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STUDIES IN PROSPECTIVE PROCESS VALIDATION OF FORMULATED DICLOFENAC SODIUM BILAYER TABLET

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ABSTRACT

The purpose of research was to study prospective process validation Diclofenac Sodium Bilayer tablet (100mg). Tablet contains two layers fast disintegrating release layer and sustained release layer. The critical process parameter for individual layer was identified with the help of process capability and evaluated by challenging its lower & upper release specification. Three initial process validation batches (PVB1, PVB2, PVB3) of same size, method, equipment & validation criteria were taken. The critical parameter involved in fast disintegrating layer like sifting, dry mixing, drying, sizing & compression stages were identified and evaluated as per validation master plan. The critical parameter involved in sustained release layer like sifting, dry mixing, preparation of granulating agent, wet mixing, wet milling, drying, sizing, lubrication & compression stages were identified and evaluated as per validation master plan. The outcome indicated that this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes.

KEYWORDS : *Diclofenac Sodium, Prospective process validation, Bilayer tablet.*

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INTRODUCTION

Diclofenac sodium delayed-release tablets are indicated for relief of signs and symptoms of osteoarthritis, relief of signs and symptoms of rheumatoid arthritis, acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis. The mechanism of action of Diclofenac Sodium may be related to prostaglandin synthetase inhibition. So for quick & long time relief of pain it is necessary to maintain level of diclofenac sodium in blood stream. So, by this novel bi layer formulation, diclofenac sodium level in blood is maintained & patient can get relief from pain for longer time. So, it is necessary that formulated Diclofenac Sodium tablet produces with its predetermined specifications and quality attributes.

As per the ICH guidelines defines as Process validation: ‘ 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'[1].

Quality cannot be adequately assured by in-process and finished inspections and testing but it should be built in to the manufacturing process. These processes should be controlled in order that the finished product meets all quality specifications. The quality system regulation defines process validation by establishing evidence that a process consistently produces a result or product meeting its predetermined specifications. The goal of quality system is to consistently produce products that are suitable for their intended use. In this study prospective process validation was carried out for one product. In tablet dosage form, critical parameters like dry mixing, lubrication, drying, granulation, compression were taken up for validation studies[1].

MATERIALS:

Diclofenac sodium obtained as a gift sample Centurion Laboratories, Vadodara. PVP K-30 & all other materials are obtained through commercial sources.

INSTRUMENTATION:

A UV visible spectrophotometer (Shimadzu 1800) with spectral bandwidth 1nm was employed for all spectroscopic measurements, using a pair of 10 mm matched quartz cells. Electro Lab ED-2L Disintegration tester, Shimadzu AUX 220 weighing balance, Electro Lab EF-2 friabilator, PLC dissolution rate test apparatus, Yorco PDA-65 hot air oven, Lab Press tablet compression machine, Monsanto tester, V-cone mixer.

METHODOLOGY:

Formula:[2-5]

Table 1-For matrix tablet:

Sr.no	Ingredients	Quantity given (mg/tablet)
1	Diclofenac Sodium	75
2	HPMC	150
3	Sodium CMC	22
4	Talc	1
5	Magnesium Stearate	2
6	PVP K30	50
7	Alcohol	q.s.

Table 2-For Fast Disintegrating Tablet:

Sr.no	Ingredients	Quantity given (mg/tablet)
1	Diclofenac Sodium	25
2	MCC	68
3	Crospovidone	2
4	Sodium Saccharine	2
5	Talc	1
6	Magnesium Stearate	2

Procedure:[6-14]

For matrix tablet:

Tablets were prepared by Wet Granulation method. Diclofenac Sodium, HPMC, sodium CMC & PVP K30 were weighed accurately & mixed homogeneously. Required quantity of alcohol drop wise incorporated to the blend. Wet granules were passed through sieve # 10 & air dried for 15 minutes. The dried granules were then passed through sieve # 22 & # 44, where the granules were retained on 44 mesh & fines were passed through # 44. Retained granules were weighed. Fines of 10% were incorporated to retained granules. Required quantity of magnesium stearate

& talc were added to the granules, mixed for five minutes & the blend was compressed using 9 mm flat punch to an average weight of 300 mg.

For Fast disintegrating tablet:

Fast disintegrating tablets of Diclofenac Sodium were prepared by direct compression method. All the excipients without magnesium stearate and talc were mixed uniformly followed by addition of magnesium stearate and talc.

