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Studies in Prospective Process Validation of Metformin HCl Tablet Dosage Formulation

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Abstract : 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 (PVB1,PVB2 & PVB3) 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- Metformin HCL, Prospective process validation, Uniformity of mixing, CI.

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 [3] .The trial are then performed and evaluated & overall assessment is made. If at the end result are acceptable the process is satisfactory[4]. 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 [5]. This present work deals with identification of critical stage and their consequent evaluation by challenging its upper and lower specifications[6].

Materials and Methods:

Metformin HCL (Shree Maa), Maize Starch (universal starch), Dicalcium phosphate (Enar chemie), PVP-K30 (ISP technology), Sodium benzoate (Navyog pharmaceuticals), Purified Talc (Gujarat mineral industry), Magnesium sterate (Nikita chemical), sodium starch glycolate (Aditya chemical) and purified Water (INH) was used for this Formulation. All raw material used of BP grade and chemicals used in the analysis in the 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.

Fig no:1 Illustrative diagram of RMG and sampling locations.

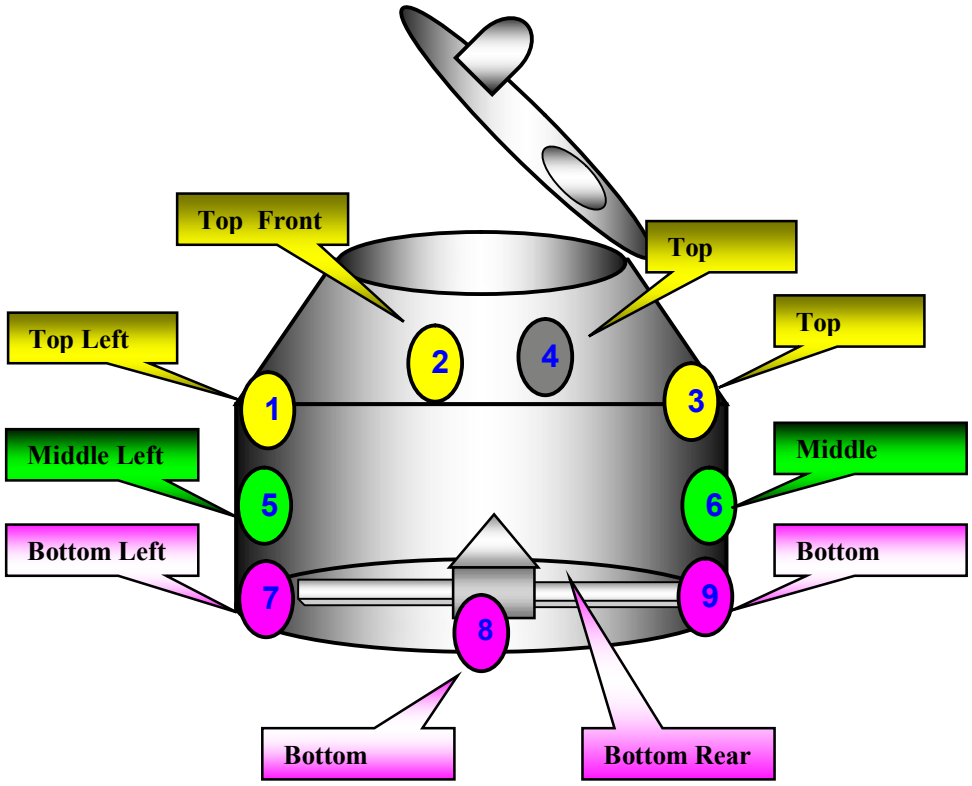
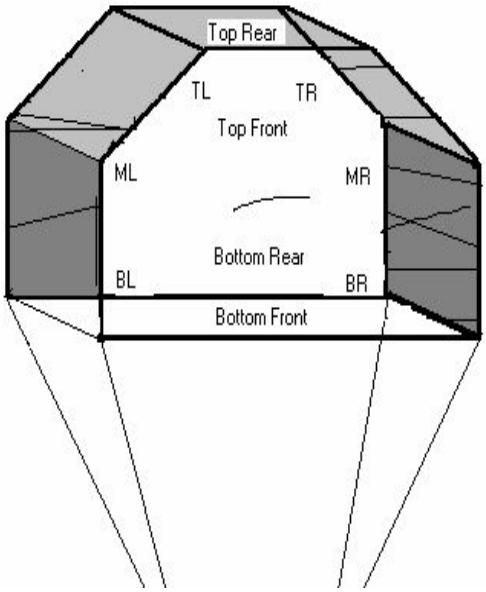


Fig :2 Illustrative diagram of octagonal blender and sampling locations.



