Research Article

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PROCESS VALIDATION OF DICLOFENAC SODIUM, PARACETAMOL AND CHLORZOXAZONE TABLETS

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Abstract

Validation is a tool of quality assurance which provides confirmation of the quality in equipment systems, manufacturing processes, software and testing methods. Validation of the individual steps of the processes is called the process validation. In this study the process validation was carried out for the combined tablet dosage form which contains Diclofenac sodium 50mg, Paracetamol 325 mg and Chlorzoxazone 250 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, hardness test and friability and assay were checked and results found within the acceptance criteria. During packing operation, blisters were checked and found satisfactory. Thus process validation of Diclofenac sodium 50mg, Paracetamol 325 mg and Chlorzoxazone 250 mg in combined solid dosage form was successfully completed and found within the specifications.

Keywords: Process validation, Diclofenac sodium, Paracetamol, Chlorzoxazone, Tablet dosage form.

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. Validation is also be defined as documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results as per WHO guidelines. Process validation is a requirement of the current good manufacturing practices regulation for the finished pharmaceuticals. The different types of process validation 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.

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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 combined tablet dosage form which contains Diclofenac sodium 50mg, Paracetamol 325 mg and Chlorzoxazone 250 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, 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 No. 01: List of raw materials and their functions

S.No	Ingredients	Function
1.	Paracetomol	API (Antipyretic, Analgesic & Anti inflammatory)
2.	Starch	Binder
3.	Chlorzoxazone	API (Muscle relaxant)
4.	Starch (P)	Binder/Diluent
5.	Citric acid	Buffer
6.	Methyl paraben sodium	Anti microbial Preservative
7.	Propyl paraben sodium	Anti microbial Preservative
8.	Sunset yellow (S)	Colourant
9.	Purified Water	Vehicle
10.	Diclofenac sodium	API (Analgesic & Anti inflammatory)
11.	Cellulose acetate phthalate	Polymer
12.	Talc	Glidant
13.	Magnesium sterate	Lubricant
14.	Sodium lauryl sulphate	Surfactant

Table No. 02: 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 No. 03: 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 Diclofenac sodium 50mg, Paracetamol 325 mg and Chlorzoxazone 250 mg in tablets were Dry mixing, Drying, Lubrication Compression, Blister 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 Paracetamol, Chlorzoxazone 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 parameters like Assay of paracetamol and chlorzoxazone. 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 form 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.

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 simultaneous determination of diclofenac sodium, paracetamol and chlorzoxazone and in tablets.

Chromatographic Condition

The mobile phase was prepared by mixing solvents, Methanol and Buffer (70:30) v/v ratio. The Buffer consists of equal volume of 0.01 (M) ortho Phosphoric Acid and 0.01 (M) Monobasic Sodium Phosphate, pH adjusted to (2.5±0.2) with orthophosphoric acid. The prepared mobile phase was filtered through a Millipore 0.45 µm membrane filter and ultrasonically degassed prior to use. Methanol and Water in the ratio of 70:30 (v/v) was used as diluent throughout the experiment. The detection wavelength was set at 254 nm. The elution was done at a flow rate of 1.0 ml/min under ambient condition.

Standard Solution

A standard stock solution of Paracetamol (1000 mcg/ml), Diclofenac sodium (120 mcg/ml) and Chlorzoxazone (1000 mcg/ml) were prepared in diluent. Subsequent dilutions were made in diluent to prepare the concentrations 40,42,44,46,48 and 50 mcg/ml for Paracetamol; 10,12,14,16,18 and 20 mcg/ml for Diclofenac sodium and 45,48,51,54,57 and 60 mcg/ml for Chlorzoxazone. The calibration curve was done by plotting peak area against sample concentration for each ingredient.

Procedure

Twenty tablets were finely powdered and weighed accurately in the electronic balance (model Metler Toledo AG285). The powder equivalent to 325 mg of paracetamol, 250 mg of chlorozoxazone and 50 mg of diclofenac sodium was weighed accurately and dissolved in 250 ml methanol (HPLC Grade). The solution was filtered through 0.45 µm Millex-HV syringe driven membrane filter unit. Further appropriate dilutions have been made to get concentration of 50µg/ml of paracetamol, 60 µg/ml of chlorzoxazone, 20-µg/ ml of diclofenac sodium. 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

Results and discussion

Dry mixing: The content of Paracetamol (Para), Chlorzoxazone (Chlor) 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. Dry mixing result of all the batches was well within the acceptance criteria and shown in Table 4.

