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DEVELOPMENT OF GENERIC CONTROLLED RELEASE TABLET: AN INDUSTRIAL APPROACH

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ABSTRACT The purpose of this study was to develop a generic prolonged release tablet formulation using Gliclazide for Europe market, which is stable and bioequivalent to Diamicron MR 30 mg tablet of Servier laboratories, France. This paper will provide a summary of the different development stages of gliclazide prolonged release tablet and elloborate formulation and process factors impacting drug release pattern. Tablets were prepared through wet granulation in high shear granulator by using Hypromellose K 4 M and Hypromellose E 15 LV with hydrophobic diluent dibasic calcium phosphate. A non aqueous solution of low viscosity Hypromellose 2910 (5cps) (HPMC E-5) is used as binder. The manufacturing process (Effect of Active particle size distribution, Effect of dry mixing in RMG, Effect of Kneading time, Effect of Loss on drying (LOD), Sifting and milling, Effect of pre lubrication and Lubrication time and hardness challenges were carried to check the desired impact on drug release of prolonged release tablet in order to recommend Control strategy. Tablets were analyzed for multimedia dissolution in pH 7.4, pH 6.8 and pH 5.5 phosphate buffer, assay, related substances initially as well as in stability study. Similarity factor (f2) value of generic tablet to marketed product in pH 7.4, 6.8 and 5.5 phosphate buffer is 70.15, 68.36 and 61.59 respectively. Final formulation showed similar dissolution profile in multimedia with the marketed formulation.

KEYWORDS : Gliclazide, matrix tablet, formulation optimization, process optimization, alcohol dose dumping, Multimedia dissolution.

1. Introduction

Diabetes caused due to the inappropriate functioning of pancreatic cells where person suffer from high sugar levels in the bloodstream and which leads to decrease or absence of secretion of insulin in the body or the cells of the body become insensitive to the insulin, produced by the pancreatic cells[1]. Middle-aged persons are suffering mainly from diabetes. [2] millions of patient are increasing per year as per report of World health organization (WHO)[3,4]. Gliclazide, a sulphonylurea used when dieting and exercise are not enough to handle the rise in glucose level. PKa value of 5.8 confirms it weak acid nature and also lipophilicity is confirmed by log P value of 2.6 and shows different solubility at different pH [5]. Biopharmaceutical system (BCS) classifies Gliclazide as Class II molecule. [6]

Extended release drug delivery systems can be used to overcome the above mentioned limitations. Extended release drug delivery systems are designed to deliver drugs specific target tissues at the right amount, at and for the right amount of time and with minimum of side effects. These systems help to achieve prolonged therapeutic effect by continuously releasing the drug over an extended period of time after administration of a single dose. The blood level oscillations by multiple dosing of conventional dosage forms are reduced as a more even and effective drug level is maintained. The safety margin of high potency drugs can be increased and incidence of both local and systemic side effects can be reduced in sensitive patients.

Hydroxypropyl methylcellulose (HPMC) is most commonly used water swellable release retardant [11] among the other available polymers used nowadays in the pharmaceutical industry for developing modified release drug delivery. [12]. High aqueous and pH-independent solubility are best behaviors of hypromellose. Gel forms after swelling of HPMC due to absorption of water and which help to form pores and through which drug start permeating at predetermined rate and time. Different grades of HPMC were used as a release retardant in the design of this matrix based modified release Gliclazide tablet.

The inventive concept was a patent non infringing, matrix tablet as generic for Europe/US/ROW (Rest of world) markets prepared through aqueous wet granulation technique using cellulose derivative without any binder. Gliclazide modified release tablet 30 mg is capable of maintaining the desired dissolution profile upto 24 hours after beginning of dissolution, has identical dissolution profile as compared to reference product Diamicron MR 30 mg tablet of Servier lab, France which is one the most important factor for acceptance of generic tablet in market?

Rationale and objective of the research work were to develop a generic prolonged release hydrophilic matrix tablet containing 30 mg of Gliclazide which will be comparable to reference product Diamicron MR 30 mg tablet of Servier lab, France in terms of quality, safety and efficacy. F2 value (similarity study) of the in vitro dissolution of these two formulations (test and reference prolonged release tablet) have been performed in four different dissolution media (pH 5.5 phosphate buffer, pH 6.8 phosphate buffer and pH 7.4 Phosphate buffer) and found comparable. In vitro alcohol dose dumping studies were performed on test tablets using 0 %, 5 %, 20 % and 40 % ethanol with pH 7.4 phosphate buffer and found test product is alcohol resistant. The investigators found that the studied formulation enables the prolonged and reproducible release of Gliclazide and having identical in vitro dissolution profile as comparAed to reference formulation.

2. Materials & methods

2.1. Materials

The detailed list of the excipients/raw materials used in the preparation of Gliclazide 30 mg, prolonged drug release tablet is given in Table 1. Diamicron modified release tablet 30 mg, (Reference listed drug-RLD) procured form Servier laboratories Ireland. All other solvents and reagents were of analytical grade and used as provided.