Wet Granulation :

Tablet was manufactured by wet granulation method using ingredients shown in table no 1 . During manufacturing temperature NMT 25^{0}c & RH NMT 50% was maintained.. After dispensing of material they were sifted through sifter as shown in table no. 1 Metformin HCL, D.C.P & maize starch was dry mixed in RMG at slow speed for time intervals 5min, 10min & 15min. Granulating agent was prepared in steam kettle, maize starch for paste was dispersed in 1/3 quantity of P/W, remaining quantity in steam kettle with boiling to this sodium benzoate, PVP-K 30 & starch mucilage was added with stirring and cool 45 -50 ^{0}c. To

dry mix granulating agent was added and mixed on slow and high speed till desired consistency of dough mass was formed. Then this material was wet milled with multimill without mesh with impact forward slow speed. Drying in FBD was done at inlet temp 65^0c till outlet temp reaches 38-40^0c & LOD 2-3% w/w for 20min, 25min & 30min. Sizing was done by passing dried mass through 20 mesh sieve & retention generated passed through 1.5mm mesh of multimill knives forward, slow speed. Lubrication was done in octagonal blender after geometric mixing of sifted lubricant with sized granules at 14RPM, slow speed for 5min, 10min & 15min intervals.

Compression of Batches:

Tablets were compressed using 12.7mm, FB round Punch, having break line on

Upper punch & lower Punches plain. Each 605mg tablet contains 500mg metformin HCl. The specification for tablet was average weight 605mg(±5%) , hardness NLT 3kg/cm^2, thickness 3.60mm(±0.3mm), friability NMT 1%w/w, DT NMT 15

Min, Assay 100%(± 5%), Dissolution NLT 70% of stated amount released in 45 min.

Analysis[7-11]**:**

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 70ml p/w, sonicated & made volume 100ml, filtered it and from filtrate pipette out 10ml and diluted to 100ml with p/w again pipette out 10ml and diluted it 100ml with p/w and record absorbance .

Process validation stage, control variables and measuring justification[7-11]:

In sifting sieve integrity before and after. Dry mixing uniformity, the samples are withdrawn (5,10&15min) as shown in fig 1 and analyzed. Consistency of paste was evaluated in preparation of granulating agent. Wet mixing dough mass consistency was evaluated by studying speed of chopper & beater, time of mixing and ampere reading. Drying stage LOD obtained within predefined interval of drying. Representative samples was selected for evaluation of % fine, LOD, BD & CI. Lubrication stage uniformity of mixing, the samples were withdrawn as per fig 2 with predefined time interval (5,10&15min) and representative samples was studied for %fine, LOD, BD & CI. Compression stage speed challenge study was done by compression of 30% batch at minimum speed (16 RPM), 30% at maximum speed (35 RPM) & remaining at optimum speed (25RPM) & parameter evaluated were appearance, weight variation, thickness, hardness, DT, friability, assay & dissolution.

Table No 1:Composition of various process validation batches.

Ingredient	PVB -1	PVB -2	PVB-3	Mesh
Metformine HCL	100kg	100kg	100kg	40
Maize Starch	1.640kg	1.640kg	1.640kg	60
DCP	7.600kg	7.600kg	7.600kg	100
PVP-K30	1.100kg	1.100kg	1.100kg	100
Maize Starch (Paste)	5.500kg	5.500kg	5.500kg	100
Sodium benzoate	0.080kg	0.080kg	0.080kg	100
Purified water	12 L	12 L	12 L	-
Purified Talc	1.436kg	1.436kg	1.436kg	80
Magnesium Sterate	1.494kg	1.494kg	1.494kg	80
SSG	2.150kg	2.150kg	2.150kg	80
Total Batch Size	121g	121g	121g	

DCP= Dicalcium phosphate,SSG=Sodium starch Glycolate,P/W=purified water.

Table No2 :Dry mixing results.

PVB No.	% RSD		
	5 min	**10 min**	**15 min**
1	1.9276	0.4370	1.3063
2	1.8185	0.9036	1.0952
3	1.7845	0.8695	1.2213

% RSD was calculated by taking mean of assay of all 10 locations [{Top(Four location), middle(Two location) & bottom(Four location)}].

Table No 3:Wet mixing results.

