tablet and shake constantly for 1 hour. Now, add sufficient amount of water to produce 100.0ml, mix to form a solution and centrifuge. Dilute the solution further with water, if required in order to produce

a solution comprising 0.002 percent w/v of salbutamol.

Reference Solution: A 0.0024 percent w/v of salbutamol sulphate RS in water

Chromatographic System

- Column: stainless column 20cm×5mm, packed with spherical particles of silica, 5µm in diameter, the surface of which has been modified with chemically – bonded nitrile groups (such as spherisorb CN)
- Mobile phase: a mixture of 65 volumes of water, 30 volumes of 0.05 M ammonium acetate and 5 volumes of 2 – propanol, the pH of the mixture being adjusted to 4.5 with glacial acetic acid
- Flow rate: 2ml per minute
- Spectrophotometer set at 276nm
- Injection volume: 20µl

The resolution between two principal peaks in the chromatogram gained with reference solution (b) should be at least 1.5.

Calculate the content of $C_{13}H_{21}NO_3$ in the tablet.

Calculation

$$\frac{T}{S} \times \frac{std\ wt}{std\ dilution} \times \frac{sample\ dilution}{sample\ wt} \times \%purity\ of\ std \times 0.829 \times avg.wt \frac{mg}{tab}$$

Content Uniformity

Test solution: Place 10 tablets or required number of tablets containing 4.0mg of salbutamol in the volumetric flask and shake it with about 60ml of water for 1 hour. Then, add sufficient amount of water to produce 250.0ml. Now, mix and centrifuge about 10ml of the mixture. From the centrifuge mixture use the supernatant liquid.

Reference Solution: A 0.0024 percent w/v of salbutamol sulphate RS in water. For the determination of content uniformity, follow the chromatographic method described for it. The resolution between the two principal peaks in the chromatogram gained with reference solution (b) should be at least 1.5. Calculate the content of $C_{13}H_{21}NO_3$ in the tablet.

Calculation

$$\frac{T}{S} \times \frac{std\ wt}{std\ dilution} \times \frac{sample\ dilution}{sample\ wt} \times \%purity\ of\ std \times 0.829 \times avg.wt \frac{mg}{tab}$$

RESULTS

All the results are tabulated from table no 3 to 19.

Table 1. Details of Raw Materials

S.no.	Ingredients	Grade	Quantity/tab (mg)
1.	Salbutamol sulphate*	API	4
2.	MCCP 102	IP	7.6
3.	Di calcium phosphate	IP	150
4.	Polyvinyl pyrolidone	IP	3.6
5.	Sodium starch glycolate	IP	4.4
6.	Magnesium stearate	IP	1.6
7.	Purified talc	IP	3.2
8.	Colloidal silicon dioxide	IP	0.8

9.	R.O. water	IP	……

Table 2. Equipments to be used during Validation

S. no	Processing stage	Equipment	Capacity
1.	Weight Verification	Weighing balance	60kg
2.	Sifting	Powder sifter	30 inches
3.	Dry mixing	RMG	60kg
4.	Drying	FBD	60kg
5.	Blending & Lubrication	DCB	150kg
6.	Tablet Compression	Rotatory Compression Machine	27 station
7.	Assay Testing	HPLC	

Table 3. Blending and Lubrication Result at 10mins

Batch no.	Sampling Time	Parameters					
		Assay (%)	Average Assay (%)	Standard Deviation	Average Standard Deviation	RSD (%)	Average RSD (%)
SL 301	10mins	105.40%	104.37%	0.01031	0.00864	0.1718	0.1440
SL 302		103.20%		0.01135		0.1891	
SL 303		104.52%		0.00426		0.0711	

Table 4. Blending and Lubrication Result at 20mins

Batch no.	Sampling Time	Parameters					
		Assay (%)	Average Assay (%)	Standard Deviation	Average Standard Deviation	RSD (%)	Average RSD (%)
SL 301	20mins	104.97%	103.14%	0.01460	0.011197	0.2433	0.1866
SL 302		102.73%		0.00814		0.1357	
SL 303		101.73%		0.01085		0.1809	

Table 5. Blending and Lubrication Result at 30mins

Batch no.	Sampling time	Parameters					
		Assay (%)	Average Assay (%)	Standard Deviation	Average standard Deviation	RSD (%)	Average RSD (%)
SL 301	30mins	100.20%	100.05%	0.00393	0.00313	0.0655	0.0526
SL 302		101.23%		0.00146		0.0244	
SL 303		98.72%		0.0040		0.0679	

Table 6. Summary (Average of all Three Batches)

Sampling Time	Average Assay (%)	Average Standard Deviation	Average RSD (%)
10mins	104.37%	0.00864	0.1440
20mins	103.14%	0.011197	0.1866
30mins	100.05%	0.00313	0.0526

Table 7. Flow Property Parameters at 10mins

Batch no.	Time	Parameters				
		Angle of Repose	Tapped Density	Compressibility Index	Haussner Ratio	Remarks
SL 301	10mins	31	0.73	23.28	1.3	Excellent
SL 302		33	0.75	22.66	1.29	Excellent
SL 303		32	0.74	22.97	1.29	Excellent

