World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

PREPARATION AND PROCESS VALIDATION OF METFORMIN HYDROCHLORIDE TABLET

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Article Received on 04/09/2020 **Article Revised on 25/09/2020** **Article Accepted on 15/10/2020**

ABSTRACT

The validation is a fundamental segment that supports to a commitment of company towards quality assurance. It also assures that product meets its predetermined quality specification and quality characteristics. Validation of individual step of manufacturing is called as process validation. It is concerns with the process validation of tablet dosage form which has a numerous advantages over other dosage forms. The purpose of research was to study prospective process validation metformin HCl 500mg tablet dosage formulation. The critical process parameter was identified with the help of process capability and evaluated by challenging its lower & upper release specification. Three initial process validation batches (X, Y & Z) of same size, method, equipment & validation criteria were 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.

KEYWORDS: Metformin HCL, Process validation, Uniformity of mixing, Quality attributes.

INTRODUCTION

According to Indian GMP validation study is essential part of GMP. Those required to be done as per predetermined protocols. Prospective process validation is carried out during the development stage by means of risk analysis of the production process which is broken down into individual steps.[1] These are then evaluated on basis of past experience to determine whether they might lead to critical situation are identified, the risk is evaluated, the potential cause are investigated and assessed for probability & extent, the teal plan are drawn up, & priorities are set. The trial are then performed and evaluated & overall assessment is made. If at the end result are acceptable the process is satisfactory. Unsatisfactory processes must be modified & improved until a validation exercise proves them to be satisfactory this form of validation is essential in order to limit the risk of error occurring on the production scale. This present work deals with identification of critical stage and their consequent evaluation by challenging its upper and lower specifications.[2-6]

MATERIALS AND METHODS

Material

Metformin HCL was gifted by Aurobindo Pharma Limited, Hyderabad A.P, India. All the chemicals used in this study were obtained from Hi Media Laboratories Pvt. Ltd. (Mumbai, India), Sigma Aldrich Chemical Co. (Milwaukee, WI, USA), SD Fine-Chem. Ltd. (Mumbai, India) and SRL Pvt. Ltd. (Mumbai, India).All the chemicals used in this study were of analytical grade.

Machineries

Machineries and equipments used was as sifter, multimill (Ganson Ltd), rapid mixing granulator [RMG] (250L, Kevin make), steam kettle (Anchor mark), fluid bed drier [FBD] (250L,saffhire), octagonal blender (250L, Anchor mark), compression machine 27 station single rotatory (Cadmach), UV visible spectrophotometer (Shimadzu 1800), six stage dissolution rate test apparatus IP/BP/USP (Tab machine), Monsanto hardness tester (Rollex), disintegration and friability test apparatus (Electo lab), Mitutoyo thickness tester.

Experimental[7-12]

Material shifting and dry mixing

Transfer the Raw material to granulation area and sift the all material with shifter. Load the previously weighed

and sifted materials; Metformin, 0.5 mm multimill; sequentially in RMG & mix for 10 min. at slow speed. Record the integrity of the sieve before and after sifting of material.

Binding and wet mixing

Binder preparation

Transfer the previously weighed and sifted materials to the Binder Preparation area. Take 5.60 Lt Purified Water. Add and dissolve Polyvinyl Pyrrolidone in above purified water under stirring and check the clarity of the solution.

Binding

Start RMG containing dry mixed powder at slow speed for 10 min, add binder in RMG &and at slow speed 7-8 min. Continue mixing at fast speed with fast chopper for 2-3 min, till the granulation end point is reached (to get required consistency of dough mass).

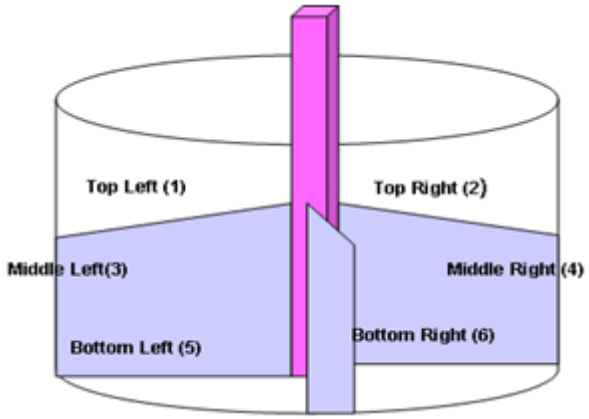

Figure 1: Rapid Mixer Granulator sampling locations.

Drying

Perform drying in FBD: Load the wet mass in FBD bowl. Dry the wet mass at ambient temperature for 10-15 min. Rake the mass of the bowl. Then dry at 55 – 60°C temperature for 10 – 15 minute with intermediate raking. Drying time can be adjusted according to the climate to obtain LOD 2.5 – 3.5 % w/w. Incase LOD is not within limit, continue drying or add moisture, as the case may be, to bring the LOD within limit. After drying collect 5 gm sample at 5 different locations from the FBD bowl as per given below.

Sifting & sizing

After drying sift the granules through 16# sieve using vibratory sifter and over sized granules should be passed through Multi-mill using 1.8 mm S.S. screen.

