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Prashant B Patil, Vivekanand K Chatap, Mahesh P More and Zamir G Khan
Department of Pharmacy, H. R. Patel Institute of Pharmaceutical Education & Research, Shirpur, Dist: Dhule (MS) 425 405 India

Correspondence

Zamir G Khan
Department of Pharmaceutical Chemistry, H. R. Patel Institute of Pharmaceutical Education & Research, Shirpur, Dist: Dhule (MS) 425 405 India

Email: khanzamir.5588@gmail.com

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Prospective Process Validation Study of Glibenclamide 2.5 mg Tablets

Prashant B Patil, Vivekanand K Chatap, Mahesh P More and Zamir G Khan

ABSTRACT

The present study provides a high degree of assurance that a specific process for manufacturing of Glibenclamide Tablets will consistently produce a product meeting its predetermined quality attributes and specifications. It mainly comprises the stages to be followed to evaluate and qualify the acceptability of manufacturing process of Glibenclamide 2.5 mg tablets. The process is limited to the three batches manufactured of specific batch size with specified equipments and control parameters for tablets. It involves All parameters related to the each step were evaluated by respective standard test involved in the manufacturing. Sampling, testing plan and acceptance criteria for each step were monitored. The analytical results of all stages were found to be within the acceptable limit. Other tests related to compression such as hardness, thickness, disintegration and dissolution for all three batches were found within the acceptable limit.

Key words: Glibenclamide, Blend Uniformity, Assay of Glibenclamide, Process validation of Glibenclamide, Glibenclamide tablets.

1. INTRODUCTION

Validation is defined as process of founding through a documented database programme, which provides a high degree of assurance that a specific process will constantly produce, a product meeting its pre-determined specifications and critical quality attributes. The word validation simply means, ‘assessment of validity’ or ‘action of proving effectiveness’ a validated manufacturing process is one, which has been proved to do what it purports to or is represented to do. Validation essentially contains process qualification (the qualification of materials, equipment, system, buildings and personnel i.e. Design Qualification, Installation Qualification, Operation Qualification, Performance Qualification).

Process Validation is defined as the collection and evolution of data from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. It assures Quality, Safety, and efficacy. (According to 2011 United State of Food and Drug Administration (USFDA) guideline). The process validation is the analysis of data collected throughout the design and manufacturing of a product in order to endorse that the process gives consistent production of products with given standard. The main aim of process validation of Glibenclamide is to ensure various inputs lead to consistent and great quality productions and it continuing process that must be regularly improved as manufacturing feedback is gathered. Glibenclamide, also known as glyburide, is an anti-diabetic drug in the class of medications known as sulfonylurea and thoroughly related with sulfonamide antibiotics.

Glibenclamide is a sulfonylurea derivative and is recommended for the treatment of type II diabetes mellitus. In its oral administration, Glibenclamide go through the hepatic first pass effect; such that only 45% of the drug is absorbed and considering its short half-life, the persistent has to take the drug in several divided doses to maintain the desired therapeutic effect. Gastrointestinal adverse effects of Glibenclamide have been reported for the drug, which decreases the patients' compliance. The Glibenclamide fall in class II of the biopharmaceutical classification system, which means the drug is poorly water soluble and soluble in ethanol (5 mg/mL), Dimethyl sulfoxide - DMSO (25 mg/mL), chloroform (1:36), methanol (1:250), while showing a good permeability in the gastrointestinal mucosa[1-8].

1.1 Stages of Process Validation

- Process Design Stage
- Process Qualification Stage
- Continued Process Verification Stage

1.2 Process Validation should be considered in following situation

- When implementing new processes for manufacturing
- When new equipment's installed in manufacturing plant
- Process and equipment which are having altered suit changing the priority
- Processes were ended product test is poor

2. MATERIALS AND METHODS

Prospective process validation was performed on the three batches of Glibenclamide 2.5 mg Tablets. The three consecutive batches were labeled as (Batch X, Batch Y, and Batch Z) [3-9].

List of Equipment and Stages indicate list of equipment's which are used in manufacturing process of glibenclamide 2.5 mg tablets and give the involvement of equipment in which manufacturing stage with their make which are mentioned in table 1.

Details of Input Material indicates material or ingredients which are used in the manufacturing of glibenclamide 2.5 mg tablets with their category which shows in table 2.

Sampling and Testing Plan indicates the planning for sampling and testing with their manufacturing stage, procedure, quantity to be sampled and acceptance criteria for sampling for the manufacturing of glibenclamide 2.5 mg tablets which describe in table 3.