Table 8. Flow Property Parameters at 20mins

Batch no.	Time	Parameters				
		Angle of repose	Tapped density	Compressibility index	Haussner ratio	Remarks
SL 301	20mins	32	0.74	22.98	1.3	Excellent
SL 302		33	0.76	22.67	1.28	Excellent
SL 303		31	0.74	24.32	1.32	Excellent

Table 9. Flow Property Parameters at 30mins

Batch no.	Time	Parameters				
		Angle of repose	Tapped density	Compressibility index	Haussner ratio	Remarks
SL 301	10mins	31	0.73	23.28	1.3	Excellent
SL 302		33	0.75	25.33	1.33	Excellent
SL 303		32	0.73	21.91	1.28	Excellent

Table 10. Temperature of FBD

Batch no.	Parameters		
	Inlet temperature (ºC)	Outlet temperature (ºC)	Moisture Content (%)
SL 301	61	47	1.5
SL 302	63	47	1.6
SL 303	62	48	1.5

Table 11. Weight Variation of the Compressed Tablets

SAMPLE NO	SL 301(Gm)	SL 302(Gm)	SL 303(Gm)
1	0.2145	0.2102	0.2184
2	0.2161	0.2140	0.2140
3	0.2085	0.2208	0.2167
4	0.2167	0.2158	0.2154
5	0.2124	0.2134	0.2135
6	0.2161	0.2099	0.2167
7	0.2134	0.2153	0.2122
8	0.2145	0.2098	0.2128
9	0.2149	0.2129	0.2136
10	0.2208	0.2131	0.2103
11	0.2240	0.2133	0.2084

12	0.2160	0.2166	0.2111
13	0.2143	0.2107	0.2107
14	0.2136	0.2096	0.2146
15	0.2131	0.2116	0.2148
16	0.2132	0.2108	0.2181
17	0.2089	0.2067	0.2125
18	0.2157	0.2225	0.2144
19	0.2169	0.2146	0.2158
20	0.2165	0.2139	0.2186
Average	**0.2149**	**0.2133**	**0.2141**
Maximum deviation	**4.23%**	**3.56%**	**2.10%**
Minimum deviation	**2.97%**	**3.07%**	**2.66%**

Table 12. Thickness of the Compressed Tablets

SAMPLE NO	SL 301 (MM)	SL 302 (MM)	SL 303 (MM)
1	2.95	2.98	2.99
2	2.99	2.99	3.02
3	2.98	3.01	2.99
4	2.96	2.99	2.98
5	2.99	3.01	2.99
6	3.01	3.02	3.03
7	2.99	2.98	3.02
8	3.03	2.98	2.98
9	3.02	2.99	2.99
10	2.98	3.02	3.02
11	2.99	2.99	2.99
12	3.01	2.98	3.01
13	3.03	2.96	2.98
14	2.99	3.03	2.98
15	2.99	3.02	2.99
16	2.98	2.99	3.02
17	3.03	3.01	2.99
18	2.99	3.02	2.99
19	3.02	2.99	3.01
20	3.01	2.98	3.02
Average	**2.99**	**2.99**	**3.00**
Max. Deviation	**1.33%**	**1.34%**	**1.00%**
Min. Deviation	**1.33%**	**1.00%**	**0.66%**

Table 13. Hardness Calculation and Results of Compressed Tablets

SAMPLE NO.	SL 301 (Kg/cm^2)	SL 302 (Kg/cm^2)	SL 303(Kg/cm^2)
1	4.56	4.90	4.96
2	4.78	4.89	4.88
3	4.88	4.79	4.56
4	4.76	4.81	4.78
5	4.89	4.88	4.88
6	4.99	4.99	4.76
7	4.98	5.01	4.89
8	4.76	4.87	4.99
9	4.57	4.78	4.88
10	4.82	4.88	4.99
11	4.90	4.76	5.01
11	4.89	4.89	4.87
13	4.79	4.99	4.78
14	4.81	5.01	4.88
15	4.88	4.99	4.76
16	4.99	5.02	4.99
17	5.01	4.98	5.02
18	4.87	4.78	5.01
19	4.97	4.89	4.98
20	4.99	4.88	4.99
Average	**4.85**	**4.90**	**4.90**
Maximum	**3.30%**	**2.45%**	**2.45%**
Minimum	**5.97%**	**2.85%**	**6.93%**

Table 14. Disintegration Time of Compressed Tablet

SAMPLE NO	SL 301 (MIN)	SL 302 (MIN)	SL 303 (MIN)
1	8:13	8:12	8:14
2	8:10	8:10	8:00
3	8:00	8:11	7:54
4	8:09	8:11	7:45
5	8:01	8:00	8:13
6	8:12	7:54	8:11
7	7:48	7:58	7:57
8	8:05	8:09	8:10
9	7:56	8:01	8:04
10	8:10	8:09	8:12
Average	**8.07**	**8:09**	**8:06**
Minimum	**7:48**	**7:54**	**7:45**
Maximum	**8:13**	**8:12**	**8:14**