Lubrication

Load the dried Granules in octagonal blender and mix for 5 minutes. Collect the composite sample from 10 different locations and check LOD. LOD should be between 2.5-3.5% w/w. If LOD exceeds 3.5 % w/w, granules should be re-dried to get 2.5 – 3.5 %w/w LOD. Load all the lubricants except Magnesium Stearate and mix for 10 min. Magnesium Stearate is to be added in octagonal Blender and mix for 3 minutes at slow speed. Collect the Bulk sample (Approx. 1899 mg) from 10 different locations. For analysis of B.U. &assay, after lubrication unload the granules into suitable containers duly labeled.

Compression

Set the Compression Machine on following parameter and compressed the tablet.

S. No.	Tablet Test Parameter	Set Specifications
1	Appearance	White to off white, oval, beveled edged uncoated tablets having break line on one side, plain on other side.
2	Average weight	633 mg ± 5%
3	Uniformity of weight	within ± 5.0 % of average weight.
4	Diameter	14.2 x 9.7mm ±0.2mm
5	Thickness	4.50mm ±0.3mm
6	Hardness	4.5 – 9.0 Kg/cm2
7	Friability	NMT 1.0 % w/w
8	Disintegration	NMT 15 Minutes

Blister/ strip packing machine setting and operation details

Set the machine as per standard operating procedure. After setting the machine, operate on different temperature & speed. Following parameters shall to be checked during stripping.

Appearance of Blister: Aesthetically good legible over coding, no colour smudging of Blister.

Sealing and cutting: Proper sealing, uniform cutting.
Cut pocket: Free from hollow pocket, no damaged pocket.

Leak test: No single pocket should wet.

Appearance of tablet (after Blister packing): Appearance of tablet should match as per description of tablet.

Manufacturing of validation batch (X, Y & Z)
Granulation raw materials

Ingredient & Specification	Mg/tab.	Net Weight
Granulation Raw Material [1, 50,000 Tablets]		
Metformin Hydrochloride# IP	500.00	75.0 Kg
Sodium Starch Glycollate IP	20.00	3.0 Kg
Starch IP	10.00	1.500 Kg
Purified Water	qs	5.60 Ltr.
Polyvinyl Pyrrolidone IP	40.00	6.0 Kg
Ingredient & Specification	Mg/tab.	Net Weight
Lubrication Raw Material [1,50,000Tablets]		
Colloidal Silicon Dioxide IP	7.00	1.05 Kg
Microcrystalline Cellulose IP	53.00	7.95 Kg
Magnesium Stearate IP	3.00	0.450

RM dispensing: Dispensed the raw material as per above Bill of material according to their respective A.R. number.

RM sifting details: Transfer the Raw material to granulation area and sift the all material with sifter. Load the previously weighed and sifted materials; mill Metformin through 0.5 mm multimill.

Binder preparation: Take 5.60 Lt Purified Water. Add and dissolve Polyvinyl Pyrrolidone in above purified water under stirring and check the clarity of the solution.

Mixing & binding details: Start RMG containing dry mixed powder at slow speed for 10 min , add binder in RMG & and at slow speed 7- 8 min. Continue mixing at fast speed with fast chopper for 2-3 min. , till the granulation end point is reached. (to get required consistency of dough mass).

Ingredient	Qty,	Mixing type	Std. Time	Batch X	Batch Y	Batch Z
Metformin Hydrochloride IP	75.0 Kg	Dry mix (slow)	**10 min.**	10 min.	10 min.	10 min.
Sodium Starch Glycollate IP	3.0 Kg					
Binder Paste	12.100 Ltr.	Binding a) Slow impeller b) Fast impeller with chopper	**7-8 min.** **2-3 min.**	8 min. 3 min.	8 min. 3 min.	8 min. 3 min.
Ampere Load - 32 amps.						

Drying: Perform drying in FBD: Load the wet mass in FBD bowl. Dry the wet mass at ambient temperature for 10-15 min. Rake the mass of the bowl. Then dry at 55 – 60°C temperature for 10 – 15 minute with intermediate raking. Drying time can be adjusted according to the climate to obtain LOD 2.5 – 3.5 % w/w. Incase LOD is not within limit, continue drying or add moisture, as the case may be, to bring the LOD within limit. After drying collect 5 gm sample at 5 different locations from the FBD bowl as per given below.

Cycle	Std. time Initial 10-15 min. Final 10-15 min.			Std. Inlet temp. 55-60°C	LOD Std. 2.5 – 3.5 %		
	X	Y	Z	X,Y&Z	X	Y	Z
Initial	**10**	**10**	**10**	**60°C**	**2.85%**	**2.67%**	**2.91%**
Final	**10**	**10**	**10**				

Sifting &sizing: After drying sift the granules through 16# sieve using vibratory sifter and oversized granules passed through Multi-mill using 1.8 mm S.S. screen.

Sifting of lubricants: Sift all lubricants through vibratory sifter as MCC through 40#, Colloidal silicone dioxide through 30# and Magnesium stearate through 60 #.

Lubrication: Load the dried Granules in octagonal blender and mix for 5 minutes. Collect the composite sample from 10 different locations and check LOD. LOD should be between --2.5- 3.5% w/w. If LOD exceeds 3.5 % w/w, granules should be re-dried to get 2.5-3.5 %w/w LOD. Load all the lubricants except Magnesium Stearate and mix for 10 min. Magnesium Stearate is to be added in octagonal blender and mix for 3 minutes at slow speed. Collect the Bulk sample (Approx. 1899 mg) from 10 different locations. For analysis of B.U. & assay, after lubrication unload the granules into suitable containers duly labeled.