Manufacturing Process flow chart indicates the manufacturing stages of manufacturing process of glibenclamide 2.5 mg tablets depicted in Figure 1.

3. RESULT AND DISCUSSION

This results and discussion is limited to evaluation of three consecutive batches of glibenclamide 2.5 mg tablets for prospective process validation. Three manufacturing batches are validated in prospective process validation the batches are labeled as Batch X, Batch Yand BatchZ at blend stage, compression stage and packing stage.

Product Details
Product Name: Glibenclamide Tablets 2.5 mg
Label Claim: Each tablet contains Glibenclamide BP 2.5 mg.

3.1 Dry Mixing

Dry mixing was carried out in Rapid Mixer Granulator for 10 minutes and samples were collected from eleven different six locations for Blend Uniformity. The blend uniformity test was performed and acceptance criteria for it is individual values should be between 90.0 % to 110.0 % of the labeled amount of Glibenclamide with RSD not more than 5 % the results are described in table 4.

% RSD of Glibenclamide Tablets for all three validation batches were within found within the specification. Based on % RSD data of Glibenclamide Tablets for three validation batches, it was evident that the dry mixing throughout the sampling locations and all results are found within acceptable limit.

3.2 Drying Analysis

The drying analysis carried for the % LOD of dried granules of Glibenclamide analysis. The samples were collected from the fluidized bed dryer bowl from top, middle bottom side the results are shown in table 5.

% loss of drying of dried granules of Glibenclamide was within the range 7.30 to 7.89 w/w at 120 0C for 20 minutes respectively for all three validation batches, which were within the acceptable limit.

3.3 Analytical Data for Lubricated Blend

Blending was carried out by Octagonal Blender for 13 minutes and samples were collected from 12 different locations (12-points) for test Blend Uniformity such as upper site, middle site, lower site and bottom. The results are as follows in table 6.

% RSD of Glibenclamide for all three validation batches were within the range 1.07 to 1.15, which were found within the acceptance criteria. % RSD of Glibenclamide for all three validation batches, it was evident that there was no segregation occurs in the blender and mixing is homogeneous throughout the sampling locations.

3.4 Analysis of Lubricated Blend

Lubricated blend analysis is done by description of blend, assay, loss on drying, bulk density, tapped density and sieve test parameters their results are described in table 7.

Description, Assay, loss on drying, bulked density, tapped density sieve test of lubricated blend of Glibenclamide for three validation batches was within the acceptable specification and criteria.

3.5 Physical Characteristics of Lubricated Blend

Physical characteristics of lubricated blend were done by description of lubricated blend, bulk density, tapped density, loss on drying, angle of repose and particle size distribution parameters and their results are shown in table 8.

The physical parameter of lubricated blend such as description, bulk density, tapped density, loss on drying and particle size distribution for three validation batches were satisfactory and found consistent within acceptable limit. No significant observation related to the flow of the blend was observed throughout the compression activity.

3.6 Compression stage physical parameters

During compression, samples from compression machine at minimum speed and maximum speed were collected of three consecutive batches for performing physical parameters. The physical parameters checks as description, average weight, uniformity of weights, thickness, hardness, friability, disintegration, assay, dissolution test performed. The results are as follows of table 9.

Physical parameter of Glibenclamide tablet at Minimum Speed (2200 Tabs/min) and Maximum Speed (2750 Tabs/ Min) of compression for three validation batches X, Y, Z were found in the range within the acceptance criteria and specification.

3.7 Compression stage analytical results

Compression stage analysis in their content uniformity, assay by HPLC and dissolution were checked at minimum speed and maximum speed as same as to physical parameters and results describe in table 10.

% dissolution of Glibenclamide at Optimum speed of compression for three validation batches X, Y, Z were found in the range which were within the acceptance criteria.

3.8 Analysis of Compressed Tablet

The analysis of compressed tables is done by assay, content uniformity and dissolution rate of Glibenclamide compressed tablets results are shown in table 11.

Assay, content uniformity and dissolution rate of Glibenclamide at initial, middle, end and composite stage of compression at optimum were found within the acceptable limit that is Glibenclamide2.38 to 2.63 mg/tablets.

4. CONCLUSION

The prospective process validation of Glibenclamide 2.5 mg tablet has been performed for three batches and all the parameters and results were found within the acceptance limit at all stages such as dry mixing, wet granulation, drying, milling, lubrication, and compression. Based on the results of the validation data for three batches, it was concluded that the manufacturing process used for formulation of Glibenclamide 2.5 mg tablet will consistently producing the stable product meeting its predetermined specifications and quality attributes. Hence, it can be concluded that the method employed in the manufacture of the given product is considered to be validated and can be routinely followed.

5. ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

Table 1. List of Equipments

Sr. No.	Equipment	Make	Stages Involved In
1	Weighing balance	Mettler Toledo	All stages
2	Vibratory sifter (30inch)	PHARMA FAB	Sifting of raw materials
3	Rapid Mixer Granulator	BOWMEN & ARCHER	Dry mixing and granulation
4	Fluid bed drier (250 kg)	BOWMEN & ARCHER	Drying
5	Multi-mill(50 T0 250 Kg/Hrs)	PHARMA FAB	Sizing
6	Octagonal Blender (1200 Lit)	BECTOCHEM	Blending
7	Compression machine.	CALMACH	Compression
8	Friability test apparatus	ELECTROLAB	To check friability
9	Hardness tester	ELECTROLAB	To check hardness
10	Dissolution Apparatus	Electrolab(USP)	Dissolution Testing
11	Disintegration apparatus	Electrolab (USP)	To check disintegration time
12	Blister Packing Machine	Elmach Pack	For Packing of Tablets
13	Metal Detector	Sivo System PVT LTD	To Detect metal traces in tablets
14	UV Spectrophotometer	Shimadzu	For Analysis
15	HPLC	Shimadzu	For Analysis

Table 2. Detail input of material

Sr. No	Ingredients	Specification	Category
1	Glibenclamide	BP	Active Ingredient
2	Lactose Monohydrate	Ph. Eur	Diluents
3	Maize Starch	Ph. Eur	Binder
4	Povidone K30	BP	Diluents
5	Magnesium Stearate (Vegetable Grade)	EP	Lubricant
6	Purified Water	BP	Solvent

Table 3. Sampling and testing plan

Stage	Sample Location	Sample Size	Test
Dry mixing	After completion of drying, draw composite sample from 11 different location of RMG after 5,10,15 min. of mixing of API and excipients	Approx. 300 mg /each location	Blend uniformity
Drying	Samples of dried granules shall be withdrawn from 5 sampling points comprising left, right, center, front, back layer of FBD bowl.	Approx. 5.0 g /each location	Loss on Drying
Lubrication Stage	Unit dose samples shall be withdrawn from 11 different location of the blender comprising of upper, middle, lower layer and bottom layer after 3 minutes mixing with Lubricant in Octagonal blender.	Approx. 1100 mg.	Blend uniformity
Lubricated Blend	Approximately 300 g of lubricated bulk blend to be sampled for physical characteristic evaluation.	Approx. 300 g	Physical characteristics 1. Description 2. Bulk density Tapped density 3. Angle of repose 4. Particle size analysis 5. Assay 6. Sieve analysis.
Compression Stage a. Minimum speed b. Optimum speed c. Maximum speed	During compression, samples to be collected & mixed from both sides of press(RHS and LHS) at initial, middle and at the end of compression operation	150 Tablets at each stage	1. Description 2. Average weight 3. Uniformity of Weigh. 4. Friability 5. Hardness 6. Thickness 7. Dissolution 8. Content uniformity
Finished Product	After final compression of tablets before packing this analysis is carried.	150 Tablets	1. Assay 2. Dissolution 3. Content Uniformity

Table 4. Dry mixing stage blend uniformity results

Sr. No.	Location	Acceptance Criteria	Batch X	Batch Y	Batch Z
1	T1	Individual values should be between 90.0 % to 110.0 % of labeled amount of Glibenclamide with RSD NMT 5 %.	101.5	101.5	101.5
2	T2		101.1	101.1	101.1
3	T3		100.8	100.8	100.8
4	B1		100.4	100.4	100.4
5	B2		100.9	100.9	100.9
6	B3		101.1	101.1	101.1
		Minimum	100.4	100.5	100.4
		Maximum	101.5	101.6	101.5
		Mean	100.9	100.9	101
		% RSD	0.3	0.3	0.4

T: Top, B: Bottom

Table 5. Results of Drying Homogeneity Analysis

Sr. No	Limit 7.3 to 8.0 w/w at 120 ^{0}C for 20 minutes	Batch X	Batch Y	Batch Z
1	Top	7.31	7.30	7.33
2	Middle	7.80	7.82	7.81
3	Bottom	7.87	7.86	7.89