Table 1: Suppliers for raw material

Excipient		Function	Purchased/ Procured from
Gliclazide	PSD : D_{50} : 15.20 micron D_{90} : 51.25 micron	Active drug substance	Bal Pharma Limited, Mumbai, India
	PSD : D_{50} : 5.25 micron D_{90} : 11.02 micron		

Hypromellose (Methocel E15 LV) 15 cps	Release retardant	Colorcon, India
Hypromellose (Methocel K 4 CR) 4000 cps	Release retardant	Colorcon, India
Hypromellose (Methocel E5) 5 cps	Binder	Colorcon, India
PVP K-30	Binder	Signet
Dibasic calcium phosphate (Calipharm A)	Diluent	Innophos, USA
Isopropyl Alcohol	Granulation agent	Merck
Methylene Chloride	Granulation agent	Merck
Magnesium Stearate	Lubricant	Peter greven, Germany.

2.2. Methods

2.2.1.Preparation of matrix tablet

Eight different formulations were prepared, by varying the type of release retardant and keeping the drug amount (18.75% w/w) and the total tablet weight constant. Tablets were prepared using different grades of Hypromellose in intragranular and extragranular phase through wet granulation using Isopropyl alcohol and methylene chloride as granulating fluid. Compression (with a rotary tablet press at a force of 80-100 N) of the components previously sieved i.e., Gliclazide, HPMC K4 M (#40 mesh) and Dibasic calcium phosphate (#60 mesh) and mixed for 10 min in a rapid mixer granulator (Bowman and Archer pharma machines, Mumbai, India). Granulate the dry blend with binder solution of HPMC E 5/ PVP K30 (Bathc #002) for 10 minutes. Dry the granules in FBD (Bowman and Archer pharma machines, Mumbai, India) at 40˚ C ± 5 to obtain LOD of NMT 1.5 %. Dried granules were then passed through 30 mesh and retains were milled through a 0.8 mm screen and again pass through (#30 mesh). Put the sifted granules in double cone blender. Pass the dried granules from (#60) mesh using Vibro sifter without force, collect (#60) retain and (#60) pass granules separately. Add previously sifted HPMC E15 LV to dried #60 pass granules in double cone blender at 20 RPM for 10 minutes. Add (#60) retain granules and previously sifted (#60) mesh magnesium stearate to double cone blender and blend in double cone blender at 20 RPM for 5 minutes. The mixtures were checked for blend uniformity prior to tabletting (coefficient of variation (C.V.) of the mixing index 5%) and particle size distribution, bulk density, tapped density, Haunser ratio and compressibility index. Weight uniformity of the tablets was controlled (OHAUS CORPORATION USA, PAG413C) (C.V.±2%). Qualitative and quantitative composition of development batches is given in table 2.

Table 2: Qualitative and quantitative composition of the development batches

Ingredients	Spec	30 mg prolonged release tablet								
		#001	#002	#003	#004	#005	#006	#007	#008	#009
Intragranular										
Gliclazide	Ph.Eur	30	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30
DCP (Calipharm A)	Ph.Eur	85.69	86.8	93.25	93.25	93.25	93.25	93.25	93.25	58.93
HPMC K 4M	Ph.Eur	18.41	17.30	17.30	17.30	17.30	17.30	17.30	17.30	17.30
HPMC E15 LV	Ph.Eur	14.7								
Binder										
HPMC E5	Ph.Eur	--	--	2.15	2.15	2.15	2.15	2.15	2.15	2.15
PVPK-30	Ph.Eur	9.60	8.60	--	--	--	--	--	--	
Methylene Chloride	Ph.Eur	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	
Extragranular										
HPMC E15 LV	Ph.Eur	--	15.70	15.70	15.70	15.70	15.70	15.70	15.70	50.02
Magnesium stearate	Ph.Eur	1.60	1.60	1.60	1.60	1.60	1.60	1.60	1.60	1.60
Tablet Weight		160.0	160.0	160.0	160.0	160.0	160.0	160.0	160.0	160.0
Intra batch Variability		Trial as per available patents and literatures	Trial reducing concentration of PVP K 30 to increase release.	Trail using HPMC E5 as High impurity level with combination of PVP K30 and magnesium stearate	D50 : 15.20 micron D90 : 51.25 micron	D50 : 5.25 micron D90 : 11.02 micron	Kneading time 5 min	Kneading time 8 min	Optimization of Blending time (5/10 /15 min) and Lubrication time (3/5 min) and Hardness challenges (40-60/60-100/80-100)	Discriminatory dissolution study (Negative Trial)

2.2.3Measurement of flow of granules

2.2.3.1Hausner ratio and Carr's compressibility index (CI): The bulk and tapped densities of granules of respective formulation were determined as the volume before and after 100 taps, respectively. The Hausner ratio was determined as the ratio of the bulk density to the tapped density as per given formula.

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

CI was determined as the percentage ratio at which the granules were packed down to the tapped density. The Hausner ratio may be related to the compressibility of the powder and values of <1.25 is indicative of good compressibility. The CI may be indicative of flowability and degree of packing of the material, which are relevant properties when filling the matrices of the tablet press. CI of <15% indicates an adequate flow of powders and stable packing, while values of >25% are characteristic of poor flow properties.

$$CI = 100 X \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}}$$

2.2.4Physicochemical characterization of matrix tablet

2.2.4.1.*Thickness*: The thickness of the tablets was determined using Vernier calliper and the results were expressed as mean values of 10 determinations, with standard deviations.

