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Research Paper

Process Validation of Clopidogrel Bisulphate USP Tablet

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Drugs are significant elements for human health. They must be manufactured to the maximum quality levels. Validation is best viewed as an impartment and integral part of cGMP. It is an important step in achieving and maintaining the quality of the final product. If each step of production process is validated we can assure that the final product is of the best quality. Validation of product should be performed as per guideline. In this study the concurrent process validation of Clopidogrel Bisulphate USP 75mg tablet was performed. It gives detail about the validation of each step of the manufacturing process like blending, lubrication, compression, analysis of finished product. During this process critical parameters such as blend uniformity, bulk density, flow property of drug, uniformity of dosage unit, uniformity of weight, average weight, hardness test, thickness, disintegration time, friability, dissolution test and assay were studied. Based on result and conclusion, it is established that the employed manufacturing process is capable to produce the product consistently which meets all the predetermined specification and quality attributes. Hence the manufacturing process stands validated and can be used for routine manufacturing of Clopidogrel bisulphate USP tablet.

Key Words: Validation, concurrent process validation, cGMP, Quality, Manufacturing process.

INTRODUCTION

USFDA Defines validation as "Establishing documented evidence, which provides a high degree of assurance that specific process, will consistently produce a product meets its predetermined specification and quality characteristics.[1]

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. [2]

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Essentials of Pharmaceutical Validation

Validation is beneficial to the manufacturer in many ways

- It deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.
- It decreases the risk of defect costs.
- It decreases the risk of regulatory noncompliance.
- A fully validated process may require less inprocess controls and endproduct testing. [3]

Objectives of process validation

1) The manufacturing process, in addition to the individual equipment, must be validated.

2) The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.

3) A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.

5) In the end, process validation will ensure a robust product that is highly reproducible over time. [4]

Elements of Process Validation

Process validation involves a series of activities taking place over the lifecycle of the product and process. All the activities of the process validation were divided into three stages,

- Process Design
- Process Qualification
- Continued Process Verification [5]

Benefits of Validation

- Process improvement, technology transfer, rapid failure investigations.
- Improve employee awareness and increased outputs.
- Find approved products
- Fewer rejects and reworks and avoidance of capital expenditures.
- Increased efficiency, shortening lead time resulting in lower inventories.
- Reduction in utility costs.
- Possible reduced testing of raw materials bulk formulations and finished products.
- Reduced testing in process and finished goods.
- More rapid and accurate investigations into process deviations.
- More rapid automation.[6-7]

MATERIALS AND METHODS

Clopidogrel Bisulphate was obtained from Mepro Pharmaceuticals. All other chemicals and reagents are of analytical grade.

Methods:

1. Sifting

Sift Clopidogrel Bisulphate USP & Betadex BP through 40 # sieve by using sifter. Sift Microcrystalline cellulose (pH 102) BP through 20 # sieve by using sifter. Sift Ac-Di-Sol (Croscarmellose sodium) BP through 30 # sieve by using sifter. Sift Maize Starch BP through 60 # sieve by using sifter. Sift Purified Talc BP & Magnesium stearate BP through 60 # sieve.

2. Blending

Blending was carried out for 30 minutes.

All sifted ingredients are mixed in rapid contra blender for 30 minutes.

3. Lubrication

Lubrication step is followed by blending process, in lubrication stage the mixed ingredients are lubricated with magnesium stearate and talc in contra blender. This lubrication stage is carried out for proper compression of the blended material.

4. Compression

This step involves conversion of blended material into tablets as per specifications. Upper punch and lower punch and dies were checked before starting the machine. Blended granules were loaded into machine hopper and compressed the blended granules into tablets using 9.00 mm heart shaped punch, plain on both sides. All the parameters are checked.

5. Coating

Step 1: Suspend Hypromellose BP in Isopropyl alcohol BP by using a mechanical stirrer.

Step 2: Add Dichloromethane BP in step 1 & continuous stirring till clear mucilage is formed.

Step 3: Add Titanium Dioxide BP & Red oxide of Iron NF in Isopropyl alcohol BP with continuous stirring till dispersed uniformly. Then the mixture passes through double muslin clothes 200# & collected in clean dry S.S container.

Step 4: Add step 3 to step 2 with constant stirring for complete distribution.

Step 5: Then add propylene glycol BP in step 4 with continuous stirring.

Step 6: Pass the final solution through colloid mill & keep in well-closed container.

Place uncoated dedusted tablets in a clean, dry coating pan. Heat the tablets by inching the coating pan. Tablets are coated to give in average coat of 5 to 6 mg. When the weight is achieved, stop the spray & dry the tablets in the pan using hot air.

6. Packing

This process involves packing of tablets in polythene lined aluminium foils and blister bottom cold form aluminium foil blister pack. Sealing roller temperature & speed of machine are critical variables.

