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Studies in Prospective Process Validation of Gliclazide Tablet 80 mg Dosage Formulation

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Abstract: The purpose of research was to study prospective process validation of Gliclazide Tablet 80 mg after successful completion of the Optimization batch of solid dosage formulation. The critical process parameter was identified with the help of optimization batch(s) of process capability and evaluated by challenging specification. Three process validation batches (1009G0519, 1009G0520 & 1009G0521) of same size, manufacturing process, 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. 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 - Gliclazide, 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 results 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:

Gliclazide BP (Bal Pharma Ltd.), Microcrystalline cellulose (Avicel PH 102) USP/NF (FMC Biopolymer), Maize Starch BP/EP (Roquette,Signet), Povidone (Plasdone K 29/32) USP/ NF (ISP Technologies), Sodium Starch Glycolate USP/NF(Roquette,Signet), Purified Talc (Lozenac pharma, Signet), Colloidal Anhydrous Silica (Aerosil 200) BP/EP (Evonik Industeries), Magnesium sterate (Healthcare Ltd.) and Purified Water was used for this Formulation. All material used of USP/NF/BP grade and chemicals used in the analysis in the study were of analytical grade.

Machineries:

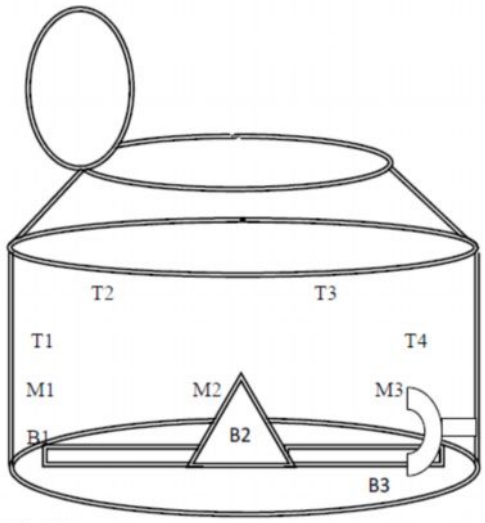
Machineries and equipments used was as sifter, multimill (Ganson Ltd), rapid mixing granulator [RMG] (100L, Kevin make), steam kettle (Anchor mark), drier [trey], octagonal blender (100L, Anchor mark), compression machine 16 station single rotatory (Cadmach), UVvisible spectrophotometer (Jasco), HPLC (Shimadzu 1800), six stage dissolution rate test apparatus (Tab machine), Monsanto hardness tester (Rollex), disintegration and friability test apparatus (Electo lab), Mitutoyo thickness tester.

Table No 1: Composition of various process validation batches.

Ingredients	Process Validation Batch No.			Mesh
	1009G0519	1009G0520	1009G0521	
Gliclazide	4.000	4.000	4.000	20
Microcrystalline cellulose (Avicel PH 102)	5.095	5.095	5.095	20
Maize Starch	1.485	1.485	1.485	60
Povidone (Plasdone K 29/32)	0.100	0.100	0.100	60
Sodium Starch Glycolate	0.150	0.150	0.150	40
Purified Talc	0.090	0.090	0.090	40
Colloidal Anhydrous Silica	0.0150	0.0150	0.0150	40
Magnesium sterate	0.050	0.050	0.050	60
Purified Water	4.000	4.000	4.000	---

MCC- Microcrystalline Cellulose, SSG- Sodium Starch Glycolate, P/W- Purified Water.

Fig no:1 Illustrative diagram of RMG and sampling locations

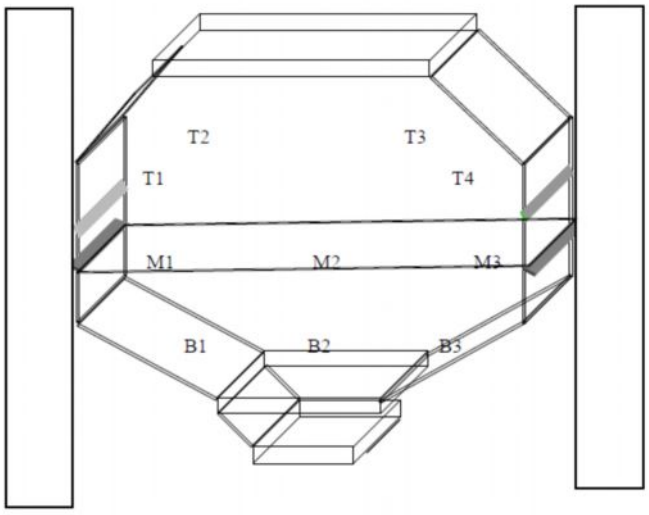


Top: - T1, T2, T3, T4

Middle:-M1, M2, M3

Bottom: - B1, B2, B3

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



Top: - T1, T2, T3, T4

Middle: - M1, M2, M3

Bottom: - B1, B2, B3

Wet Granulation:

