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PROCESS VALIDATION OF METFORMIN HYDROCHLORIDE EXTENDED RELEASE TABLETS USP 500MG

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ABSTRACT

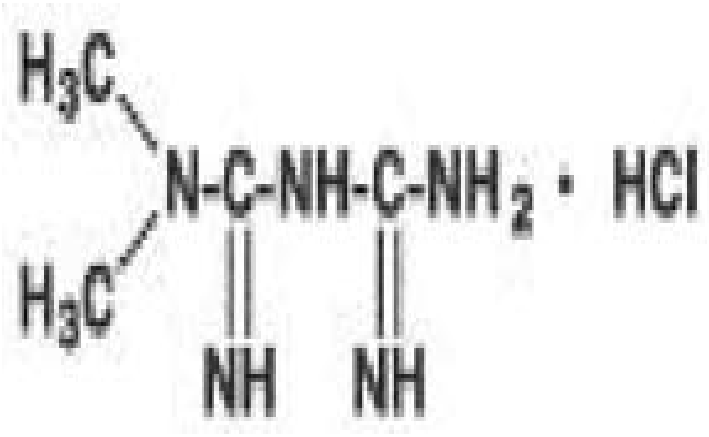
Process Validation is a reqirement of the cGMP regulations for the finished pharmaceuticals. Purpose of research was to study Process Validation of Metformin HCL 500mg tablets dosage formulation, which acts as a type 2 diabetes. Three initial process validation batches (MF2001, MF2002 & MF3001) of same size, method, equipment & validation criteria was taken. The critical parameter involved in 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.

KEY WORDS: cGMP, process validation, MF, HCL.

INTRODUCTION

Process development is actual transfer of the manufacturing process from R & D to production along with necessary knowledge & skill to be able to make the product, is referred to as technology transfer. The ultimate objective for successful technology transfer is to have documented proof that the process is robust and effective in producing product meeting with registered specification & cGMP requirements. Metformin hydrochloride extended-release tablets contain an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (N, N dimethylimidodicarbonimidic diamide hydrochloride) is a member of the biguanide class of oral antihyperglycemic and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents. The empirical

formula of metformin hydrochloride is $C_4H_{11}N_5$.HCl and its molecular weight is 165.63. Its structural formula is:



MATERIALS AND METHOD

Metformin HCL, HPMC-K100M, PVP-K30, Isopropyl alcohol, Dichloromethane, Ethyl cellulose, Purified Talc, Magnesium stearate, was used for this Formulation. All raw material used of USP& BP grade and chemicals used in the analysis in the study were of analytical grade.

Machineries

Machineries and equipments used was as vibratory sifter (Pharma fab), rapid mixing granulator [RMG] (Bowmen & Archer), multimill (Pharma fab), Binder preparation vessel (Pharma fab), fluid bed drier [FBD] (Bowmen & Archer), Blender (Bectochem), compression machine 27 station double rotary (Cadmach), UV-visible spectrophotometer (Shimadzu 1800), six stage dissolution rate test apparatus IP/BP/USP (Electro lab), hardness tester (Electro lab), disintegration and friability test apparatus (Electro lab), Vernier caliper (Mitotoyo).

Wet Granulation Method

Tablet was manufactured by wet granulation method using ingredients shown in table no 1. During manufacturing temperature NMT 25^0C & RH NMT 50% were maintained.Sifting: Vibratory sifter After dispensing of required material they were sifted through vibratory sifter as shown in table no.1. Dry Mixing: Rapid Mixing Granulator Metformin HCL & HPMC-K100M was dry mixed in RMG at slow speed for 10min. Binding solution Preparation: Steam Kettle Binding solution was prepared in steam kettle, take isopropyl alcohol, Dichloromethane & PVP-K30 was added with continuous stirring for 1hr till clear solution is

obtained. Then add ethyl cellulose into the above solution with continuous stirring till a smooth paste is obtained. Wet Granulation: Slowly add this paste into the above dry mix in RMG till dough like consistency formed. Multi Mill: Pass the wet mass through multimill fitted with 10mm screen at slow speed. Drying: Fluidized Bed Dryer Dry the wet granules at 60^0C in FBD till LOD is 1.0 to 2.0%. Sizing: Pass the dried granules through 16#. Milling: Mill the retained granules on the sifter through multi mill using 1.50/2.00mm screen. Lubrication: Octagonal Blender Transfer the milled and sieved granules to the Octagonal blender and mix for 1min, add to the above purified talc & mix for 05min. To the above add magnesium stearate, mix for 03 min at slow speed in Octagonal blender.Compression: Compression Machine Set the compression machine according to the tablet specifications and compressed the lubricated granules.Tablets were compressed using 17.5mm×8.5mm standard concave capsule shape Punches plain on 27 Station double rotary compression machine. Each 890mg tablet contains 500mg Metformin HCl. The specification for tablet was average weight 890mg (±2%) , hardness NLT 140N, thickness 6.80mm (±0.2mm), friability NMT 1%w/w, Assay 90-110%, Dissolution NLT 85% of stated amount released in 10hr.