Evaluation Parameters:

1. Bulk Density

A. Untapped density

Weigh accurately 25 g of powder and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume}}$$

B. Tapped bulk density

Weigh accurately 25 g of powder and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_2). Calculate the tapped bulk density in gm/ml by the following formula:

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

2. Carr's index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = \frac{[(TD - BD)*100]}{TD}$$

3. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

4. Angle of Repose

The angle of repose of API powder was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan\theta = \frac{h}{r}$$

Where, h and r are the height and radius of the powder cone respectively.

5. Average Weight

Take 20 tablets & weigh the tablets on the balance & then weight of 20 tablets were divided with the number of tablets.

6. Thickness

Ensure that the instrument is clean. Check for zero setting. Open the jaws slowly & insert the object between it & then close the jaws. Take the reading. The least count of the apparatus is 0.01 mm.

7. Hardness

Hardness is measured using tablet hardness tester. From the composite sample 10 tablets are selected

randomly to check the hardness. Ensure that the instrument is clean & free from any residue of dust or tablets. Hold the tablets between the jaw & nozzle in edgewise position. Adjust the scale by sliding, so that the zero on the scale coincides with the pointer. Turn the screw knob slowly till the tablet breaks. The pressure indicated on the dial is in kg /cm^2.

8. Friability

Switch on the friability apparatus. Take a sample of whole tablets corresponding as near as possible to 6.5 g. The tablets are carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

9. Disintegration Time

Fill up the beaker of the disintegration apparatus with water & allow it to equilibrate to 37 ± 2°C. After reaching the temperature 37 ± 2°C, put one tablet in each tube of the disintegration test apparatus. Then start the DT apparatus & note down the disintegration time. The disintegration time of the uncoated tablet should be not more than 15 minutes. If one or two tablets failed to disintegrate completely repeat the test on 12 additional tablets. Not less than 16 of the total 18 tablets tested should disintegrate completely.

10. Dissolution

Procedure:

Fill up the dissolution apparatus with 0.1 N HCl and allow it to warm up to 37 $\pm$ 0.5°C. Add one tablet & rotate the paddle at 50 RPM for 30 minutes. After 30 minutes withdraw 20 ml and filter it with whatmann filter paper #1. From the above filtrates take 10 ml & transfer to a 50 ml volumetric flask & make up the volume with dissolution media i.e. 15 µg/ml. Simultaneously make the working standard, accurately weigh 75.0 mg of Clopidogrel WS (equivalent to 97.8 mg Clopidogrel bisulphate) & transfer to a 100 ml volumetric flask. Add 20 ml of methanol and dilute to stepwise with medium. Take 1 ml in to 50 ml volumetric flask and make up volume to 50 ml with medium. So final concentration of test and standard is 15 µg/ml. Measure the absorbance at 240 nm both standard & sample solution-using dissolution media as a blank.

11. Assay

Assay preparation:

Weight and finely powder not less than 20 Tablets. Transfer an accurately weighed portion of the powder, eq. to about 75 mg of Clopidogrel to a 100 ml volumetric flask, and add 50 ml of

methanol. Sonicate for 5 minutes, and stir for 30 minutes Dilute with methanol to volume, and mix. Transfer 5.0 ml of this solution to the flask, dilute with methanol to 50 ml and mix. Pass a portion of this solution through a filter having a 0.45 µm or finer porosity. And use the filtrate after discarding the first 5 ml.

Procedure:

Separately inject equal volumes (about 10 µl) of the standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the analyte peaks. Calculate the quantity in mg of Clopidogrel ($C_{16}H_{16}ClNO_{21}S$) in the portion of Tablets taken.

12. Uniformity of Weight

The test is provides limits for the permissible variation in the mass of individual dosage units, expressed in terms of allowable deviation from the average mass of a sample.

Procedure:

Select 20 tablets at random from a particular batch. Weigh the tablets individually. Determine the average mass.

13. Uniformity of Dosage Unit

Standard preparation:

Weigh accurately 97.8 mg of USP Clopidogrel Bisulfate RS equivalent to 75 mg of Clopidogrel and transfer to a 50 ml volumetric flask. Sonicate for 5 minutes with 50 ml 0.1 N HCl and cool. Take 5 ml of the above solution to a 50 ml volumetric flask and make the volume up to the mark with 0.1 N HCl. Filter the solution through a 0.45 micron filter paper. Discard the first 5 ml of the filtrate. So the final concentration will be 150 µg/ml.

Test preparation:

Place one tablet in a standard 50 ml volumetric flask. Sonicate for 5 minutes with 50 ml 0.1 N HCl and cool. Take 5 ml of the above solution to a 50 ml volumetric flask and make the volume up to the mark with 0.1 N HCl. Filter the solution through a 0.45 micron filter paper. Discard the first 5 ml of the filtrate. So the final concentration will be 150 µg/ml.

Procedure:

Start suitable spectrophotometer and measure the absorbance of standard solution and test solution at 240 nm using 0.1 N HCl as a blank. Same way repeat the procedure for further 9 tablets.

RESULTS AND DISCUSSION

1. Sieve integrity and % retention in sifting process:

All sieves used before and after sifting process shows integrity within acceptance criteria.

