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Process validation of clopidogrel bisulphate 75 mg tablets

L. Jebalsy Lalitha[1], A. Chenthilnathan[1*] and V. Vidyasagar[2]

[1]*Department of Pharmaceutical Chemistry, Manonmaniam Sundaranar University, Tirunelveli –Tamil Nadu, India*
[2]*Surien Pharmaceuticals (P) Ltd., Chennai, Tamil Nadu, India*

ABSTRACT

Validation of the individual steps of the processes is called the process validation. In this study the process validation was carried out for the tablet dosage form which contains Clopidogrel bisulphate 75 mg. In tablet dosage form, critical parameters like dry mixing, drying, lubrication and compression were taken up for validation studies. In -process quality monitoring of all critical processing steps was done for three production batches. Assay after lubrication was within the specified limit, indicating blend uniformity. Physical parameters such as weight variation, Thickness, hardness test, friability, disintegration time and assay were checked and results found within the acceptance criteria. During packing operation, strips were checked and found satisfactory. Thus process validation of Clopidogrel bisulphate 75 mg in tablets was successfully completed and found within the specifications.

Keywords: Process validation, Clopidogrel bisulphate, Tablet, Quality, Process parameters.

INTRODUCTION

As per USFDA, Validation [1-7] is defined as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre- determined specifications and quality characteristics. Process validation is a requirement of the current good manufacturing practices regulation for the finished pharmaceuticals. The different types of process validation, Prospective, Retrospective, Concurrent and Revalidations, which are described below:

***Prospective validation*:** Normally it is undertaken whenever the process for a new formula (or within facility) must be validated before routine pharmaceutical production commences.

Retrospective validation: Achieving validation by documenting all the historical information (e.g., release data) for existing products and using that data to support the position that the process is under control.

Concurrent validation*:* Documenting the evidence that a process does what it purports to do base on information generated during actual implementation of the process.

Revalidation: *Indicates* that the process must be validated once again, may not necessarily mean the original program must be repeated however.

In this study the process validation was carried out for the tablet dosage form which contains Clopidogrel bisulphate 75 mg. The critical parameters like dry mixing, drying, lubrication and compression were taken up for validation studies. In -process quality monitoring of all critical processing steps was done for three production batches. Physical parameters such as weight variation, hardness test and friability, dissolution and assay were checked and results found within the acceptance criteria. During packing operation, blisters were checked and found satisfactory.

MATERIALS AND METHODS

Materials used in the manufacturing of tablets are shown in Table 1 and the equipments and instruments used in the production are mentioned in Table 2 &3 respectively.

Table 1: List of Raw materials and their functions

S.No	Ingredients	Function
1.	Clopidogrel bisulphate	API (Antithrombotic, platelet aggregation inhibitor)
2.	Methyl crystalline cellulose	Binder
3.	Lactose	Diluent
4.	Poly vinyl pyrolidone k-30	Binder
5.	Iso propyl alcohol	Vehicle
6.	Cross carmellulose sodium	Disintegrant
7.	Talc	Lubricant
8.	Sodium starch glycolate	Disintegrant
9.	Aerosil	Glidant

Table 2: List of Equipment and their uses

S.No	Name of Equipment	Uses
1.	Rabid mixer granulator	Dry Mixing
2.	Sifter with SS sieves 16#,40#,60#	Sifting
3.	Balance	Weighing
4.	Fluid bed drier	Drying
5.	Octagonal blender	Blending
6.	Multimill with 1.5mm Screen	Sifting
7.	Jacketed stainless steel kettle for starch paste preparation	Binding
8.	Rotary Tablet Press	Compression

Table 3: List of Instruments and their Uses

S.No	Instrument Name	Uses
1.	Analytical balance	Weighing
2.	Disintegration Test apparatus	Disintegration time
3.	Vernier caliper	Thickness
4.	Tablet friability test apparatus	Friability
5.	Monsanto Hardness Tester	Hardness

EVALUATION OF TABLETS

The critical parameters considered during the process validation of Clopidogrel bisulphate 75 mg in tablets were Dry mixing, Drying, Lubrication Compression, Strip packing, Weight variation, Hardness Test, Thickness, Friability, Disintegration Time and Assay.