Analysis

Metformin HCL was estimated by using U.V. Spectrophotometer at 232nm (A1%=798) formulation samples was Subjected to U.V spectroscopy. Quantity equivalent to 100mg of metformin HCL was taken for assay. Dissolved this in 70 ml p/w, sonicated & made volume 100ml, filtered it and from filtrate pipette out 10 ml and diluted to 100ml with p/w again pipette out 10ml and diluted it 100 ml with p/w and record absorbance .

RESULTS AND DISCUSSION

Integrity of sieve before and after was satisfactory for all MFs. Uniformity of dry mixing was obtained by assay of 30 locations per batch & % RSD (must be NMT 2% for effective mixing) was calculated by mean assay of all location as shown in table no 2. Consistency of granulating agent was found excellent with given proportion. Dough mass consistency was excellent with respect to speed of impeller & choppers as per table no 3. Drying stage LOD obtained at different time interval was shown in table no 4. Sizing process evaluation result was as per table no 5. Uniformity of mixing in lubrication stage obtained by assay of 30 locations per batch & % RSD was calculated by mean assay of all locations. The LOD, Angle of repose, BD & Angle of Repose result was shown in table no 6. Compression stage speed challenge study shown in table no. 8a & 8b.

Table No 1: Composition of various process validation batches.

Ingredient	MF 2001	MF 2002	MF 3001
Dry Mixing			
Metformin HCL	300kg	300kg	300kg
HPMC K100M	174kg	174kg	174kg
Wet Granulation			
PVP K30	15kg	15kg	15kg
Isopropyl Alcohol	170.001kg	170.001kg	170.001kg
Dichloromethane	80.001kg	80.001kg	80.001kg
Ethyl Cellulose	36kg	36kg	36kg
Lubrication			
Purified Talc	3	3	3
Magnesium Stearate	6	6	6

Table No 2: Dry Mixing Results.

Batch No.	% RSD		
	5Min	10 Min	15 Min
MF 2001	0.91	0.88	1.15
MF 2002	1.86	0.94	1.65
MF 3001	1.57	0.90	0.89

% RSD was calculated by taking mean of assay of all locations.

Table No 3: Wet Mixing Results.

Batch No.	Duration	Chopper	Impeller	Ampere Reading	Dough Mass Consistency
MF 2001	4min	Off	Slow	22.0	Excellent
	2:30min	Slow	Slow		
	0:30min	Slow	Fast		
MF 2002	4min	Off	Slow	22.4	Excellent
	2:30min	Slow	Slow		
	0:30min	Slow	Fast		
MF 3001	4min	Off	Slow	22.3	Excellent
	2:30min	Slow	Slow		
	0:30min	Slow	Fast		

LOD % W/W (60^0C)															
Time	**70 min**					**75 min**					**85 min**				
Location	L	R	C	F	B	L	R	C	F	B	L	R	C	F	B
MF 2001	2.16	2.19	2.21	2.14	2.20	2.08	2.11	2.04	2.09	2.06	1.49	1.60	1.55	1.52	1.56

MF 2002	2.09	2.12	2.16	2.19	2.14	2.06	2.10	2.04	2.09	2.07	1.58	1.61	1.57	1.60	1.55
MF 3001	2.14	2.10	2.12	2.16	2.20	2.05	2.07	2.09	2.11	2.00	1.40	1.48	1.48	1.44	1.49

Table No 4: Drying Stage Results.

L-Left, R-Right, C-Centre, F-Front, B-Back

Table No 5: Sizing Stage Results.

Batch No.	% LOD	Screen Size	Duration
MF 2001	1.54	2mm	30min
MF 2002	1.58	2mm	30min
MF 3001	1.45	2 mm	30min

Table No 6: Lubrication stage Results.

Batch No.	% RSD	% LOD	Avg. Assay of Drug	BD (gm/ml) untapped	BD Tapped	Angle of Repose	Sieve Analysis			
							20 #	60#	80#	100#
MF 2001	1.62	1.52	98.1	0.658	0.685	24.09	98.10	24.59	40.6	45.56
MF 2002	1.77	1.55	98.4	0.628	0.688	23.38	98.3	49.4	26.2	59.40
MF 3001	1.29	1.40	95.3	0.654	0.698	24.09	98.3	75.4	59.4	54.60

Lubrication Time 8 min % RSD was calculated by taking mean of assay of all locations.

Table No 7: Compression stage. Acceptance criteria for Inprocess Test

Test		Acceptance criteria
Appearance		White coloured, uncoated capsules shaped, biconvex tablets plain on both side.
Avg.Wt (mg)		890.0 ±2%
Uniformity of weight		890.0 mg ±3%
Dimension (mm)		17.40×8.40 mm- 17.60×8.60 mm
Hardness (Avg)		NLT 140.0N
Thickness		6.80 mm ± 0.2 mm
Friability		NMT 1.0% w/w
Assay		90 – 110%
Dissolution	1 hr	20 – 40%
	3 hr	45 – 65%
	10 hr	NLT 85%

Table No 8a: Compression stage Results.

