ISSN: 2347-4742

Research Article
Journal of Pharmaceutical and Biomedical Analysis Letters
www.pharmaresearchlibrary.com/jpbmal

Process Validation of Aspirin 75 mg Tablets

C. Iniya [1], A. Chenthilnathan[1*] and V. Vidyasagar[2]

[1]*Department of Pharmaceutical Chemistry, Manonmaniam Sundaranar University, Tirunelveli–627 012, Tamil Nadu, India.*
[2]*Surien Pharmaceuticals (P) Ltd., Chennai–600 122, Tamil Nadu, India.*
Received: 8 May 2014, Accepted: 29 June 2014, Published Online: 18 June2014

Abstract
Process validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of required quality. In this study, the process validation was carried out for the coated tablet dosage form which contains aspirin 75 mg. In tablet dosage form, critical parameters like 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, friability, disintegration time and assay were checked and results found within the acceptance criteria. During packing operation, blisters were checked and found satisfactory. Thus process validation of aspirin 75 mg in tablets was successfully completed and found within the specifications.
Keywords Aspirin, Process validation, Coated tablet, Process parameters.

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***Corresponding author**
A. Chenthilnathan
Department of Pharmaceutical Chemistry
Manonmaniam Sundaranar University,
Tirunelveli–627 012, Tamil Nadu, India.
Manuscript ID: JPBMAL2111

PAPER-QR CODE

1. Introduction
Validation is a fundamental segment that supports to a commitment of company towards quality assurance and also assures that product meets its predetermined quality specification and quality characteristics. Validation of individual step of manufacturing is called as process validation. 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 process validation is of four types:

Prospective validation:
In prospective validation the validation protocol is executed before the process is put into the commercial use. During the product development stage the production process should be broken down into individual steps. Each step should be evaluated on the basis of Experience or theoretical considerations to determine the critical parameters that may affect the quality of finished product.

Retrospective validation:
In this historic data is taken from the records of the completed production batches are used to provide the documented evidence that the process has been in state of control prior to the request for such evidence.

Concurrent validation:
It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public as its market price. This validation involves in process monitoring of critical processing steps and product testing which helps to generate documented evidence to show that production process is in a state of control.

Revalidation:
It is the repetition of validation process or part of it. This is carried out when there is any change or replacement in formulation, equipment plan or site location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes. In this study the process validation was carried out for the coated tablet dosage form which contains aspirin 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, friability, disintegration and assay were checked and results found within the acceptance criteria. During packing operation, blisters were also checked and found satisfactory.

2. 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.	Aspirin	API (Analgesic, Anti inflammatory and Anti platelet aggregator)
2.	Methyl cellulose powder	Polymer
3.	Starch	Binder
4.	Hydroxy propyl cellulose	Polymer
5.	Ethyl cellulose	Binder
6.	Purified water	Vehicle
7.	Stearic acid	Lubricant
8.	Talc	Glidant
9.	Iso propyl alcohol	Coating solvent
10.	Titanium dioxide	Pigment for coating
11.	Sunset yellow	Colourant

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.	Fluid bed drier	Drying
4.	Octagonal blender	Blending
5.	Multimill with 1.5mm Screen	Sifting
6.	Jacketed stainless steel kettle for starch paste preparation	Binding
7.	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

Evaluation of Tablets

The critical parameters considered during the process validation of Aspirin 75 mg in coated tablets were Drying, Lubrication Compression, Blister packing, Weight variation, Thickness, Friability, Disintegration Time and Assay.

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 Aspirin. 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.

Blister 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 from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

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

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 aspirin 75 mg in tablets.

Chromatographic Condition: The mobile phase was prepared by mixing solvents, Acetonitrile and Buffer (80:20) v/v ratio. The Buffer consists of potassium dihyrogen orthophosphate and ortho phosphoric acid. 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 260 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 preparation: Accurately weighed about 75mg of aspirin and transferred in to a 100 ml volumetric flask. 40ml of the diluent was added. Sonication was made for dissolving the drug substance by sonicator. Finally it was made up with diluent and mixed well.