Ingredient	Wt.	Std. time (Min.)	Period (Min.) Batch- X	Batch- Y	Batch- Z
Unlubricated Granules	-	**5**	5	5	5
LOD of Unlubricated granule (Limit 2.5 – 3.5%)			2.92%	2.83%	3.13%
Colloidal Silicon Dioxide IP	1.05 kg	**10**	10	10	10
Microcrystalline Cellulose IP	7.95 kg				
Magnesium Stearate IP	0.450 kg	**3**	3	3	3

Compression Machine setting and operation details.

Machine Parameters	Specification	Tablet Parameters	Specification
Compression Machine	27 stations	Individual wt.	633 mg ± 5%
Punch Size	14.2x9.7 mm Oval	Wt. of 20 tablets	12.660 mg± 5%
Upper Punch	Break line	Thickness range	4.2 – 4.8 mm
Lower Punch	Plain	Hardness	4.5 – 9.0 kg/cm2
Die	14.2x9.7	D.T.	NMT 15 min.
Speed	10 to 35 RPM	Friability	NMT 1.0 %

Validation of compression machine speed

Set the compression machine at its Minimum speed (10 RPM) on which it gives all the above parameters within specifications and noted down the readings. Again set on Maximum speed i.e. 35 RPM and perform all above physical test. A composite sample of both minimum and maximum speed also sends to QC for C.U. Analysis to observe the effect of speed on tabletting.

Validation of hopper level

After speed validation Hopper full filled with powder and run the machine and perform all tests with satisfactory data. Similarly Half and bottom hopper validation performed.

Validation of hardness

Set the machine at its low hardness and perform all physical test & got satisfactory data and similarly on high hardness satisfactory data achieved. A composite sample of both LHS & RHS of low hardness and another composite sample of both LHS & RHS of high hardness send to QC for Dissolution analysis to observe the effect of hardness on Disso profile of Drug.

Validation at different time interval

Sample withdrawn from Initial , Middle and End stage of compression and perform all the physical parameters and also withdrawn composite sample of LHS & RHS from all intervals and send to QC for complete analysis including Dissolution, Assay, C.U.

Packing

Blister packing machine setting and operation details

Set the machine as per standard operating procedure. After setting the machine, operate on different temperature & speed. Following parameters shall to be checked during stripping.

➢	Appearance of Blister	:	Aesthetically good legible over coding, no colour smudging of Blister.
➢	Sealing and cutting	:	Proper sealing, uniform cutting.
➢	Cut pocket	:	Free from hollow pocket, no damaged pocket.
➢	Leak test	:	No single pocket should wet.
➢	Appearance of tablet (after Blister packing)	:	Appearance of tablet should match as per description of tablet.

RESULTS AND DISCUSSION

Dry mix performed in RMG at slow speed for 10min. Wet mixing performed at fast speed. Till the granulation end point is reached to get required consistency dough mass. Initial drying at ambient temperature for 10min. Final drying at 55 to 60°C inlet temperature for 10 min. through 1.2mm ss screen using conical mill. Lubrication performed in octagonal blender un-lubricated granules mixed for 5 minutes. Lubricated granules except magnesium stearate and mix for 10min, addition magnesium stearate & mix for 3min, blister forming roller temp. Observed 180°C and counter sealing roller kept 220°C ±20°C. All the analytical data review during process validation of metformin hydrochloride tablets found satisfactory hence process is validated.

Table 1: Dry mixing result.

Metformin Hydrochloride Tablets: Content in dry mix				
	Location	**Batch no. X**	**Batch no. Y**	**Batch no. Z**
Sample 1	Top left	99.19	99.45	98.52
Sample 2	Top right	99.56	99.11	98.12
Sample 3	Middle left	98.76	98.46	99.36
Sample 4	Middle right	96.78	97.36	97.19
Sample 5	Bottom left	98.11	99.08	99.25
Sample 6	Bottom Right	99.02	98.52	99.05
RSD (NMT 6 %)		**2.30**	**1.98**	2.31

Table 2 Results of lubrication.

% LOD OF Dried Granules		**Limit : 2.5- 3.5% w/w**		
	Batch no:	**Batch no: X**	**Batch no: Y**	**Batch no: Z**
	Location			
Sample 1	Top Left	2.69	2.59	2.95
Sample 2	Top Right	2.89	2.69	2.88
Sample 3	Middle	2.91	2.72	2.79
Sample 4	Bottom Left	3.01	2.69	2.81
Sample 5	Bottom Right	2.89	2.83	2.96
RSD (NMT 6 %)	------	**2.30**	**1.98**	2.31

Table 3: Observation and results of tablets at different speed.

Metformin content in lubricated granules With Magnesium Stearate		**Limit: 90.0% – 110.0% of L .A**		
	Location ↓	Assay Result		
	Batch no.→	X	Y	Z
Sample 1	Top Left	99.29	98.12	96.78
Sample 2	Top Middle	98.39	96.78	96.78
Sample 3	Top Right	96.28	97.18	97.89
Sample 4	Middle Left	98.23	98.13	98.13
Sample 5	Middle Middle	97.22	99.28	97.29
Sample 6	Middle Right	99.12	99.29	98.16
Sample 7	Bottom Left	98.23	97.26	97.86
Sample 8	Bottom Middle	98.11	96.28	98.45
Sample 9	Bottom Right	96.29	98.11	96.28
Random location	--------	98.12	98.35	96.78
Average	____	98.23	99.12	99.15
RSD (NMT 6%)		**2.30**	**1.98**	2.31
Composite Sample	**Limit**	**Batch No. X**	**Batch No. Y**	**Batch No. Z**
LOD	**2.5 – 3.50% w/w**	2.89	2.98	3.12
Assay: Metformin 500 mg.	**90.0% - 110.0 % of L.A.**	98.65	97.59	99.09