Parameter	Speed	MF 2001	MF 2002	MF 3001
Appearance	Min – 8rpm	Ok	ok	Ok
	Max – 12rpm	Ok	ok	Ok
	Opt – 10rpm	Ok	ok	Ok
Avg.Wt	Min – 8rpm	890.7	890.5	897.5

	Max – 12rpm	889.5	889.8	895.3
	Opt – 10rpm	890.5	890.4	896.6
Uniformity of weight	Min – 8rpm	881 – 898	882 – 899	889 – 895
	Max – 12rpm	882 – 899	883 – 898	889 – 897
	Opt – 10rpm	880 – 897	883 – 898	888 – 896
Hardness	Min – 8rpm	151.8 – 167.4	152.3 – 166.8	196.3 – 210.5
	Max – 12rpm	151.8 – 164.4	151.4 – 167.9	195.3 – 203.5
	Opt – 10rpm	152.7 – 165.5	151.4 – 167.2	194.2 – 209.8
Thickness	Min – 8rpm	6.75 – 6.82	6.80 – 6.89	6.66 – 6.70
	Max – 12rpm	6.75 – 6.82	6.81 – 6.88	6.66 – 6.70
	Opt – 10rpm	6.74 – 6.83	6.81 – 6.88	6.65 – 6.71
Friability	Min – 8rpm	0.007	0.20	0.03 %
	Max – 12rpm	0.006	0.19	0.03 %
	Opt – 10rpm	0.009	0.19	0.04 %

Table No 8b: Compression stage Results.

Parameter	Stage	MF2001	MfF2002	MF 3001
Appearance	Initial	Ok	Ok	Ok
	Middle	Ok	Ok	Ok
	End	Ok	Ok	Ok
	Composite	Ok	Ok	Ok
Average Weight	Initial	887.8	888.2	887.6
	Middle	883.4	888.2	889.1
	End	888	888.6	889.5
	Composite	887.9	889.4	889.5
Uniformity of weight	Initial	881.4 – 896.9	888.9–892.5	888.1 – 892.5
	Middle	883.4 – 891.3	881.6–892.6	881.5 – 889.3
	End	889.4 – 892.3	881.5–892.8	881.5 – 892.9
	Composite	888 – 892.3	887.8–892.1	887.9 – 892.4
Hardness	Initial	141.5 – 170.4	146.3–170.3	146.5 – 169.9
	Middle	143.3 – 165.4	141.3 – 170	144.3 – 170.2
	End	142.3 – 165.3	140.3–164.3	140.5 – 162.4
	Composite	140.4 – 164.3	143.6–170.3	143.5 – 169.9
Thickness	Initial	6.77 – 6.88	6.78 – 6.86	6.77 – 6.85
	Middle	6.74 – 6.90	6.82 – 6.88	6.80 – 6.86
	End	6.78 – 6.86	6.79 – 6.87	6.78 – 6.86
	Composite	6.78 – 6.86	6.82 – 6.87	6.83 – 6.88
Friability	Initial	0.21	0.14	0.14
	Middle	0.18	0.25	0.25
	End	0.16	0.14	0.14
	Composite	0.21	0.18	0.18
Assay	Initial	100.6	94.2	96.1
	Middle	98.3	96.5	95.1
	End	98.9	95.7	95.7
	Composite	99.1	97.9	97.4
Dissolution – Initial	1 hr – Min	31.3	30.8	30.1
	1 hr – Max	32.5	32.5	32.3
	3 hr – Min	55.6	55.7	56.7

			Max	60.5	60.0	62.9
		10 hr	Min	85.40	89.9	87.0
			Max	94.42	97.5	96.0
	Middle	1 hr	Min	30.1	31.6	30.6
			Max	32.5	33.0	32.9
		3 hr	Min	56.9	56.7	57.5
			Max	59.8	62.5	61.9
		10 hr	Min	89.9	89.8	86.7
			Max	94.6	93.6	94.1
	End	1 hr	Min	30.6	30.9	31.5
			Max	32.1	32.1	33.2
		3 hr	Min	56.8	56.8	56.9
			Max	60.4	60.4	60.3
		10 hr	Min	90.6	89.4	85.2
			Max	97.2	95.7	93.2
	Composite	1 hr	Min	30.2	31.8	31.0
			Max	35.2	33.3	32.5
		3 hr	Min	58.3	56.6	56.0
			Max	61.5	61.7	61.4
		10 hr	Min	88.6	88.7	86.0
			Max	90.3	94.2	93.0

CONCLUSION

The selected sieve was suitable for sifting. Uniformity of dry mixing is excellent in 10min because % RSD found 0.880-0.940%. Granulating agent was prepared of desired consistency. Dough mass was formed satisfactory within 7min wet mixing & ampere reading 22 – 22.4 Amp. Drying time 85 min is suitable for achieving LOD NMT 2%. Evaluation parameter of sizing shows effective LOD, %fine, BD & Angle of repose. Lubrication stage uniformity was achieved with 8min because % RSD found 1.29 – 1.77% and flow properties was satisfactoty. Compression machines optimum speed (10RPM) was satisfactory for effective compression. Therefore based on results MF at each of the stages for the specified parameters it is summarized and concluded that with the prospective process validation for the metformin HCL 500mg 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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