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.

Lubrication: 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. Lubrication of all the batches was within 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 No. 04: Result of dry mixing – mixing uniformity

Time	Sample Taken	Content					
		Batch No I		Batch No I		Batch No I	
		Para	Chlor	Para	Chlor	Para	Chlor
5 min	Top	115.87	114.26	111.35	132.43	125.65	124.35
	Middle Left	110.91	122.20	126.34	124.67	124.56	136.76
	Middle	112.85	135.46	78.90	67.89	132.78	123.87
	Middle Right	80.85	76.20	89.76	89.70	86.56	76.86
	Bottom	116.75	127.30	134.23	123.45	56.78	89.54
	Maximum	116.75	135.46	134.23	132.43	132.78	136.76
	Minimum	80.85	76.20	78.90	67.89	56.78	56.78
	Mean	107.45	115.08	108.12	107.63	105.27	110.24
	SD	0.15	0.23	0.24	0.28	0.32	0.26
	%RSD	14.0	20.0	21.8	25.7	30.0	23.3
10 min	Top	137.88	126.26	112.23	123.43	125.65	134.23
	Middle Left	126.65	142.40	134.54	135.67	154.56	136.89
	Middle	77.85	75.56	79.90	67.90	142.78	153.97
	Middle Right	135.85	145.30	65.76	89.65	86.65	76.56
	Bottom	154.75	134.30	124.23	146.45	66.80	85.65
	Maximum	154.75	75.56	134.54	146.45	154.56	153.97
	Minimum	77.85	145.30	65.76	67.90	66.80	76.56
	Mean	126.60	124.76	103.33	112.62	115.29	117.46
	SD	0.29	0.28	0.29	0.33	0.37	0.34
	%RSD	22.9	22.8	28.4	29.2	32.4	29.1
15 min	Top	99.88	98.26	96.45	99.80	97.65	99.78
	Middle Left	99.91	99.20	95.67	96.34	97.89	99.66
	Middle	99.85	98.46	98.90	97.80	97.90	99.87
	Middle Right	98.85	96.20	99.80	96.78	96.75	98.76
	Bottom	98.75	97.30	99.78	94.56	97.67	98.67
	Maximum	99.91	99.20	99.80	99.80	97.90	99.87
	Minimum	98.75	96.20	95.67	94.56	96.75	98.67
	Mean	99.45	97.88	98.12	97.06	97.57	99.35
	SD	0.005	0.01	0.01	0.01	0.004	0.005
	%RSD	0.59	1.18	1.97	1.98	0.48	0.58

Table No. 05: Result of drying

Sample Taken	Content (%)					
	Batch No I		Batch No I		Batch No I	
	Para	Chlor	Para	Chlor	Para	Chlor
Top	98.33	98.89	99.87	98.86	98.16	98.76
Middle	99.43	99.52	98.76	99.67	95.78	97.56
Bottom	99.12	99.21	96.80	97.65	96.76	98.67
Mean	98.96	99.21	98.48	98.73	96.90	98.33
Maximum	99.43	99.52	99.87	99.67	98.16	98.16
Minimum	98.33	98.89	96.80	97.65	95.78	97.56

Table No. 06: Result of lubrication

Time Interval	Content of Paracetamol,Chlorzoxazone, Diclofenac sodium			
	Test	Batch No I	Batch No II	Batch No III
10 min	Description	Complies	Complies	Complies
	Assay	Complies	Complies	Complies
15 min	Description	Complies	Complies	Complies
	Assay	Complies	Complies	Complies
20 min	Description	Complies	Complies	Complies
	Assay	Complies	Complies	Complies