Table 3-Critical Processing Steps:[15]

Fast disintegrating layer	Sustained release layer(matrix layer)
Dry mixing Sizing Compression stage	Dry Mixing Lubrication Drying Sizing Compression Stage

Table 4-Equipment used during manufacture:

Processing Stage	Processing Equipments
Weighing	AUX 220 weighing balance
Mixing	V-cone mixer
Drying	Yorco PDA-65 hot air oven
Sizing	Mechanical shaker
Compression Stage	Lab Press tablet compression machine
Friability testing	Electro Lab EF-2 friabilator
Disintegrating testing	Electro Lab ED-2L Disintegration tester
Dissolution testing	PLC dissolution rate test apparatus
Hardness testing	Monsanto tester

Process validation parameter:[15-17]

Dry Mixing:

The dry-mixing step involves mixing of active ingredients with other additives using V-cone blender. The content of Diclofenac Sodium in the dry mix shall be tested, to validate dry mixing process. Mixing speed and mixing time are the critical variables that determine content uniformity. Mixing speed is kept constant, mixing time shall be studied to validate dry mixing step. In dry mixing stage 3 batches like PVB 1, PVB 2 and PVB 3 are considered for validation. Each side sampled from top, middle, bottom layer of mixer in polyethylene bag for QC analysis of assay. Dry mixing results of all the batches should be within the acceptance criteria.

Drying of granules:

Drying of wet granules for 4 to 6 hours at 55-65°C temperature till the loss on drying is NMT 2% w/w at 105°C. (Outlet temperature would be approx.30ºC to 40°C). 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 desired LOD will be maintained in the granules which will influence the quality parameters like tablet hardness, flow properties, physical properties during compression. Drying of granules in Tray dryer controls the level of moisture. Inlet temperature of is most critical variable for the same. LOD is checked at regular interval to establish the correlation with outlet temperature. In dry stage of different time interval of each batch should be considered for validation. After mixing completed of above material take 5 gm sample material from three sides (starting from left corner,

centre, and right corner). Drying results of the batches are well within the acceptance criteria.
Acceptance criteria: NLT 2% w/w.

Lubrication:

This step involves mixing of Lubricating agent with drug granules & other blending material. The purpose of blending is to get a uniform distribution of granules and lubricating agent. This is followed by mixing of the granules with lubricant to get good flow and anti-adhesion property of the blend. Mixing speed and time are critical variables in this process. Mixing speed is kept constant & mixing time of blender should be studied for validate blending process. Mixing time is critical since under mixing would result in non-uniform distribution of drug and poor flow whereas over mixing will result affect the uniformity of mixing and leads to non-uniform distribution of drug. So, a flow property of powder is checked.

Compression of Batches:

Tablets were compressed using FB round Punch, having break line on Upper punch & lower Punches plain. Each 400 mg tablet contains 100 mg Diclofenac Sodium. The specification for tablet was average weight 400 mg(±5%) , hardness NLT 3 kg/cm2, thickness 3.80 mm(±0.3mm), friability NMT 1%w/w, DT NMT 15 Min, Assay 100% (± 5%), Dissolution NLT 50% of stated amount released in 6 hr.

Weight Variation:

Twenty tablets were randomly selected from each batch and individually weighed. 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 5%.

Thickness & Diameter:

Twenty tablets were randomly selected from each batch and there thickness and diameter was measured by using digital vernier calliper.

Hardness:

The crushing strength Kg/cm^2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto hardness tester. The average hardness and standard deviation was determined.

Friability:

Twenty tablets were weighed and placed in the Electro lab friabilator and apparatus was rotated at 100 rpm. After revolutions the tablets were deducted and weighed again.

The percentage friability was measured using the formula,

% F = {1-(Wt/W)} ×100

Where, % F = friability in percentage

W = Initial weight of tablet

Wt = weight of tablets after revolution.

Drug content:

Diclofenac Sodium was estimated by using U.V. Spectrophotometer at 267 nm formulation Samples was Subjected to U.V spectroscopy. Quantity equivalent to 300 mg of Diclofenac Sodium was taken for assay. Dissolved this in 70ml phosphate buffer pH 6.8, sonicated & made volume 100ml, filtered it and from filtrate pipette out 10ml and diluted to 100ml with phosphate buffer pH 6.8, again pipette out 10ml and diluted it 100ml with phosphate buffer pH 6.8 and record absorbance (final concentration of solution-30 µg/ml).

In-vitro disintegration studies:

It was carried out using Electro Lab ED-2L Disintegration tester using 0.1n HCl as disintegrating medium, at 37±0.5^{o}C.

In-Vitro Dissolution Studies:

In Vitro dissolution study was carried out using USP II apparatus (paddle apparatus) in 900 ml of phosphate buffer pH6.8 for 6 hrs. The temperature of the dissolution medium was kept at 37± 0.5oC and the basket was set at 50 rpm. 10 ml of sample solution was withdrawn at specified interval of time and filtered through Whatmann filter paper. The absorbance of the withdrawn samples was measured at 267 nm using UV visible spectrophotometer.

RESULTS:

All the results are tabulated in Table 5-10.