***2.2.4.2.Weight variation*:** To study weight variation, 20 tablets of each formulation were weighed individually using four decimals digital electronic balance (METTLER-TOLEDO AJ150, Switzerland).

***2.2.4.3.Resistance to crushing (Hardness)*:** For each formulation batch (#001 to #008), the resistance to crushing (hardness) of 10 whole tablets, were determined using hardness tester (ERWEKA TBH-28, Germany). The tablet is placed between the jaws, taking into account the shape, the break mark and the inscription. The tablet was oriented in the same way with respect to the direction of application of the force. The measurement was carried out on 10 tablets, taking care that all fragments have been removed before each determination. The results are expressed in the values of the forces measured; all expressed in newtons. The tablet compression machine was suitably adjusted to produce tablets of uniform weight and thickness. Tablet hardness was checked at the start, middle and end during the compression process to control an acceptable range of tablet hardness.

***2.2.4.4.Friability*:** For each formulation batch (#001 to #008) the tablets (equivalent to 6.5 gm of weight) were placed on a sieve, and any

loose dust was removed with the aid of the brush. The tablet sample was accurately weighed and placed in the drum. It was rotated 100 times, and the tablets were taken out. Any loose dust from the tablets was removed as before. The friability is expressed as the loss of the mass and it is calculated as a percentage of the initial mass.

***2.2.4.5.Uniformity of weight*:** Ten tablets of each formulation weighed individually. Minimum, maximum and average value of the weight was determined and noted.

***2.2.4.6.Drug content*:** Total 20 whole tablets were weighed and crushed to powder; tablet powder equivalent to 100 mg of Gliclazide was accurately weighted and transferred into a 100 ml volumetric flask. 70 ml of acetonitrile is added and sonicated for 10 minutes. The solution was cooled to room temperature and made up to mark with acetonitrile; the prepared sample was filtered through 0.45m PVDF filter. The 5.0ml filtered solution was diluted to 50ml with diluent in a volumetric flask (About 100 µg/ml of Gliclazide). The final samples were filtered through a 0.45 µm diameter membrane before injection into HPLC system UV/PDA detector (Agilent 1200, USA) with the following chromatographic conditions: Mobile phase: mixture of 600 ml mili-Q water, 400 ml acetonitrile , 1.0 ml of trifluoroacetic acid and 1.0ml of triethylamine, Zorbax Eclipse XDB C8 Rapid resolution (150 x 4.6 mm) 3.5G or equivalent column), mobile phase flow rate of 1.0 ml/minute at 25˚C ± 1˚C, the injection volume of 10.0 µl, and the UV detector set at a wavelength of λ = 220 nm.

***2.2.4.7.Uniformity of dosage units by content uniformity*:** The content uniformity was determined by HPLC method. Transfer 1 whole tablet individually of optimized formulation) to a 100 ml volumetric flask. Add about 40 ml of acetonitrile and sonicate for about 5 minutes. Add 20 ml of water, again sonicate for 25 minutes. Cool, and dilute to volume with water, shake well. Filter the content through 0.45 µm nylon syringe filter, discarding first 3 ml of filtrate. Dilute 7 ml filtrate to 10 ml with diluent, and mixed. (Test repeated for remaining 9 tablets). The final samples were filtered through a 0.45 µm diameter membrane before injection into HPLC system UV/PDA detector (Agilent 1200, USA) with the following chromatographic conditions: Mobile phase: mixture of 600 ml mili-Q water, 400 ml acetonitrile , 1.0 ml of trifluoroacetic acid and 1.0ml of triethylamine, Zorbax Eclipse XDB C8 Rapid resolution (150 x 4.6 mm) 3.5G or equivalent column), mobile phase flow rate of 1.0 ml/minute at 25˚C ± 1˚C, the injection volume of 10.0 µl, and the UV detector set at a wavelength of λ = 220 nm.

2.2.4.8.In vitro release studies: Dissolution studies to determine drug release from six whole tablets were performed according to the In-house method, apparatus USP type 2 (Paddle 50 rpm), 900 ml of pH 5.5 phosphate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer for dissolution. 10 ml aliquots were collected from a midway zone between the surface of the dissolution medium and the top of the rotating paddle of each vessel at specified time intervals (1,2,,3,4, 6,8,10,12,16,20 and 24 hours) for the 24 hour dissolution study. After collection, the samples were filtered through a 0.45 µm nylon syringe filter. A 5 ml of the filtrate diluted to 10 ml with dissolution medium and mixed. Absorbance at the wavelength of maximum at 226 nm for standard and 290 nm for sample solution was measured on UV Vis spectrophotometer using dissolution media as blank. As correction difference in absorbance reading at 226 nm and 290 nm is calculated. Gliclazide dissolution profiles are presented as percent drug release versus time curves. A model independent approach was recommended in FDA guidance using similarity factor (f2) as one of the mathematical models of dissolution to compare between the release data of two dissolution profiles, one is the test and the other is the reference at different time intervals (FDA, 2000), as the following equation:

$$f_2 = 50 \log_{10} \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t (Rt - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

2.2.4.9.Alcohol induced dose dumping study

To determine the effect of ethanol on drug release of optimized formulation, whole tablets and halved tablet are subjected for dissolution in pH 7.4 phosphate buffer with 0%, 5%, 20% and 40% ethanol and samples were withdrawn for 0.5,1,2,3,4,5,6,8,10,12,14,16,20 and 24 hours and analyzed with the same method given in dissolution studies.