Compression Machine						**27 Station**							
Physi calpara meter	**Acceptance criteria**	**Batch X**				**Batch Y**				**Batch Z**			
		Speed				**Speed**				**Speed**			
		10 RPM		**35 RPM**		**10 RPM**		**35 RPM**		**10 RPM**		**35 RPM**	
		Min.	**Min.**	**Max.**	**Max.**	**Min.**	**Min.**	**Max.**	**Max.**	**Min.**	**Min.**	**Max.**	**Max.**
		LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
Description:	***Conforms**	**Conforms**	**Conforms**	**Conforms**	**Conforms**	**Conforms**	**Conforms**	**Conforms**	**Conforms**	**Conforms**	**Conforms**	**Conforms**	**Conforms**
Average weight	633.0mg ± 3.0%	638.2	638.3	638	638	638.5	638	638	638.9	638	638.7	638	638
Uniformity of weight :	Within ± 5% of the Average weight	637	638	638	639	640	638	639	639	638	639	639	639
		641	639	638	638	638	635	635	638	639	638	635	635
		633	635	633	635	629	638	629	633	629	635	634	638
		658	633	634	629	630	639	623	629	631	634	639	638
		629	638	645	638	634	629	635	638	632	639	635	629
		634	641	642	628	635	638	628	638	632	641	638	638
		638	642	628	638	632	637	638	635	635	640	629	629
		639	638	622	639	638	639	629	634	630	638	631	635
		637 639	645	635	645	633	638	633	629	633	632	6329	629

		638											
		639	632	645	629	628	635	635	638	634	639	638	635
		638	628	628	633	626	633	629	629	641	638	639	629
		645	627	635	628	628	637	622	638	639	635	633	635
		641	630	628	635	635	631	635	629	638	639	635	628
		645	633	629	635	638	629	639	633	645	633	639	629
		638	625	628	638	635	633	625	629	634	632	632	635
		639	638	638	629	639	632	623	633	635	632	629	639
		633	639	625	630	622	634	633	637	639	635	634	638
		638	641	628	621	633	635	638	634	635	629	629	629
		637	640	639	629	633	638	639	635	632	639	633	629
		632	631	629	632	633	635	638	638	631	635	629	635
Minimum		637	640	639	629	633	638	639	635	632	639	633	629
Maximum		632	631	629	632	633	635	638	638	631	635	629	635
Wt. variation ± %		-0.12, +0.23	-0.12, +0.28	-0.09, +0.21	-0.12, +0.23	-0.12, +0.23	-0.12, +0.23	-0.17, +0.26	-0.12, +0.23	-0.12, +0.23	-0.12, +0.22	-0.11, +0.23	-0.12, +0.23

Dimension	9.75mm ±0.2mm	9.76	9.88	9.79	9.81	9.78	9.76	9.77	9.74	9.69	9.77	9.78	9.75
		9.77	9.74	9.75	9.69	9.79	9.81	9.71	9.76	9.89	9.76	9.68	9.76
		9.78	9.78	9.78	9.76	9.64	9.65	9.70	9.68	9.88	9.79	9.71	9.64
		9.81	9.77	9.84	9.78	9.66	9.69	9.81	9.59	9.67	9.81	9.77	9.80
		9.75	9.68	9.79	9.63	9.77	9.76	9.78	9.68	9.69	9.67	9.78	9.69
Thickness :	4.50mm ±0.3mm	4.52	4.53	4.44	4.50	4.58	4.58	4.43	4.40	4.58	4.50	4.49	4.50
		4.59	4.59	4.43	4.50	4.52	4.50	4.59	4.42	4.52	4.53	4.58	4.56
		4.44	4.51	4.55	4.56	4.44	4.52	4.52	4.51	4.53	4.55	4.46	4.40
		4.49	4.46	4.49	4.59	4.48	4.41	4.44	4.53	4.48	4.49	4.51	4.46
		4.52	4.39	4.53	4.56	4.49	4.42	4.39	4.56	4.50	4.48	4.58	4.52
Hardness :	3.0 Kg / cm 2	3.5	4.0	4.0	3.5	3.5	3.5	4.0	3.5	3.5	4.5	3.5	4.0
		3.5	4.0	4.0	3.5	4.0	3.5	4.0	4.0	3.5	4.0	3.5	4.0
		4.0	4.0	3.5	4.0	3.5	3.0	4.0	4.0	4.0	4.0	4.0	4.0
		3.5	3.5	3.5	4.0	4.0	3.5	4.0	4.0	4.5	4.0	4.0	3.5
		4.0	3.5	4.0	4.0	3.5	4.0	4.0	3.5	4.0	3.5	3.5	4.0
Friability :	NMT 1.0 % w/w	0.23	0.22	0.38	0.09	0.53	0.29	0.45	0.38	0.26	0.45	0.29	0.33
Disintegration	NMT 10min	2’22’’	3’12’’	1’22’’	1’38’’	2’01’’	03’08’’	01’56’’	01’23’’	02’23’’	03’01’’	01’12’’	02’15’’