Dry Mixing

The dry-mixing step involves mixing of active ingredients with the other additives using Rabid Mixer Granulator (RMG). The content of Clopidogrel bisulphate in the dry mix were tested and also to validate dry mixing time were the critical variables that determine content uniformity. Mixing speed was 5, 10, 15 minutes and the sample were collected at 5 stages Top, Middle left, Middle, Middle right and bottom. In dry mixing stage, 3 batches like I, II, and III were considered for validation.

Fixed Parameters

Time interval studies	:	5, 10, 15 minutes
Measured response uniformity	:	Description, blend uniformity.
Acceptance criteria	:	Not less than 90% & not more than 110% of the Label claim

Drying

The drying step involves drying of wet mass. The level of moisture in the granules is important factor. If level of moisture is more in granules then blend will have poor flow & distribution characteristics. If level of moisture in blend is less it will produce tablet with capping, high friability and chipping problems. During drying the granules which will influence the quality parameter like assay of Clopidogrel bisulphate. Drying of granules in FBD controls the levels of moisture. In drying stage, 3 batches like I, II, and III were considered for validation.

Fixed Parameters

Analysis	:	5, 10, 15 minutes
Acceptance criteria	:	Not less than 90% & not more than 110% of the Label claim

Lubrication

Lubrication is to be carried out as per batch manufacturing record. The samples were collected at various stages at top, middle, and bottom with the mixing speed at 5, 10, and 15 min. Samples were collected at the lubrication stage and carried out the testing of content uniformity Assay, Description,Tapped density, Bulk density etc. In lubrication stage, three batches such as Batch I, II and III were considered for validation.

Compression

This step involves consistent flow of an adequately lubricated, into dies where the granules are being compressed into tablets. Compression is to be carried out as per batch manufacturing record. The samples were collected at the various stages i.e. at start up, high and low RPM speed. Testing were carried out for content uniformity, Appearance, Group weight, Individual weight, Thickness, Hardness, Friability, Disintegration time, Assay, Dissolution. In compression stage, three batches such as Batch I, II and III were considered for validation.

Strip Packing

Packing is to be done as per batch packing record. In packing stage, three batches such as Batch I, II and III were considered for validation.

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

Thickness

Five tablets were randomly selected form each batch and there thickness and diameter was measured by using digital vernier caliper.

Hardness

The crushing strength kg/cm² of prepared tablets was determined for 5 tablets of each batch by using Monosanto tablet hardness tester. The average hardness and standard deviation were determined.

Friability

Five tablets were weighed and placed in the Electro lab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\%F = \{1-(Wt/W)\}\times 100$$

Where
%F= friability in percentage
W= Initial weight of tablet
Wt= Weight of tablets after revolution

Assay [8]

High performance liquid chromatography (HPLC) method used for determination of clopidogrel bisulphate 75 mg in tablets.

Chromatographic Condition

The mobile phase was prepared by mixing solvents, Acetonitrile and Buffer (25:75) v/v ratio. The Buffer consists of 1.36g of mono basic potassium phosphate in 1000 ml of water. The prepared mobile phase was filtered through a Millipore 0.45 µm membrane filter and ultrasonically degassed prior to use. Mobile phase was used as diluent throughout the experiment. The detection wavelength was set at 220 nm. The elution was done at a flow rate of 1.0 ml/min under ambient condition. Twenty µl of this solution was injected in triplicate under the specified conditions. The peak areas obtained were related to slopes and intercepts from the calibration data to calculate concentration of the drugs

Standard Solution
Accurately weighed 75mg of clopidogrel bisulphate and transferred in to a 100 ml of the methanol. 5 ml of the solution was diluted to 50 ml with the methanol and filtered.

Sample preparation
Randomly 20 tablets were selected, weighed and powdered. Accurately weighed a quantity of the powder equivalent to 75mg of clopidogrel bisulphate and it was transferred in to a 100 ml of the methanol. 5 ml of the solution was diluted to 50 ml with the methanol and filtered.

Calulation: The amount of clopidogrel bisulphate present in each tablet was found to be:

$$\% \text{ of assay} = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{5}{50} \times \frac{100}{WT} \times \frac{50}{5} \times \frac{AW}{LC} \times \frac{321.8}{419.9} \times \text{Potency}$$

RESULTS AND DISCUSSION

Dry mixing: The content of clopidogrel bisulphate in the dry mix was tested and also to validate dry mixing time, were the critical variables that determine content uniformity. Mixing speed was 15 minutes and the sample was collected at 5 stages Top, Middle left, Middle, Middle right and bottom. In dry mixing stage, 3 batches like I, II, and III were considered for validation. Dry mixing result of all the batches was well with in the acceptance criteria and shown in Table 4.