2.2.4.1.0.Release kinetics

To study the mechanism of drug release from the matrix tablet, Zero Order, First Order, Higuchi equation and Korsmeyer-Peppas equation was selected as a model dependent approach to characterize the dissolution profile [26–31]. The model which gave the highest coefficient of determination (R^2) was considered to be the most suitable kinetic model for describing the release of Gliclazide from the matrix tablet.

***2.2.4.1.1.*Discriminatory Dissolution study**

To determine if a dissolution method can discriminate product changes, the method must be challenged. In conducting the challenge, the change in the drug product is evaluated versus the change in the dissolution data. If the data show a measurable difference for the key variables, then the method may be considered a discriminating test for critical manufacturing variables. Dissolution studies to determine drug release from six whole tablets were performed according to the In-house method, apparatus USP type 2 (Paddle 50 rpm), 900 ml. Based on the solubility data, innovator dissolution profile upto 12 hours and drug retention in intestine as per literature. pH 6.8 phosphate buffer was selected as the dissolution medium to study discriminatory power. 10 ml aliquots were collected from a midway zone between the surface of the dissolution medium and the top of the rotating paddle of each vessel at specified time intervals (1,2,,3,4, 6,8,10,12,16,20 and 24 hours) for the 24 hour dissolution study.

2.2.4.1.2Process optimization study

Manufacturing process development studies were conducted at the 5 kg scale up batch, corresponding to 31,2500 units for 30 mg. Dibasic calcium phosphate (Calipharm A) is selected as diluent, Hypromellose E 15LV and Hypromellose K4 MCR as release retardant, Hypromellose E-5LV as binder and Magnesium stearate as lubricant. The manufacturing process (Effect of Active particle size distribution, Effect of Kneading time, Effect of Lubrication time and hardness challenges were carried to check the desired impact on drug release of prolonged release tablet in order to recommend Control strategy) was optimized based on optimization studies conducted to study the effect of processing parameters on the granule characteristics such as bulk and tapped density and tablet characteristics such as hardness, thickness, Assay, related substances and dissolution profile.

3. Results and discussion

3.1. Measurement of flow of granules

Bulk density and TD was found to be uniform among different batches of the granules and ranged from 0.510 gm/mL to 0.576 gm/mL and 0.645 gm/mL to 0.697 gm/ml. The Hausner ratio and Compressibility index of the granules of all batches ranged from 1.18 to 1.367 and 15.419 to 26.829, respectively (Table 3). The flow of the granules is found to be passable as per Hausner ratio.

Table 3: Measurement of flow of granules.

Physical properties	Number of Batches								
	#001	#002	#003	#004	#005	#006	#007	#008	#009
Bulk density (g/ml)	0.53	0.518	0.529	0.537	0.531	0.546	0.576	0.539	0.510
Tapped density (g/ml)	0.69	0.645	0.648	0.668	0.66	0.671	0.681	0.649	0.697
CI	22.77	19.690	18.364	19.611	19.545	18.629	15.419	16.949	26.829
HR	1.29	1.245	1.225	1.244	1.243	1.229	1.182	1.204	1.367
Flow as HR	Passable	Passable	Passable	Passable	Passable	Passable	Passable	Passable	Passable

3.2. Physicochemical Characteristics of Tablet

3.2.1.Physicochemical characterization

The produced tablets (Formulations 1–10, Table 4); had a thickness ranged from 2.77 mm to 3.18 mm. Weight variation of produced tablet ranged from 155 mg to 164 mg. The resistance to crushing and percentage friability of the tablets of all batches ranged from 80 N to 120 N and 0.07% to 0.12%, respectively. The results of drug content for tablet containing Gliclazide are summarized in Table 10 and ranged from 97.26 % to 101.71 %. The results of content uniformity studies for whole tablets containing Gliclazide are summarized in Table 11 which show the percentage of drug present in each tablet (n=3), standard deviation (S.D.) and Acceptance value (A.V.) for optimized formulation batch, Trail #006. The contents of Gliclazide in each tablet

fulfilled pharmacopeia requirements. Determination of the content uniformity of Gliclazide in our batch, both for whole and halved tablets was carried out by HPLC method. The procedure was performed on ten whole tablets and ten halves separately. According to the Ph. Eur. (Rfrnc), the content uniformity of active substance expressed as a percentage of the declared content should be within the limits of 85-115 and relative standard deviation (R.S.D.) should be equal or smaller than 6. The results of the content uniformity analysis for the whole tablets were: 98.9 % with A.V of 1.65 (NMT 15), which fulfils Pharmacopoeial requirements.