Tablet was manufactured by wet granulation method using ingredients shown in table no 1. Required quantity of Materials was weighed. Materials were sifted through sifter as shown in table no. 1 Gliclazide, MCC (PH 102) & maize starch (2.20 kg) was dry mixed in RMG at slow speed for time intervals 10min, 12min & 15min. and sampling was done to check the uniformity of Mixing and results were illustrated. Granulating agent was prepared as Purified water (6 kg) heated up to 80^{oC} and Povidone (Plasdone K 29/32) was added. Stirring was done up to complete dissolution of Povidone (Plasdone K 29/32), same time slurry of Maize starch (1.10 kg) was prepared with purified water (2 kg) and the slurry was added in the boiling solution of the Povidone (Plasdone K 29/32) under constant stirring till the time translucent, homogenous paste was obtained and cooled up to 50°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 passed through 10 # through sifter. Drying in dryer was done at temp 50^0C & LOD 3% w/w for 25min, 30min & 35min. Sizing was done by passing dried mass through 20 mesh sieve & retention generated passed through 1.5mm screen of multimill knives forward, slow speed. Lubrication was done in octagonal blender mixing of sifted lubricant with sized granules at 12 RPM, slow speed for 10min, 12min & 15min intervals and sampling were done and results were illustrated. After that by adding Magnesium Stearate 5 min. mixing was done and sampling was done after 5 min. and results were illustrated.

Compression of Batches:

Tablets were compressed using 8.5mm, round shape, flat Punch, having break line on Upper punch & lower Punches plain. Each 220mg tablet contains 80mg Gliclazide. The specification for Dry mixed & Lubricated Blend was between 95% to 105 % of label claim for Assay and for tablets tablet was average weight 220 mg (±7.5%) , hardness NLT 4kg/cm^2, thickness 3.00mm (±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]:

Formulation Samples was Subjected to HPLC by keeping flow rate 0.9 ml/min, wave length 235 nm, injection volume 20 µl, column 250mm X4.0mm X4µm with compartment temperature Ambient. Quantity equivalent to 800mg of Gliclazide in 200 ml Acetonitrile, concentration of Gliclazide was about 0.8mg/ml taken for assay.

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

In sifting sieve integrity before and after. Dry mixing uniformity, the samples are withdrawn (10, 12&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 were selected for evaluation of % fine, LOD, BD & CI. Pre-Lubrication stage uniformity of mixing, the samples were withdrawn as per fig.2 with predefined time interval (10, 12&15min). Lubricated stage composite sample collected after 5 min of addition of Magnesium Stearate, representative samples was studied for % fine, BD & CI. Compression stage speed challenge study was done by compression of 30% batch at minimum speed (10 RPM), 30% at maximum speed (25 RPM) & remaining at optimum speed (20RPM) & parameter evaluated were appearance, weight variation, thickness, hardness, DT, friability, assay & dissolution.

Table No 2: Dry Mixing Results

Process Validation Batch No.	% RSD		
	10 min	**12 min**	**15 min**
1009G0519	1.2400	1.0099	0.3998
1009G0520	0.4659	0.9638	1.4857
1009G0521	0.7182	0.8721	1.3527

% RSD calculated by taking mean of the assay of all 10 locations
[{Top (Four Location), Middle (Three Location) & Bottom (Three Location)}].