Table 15. Friability of Compressed Tablet

SAMPLE NO	SL 301 (%)	SL 302 (%)	SL 303 (%)
1	0.37	0.24	0.36
2	0.35	0.12	0.26
3	0.24	0.26	0.27
4	0.35	0.32	0.23
5	0.40	0.33	0.34
6	0.16	0.32	0.16
7	0.24	0.24	0.35
8	0.45	0.42	0.34
9	0.10	0.52	0.18
10	0.34	0.28	0.24
Average	**0.3**	**0.30**	**0.28**
Minimum	**0.10**	**0.12**	**0.16**
Maximum	**0.45**	**0.42**	**0.35**

Table 16. Assay of Compressed Tablet

Batch no.	Sampling points	Standard weight (mg)	Sample weight (mg)	Standard area	Sample area	Assay (%)
SL 301	S1	25.3mg	268.7	107282	104900	102.59%
	S2		270.1		106669	104.21%
	Average					103.41%
SL 302	S1	25.4	267.3	88527	87408	103.54%
	S2		267.0		85108	101.16%
	Average					102.35%
SL 303	S1	25.3	267.6	25.548	25.415	104.85%
	S2		267.7		25.959	107.06%
	Average					105.95%

Table 17. Content Uniformity Test of compressed tablet (SL-301)

Batch no.	Sampling points	Standard weight (mg)	Standard area	Sample area	Assay (%)
SL 301	Sp1	25.3mg	107282	103979	102.14%
	Sp2			97241	95.52%
	Sp3			104814	102.97%
	Sp4			93804	92.15%
	Sp5			105226	103.37%
	Sp6			105235	103.38%
	Sp7			103259	101.44%
	Sp8			106626	104.74%
	Sp9			104062	102.22%
	Sp10			102654	100.840%
	Minimum Deviation				92.15%
	Maximum Deviation				104.74%

Table 18. Content Uniformity Test of Compressed Tablet (SL-302)

Batch no.	Sampling Points	Standard Weight (mg)	Standard Area	Sample area	Assay (%)
SL 302	Sp01	25.4	88527	83690	99.63%
	Sp02			83462	99.36%
	Sp03			79351	94.46%
	Sp04			83810	99.77%
	Sp05			79666	94.84%
	Sp06			86544	103.03%
	Sp07			82473	98.18%
	Sp08			80957	96.38%
	Sp09			8340	99.06%
	Sp10			83249	99.11%
	Minimum Deviation				94.46%
	Maximum Deviation				103.03%

Table 19. Content Uniformity Test of Compressed Tablet (SL-303)

Batch no.	Sampling points	Standard weight (mg)	Standard area	Sample area	Assay (%)
SL 303	Sp01	25.3mg	25.548	24.934	102.85%
	Sp02			25.543	105.37%
	Sp03			24.022	99.09%
	Sp04			24.202	99.84%
	Sp05			24.467	100.93%
	Sp06			24.953	102.93%
	Sp07			24.501	101.07%
	Sp08			24.753	102.11%
	Sp09			25.269	104.24%
	Sp10			24.703	101.90%
	Minimum Deviation				99.09%
	Maximum Deviation				105.37%

CONCLUSION

In this study process validation was executed for the three successive batches of salbutamol 4mg tablet. Different parameters were checked and validated during this research work; dispensing, sifting, mixing, granulation, drying, lubrication, compression, labelling and packaging. The various critical parameters are:

1) Dry mixing
2) Granulation
3) Drying
4) Lubrication
5) Compression

Dry Mixing

Excipients; di calcium phosphate, polyvinyl pyrolidone k30 and MCCP were mixed uniformly in the rapid mixer granulator for about 30 minutes. The mixing of all the ingredients depends upon the speed and time of mixing.

Granulation

The granulating solution was prepared dissolving salbutamol sulphate (API) in sufficient quantity of R.O. water. The granulating solution was mixed with mixture of dry mixing. The mixing of the active ingredient depends upon the proper mixing of drug during mixing.

Drying

Drying of the granules is the important step as moisture in the granules plays a vital role. Presence of excessive moisture results in sticking and poor flow problem whereas presence of less amount of moisture leads to capping, chipping and high friability. The inlet and outlet temperature should be controlled and monitored in FBD.

Lubrication

All the three different batches were blended uniformly in the double cone blender and the samples were collected from the different location of the DCB at different time intervals *i.e.* 10mins, 20mins and 30mins to determine the RSD values and content uniformity of salbutamol sulphate. From the study, the best lubrication time was confirmed to be 30 minutes.

Compression

Sequential in process check was carried out as per in process specification of compressed tablets and the data is recorded in the BMR. The physical parameters, results of dissolution and content uniformity of tablets were found to be within the accepted criteria. The results of three batches were comparable.

Strip packaging

Strip packaging involves the packing of the prepared compressed tablets inside the aluminum foil. Various parameters related to packaging such as speed of the machine, sealing, temperature, pocket formation, knurling and cutting were evaluated.

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