Table 4: Physiochemical characterization for Matrix tablets.

Compression parameters	Batch Number								
	#001	#002	#003	#004	#005	#006	#007	#008C	#009
Thickness (mm)	2.78-3.06	2.88-3.18	2.77-3.05	2.9-3.1	2.89-3.08	2.91-3.11	2.91-3.10	2.88-3.12	2.8-3.1
Resistance to crushing (N)	80-110	80-120	100-120	100-120	100-120	100-120	100-120	100-120	110-140
Friability (%) at 100 rev	0.09	0.1	0.11	0.09	0.1	0.08	0.12	0.1	0.07
Uniformity of weight (mg)	157.162	155-163	159-164	156-162	158-162	159-160	157-162	158-164	157-163
Assay (Drug content) %	99.9	97.26	98.36	99.15	100.25	100.7	101.45	100.36	101.71
Punch dimension (mm)	105.0 X 4.5 mm, concave, oval shaped ,upper punch and lower punches plain								
Length (mm)	15.06	15.04	15.1	15.05	15.08	15.06	15.1	15.1	15.1
Width (mm)	7.49	7.51	7.52	7.48	7.49	7.49	7.51	7.51	7.5

Table 5: Uniformity of dosage units (by content uniformity) for final formulation Trail #008C.

Units	1	2	3	4	5	6	7	8	9	10	Average	SD	K	A. value
% drug	98.1	96.9	98.2	98.8	100.6	98.5	98.3	97.8	96.7	100.3	98.42	1.26	2.4	3.02

3.2.2.In-vitro drug release

Dissolution profile comparison in pH 7.4 phosphate buffer clearly distinguishes the dissolution profile of other formulations. Table 6 and figure 1indicates dissolution of RLD in pH 5.5, 6.8 and pH 7.4 phosphate buffer. Dissolution profile of optimized formulation (#008C) was found to be most comparable to reference listed drug Diamicron MR 30 mg tablet with the highest F2 value of 73.90 in pH 7.4 phosphate buffer amongst all the other studied batches. But other formulations don't show a desired dissolution pattern. Some are showing faster dissolution than Diamicron MR 30 mg tablet where others showing slower dissolution except Run Trial #006, which shows essentially similar dissolution profile when compared with RLD, F2 value is 67.82. Drug release in pH 7.4 buffer (Figure. 2) of development batches, in comparison to RLD is given Table 7. Drug release in pH 5.5 phosphate buffer and pH 6.8 phosphate buffer of optimized Tablet (Trail #008C) in comparison to RLD is given Table 8 and 9. When dissolution studies are carried out in pH pH 5.5 phosphate buffer (Figure 3) and 6.8 phosphate buffer (Figure 4) complete drug release achieved i.e. more than 85 % % in 24 hours , similarity factor, F2 is 72.47 and 69.34 where dissimilarity factor, F1 is below 15 i.e. 7.47 and 10.36 when compared with Reference listed drug.

Table 6: Dissolution of RLD in multimedia pH 5.5, 6.8 and 7.4 phosphate buffer.

Drug release in pH 5.5 ,6.8 and 7.4 phosphate buffer /900ml/paddle/50 rpm			
Time in Hours	RLD (153779) (pH 5.5 Phosphate buffer)	RLD (153779) (pH 6.8 Phosphate buffer)	RLD (153779) (pH7.4 phosphate buffer)
0	0	0	0
1	3.15	4.80	5.6
2	7.02	11.25	13.54
3	11.95	17.75	20.17
4	16.20	25.10	29.41
6	26.00	36.90	40.10
8	36.10	48.10	56.71
10	46.50	57.69	62.92
12	53.50	68.94	75.16
16	67.10	79.43	84.37
20	77.35	92.12	95.35
24	85.50	95.40	99.17

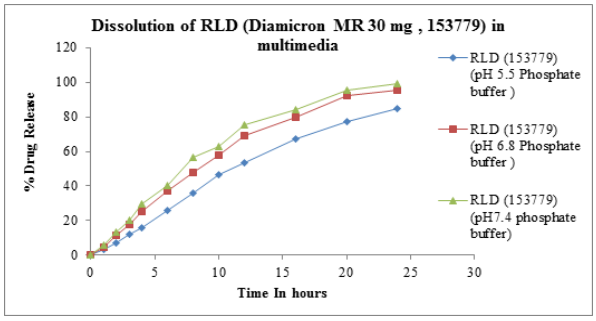

Figure 1. Dissolution of RLD (Diamicron MR 30, 153779) in multimedia

Table 7: Dissolution of RLD and Trial (1-9) in pH 7.4 phosphate buffer (Release media)