Sample preparation

Randomly 20 tablets were selected, weighed and powdered. Accurately weighed a quantity of the powder equivalent to 75mg of aspirin and it was transferred in to a 200 ml volumetric flask. 140ml of diluent was added and sonicated for 1 hour with intermittent shaking, cool and make up the volume up to the mark with diluent and mixed well. The resulting solution was filtered through 0.45µ nylon filter. 5 ml of the solution was diluted to 25ml.

Calculation

The amount of aspirin present in each tablet was found to be:

$$\%\ \text{of assay} = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{200}{WT} \times \frac{25}{5} \times \frac{AW}{LC} \times \text{Potency}$$

3. Results and Discussion

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

Table 5. Result of Drying

Sample Taken	Content (%)		
	Batch No		
	I	II	III
Top	98.33%	98.89%	99.87%
Middle	99.43%	99.52%	98.76%
Bottom	99.12%	99.21%	96.80%
Mean	98.96%	99.21%	98.48%
Maximum	99.43%	99.52%	99.87%
Minimum	98.33%	98.89%	96.80%

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 within the acceptance criteria and shown in Table 6.

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

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 within 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)	109.0	108.9	109.1
Uniformity of weight(mg)	Complies	Complies	Complies
Thickness (mm)	3.02	3.13	3.17
Friability (%w/w)	0.08	0.07	0.09
Assay	99.88	97.89	98.78
Disintegration Time	4'44''	4'56''	4'67''

Weight variation:

Twenty tablets were randomly selected from 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 within 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.	105.4	108.4	109.8
2.	111.8	109.8	104.6
3.	107.1	105.8	106.5
4.	109.7	107.9	107.9
5.	110.3	111.2	109.8

6.	108.8	106.7	112.6
7.	109.0	108.9	110.3
8.	105.6	107.5	113.7
9.	108.1	108.2	106.5
10.	108.5	109.7	108.2
11.	108.3	107.6	109.8
12.	107.6	112.6	107.2
13.	111.9	103.5	115.2
14.	110.3	109.2	113.7
15.	109.2	110.2	107.2
16.	111.3	108.2	110.1
17.	109.0	110.5	109.3
18.	107.2	109.8	107.8
19.	109.2	106.5	106.9
20.	111.2	106.9	105.8
Maximum	**111.9**	**113.5**	**115.2**
Minimum	**105.4**	**105.8**	**104.6**
Average	**109.0**	**108.9**	**109.1**

Thickness:

Five tablets were randomly selected from each batch and their thickness were measured by using digital vernier caliper. The Thickness of all the batches of tablets was within 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.	2.98	3.12	2.95
2.	3.12	2.98	3.30
3.	2.91	3.00	3.15
4.	2.99	3.13	2.99
5.	3.10	3.45	3.47
Average	**3.02**	**3.13**	**3.17**
Maximum	**3.12**	**3.45**	**3.47**
Minimum	**2.91**	**2.98**	**2.95**

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 10.

Table 10. 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 from each batch and their disintegration time were determined by using Tablet Disintegration Test apparatus. The disintegration time of all the batches of tablets was within the acceptance criteria and the results were shown in Table 11.

Table 11. Result of Disintegration Time

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

Assay:

High performance liquid chromatography (HPLC) method used for determination of aspirin 75 mg in tablets. The assay of all the batches was within the acceptance criteria and shown in Table 12.

Table 12. Results of HPLC assay

Aspirin		
Amt. claimed (mg/tablet)	**Amt. found mg/tablet)**	**%Purity**
75	76.27	101.69
	74.68	99.57
	74.88	99.88
Mean	**75.27**	**100.38**
SD	**0.70**	**1.14**
RSD	**0.93**	**1.13**

4. Conclusion

Based on the results obtained, it was concluded that three validation batches of Tablets containing Aspirin 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.

5. Acknowledgements

The authors are thankful to the management of Surien Pharmaceuticals (P) Ltd., Chennai – 122, Tamil Nadu, India for providing the necessary facilities to carry out for the research work.

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