Table 6. Result of Blend Uniformity of Lubricated Blend

Sr. No.	Location	Acceptance Criteria	Batch X	Batch Y	Batch Z
1	U1	Individual values should be between 90.0 % and 110.0 % of labeled amount of Glibenclamide with RSD not more than 5.0 %	96.9	96.8	96.7
2	U2		98.8	98.9	98.7
3	U3		98.2	98.3	98.5
4	M1		100.1	100.3	100.2
5	M2		98.3	98.2	98.4
6	M3		98.3	98.5	98.3
7	L1		98.6	98.5	98.4
8	L2		100.4	100.6	100.5
9	L3		100	99.9	100.1
11	BO		99	99.2	99.3
		Minimum	96.9	96.8	96.7
		Maximum	100.4	100.6	100.5
		Mean	98.86	98.92	98.91
		% RSD	1.07	1.14	1.15

Table 7. Results of Assay of Lubricated Blend

Test	Acceptance Criteria		Observation		
			Batch X	**Batch Y**	**Batch Z**
Description	White granules free from extraneous matter (Blend)		Complies	Complies	Complies
Assay	2.375 mg to 2.625 mg of Glibenclamide per average weight of Blend NMT 95.0 % and NMT 105.0 % of label claim of Glibenclamide		97.2	97.8	98.1
Loss on Drying	For information only		8.65	8.78	8.33
Bulk Density	For information only		0.6946 mg/ml	0.7130 mg/ml	0.6888 mg/ml
Tapped Density	For information only		0.81 g/ml	0.86 g/ml	0.79 g/ml
Sieve Test	For information only	Sieve No.	% of Sample passes		
		20 #	93.1 %	94.3 %	93.4 %
		40 #	68.0 %	68.8 %	69.2 %
		60 #	60.1 %	59.8 %	61.2 %
		80 #	56.9 %	57.2 %	56.7 %
		100 #	46.8 %	47.2 %	46.3 %

Table 8. Physical Characteristic of Lubricated Blend

Sr. No.	Parameter	Batch X	Batch Y	Batch Z
1	Description	White Colored Powder Blend	White Colored Powder Blend	White Colored Powder Blend
2	Bulk density gm/ml	0.65	0.62	0.65
3	Tapped density gm/ml (500taps)	0.68	0.68	0.69
4	Loss On Drying	1.98%	1.51%	1.55%
5	Angle of Repose	24.09	23.38	24.09
6	Particle Size Distribution	Cumulative Retention (%)	Cumulative Retention (%)	Cumulative Retention (%)
	Above 20#	1.72 %	98.3 %	98.3 %
	Above 60#	24.59 %	49.4 %	75.4 %
	Above 80#	40.61 %	28.2 %	59.4 %
	Above 100#	45.56 %	24.1 %	54.6 %