Time in Hours	RLD	#001	#002	#003	#004	#005	#006	#007	#008A (40-60N)	#008B (60-100N)	#008C (100-140N)	#009
0	0	0	0	0	0	0	0	0	0	0	0	0
1	5.6	6.15	6.12	7.15	7.62	6.98	6.00	5.96	3.50	4.12	5.50	2.30
2	13.54	15.6	14.6	15.64	16.45	14.39	14.01	15.36	10.31	11.36	13.64	10.64
3	20.17	20.1	19.3	20.72	23.14	21.90	20.41	18.45	16.15	18.24	19.13	15.47
4	29.41	26. 3	25.6	24.36	25.31	27.31	26.71	24.62	23.31	26.15	28.17	20.67
6	40.10	32.5	31.5	36.15	35.63	36.45	37.17	33.23	34.46	37.61	39.51	32.34
8	56.71	49.5	50.1	50.52	48.15	51.03	45.31	40.15	48.36	51.37	53.61	42.67
10	62.92	52.36	53.61	56.34	54.39	55.42	60.15	55.46	55.91	57.34	59.27	51.70
12	75.16	58.36	61.70	70.38	68.37	66.31	71.36	62.51	66.38	69.17	69.79	60.78
16	84.37	74.10	72.15	77.42	75.96	76.13	80.96	69.43	78.52	82.67	78.38	68.64
20	95.35	77.30	83.10	87.42	84.91	86.11	93.40	88.15	81.34	84.93	94.39	76.18
24	99.17	84. 1	83.1	87.15	88.91	90.37	95.14	93.41	90.8	92.67	99.37	84.37
F1		**15.78**	**14.21**	**10.87**	**12.25**	**10.18**	**6.22**	**15.39**	**10.87**	**13.47**	**5.46**	**21.09**
F2	**NA**	**50.46**	**53.70**	**59.92**	**58.92**	**61.30**	**67.82**	**51.75**	**56.766**	**65.39**	**73.90**	**46.88**
Time points considered		**1-20 hrs**	**1-20 hrs**	**1-20 hrs**	**1-20 hrs**	**1-16 hrs**	**1-16 hrs**	**1-16 hrs**	**1-20 hrs**	**1-16 hrs**	**1-16 hrs**	**1-20 hrs**

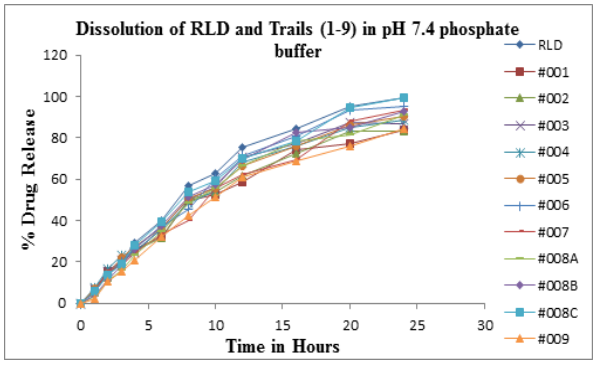

Figure 2: Dissolution of RLD and Trial (1-9) in pH 7.4 phosphate buffer (Release media)

Table 8: Dissolution of RLD and trial #008C in multimedia pH 5.5 phosphate buffer.

Drug release in pH 5.5 phosphate buffer /900ml/paddle/50 rpm		
Time in Hours	**RLD (153779)**	**Trial (008C)**
0	0	0
1	3.15	4.62
2	7.02	9.15
3	11.95	13.4
4	16.20	19.37
6	26.00	29.37
8	36.10	40.84
10	46.50	52.37
12	53.50	58.34
16	67.10	69.71
20	77.35	81.36
24	85.50	87.36
F1		**9.76**
F2		**71.08**
Time points 1-20 hrs		

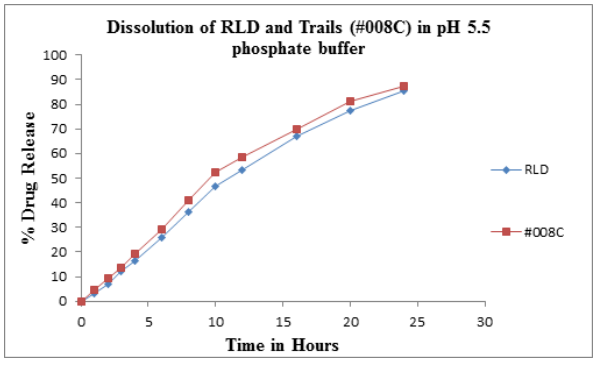

Figure 3: Dissolution of RLD and trial #008C in multimedia pH 5.5 phosphate buffer.

Table 9: Dissolution of RLD and trial #008C in multimedia pH 6.8 phosphate buffer.

Drug release in pH 6.8 phosphate buffer /900ml/paddle/50 rpm		
Time in Hours	**RLD (153779)**	**Trial (008C)**
0	0	0
1	4.80	5.21
2	11.25	13.65
3	17.75	20.35
4	25.10	29.15
6	36.90	39.13
8	48.10	59.34
10	57.69	64.24
12	68.94	73.45
16	79.43	82.54
20	92.12	94.23
24	95.40	97.35
F1		**8.88**
F2		**65.04**
Time points 1-20 hrs		

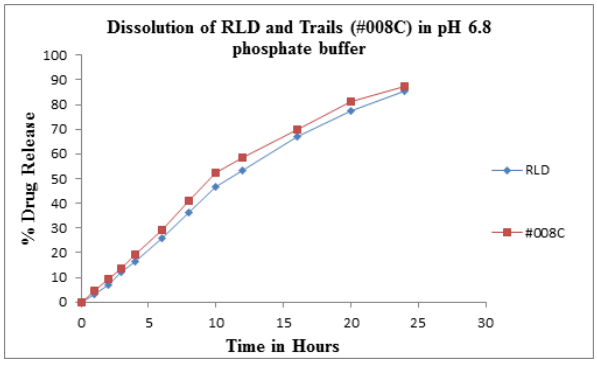

Figure 4: Dissolution of RLD and trial #008C in multimedia pH 6.8 phosphate buffer.