Table No 3: Wet Mixing Results

Process Validation Batch No.	Chopper (Speed & Time)		Beater (Speed & Time)		Ampere Reading	Dough Mass Consistency
Speed	Slow	Fast	Slow	Fast		
1009G0519	3 min	5 min	4 min	6 min	14 Amp	Excellent
1009G0520	3 min	5 min	4 min	6 min	14 Amp	Excellent
1009G0521	3 min	5 min	4 min	6 min	14 Amp	Excellent

Table No 4: Drying stage Results

Process Validation Batch No.	Loss on drying LOD (% W/W)								
Time	25 min			30 min			35 min		
Layer	T	M	B	T	M	B	T	M	B
1009G0519	2.80	2.76	2.82	2.75	2.70	2.79	2.64	2.59	2.53
1009G0520	2.90	2.86	2.82	2.80	2.76	2.75	2.60	2.65	2.63
1009G0521	2.85	2.71	2.83	2.69	2.61	2.72	2.59	2.68	2.60

T =Top, M=Middle, B= Bottom

Table No 5: Sizing stage results

PVB No.	**% Fine**	**BD**	**CI %**
1009G0519	34.10	0.823	3.475
1009G0520	38.90	0.806	3.808
1009G0521	36.04	0.807	4.205

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

Table No 6: Pre-Lubrication stage results

PVB No.	**% RSD**		
Time	10 min	12 min	15 min
1009G0519	0.5370	2.7316	1.1286
1009G0520	0.2595	0.8876	0.6088
1009G0521	1.4691	0.4867	0.3510

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

Table No 7: Lubrication stage results

PVB No.	Assay %	**% Fine**	**BD (gm/ml)**	**% CI**
Time	5 mins.			
1009G0519	100.62	36.25	0.765	2.873
1009G0520	99.74	34.67	0.679	2.579
1009G0521	99.52	37.24	0.704	3.025

 # Composite sample results of Assay, % Fine, BD, % CI

Table No 8: Compression stage results

Parameter	Speed	Batch No.		
		1009G0519	1009G0520	1009G0521
Appearance	Minimum	Ok	Ok	Ok
	Maximum	Ok	Ok	Ok
	Optimum	Ok	Ok	Ok
Uniformity of weight (%)	Minimum	± 4.0	± 4.2	± 4.4
	Maximum	± 4.4	± 4.0	± 4.4
	Optimum	± 3.5	± 3.4	± 2.8
Thickness (mm)	Minimum	2.90 -3.10	2.98 -3.15	2.86 -3.09
	Maximum	2.85 -3.14	2.92 -3.19	2.89 -3.21
	Optimum	2.87 -3.12	2.88 -3.17	2.96 -3.20
Hardness (Kg/cm^2)	Minimum	5- 8	6-7.5	6-8.5
	Maximum	5.5-7.5	5-8	5.5-8
	Optimum	6- 8	6-8.5	6-7.5
Disintegration time(min)	Minimum	6 min 12 sec	6 min 20 sec	6 min 19 sec
	Maximum	6 min 10 sec	5 min 59 sec	6 min 25 sec
	Optimum	6 min 29 sec	6 min 09 sec	6 min 11 sec
Friability (%w/w)	Minimum	0.35	0.43	0.39
	Maximum	0.45	0.39	0.40
	Optimum	0.49	0.37	0.32
Assay (%w/w)	Minimum	100.12	99.89	100.45
	Maximum	99.20	98.67	99.58
	Optimum	99.50	99.94	100.38
Dissolution (%)	Minimum	98.12	99.02	97.15
	Maximum	97.42	98.65	99.35
	Optimum	98.52	99.82	97.85

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 4% 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. At Pre-Lubrication stage uniformity of mixing was obtained by assay of 30 locations per batch & % RSD (must be NMT 4% for effective mixing) was calculated by mean assay of all location as shown in table no 6.At the lubrication stage blend obtained by assay composite locations per batch & results were illustrated . The % fine, BD & CI result was shown in table no 7. Compression stage speed challenge study has shown in table no 8.

Conclusion:

The selected sieve was suitable for sifting. Uniformity of dry mixing is excellent in 12 min because % RSD found between 0.8721 1.0099. Granulating agent was prepared of desired consistency. Dough mass was formed satisfactory within 7min wet mixing & ampere reading 14 Amp. Drying time 30 min is suitable for achieving LOD NMT 3%. Evaluation parameter of sizing shows effective LOD, %fine, BD & CI. Pre-Lubrication stage uniformity was achieved with 15min because % RSD found 0.3510% to 1.1286 % and flow properties were satisfactory. 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 Gliclazide 80 mg 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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