Table 4: Observation and results of uncoated tablets.
(A)Batch No: X

Physical parameter &	Acceptance criteria	Initial		Middle		End	
		LHS	RHS	LHS	RHS	LHS	RHS
Description :	*** Conforms**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**
Average weight	**633.0mg ± 3.0%**	**633.5**	**633.9**	**629.8**	**630.8**	**633.5**	**637.2**
Uniformity of weight :	Within ± 5% of the Average weight	638	639	640	638	638	638
		639	638	638	635	639	638
		629	635	629	638	635	633
		631	629	630	639	633	634
		632	638	634	629	638	645
		632	628	635	638	641	642
		635	638	632	637	642	628
		630	639	638	639	638	622
		633	645	633	638	645	635
		634	629	628	635	632	645
		641	633	626	633	628	628
		639	628	628	637	627	635
		638	635	635	631	630	628
		645	635	638	629	633	629
		634	638	635	633	625	628
		635	629	639	632	638	638
		639	630	622	634	639	625
		635	621	633	635	641	628
		632	629	633	638	640	639
		631	632	633	635	631	629

Minimum		632	629	633	638	640	639
Maximum		631	632	633	635	631	629
Wt. variation ± %		-0.12, +0.23	-0.12, +0.28	-0.09, +0.21	-0.12, +0.23	-0.12, +0.23	-0.12, +0.23
Dimension	9.75mm ±0.2mm	9.76	9.79	9.81	9.74	9.69	9.77
		9.77	9.75	9.69	9.76	9.89	9.76
		9.78	9.78	9.76	9.68	9.88	9.79
		9.81	9.84	9.78	9.59	9.67	9.81
		9.75	9.79	9.63	9.68	9.69	9.67
Thickness :	4.50mm ±0.3mm	4.49	4.50	4.53	4.43	4.40	4.50
		4.58	4.56	4.59	4.59	4.42	4.50
		4.46	4.40	4.51	4.52	4.51	4.56
		4.51	4.46	4.46	4.44	4.53	4.59
		4.58	4.52	4.39	4.39	4.56	4.56
Hardness :	3.0 Kg / cm 2	3.5	3.5	3.5	4.0	3.5	3.5
		3.5	4.0	3.5	4.0	4.0	3.5
		4.0	3.5	3.0	3.5	4.0	4.0
		4.0	4.0	3.5	3.5	4.0	4.0
		4.0	3.5	4.0	4.0	3.5	3.5
Friability :	NMT 1.0 % w/w	0.12	0.39	0.25	0.28	0.09	0.24
Disintegration	NMT 10 min	01’56’’	02’12’’	03’01’’	02’23’’	01’46’’	02’13’’

(B)Batch No: Y

Physical parameter &	**Acceptance criteria**	**Initial**		**Middle**		**End**	
		LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
Description :	*** Conforms**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**
Average weight	**633.0mg ± 5.0%**	**633.5**	**633.9**	**629.8**	**630.8**	**633.5**	**637.2**
Uniformity of weight :	Within ± 5% of the Average weight	639	639	639	639	640	638
		638	635	635	638	638	635
		635	634	638	635	629	638
		634	639	638	629	630	639
		639	635	629	638	634	629
		641	638	638	628	635	638
		640	629	629	638	632	637
		638	631	635	639	638	639
		632	6329	629	645	633	638
		639	638	635	629	628	635
		638	639	629	633	626	633
		635	633	635	628	628	637
		639	635	628	635	635	631
		633	639	629	635	638	629
		632	632	635	638	635	633
		632	629	639	629	639	632
		635	634	638	630	622	634
		629	629	629	621	633	635
		639	633	629	629	633	638
		635	629	635	632	633	635
Minimum		632	629	633	638	640	639
Maximum		631	632	633	635	631	629
Wt. variation ± %		-0.12, +0.23	-0.12, +0.28	-0.09, +0.21	-0.12, +0.23	-0.12, +0.23	-0.12, +0.23
Dimension	9.75mm ±0.2mm	9.77	9.83	9.76	9.76	9.77	9.74
		9.76	9.74	9.81	9.81	9.71	9.76
		9.79	9.78	9.65	9.65	9.70	9.68
		9.81	9.77	9.69	9.69	9.81	9.59
		9.67	9.68	9.76	9.76	9.78	9.68
	4.50mm ±0.3mm	4.40	4.44	4.50	4.58	4.49	4.50
		4.42	4.43	4.50	4.52	4.58	4.56

Thickness :		4.51	4.55	4.56	4.44	4.46	4.40
		4.53	4.49	4.59	4.48	4.51	4.46
		4.56	4.53	4.56	4.49	4.58	4.52
Hardness :	3.0 Kg / cm 2	3.5	4.0	3.5	3.5	4.0	4.0
		3.5	4.0	3.5	3.5	4.0	4.0
		4.0	3.5	4.0	4.0	4.0	3.5
		4.5	3.5	4.0	3.5	3.5	3.5
		4.0	4.0	4.0	4.0	3.5	4.0
Friability :	NMT 1.0 % w/w	0.26	0.31	0.46	0.20	0.19	0.26
Disintegration	NMT 10 min	2’12’’	2’25’’	01’36’’	3’01’’	02’49’’	03’04’’