3.2.3. Alcohol induced dose dumping study

To determine the effect of ethanol on drug release of optimized formulation, whole tablets are subjected for dissolution in pH 7.4 phosphate buffer with 0%, 5%, 20% and 40% ethanol and samples were withdrawn for 0.5,1,2,3,4,5,6,8,10,12,16,20 and 24 hours (figure 5). Results show that ethanol has no effect on the dissolution performance of tablets which is confirmed through similarity factor keeping pH 7.4 with 0% alcohol as reference. Similarity factor (F2 value) is 68.77, 68.32 and 64.12 for 5 %, 20% and 40 % ethanol respectively. Drug release in pH 7.4 phosphate buffer with 0, 5, 20, and 40% of ethanol for optimized formulation (whole tablet) is given Table 10.

Table 10: Alcohol induced dose dumping for Whole and halved tablet, Run 10

Trial #008C (30 mg)														
Dissolution conditions	**Apparatus Paddle Type (II), Speed : 50 rpm, Medium 7.4 pH, Method UV**													
Dissolution medium	Time in hours													
	0.5	1	2	3	4	5	6	8	10	12	16	20	24	F2 value *
	% Drug release													
pH 7.4 + 0 % ethanol	2.3	5.5	13.64	19.13	28.17	34.15	39.51	53.61	59.27	69.79	78.38	94.39	99.37	
pH 7.4 + 40 % ethanol	2.1	5.2	11.35	17.35	30.15	32.14	37.10	50.21	57.15	65.1	72.69	92 34	96.78	74.88
pH 7.4 + 20 % ethanol	2.5	5.6	12.64	19.15	31.65	33.48	36.64	49.37	55.1	66.37	74.39	90.37	100 .8	75.81
pH 7.4 + 5 % ethanol	3.1	6.1	15.02	20.14	30.20	36.35	42.36	56.37	65.17	75.37	82.34	96.79	102	72.86

*** F2 value calculated against drug release in pH 7.4 + 0 %, Time points considered for whole tablet are 1, 2, 3, 4, 5, 6, 8,10,12,16 hours.**

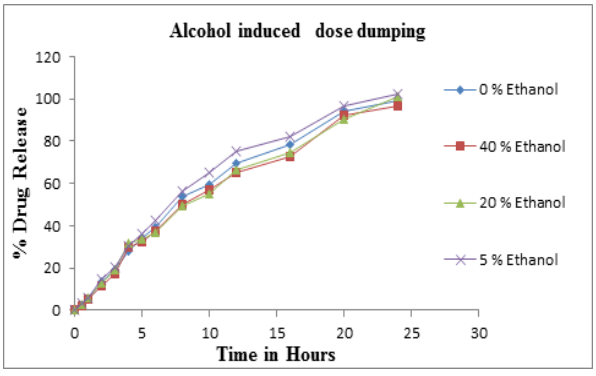

Figure 5: Alcohol induced Dose Dumping

3.2.4. In vitro drug release kinetic studies

The *in vitro* drug release studies of the Trial #008C having optimum and similar drug release compared to RLD were performed in phosphate buffer (pH-7.4) for 24 hours. Figure 4 shows the % cumulative drug release as a function of the dissolution time from the Gliclazide modified release tablet. HPMC E15 LV and HPMC K 4M are hydrophilic polymers and able to control drug release from Gliclazide modified release tablet. From the figure 4, it was found that the release rate of Gliclazide was extremely comparable to RLD in phosphate buffer (pH 7.4). The modified release tablet showed drug release restricted to Not more than NMT 20 % in 2 hrs 4 35 % to 65 % in 10 hrs and NLT 80 % in hrs . Different kinetic models were employed to evaluate the possible changes in the release mechanism. Table 11 indicates the release kinetic model having a value of regression coefficient R^2>0.75. The data were fitted into Korsmeyer-Peppas model. The sample showed good linearity (R^2: 0.9890) with a value of the slope (n) $\geq$ 0.43. This n value, however, appears to indicate that anomalous transport is the dominant mechanism of drug release with these formulations. It indicates that the drug was entrapped in the polymer matrix like network and released by diffusion coupled with the erosion mechanism from HPMC based matrix tablet.

Table 11: Drug release kinetics with model fitting for optimized formulation Trail #008 C in pH 7.4 phosphate buffer.