Table 9. Compression stage Physical parameters Bach X, Batch Y and Batch Z

Test	**Acceptance Criteria**	**Minimum Speed (2200 Tabs/min)**		**Maximum Speed (2750 Tabs/ Min)**	
		LHS	**RHS**	**LHS**	**RHS**
		Batch X			
Description	White circular tablets debossed with GL/2.5 on one side	Complies	Complies	Complies	Complies
Average Weight	80.0 mg ± 5 % (76.0 to 84.0 mg)	83.7 mg	82.3 mg	80.9 mg	80.7 mg
Uniformity Weight	NMT 2 tablets deviate by more than ± 10 % from the average weight and none deviate by ±20 % from the average weight.	-2.03 to + 1.55 %	-1.58 % to +2.07 %	- 2.35 % to +2.60 %	- 3.35 % to +5.33 %
Hardness	19.6 N to 49.0 N	Min – 32 Max - 44	Min – 31 Max - 35	Min – 29 Max - 35	Min – 28 Max – 32
Thickness	2.50 to 3.00 mm	Min – 2.79 Max – 2.85	Min – 2.74 Max – 2.79	Min – 2.73 Max – 2.79	Min – 2.72 Max – 2.81
Friability	Not more than 1 % w/w	0.28 %	0.24 %	0.26 %	0.24 %
Disintegration	Not more than 8 minutes	01 min 44 sec	01 min 02 sec	01 min 12 sec	01 min 32 sec
		Batch Y			
Description	White circular tablets debossed with GL/2.5 on one side	Complies	Complies	Complies	Complies
Average Weight	80.0 mg ± 5 % (76.0 to 84.0 mg)	82.8 mg	83.5 mg	81.8 mg	84.2 mg
Uniformity Weight	NMT 2 tablets deviate by more than ± 10 % from the average weight and none deviate by ± 20 % from the average weight.	- 2.04 to + 1.52 %	-1.55 % to +2.09 %	- 2.28 % to +2.59 %	- 3.33 % to +5.36 %
Hardness	19.6 N to 49.0 N	Min – 33 Max - 42	Min – 31 Max - 36	Min – 32 Max - 39	Min – 27 Max – 31
Thickness	2.50 to 3.00 mm	Min – 2.55 Max – 2.86	Min – 2.64 Max – 2.78	Min – 2.76 Max – 2.98	Min – 2.69 Max – 2.83
Friability	Not more than 1 % w/w	0.31 %	0.29 %	0.28 %	0.26 %
Disintegration	Not more than 8 minutes	01 min 38 sec	01 min 22 sec	01 min 18 sec	01 min 23 sec
		Batch Z			
Description	White circular tablets debossed with GL/2.5 on one side	Complies	Complies	Complies	Complies
Average Weight	80.0 mg ± 5 % (76.0 to 84.0 mg)	84.6 mg	82.8 mg	82.8 mg	83.8 mg
Uniformity Weight	NMT 2 tablets deviate by more than ± 10 % from the average weight and none deviate by ± 20 % from the average weight.	- 2.11 to + 1.53 %	-1.49 % to +2.07 %	- 2.25 % to +2.60 %	- 3.34 % to +5.34 %
Hardness	19.6 N to 49.0 N	Min – 35 Max - 41	Min – 31 Max - 39	Min – 29 Max - 36	Min – 29 Max – 33
Thickness	2.50 to 3.00 mm	Min – 2.54 Max – 2.76	Min – 2.70 Max – 2.83	Min – 2.66 Max – 2.86	Min – 2.71 Max – 2.86

Friability	Not more than 1 % w/w	0.33 %	0.27 %	0.29 %	0.25 %
Disintegration	Not more than 8 minutes	01 min 33 sec	01 min 29 sec	01 min 21 sec	01 min 26 sec

Table 10. Compression stage analytical results

Test	**Acceptance Criteria**		**Batch X**		**Batch Y**		**Batch Z**	
			Min Speed	Max Speed	Min Speed	Max Speed	Min Speed	Max Speed
Uniformity of dosage (by content uniformity)	Less than or equal to 15.0		4.6	4.2	4.3	5.1	4.8	4.9
Assay (By HPLC)	95.0 % to 105.0 % of label amount of glibenclamide		97.6 %	96.0 %	97.0 %	98.8 %	97.2 %	98.6 %
Dissolution Profile in %	Limit between 45 % to 70 % after 30 mins	Min	54	56	55	57	56	57
		Max	58	60	59	61	57	59
		Avg	56	58	57	59	57	58

Table 11. Results of analysis of compressed tablet

Parameter	**Acceptance limit**	**Observation**		
		Batch X	**Batch Y**	**Batch Z**
Assay (HPLC)	Glibenclamide 2.38 to 2.63 mg/tablets	2.44 mg/tablets	2.49 mg/tablets	2.48 mg/tablets
Content Uniformity	Less than or equal to 15.0	4.7	4.8	4.7
Dissolution	45 to 70 % after 30 mins	Min – 58 % Max- 62 % Avg – 60 %	Min – 59 % Max- 62 % Avg– 61 %	Min – 58 % Max- 63 % Avg - 60

*Min: Minimum, Max: Maximum, Avg: Average

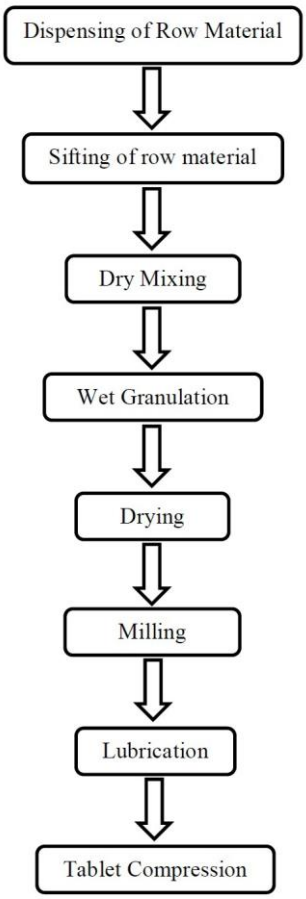

Fig 1. Manufacturing process flow chart of Glibenclamide 2.5 mg tablet

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