Table 4: Result of Dry mixing – Mixing Uniformity

Time	Sample Taken	Content					
		Batch No I		Batch No II		Batch No III	
15 min	Top	98.26	98.43	99.23	98.26	98.43	99.23
	Middle Left	99.88	98.53	99.69	99.88	98.53	99.69
	Middle	99.85	99.45	98.76	99.85	99.45	98.76
	Middle Right	98.54	99.32	98.31	98.54	99.32	98.31
	Bottom	99.51	99.64	99.45	99.51	99.64	99.45
	Maximum	99.88	99.64	99.69	99.88	99.64	99.69
	Minimum	98.26	98.43	98.31	98.26	98.43	98.31
	Mean	99.20	99.07	99.08	99.20	99.07	99.08
	SD	0.758	0.555	0.553	0.758	0.555	0.553
	%RSD	0.764	0.560	0.558	0.764	0.560	0.558

Drying: In drying stage, 3 batches like I, II, and III were considered for validation. Drying of all the batches was with in the acceptance criteria and shown in Table 5.

Table 5: Result of Drying

Sample Taken	Content (%)		
	Batch No		
	I	II	III
Top	98.43%	98.89%	99.77%
Middle	99.63%	99.22%	98.96%
Bottom	99.22%	99.61%	96.80%
Mean	98.96%	99.21%	98.48%
Maximum	99.43%	99.52%	99.87%
Minimum	98.33%	98.89%	96.80%

Table 6: Result of Lubrication

Time Interval	Content of Clopidogrel bisulphate			
	Test	Batch No I	Batch No II	Batch No III
10 min	Description	Doesn't comply	Doesn't comply	Doesn't comply
	Assay	Doesn't comply	Doesn't comply	Doesn't comply
15 min	Description	Doesn't comply	Doesn't comply	Doesn't comply
	Assay	Doesn't comply	Doesn't comply	Doesn't comply
20 min	Description	Complies	Complies	Complies
	Assay	Complies	Complies	Complies

Lubrication: The samples were collected at various stages at top, middle, and bottom with the mixing speed at 10, 15, and 20min. Samples were collected at the lubrication stage and carried out the testing of content uniformity Assay, Description, Tapped density, Bulk density etc. In lubrication stage, three batches such as Batch I, II and III were considered for validation. Lubrication of all the batches was with in the acceptance criteria and shown in Table 6.

Compression : The samples were collected at the various stages i.e. at start up, high and low RPM speed. Testing were carried out for content uniformity, Appearance, Group weight, Individual weight, Thickness, Hardness, Friability, Disintegration time, Assay, Dissolution. In compression stage, three batches such as Batch I, II and III were considered for validation. Compression of all the batches of tablets was with in the acceptance criteria and results were shown in Table 7.

Table 7: Result of Compression

Test	Batch Number		
	Batch No I	**Batch No II**	**Batch No III**
Description	Complies	Complies	Complies
Average Weight(mg)	147.4	148.1	147.8
Uniformity of weight(mg)	Complies	Complies	Complies
Thickness (mm)	3.16	3.11	3.09
Friability (%w/w)	0.07%	0.08%	0.07%
Hardness	3.7	3.9	3.8
Assay	100.39%	101.36%	99.36%
Disintegration Time	10’25’’	10’46’’	9’30’’

Weight variation: Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. Weight variation of all the batches of tablets was with in the acceptance criteria and the results were shown in Table 8.