RESULTS:

MFG STEPS	PARAMETERS	ACCEPTANCE CRITERIA	VALIDATION RESULTS (3 Batches)		
			X	Y	Z
SIFTING	Sieve integrity	Ok or not ok	Ok	Ok	Ok
	% Retension	% Retention over sieve- No	Nil	Nil	Nil
BLENDING	Bulk of uniformity	95% -105% of LC	99.47	99.49	99.55
	RSD(%)	Less than or equal to 6%	0.239	0.412	0.312
	Carr's index	NMT 15 %	10.00	11.53	14.28
	Hausner's ratio	NMT 1.18	1.11	1.13	1.16
	Flow property	Must be excellent	OK	OK	OK
LUBRICATION	Bulk of Uniformity	85 %-115 % of LC	99.69	99.71	99.76
	RSD(%)	Less than or equal to 6%	0.425	0.451	0.459
	Carr's index	NMT 15 %	6.12	9.80	10.90
	Hausner's ratio	NMT 1.18	1.06	1.10	1.12
	Flow property	Must be excellent	OK	OK	OK
COMPRESSION	Assay	95%-105% of LC	100.60	101.19	102.25
	Uniformity of weight	250mg ± 5%	250.12	250.34	250.44
	Average weight of 20 tablets	250mg ± 5.0%	250.13	250.02	250.08
	Thickness	4.2 ± 0.2mm	4.30	4.26	4.25
	Disintegration time	NMT 15 minutes	08 min 06 sec	07 min 42 sec	07 min 52 sec
	Hardness	NLT 3kg/cm^2	4.03	4.08	4.07
	Friability	NMT 1.0%	0.29	0.35	0.36
	Dissolution	NLT 85% of LC	98.10	96.93	98.85
	Uniformity o dosage units	85%-115% of LC	98.94	98.83	98.93
	RSD(%)	Less than or equal to 6%	2.26	1.97	1.85
COATING	Uniformity of weight	255 mg ± 5.0%	257.95	255.78	257.01
	Average weight	255 mg ± 5.0%	257.38	255.87	256.55
	Thickness	4.3 ± 0.2mm	4.39	4.33	4.37
	Disintegration time	NMT 30 minute	08 min 35 sec	07 min 47 sec	08 min 09 sec
	Dissolution	NLT 85% of LC	98.32	99.40	98.58
	Assay	95%-105% of LC	101.25	100.24	100.75
	Hardness	NLT 4.0 kg/cm^2	4.20	4.25	4.23
PACKING	Leak test	Leak must be not present	No leak were found	No leak were found	No leak were found
	Printing quality	Must be clear	Ok	Ok	Ok

2. Blending: The blending of the ingredients was done for 30 minutes for three different batches. Content uniformity of Clopidogrel bisulphate and the corresponding RSD values, bulk density, Carr's index, Hausner's ratio and flow property are well within the limits of acceptance criteria, when blended for 30 minutes which indicates that 30 minutes of blending gives an acceptable drug distribution pattern.

3. Lubrication: The lubrication of three batches was performed and the samples at the designated locations were drawn for determining the content uniformity and RSD, bulk density, Carr's index,

Hausner's ratio and flow property values of Clopidogrel bisulphate. The RSD values met the acceptance criteria after lubrication for 5 minutes. From the analytical results it is clear that an acceptable drug distribution pattern of the drug in the blend is obtained when lubricated for 5 minutes.

4.Compression: The compression for the first three batches was done considering the validation aspects of compression process. The Compression was carried out between the speed limits mentioned in the Batch manufacturing record and the physical parameters of the tablets were studied at this speed. The parameters checked included uniformity of weight, average weight, and thickness of tablets, hardness of tablets, tablet friability, tablet disintegration time, assay, uniformity of dosage unit, dissolution. The parameters studied were well within the limits of acceptance criteria at the speed studied. Hence the Compression stage of Clopidogrel bisulphate USP tablets is found to be consistent and reproducible.

5.Coating: The coating validation was performed for three consecutive lots. It was concluded that the coating has to be performed in two lots keeping the coating parameters in accordance with the batch manufacturing record. It is recommended to carry out the coating process at the pan RPM set in between 5-7 at the Exhaust temperature of 40 – 45°C. The parameters checked included assay, dissolution, tablet disintegration time, uniformity of weight, average weight of 20 tablet, hardness of tablet, and thickness of tablets. The parameters studied were well within the limits of acceptance criteria at the speed studied. Hence the coating stage of Clopidogrel bisulphate USP tablets is found to be consistent and reproducible.

6. Packing: The packing of three batches were performed and samples were drawn for printing quality and leak test. It was concluded that no leak of blister were found. It was concluded that the blister packing has to be performed at the speed of 60-80 cuts/min, at the sealing temperature 170°C –180°C and forming temperature 140 °C -150 °C.

CONCLUSION

Based on result and discussion, it can be concluded that that the employed manufacturing process is capable to produce the product consistently which meets all the predetermined specification and quality attributes. Hence the manufacturing process stands validated and can be used for routine manufacturing of Clopidogrel bisulphate USP tablet.

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