Table 5-Dry mixing process results

Layer	Fast disintegrating layer	Matrix layer

	PVB1	PVB2	PVB3	PVB1	PVB2	PVB3
Assay result after mixing	96.89	99.78	99.56	98.85	102.30	100.12
	98.89	98.94	98.54	97.87	102.13	102.13
	102.30	100.12	98.94	100.12	97.87	96.89
	99.56	97.89	98.85	99.13	100.12	98.89
	98.54	97.9	98.89	100.14	99.67	97.87
	97.87	99.13	101.15	102.13	98.89	100.12
	100.12	100.14	102.30	100.12	101.15	101.15
	101.15	102.13	99.13	99.92	102.30	100.12
	99.92	98.85	100.14	99.13	99.13	96.89
% RSD	1.6539	1.3120	1.2599	1.1842	1.6462	1.8457

Table 6-Drying stage result (matrix layer)

Loss on drying(%w/w)									
Time	After 4 hr			After 5 hr			After 6 hr		
Layer	T	M	B	T	M	B	T	M	B
PVB1	2.50	2.35	2.45	2.60	2.47	2.52	2.78	2.56	2.62
PVB2	2.46	2.43	2.41	2.64	2.52	2.57	2.68	2.58	2.65
PVB3	2.58	2.42	2.48	2.67	2.57	2.62	2.52	2.56	2.76

Table 7-Illustrated the Result of the Compression Process

Parameter	Level	PVB 1	PVB 2	PVB 3	Specification
Appearance		OK	OK	OK	Round shape, plain on both side
Weight variation	Minimum	397	398	398	Select 20 tablets at random, weigh each one individually and obtain an average weight. Not more than two of the individual weights deviate from the average weight by more than ± 5%
	Maximum	404	403	404	
	Average	400.3	400.45	401.15	
Diameter (mm)	Minimum	8.5	8.6	8.7	8.5 mm to 9.0 mm
	Maximum	9.0	8.9	9.0	
	Average	8.8	8.7	8.8	
Thickmess (mm)	Minimum	4.03	4.05	4.03	3.70 mm to 4.50 mm
	Maximum	4.30	4.50	4.40	
	Average	3.80	3.80	3.70	
Hardness(kg/cm^2)	Minimum	4.8	4.7	5.9	Not less than 3 kg/cm2
	Maximum	5.6	5.7	4.7	
	Average	5.11	5.06	5.14	
Disintegration time(min)	Minimum	3	4	5	Not more than 15 minutes
	Maximum	7	9	8	
	Average	5.4	6.2	6.4	
Friability(%w/w)	Minimum	0.49	0.45	0.56	Not more than 1.0 % w/w.
	Maximum	0.89	0.79	0.78	
	Average	0.74	0.65	0.68	
Drug content (%w/w)	Minimum	98.39	98.39	98.39	95.00% to 105.00 %
	Maximum	98.02	98.02	98.02	
	Average	98.39	98.39	98.39	

% Dissolution (after 6 hr)	Minimum	65.89	68.92	66.70	Not less than 50 % of the labeled amount(after 6 hr)
	Maximum	72.34	75.05	76.35	
	Average	69.22	71.22	68.59	

Table 8-Flow properties of powder/granules

Type of layer	Batch no.	Angle of repose	Bulk density(gm/ml)	Tap density(gm/ml)	Hausner's ratio	Carr's index
For matrix tablet(granules)	1	22.61	0.46	0.54	1.17	14.81
	2	21.89	0.54	0.52	1.13	13.97
	3	22.32	0.58	0.53	1.15	13.67
For fast disintegrating tablet(powder)	1	21.80	0.48	0.53	1.10	9.43
	2	21.99	0.56	0.51	1.13	8.99
	3	22.80	0.49	0.56	1.11	9.60

Table 9-sizing stage result

Batch	% fine (fast disintegrating layer powder)	% fine(matrix tablet layer granules)
PVB1	65	54
PVB2	72	48
PVB3	61	52

Table 10-overall summary of tablet prospective validation

Validation Parameter	Validation standards	Inference
Flow properties a. Angle of repose b. Hausner's ratio	Less than 25 which indicates good flow Less than 1.25 which indicates good flow	Comply to Validation standard
Dry mixing	NMT 6% RSD	Comply to Validation standard
Drying	NLT 2%	Comply to Validation standard
Sizing	% fine should be NLT 40	Comply to Validation standard
Weight variation	Should not deviate more than 5%	Comply to Validation standard
Friability	Less than 1%	Comply to Validation standard
Hardness	Greater than 4%	Comply to Validation standard
Drug content	Should be in between 95-105% w/w of diclofenac sodium	Comply to Validation standard
In vitro disintegration	NMT 15 min	Comply to Validation standard
In vitro dissolution	NLT 50% after 6 hr	Comply to Validation standard

CONCLUSION:

From results PVBs at each of the stages for the specified parameters it is summarized and concluded that with the prospective process validation for the Diclofenac Sodium 100 mg bilayer tablet produces the batches with no significant deviation and reported documented evidence, that process can be effectively produce a product which complies with the present specification & reproducible quality standards.

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