Table 8: Result of Weight Variation

S.No	Batch No I (mg)	Batch No II (mg)	Batch No III (mg)
1.	152.5	152.4	147.3
2.	150.5	147.8	148.9
3.	145.8	145.3	151.6
4.	146.8	146.9	142.9
5.	145.6	150.3	150.1
6.	148.1	148.3	146.3
7.	150.0	149.2	151.6
8.	145.5	150.5	144.0
9.	147.9	146.8	145.9
10.	146.8	151.8	144.0
11.	148.9	145.9	145.9
12.	146.9	149.2	148.3
13.	144.5	146.8	151.5
14.	145.2	151.5	150.6
15.	142.2	142.5	146.9
16.	148.3	145.2	149.7
17.	150.0	145.7	151.5
18.	147.8	149.9	147.8
19.	145.5	151.5	146.8
20.	148.9	145.5	147.9
Maximum	**142.2**	**142.5**	**142.9**
Minimum	**152.5**	**152.4**	**151.6**
Average	**147.4**	**148.1**	**147.8**

Thickness: Five tablets were randomly selected form each batch and their thickness were measured by using digital vernier caliper. The Thickness of all the batches of tablets was with in the acceptance criteria and the results were shown in Table 9.

Table 9: Result of Thickness

S.No	Thickness(2.9mm-3.5mm) Batch number		
	I	II	III
1.	3.12	3.14	3.09
2.	3.29	3.17	3.15
3.	3.10	3.07	3.08
4.	3.33	3.19	3.15
5.	2.98	3.01	3.00
Average	**3.16**	**3.11**	**3.09**
Maximum	**3.33**	**3.19**	**3.15**
Minimum	**2.98**	**3.01**	**3.00**

Hardness: The crushing strength kg/cm² of prepared tablets was determined for 5 tablets of each batch by using Monosanto tablet hardness tester. The average hardness and standard deviation were determined. The hardness of all the batches of tablets was with in the acceptance criteria and the results were shown in Table 10.

Table 10: Result of Hardness

S.No	Hardness (3.5kg/cm²-10.0 kg/cm²) Batch number		
	I	II	III
1.	3.5	4.2	3.6
2.	3.8	4.0	4.0
3.	4.0	4.1	3.7
4.	3.5	3.5	3.6
5.	3.9	3.9	4.5
Average	**3.7**	**3.9**	**3.8**
Maximum	**4.0**	**6.1**	**4.5**
Minimum	**3.5**	**4.6**	**3.5**

Friability: Five tablets were weighed and placed in the Electro lab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The friability of all the batches of tablets was with in the acceptance criteria and the results were shown in Table 11.

Table 11: Result of Friability

S.No	Friability (Not more than 1%) Batch number		
	I	II	III
1.	0.08	0.07	0.08
2.	0.06	0.08	0.06
3.	0.07	0.09	0.07
4.	0.08	0.07	0.08
5.	0.09	0.08	0.06
Average	**0.07**	**0.08**	**0.07**
Maximum	**0.09**	**0.09**	**0.08**
Minimum	**0.06**	**0.07**	**0.06**

Disintegration Time: Five tablets were randomly selected form each batch and their disintegration time were determined by using Tablet Disintegration Test apparatus. The disintegration time of all the batches of tablets was with in the acceptance criteria and the results were shown in Table 12.

Table 12: Result of Disintegration Time

S.No	Disintegration Time (Not more than 15 min) Batch number		
	I	II	III
1.	9’44"	9’55”	10’55”
2.	10’15”	9’50”	10’15”
3.	9’20”	10’10”	9’34”
4.	10’30”	9’20”	10’35”
5.	10’25”	10’46”	9’30”
Average	**9’44"**	**9’55”**	**10’55”**
Maximum	**10’15”**	**9’50”**	**10’15”**
Minimum	**9’20”**	**10’10”**	**9’34”**

Assay:
High performance liquid chromatography (HPLC) method used for determination of clopidogrel bisulphate 75 mg in tablets. The assay of all the batches was with in the acceptance criteria and shown in Table 13.

Table 13: Results of HPLC assay

Clopidogrel bisulphate		
Amt. claimed (mg/tablet)	**Amt. found mg/tablet)**	**% Purity**
75	75.29	100.39
	76.02	101.36
	74.52	99.36
Mean	75.27	100.37
SD	0.750	1.000
RSD	0.996	0.996

CONCLUSION

Based on the results obtained, it was concluded that three validation batches of Tablets containing Clopidogrel bisulphate 75 mg, comply with the approved In-process and finished specifications defined for the product. The overall review of results shows consistency and reproducibility within and between batches. These results demonstrate that the manufacturing process was under control throughout all stages, within and between batches. Hence it was concluded that the manufacturing process and the equipments adopted were robust enough and produce product meeting predetermined standards and quality attributes. Therefore the Process stands Validated.

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