(C)Batch No: Z

Physical parameter &	**Acceptance criteria**	**Initial**		**Middle**		**End**	
		LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
Description :	*** Conforms**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**
Average weight	**633.0mg ± 5.0%**	**633.5**	**633.9**	**629.8**	**630.8**	**633.5**	**637.2**
Uniformity of weight :	Within ± 5% of the Average weight	638	638	638	639	639	639
		639	639	638	638	635	635
		629	635	633	635	634	638
		631	633	634	634	639	638
		632	638	645	639	635	629
		632	641	642	641	638	638
		635	642	628	640	629	629
		630	638	622	638	631	635
		633	645	635	632	632	629
		634	632	645	639	638	635
		641	628	628	638	639	629
		639	627	635	635	633	635
		638	630	628	639	635	628
		645	633	629	633	639	629
		634	625	628	632	632	635
		635	638	638	632	629	639
		639	639	625	635	634	638
		635	641	628	629	629	629
		632	640	639	639	633	629
		631	631	629	635	629	635
Minimum		632	629	633	638	640	639
Maximum		631	632	633	635	631	629
Wt. variation ± %		-0.12, +0.23	-0.12, +0.28	-0.09, +0.21	-0.12, +0.23	-0.12, +0.23	-0.12, +0.23
Dimension	9.75mm ±0.2mm	9.74	9.78	9.73	9.74	9.74	9.69
		9.75	9.79	9.71	9.81	9.76	9.89
		9.78	9.64	9.75	9.68	9.68	9.88
		9.84	9.66	9.81	9.59	9.59	9.67
		9.79	9.77	9.78	9.68	9.68	9.69
Thickness :	4.50mm ±0.3mm	4.58	4.58	4.58	4.49	4.50	4.49
		4.52	4.50	4.50	4.58	4.56	4.56
		4.44	4.52	4.52	4.46	4.40	4.40
		4.48	4.41	4.41	4.51	4.46	4.46
		4.49	4.42	4.42	4.58	4.52	4.52
Hardness :	3.0 Kg / cm 2	3.5	4.0	3.5	4.0	3.5	3.5
		3.5	4.0	3.5	4.0	3.5	3.5
		3.0	3.5	4.0	4.0	3.0	4.0
		3.5	3.5	4.0	3.5	3.5	3.5
		4.0	4.0	4.0	4.0	4.0	4.0
Friability :	NMT 1.0 % w/w	0.21	0.39	0.25	0.34	0.26	0.39
Disintegration	NMT 10 min	01’19’’	03’25’’	02’35’’	03’27’’	01’19’’	02’15’’

Table 5: Observation and results of different hopper level tablets.

(A)Batch No: X

Physical parameter &	Acceptance criteria	Full Hopper		Half Hopper		Middle Hopper	
		LHS	RHS	LHS	RHS	LHS	RHS
Description :	*** Conforms**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**
Average weight	**633.0mg ± 3.0%**	**633.5**	**633.9**	**629.8**	**630.8**	**633.5**	**637.2**
Uniformity of weight :	Within ± 5% of the Average weight	638	639	639	639	638	638
		639	638	635	635	639	638
		629	635	634	638	635	633
		631	634	639	638	633	634
		632	639	635	629	638	645
		632	641	638	638	641	642
		635	640	629	629	642	628
		630	638	631	635	638	622
		633	632	6329	629	645	635
		634	639	638	635	632	645
		641	638	639	629	628	628
		639	635	633	635	627	635
		638	639	635	628	630	628
		645	633	639	629	633	629
		634	632	632	635	625	628
		635	632	629	639	638	638
		639	635	634	638	639	625
		635	629	629	629	641	628
		632	639	633	629	640	639
		631	635	629	635	631	629
Minimum		632	629	633	638	640	639
Maximum		631	632	633	635	631	629
Wt. variation ± %		-0.12, +0.23	-0.12, +0.28	-0.09, +0.21	-0.12, +0.23	-0.12, +0.23	-0.12, +0.23
Dimension	9.75mm ±0.2mm	9.77	9.74	9.69	9.77	9.77	9.75
		9.71	9.76	9.89	9.76	9.76	9.76
		9.70	9.68	9.88	9.79	9.72	9.64
		9.81	9.59	9.67	9.81	9.68	9.80
		9.78	9.68	9.69	9.67	9.69	9.69
Thickness :	4.50mm ±0.3mm	4.58	4.50	4.58	4.58	4.43	4.40
		4.52	4.50	4.52	4.50	4.59	4.42
		4.53	4.56	4.44	4.52	4.52	4.51
		4.48	4.59	4.48	4.41	4.44	4.53
		4.50	4.56	4.49	4.42	4.39	4.56
Hardness :	3.0 Kg / cm 2	4.0	3.5	3.5	3.5	4.5	4.0
		4.0	3.5	4.0	3.5	4.0	4.0
		3.5	4.0	4.0	4.0	4.0	4.0
		3.5	4.0	4.0	4.5	4.0	3.5
		4.0	4.0	3.5	4.0	3.5	4.0
Friability :	NMT 1.0 % w/w	0.25	0.34	0.29	0.41	0.26	0.34
Disintegration	NMT 10 min	01’56’’	1’38’’	2’01’’	03’08’’	01’56’’	02’35’’

(B) Batch No: Y

Physical parameter	Acceptance criteria	Full Hopper		Half Hopper		Middle Hopper	
		LHS	RHS	LHS	RHS	LHS	RHS
Description :	*** Conforms**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**
Average weight	**633.0mg ± 3.0%**	**633.5**	**633.9**	**629.8**	**630.8**	**633.5**	**637.2**