PVB No.	**Chopper (Speed & Time)**		**Beater (speed & time)**		**Ampere Reading**	**Dough mass Consistency**
speed	Slow	fast	Slow	Fast		
1	2 min	4 min	3 min	4 min	12 Amp	Excellent
2	2 min	4 min	3 min	4 min	12 Amp	Excellent
3	2 min	4 min	3 min	4 min	12 Amp	Excellent

Table No 4:Drying stage results.

PVB No.	**Loss on Drying LOD (%w/w)**								
Time	20 min			25 min			30 min		
Layer	T	M	B	T	M	B	T	M	B
1	4.20	4.80	5.05	3.40	3.00	3.10	2.00	1.75	2.30
2	4.00	4.80	4.80	2.50	2.20	2.60	2.30	2.00	2.00
3	4.05	3.58	4.50	2.55	2.35	3.00	2.20	2.55	2.00

T=Top M=Middle B=Bottom

Table No 5:Sizing stage results.

PVB No	**% Fine**	**% LOD**	**BD**	**CI %**
1	34.10	2.60	0.8269	3.4750
2	38.90	2.40	0.8069	3.8080
3	36.04	2.8	0.8070	4.2050

BD= Bulk density(gm/ml), CI= Compressibility index (%)

Table No 6: Lubrication stage results.

PVB No.	**% RSD**			**% Fine**	**% LOD**	**BD (gm/ml)**	**% CI**	**%Yield Sizing**
Time	**5 min**	**10 min**	**15 min**					
1	1.9752	0.8120	1.3308	35.48	2.50	0.7878	3.1314	97.80
2	1.7845	0.8695	1.2213	32.46	2.80	0.8010	2.4010	98.70
3	1.8435	1.0842	1.2135	34.20	2.30	0.7820	3.4020	96.90

% RSD was calculated by taking mean of assay of all 10 locations [{Top(Four location), middle(Two location) & bottom(Four location)}].

Table No 7: Compression stage results.

Parameter	Speed	PVB -1	PVB-2	PVB-3
Appearance	Minimum	Ok	ok	ok
	Maximum	Ok	ok	ok
	Optimum	Ok	ok	ok
Uniformity of weight (%)	Minimum	±4.0	±4.2	±4.0
	Maximum	±4.2	±4.0	±4.4
	Optimum	±3.0	±2.8	±2.5
Thickness (mm)	Minimum	3.50-3.70	3.50-3.75	3.58-3.70
	Maximum	3.56-3.72	3.60-3.72	3.56-3.77
	Optimum	3.55-3.70	3.58-3.72	3.60-3.70
Hardness (Kg/cm^2)	Minimum	4.2-6.2	4.2-6.8	4.5-6.5
	Maximum	4.0-5.2	4.0-5.0	4.0-5.2
	Optimum	4.2-5.2	4.2-5.0	4.0-5.2
Disintegration time(min)	Minimum	8	7	8
	Maximum	7	7	8
	Optimum	7	8	7
Friability (%w/w)	Minimum	0.7270	0.7270	0.7370
	Maximum	0.6880	0.7880	0.6880
	Optimum	07876	07886	07376
Assay (%w/w)	Minimum	102.5902	100.2430	101.3365
	Maximum	99.6200	99.7420	99.4322
	Optimum	100.4970	101.4870	100.0276
Dissolution (%)	Minimum	87.9650	89.9870	89.7116
	Maximum	90.5200	90.0020	90.1178
	Optimum	90.3000	89.7190	89.7218
Yield of batch (%)		98.50	97.20	96.00

Results and discussion:

Integrity of sieve before and after was satisfactory for all PVBs. 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 beater & chopper 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 % fine, LOD, BD & CI result was shown in table no 6. Compression stage speed challenge study shown in table no 7.

Conclusion :

The selected sieve was suitable for sifting. Uniformity of dry mixing is excellent in 10min because % RSD found 0.4370-0.9050%. Granulating agent were prepared of desired consistency. Dough mass was formed satisfactory within 7min wet mixing & ampere reading 09-11 Amp. Drying time 30 min is suitable for achieving LOD 2-3%. Evaluation parameter of sizing shows effective LOD, %fine, BD & CI. Lubrication stage uniformity was achieved with 10min because % RSD found 0.8120-1.0842% and flow properties was satistisfactoty. Compression machines optimum speed (25RPM) was satisfactory for effective compression. Therefore based on results PVBs 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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