Table No. 07: Result of compression

Test	Batch Number		
	Batch No I	**Batch No II**	**Batch No III**
Description	Complies	Complies	Complies
Average Weight(mg)	918.4	918.9	918.5
Uniformity of weight(mg)	Complies	Complies	Complies
Thickness (mm)	5.98	5.84	5.75
Friability (%w/w)	0.08%	0.07%	0.09%
Hardness	6.06	6.05	7.08
Assay	Complies	Complies	Complies
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 No. 08: Result of weight variation

S.No	Batch No I (mg)	Batch No II (mg)	Batch No III (mg)
1.	916.3	914.3	917.3
2.	918.9	908.9	928.9
3.	901.6	901.6	911.6
4.	922.6	912.4	922.9
5.	919.1	919.7	920.1
6.	906.3	916.3	906.3
7.	911.6	910.6	921.6
8.	922.0	892.0	924.0
9.	925.5	925.5	925.9
10.	914.9	916.0	914.0
11.	905.2	905.9	915.2
12.	939.2	929.2	920.2
13.	926.3	926.8	926.9
14.	931.5	921.5	921.5
15.	912.5	922.5	911.5
16.	898.2	895.2	898.8
17.	935.7	915.7	915.9
18.	919.9	909.9	929.9
19.	921.2	921.5	901.2
20.	918.5	919.5	919.9
Maximum	939.2	929.2	929.9
Minimum	898.2	892.0	898.8
Average	918.4	915.6	917.6

Thickness: Five tablets were randomly selected from each batch and their thickness was 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 No. 09: Result of thickness

S.No	Thickness (5.7mm-6.5mm)		
	Batch number		
	I	**II**	**III**
1.	5.8	6.5	5.8
2.	5.9	6.4	5.7
3.	6.1	5.7	5.8
4.	6.3	5.9	6.1
5.	5.8	6.1	6.0
Average	5.98	6.12	5.88
Maximum	6.3	6.5	6.1
Minimum	5.8	5.7	5.7

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 within the acceptance criteria and the results were shown in Table 10.

Table No. 10: Result of hardness

S.No	Hardness (4.0kg/cm²-10.0 kg/cm²)		
	Batch number		
	I	II	III
1.	4.5	4.6	7.6
2.	5.8	5.0	5.0
3.	6.0	6.1	4.5
4.	7.5	5.5	5.5
5.	6.5	6.0	6.5
Average	6.6	5.44	5.82
Maximum	7.5	6.1	7.6
Minimum	4.5	4.6	4.5

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 within the acceptance criteria and the results were shown in Table 11.

Table No. 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 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 12.

Table No. 12: 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	5’ 27”	5’ 10”	5’ 24”
Maximum	5’20”	5’10”	5’55”
Minimum	4’25”	4’10”	4’15”

Assay: The powder equivalent to 325 mg of Paracetamol, 250 mg of Chlorozoxazone and 50 mg of Diclofenac sodium was weighed accurately and dissolved in 250 ml methanol (HPLC Grade). The solution was filtered through 0.45 µm Millex-HV syringe driven membrane filter unit. Further appropriate dilutions have been made to get concentration of 50µg/ml of Paracetamol, 60 µg/ml of Chlorzoxazone, 20-µg/ ml of Diclofenac sodium. Twenty µl of this solution was injected in triplicate under the specified conditions. The assay of all the batches was within the acceptance criteria and shown in Table 13.

Table No. 13: Results of HPLC assay

Diclofenac sodium		Paracetamol		Chlorzoxazone	
Amt. claimed (mg/tablet)	**Amt. found (mg/tablet)**	**Amt. claimed (mg/tablet)**	**Amt. found (mg/tablet)**	**Amt. claimed (mg/tablet)**	**Amt. found (mg/tablet)**
	49.54		324.52		249.50
	48.54		325.12		249.85
50	49.52	325	324.25	250	249.55
	50.20		325.14		250.10
	50.10		324.89		248.95
Mean	**49.58**	**Mean**	**324.78**	**Mean**	**249.59**
SD	**0.59**	**SD**	**0.34**	**SD**	**0.38**
RSD	**1.33**	**RSD**	**0.12**	**RSD**	**0.17**

Conclusion

Based on the results obtained, it was concluded that three validation batches of Tablets containing Diclofenac sodium 50mg, Paracetamol 325 mg and Chlorzoxazone 250 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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