Uniformity of weight :	Within ± 5% of the Average weight	639	638	638	638	640	638
		635	639	639	638	638	635
		634	629	635	633	629	638
		639	631	633	634	630	639
		635	632	638	645	634	629
		638	632	641	642	635	638
		629	635	642	628	632	637
		631	630	638	622	638	639
		6329	633	645	635	633	638
		638	634	632	645	628	635
		639	641	628	628	626	633
		633	639	627	635	628	637
		635	638	630	628	635	631
		639	645	633	629	638	629
		632	634	625	628	635	633
		629	635	638	638	639	632
		634	639	639	625	622	634
		629	635	641	628	633	635
		633	632	640	639	633	638
		629	631	631	629	633	635
Minimum		632	629	633	638	640	639
Maximum		631	632	633	635	631	629
Wt. variation ± %		-0.12, +0.23	-0.12, +0.28	-0.09, +0.21	-0.12, +0.23	-0.12, +0.23	-0.12, +0.23
Dimension	9.75mm ±0.2mm	9.78	9.76	9.77	9.74	9.69	9.81
		9.68	9.81	9.71	9.76	9.89	9.69
		9.71	9.65	9.70	9.68	9.88	9.76
		9.77	9.69	9.81	9.59	9.67	9.78
		9.78	9.76	9.78	9.68	9.69	9.63
Thickness :	4.50mm ±0.3mm	4.58	4.53	4.44	4.50	4.49	4.50
		4.52	4.59	4.43	4.50	4.58	4.56
		4.53	4.51	4.55	4.56	4.46	4.40
		4.48	4.46	4.49	4.59	4.51	4.46
		4.50	4.39	4.53	4.56	4.58	4.52
Hardness :	3.0 Kg / cm 2	3.5	3.5	4.5	3.5	4.0	3.5
		3.5	4.0	4.0	3.5	4.0	3.5
		4.0	3.5	4.0	4.0	4.0	4.0
		4.0	4.0	4.0	4.0	3.5	4.0
		4.0	3.5	3.5	3.5	4.0	4.0
Friability :	NMT 1.0 % w/w	0.29	0.31	0.16	0.45	0.38	0.26
Disintegration	NMT 10 min	02’50’’	02’11’’	03’08’’	01’56’’	01’12’’	03’01’’

(C) Batch No: Z

Physical parameter & Test procedure No.	**Acceptance criteria**	**Full Hopper**		**Half Hopper**		**Middle Hopper**	
		LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
Description :	*** Conforms**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**	**Conform**
Average weight	**633.0mg ± 3.0%**	**633.5**	**633.9**	**629.8**	**630.8**	**633.5**	**637.2**
Uniformity of weight :	Within ± 5% of the Average weight	638	638	638	639	639	639
		639	638	639	638	635	635
		635	633	629	635	634	638
		633	634	631	634	639	638
		638	645	632	639	635	629
		641	642	632	641	638	638
		642	628	635	640	629	629
		638	622	630	638	631	635

		645	635	633	632	632	629
		632	645	634	639	638	635
		628	628	641	638	639	629
		627	635	639	635	633	635
		630	628	638	639	635	628
		633	629	645	633	639	629
		625	628	634	632	632	635
		638	638	635	632	629	639
		639	625	639	635	634	638
		641	628	635	629	629	629
		640	639	632	639	633	629
		631	629	631	635	629	635
Minimum		632	629	633	638	640	639
Maximum		631	632	633	635	631	629
Wt. variation ± %		-0.12, +0.23	-0.12, +0.28	-0.09, +0.21	-0.12, +0.23	-0.12, +0.23	-0.12, +0.23
Dimension	14.25 x 9.75mm ±0.2mm	9.78	9.76	9.77	9.74	9.69	9.78
		9.79	9.81	9.71	9.76	9.89	9.68
		9.64	9.65	9.70	9.68	9.88	9.71
		9.66	9.69	9.81	9.59	9.67	9.77
		9.77	9.76	9.78	9.68	9.69	9.78
Thickness :	4.50mm ±0.3mm	4.58	4.58	4.43	4.40	4.49	4.50
		4.52	4.50	4.59	4.42	4.58	4.56
		4.44	4.52	4.52	4.51	4.46	4.40
		4.48	4.41	4.44	4.53	4.51	4.46
		4.49	4.42	4.39	4.56	4.58	4.52
Hardness :	3.0 Kg / cm 2	3.0	3.5	4.0	4.0	3.5	3.5
		4.0	3.5	4.0	4.0	3.5	4.0
		4.0	4.0	4.0	3.5	4.0	3.5
		4.0	3.5	3.5	3.5	4.0	4.0
		3.5	4.0	3.5	4.0	4.0	3.5
Friability :	NMT 1.0 % w/w	0.26	0.45	0.29	0.33	0.35	0.44
Disintegration	NMT 10 min	3’12’’	02’25’’	03’09’’	01’49’’	01’56’’	02’13’’

Table 7: Observations & acceptance criteria of finished products.
Batch No.: X

S. No	Test	Acceptance Criteria	Results		
1	**Description**	White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a break line on one side.	White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a break line on one side.		
2	**Average weight**	633mg ± 5%	634.9 mg		
3	**Uniformity of weight**	within ± 5% of the Average weight	Min. +0.30%	Max.-0.17%	
4	**Dimension**	9.75mm ±0.2mm	1. 9.83 2. 9.77 3. 9.69 4. 9.68	5. 9.84 6. 9.80 7. 9.77 8. 9.65	9. 9.83 10. 9.67
5	**Thickness**	4.50mm ±0.3mm	1. 4.52 2. 4.51 3. 4.56 4. 4.49	5. 4.39 6. 4.52 7. 4.56 8. 4.44	9. 4.52 10. 4.53
6	**Hardness :**	3.0Kg / cm2	1. 3.5 2. 3.0 3. 4.0 4. 3.5	5. 4.0 6. 4.0 7. 3.5 8. 4.5	9. 3.5 10. 3.5
7	**Friability**	NMT 1.0 % w/w	0.29%		
8	**Disintegration**	NMT 10 min	01’28’’		
9	**LOD**	NMT 4% w/w (at 105^{o}C for 3 hrs.)	2.89%		

10	**Dissolution**	Not less than 70% of L.A.C4H11N5. HClafter 45min	86.51%
11	**Assay: Metformin 500.0 mg.**	90.0% - 110.0 % of L.A.	98.56%
12 A	**TBC**	NMT 1000 CFU / g	10 CFU / g
B	**Mould& Yeast**	NMT 100 CFU / g	10 CFU / g
C	**Pathogen**	Absent /g	Absent /g

(B) Batch No.: Y

S. No	Test	Acceptance Criteria	Results		
1	**Description**	White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a break line on one side.	White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a break line on one side.		
2	**Average weight**	633mg ± 5%	633.4 mg		
3	**Uniformity of weight**	within ± 5% of the Average weight	Min. +0.21%	Min. +0.34%	
4	**Dimension**	9.75mm ±0.2mm	1. 9.73 2. 9.75 3. 9.81 4. 9.68	1. 9.87 2. 9.74 3. 9.63 4. 9.68	1. 9.81 2. 9.72 3. 9.69 4. 9.68
5	**Thickness**	4.50mm ±0.3mm	1. 4.66 2. 4.52 3. 4.56 4. 4.49	1. 4.48 2. 4.51 3. 4.59 4. 4.49	1. 4.52 2. 4.43 3. 4.58 4. 4.51
6	**Hardness :**	3.0Kg / cm^2	1. 3.0 2. 4.0 3. 4.0 4. 3.5	1. 3.5 2. 3.5 3. 4.0 4. 3.5	1. 4.5 2. 3.5 3. 4.0 4. 4.0
7	**Friability**	NMT 1.0 % w/w	0.35%		
8	**Disintegration**	NMT 10 min	02’11’’		
9	**LOD**	NMT 4% w/w (at 105^oC for 3 hrs.)	2.59%		
10	**Dissolution**	Not less than 70% of L.A.$C_4H_{11}N_5$. HClafter 45min	89.33%		
11	**Assay: Metformin 500.0 mg.**	90.0% - 110.0 % of L.A.	99.09%		
12 A	**TBC**	NMT 1000 CFU / g	10 CFU / g		
B	**Mould& Yeast**	NMT 100 CFU / g	10 CFU / g		
C	**Pathogen**	Absent /g	Absent /g		

(C) Batch No. : Z

S. No	Test	Acceptance Criteria	Results		
1	Description	White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a breakline on one side.	White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a break line on one side.		
3	Average weight	633mg ± 5%	629.3 mg		
4	Uniformity of weight	within ± 5% of the Average weight	Min. +0.17%	Min. +0.28%	
5	Dimension	9.75mm ±0.2mm	1. 9.73 2. 9.69 3. 9.62 4. 9.68	1. 9.71 2. 9.63 3. 9.70 4. 9.68	1. 9.85 2. 9.72 3. 9.68 4. 9.63
6	Thickness	4.50mm ±0.3mm	1. 4.58 2. 4.47 3. 4.51 4. 4.48	1. 4.52 2. 4.44 3. 4.39 4. 4.42	1. 4.45 2. 4.61 3. 4.56 4. 4.63

7	Hardness :	NLT 3.0Kg / cm^2	1. 3.5 2. 4.0 3. 4.0 4. 4.5	1. 4.5 2. 3.5 3. 4.0 4. 4.5	1. 4.5 2. 3.5 3. 4.0 4. 4.0
8	Friability	NMT 1.0 % w/w	0.16%		
9	Disintegration	NMT 10 min	01'52''		
10	LOD	NMT 4% w/w (at 105^oC for 3 hrs.)	3.02%		
11	Dissolution	Not less than 70% of L.A.L.A.$C_4H_{11}N_5$. HClafter 45min	90.83%		
12	Assay: Metformin 500.0 mg.	98.0% - 103.0 % of L.A.	99.15%		
13 A	TBC	NMT 1000 CFU / g	10 CFU / g		
B	Mould& Yeast	NMT 100 CFU / g	10 CFU / g		
C	Pathogen	Absent /g	Absent /g		

CONCLUSION

Process validation of a production process utilizes information generated during the entire developmental sequence that produced the final process. Validation starts at the first indication that a final production process will evolve from a potential product concept. As a potential product moves through various developmental stages, information was continually generated and incorporated into a master documentation file. Three batches of metformin hydrochloride tablets were studied. Different control parameters were checked, which could affect the quality of the process and product. The Dissolution results of lower and higher thickness are found within the specification limits for the batches 01&02&03. Hopper study results show that no segregation of the blend has been taken place during the compression. All parameters were evaluated and were found to be within the limits. This report overall summarizes the data of three batches of metformin hydrochloride tablets. The parameters were observed during the processing of these three validation batches and the same parameters were recommended for the subsequent commercial batches.

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