Drug release kinetics					
Sr no.	**Time**	**%CDR**	**Model Fitting**	**R2**	**k**
1	0.0	0.00	Zero order	0.9538	4.2892
2	1.0	5.50	1st order	0.8668	-0.1770
3	2.0	13.64	Higuchi Matrix	0.9728	23.0148
4	3.0	19.13	Peppas	0.9773	7.0475
5	4.0	28.17	Hix.Crow.	0.9775	0.0321
6	6.0	39.51	Parameters for Korsmeyer-Peppas Equation	n=	0.8960
7	8.0	53.61		k=	7.0475
8	10.0	59.27	Best fit model	Peppas Korsmeyer	
9	12.0	69.79	Mechanism of release	Anomalous Transport	
10	16.0	78.38			
11	20.0	94.39			
12	24.0	99.37			

3.2.5.Discriminatory Dissolution Study

In current formulation discriminatory power of the method is checked by change in concentration of release controlling polymer Hypromellose. HPMC E 15 LV increased in extragranular part from 15.70 mg per tablet to 50.02 mg per tablet. This batch clearly shows lower drug release almost at all-time points. This clearly shows that our dissolution medium is sufficient enough to show slight changes in formulation.As observed from the above results that changes in release controlling excipient having impact on drug release of drug. As expected, relatively lower drug release achieved in batch #009due to higher concentration of release controlling excipient in comparison to optimized batch #008C. This clearly establishes that the dissolution media selected is able to discriminate the changes in the product. Results are tabulated in table no 12 and figure 6.

Table no. 12: Discriminatory Dissolution Study ofTrial (#008C and #009) in pH 6.8 phosphate buffer.

Time in Hours	#008C (100-140N)	#009 (Discriminative batch)
0	0	0
1	5.21	2.30
2	13.65	9.15
3	20.35	15.47
4	29.15	20.67
6	39.13	30.56
8	59.34	41.02
10	64.24	50.35
12	73.45	58.68
16	82.54	67.15
20	94.23	74.29
24	97.35	84.37
F1		**23.20 Fail**
F2		**44.97 Fail**
Time points considered		1-20 hrs F2 value calculated against #008 C

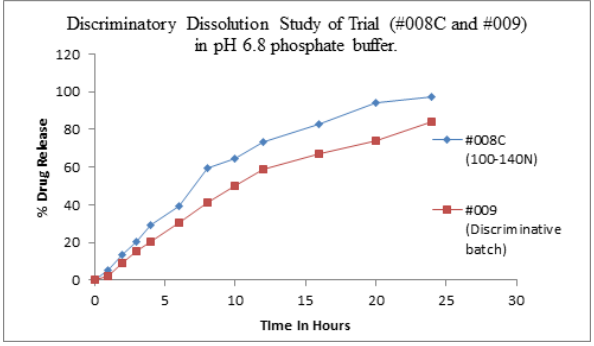

Figure 6: Discriminatory Dissolution Study of Trial (#008C and #009) in pH 6.8 phosphate buffer.

3.2.6.Manufacturing process development and Process Optimization Trial

Once the formulation was finalized, a scale up process 7500 tablets of Gliclazide MR 30 mg) was developed to begin to identify critical process parameters. The scale up batch equipment's used was same as that of expected pivotal batch and commercial equipment's. The effect of some of the critical parameters, such as blending time, tablet hardness and machine speed on critical physicochemical parameters such as blend uniformity, bulk density, tapped density, particle size distribution of the blend, dissolution and uniformity of dosage units were studied.

3.2.7.1 *Effect of Dry mixing time on Content Uniformity:*

Dry mixing in rapid mixer granulator is carried out with impeller at slow speed and chopper off. The blend uniformity samples were carried out at 5 minutes, 10 minutes and 15 minutes time points interval to check the content uniformity of Gliclazide in dry mix blend. The results are mentioned below in Table no.13.

Table No. 13 Content uniformity (in %) of Gliclazide in the Dry mixing- Granulation process

Gliclazide MR Tablet 30 mg Batch No. #006			
Sampling Location	**#006A**	**#006B**	**#006C**
	5 Minutes	**10 Minutes**	**15 Minutes**
Top (Front)	96.7	97.65	98.6
Top (Left)	98.5	99.56	102.4
Top (Right)	98.6	99.45	100.76
Top (Back)	99.1	101.6	96.54
Middle (Left)	100.6	100.02	98.78
Middle (Right)	98.12	99.65	102.18
Bottom (Front)	99.02	98.68	99.16
Bottom (Left)	100.6	99.84	98.39
Bottom (Right)	99.96	100.65	99.67
Bottom (Back)	97.62	97.65	98.37
Minimum	96.70	97.65	96.54
Maximum	100.6	101.6	102.18
Average	98.882	99.655	99.485
%RSD (Specification: NMT 5.0%)	1.274	1.057	1.832

Conclusion- The content uniformity of Gliclazide in Dry mixing stage was carried out for 5min, 10min and 15min. In Lot #006A, RSD at all three time points (5, 10, 15 min) is coming less than 2%, so middle time point has been finalized i.e., 10 min. and the results were within the specifications.

3.2.7.2 Effect of granulation time on Drug Release and physicochemical properties:

Two different trials were carried out on 30mg strength to understand the effect of kneading at different time of 5min and 8min. The blend is evaluated for particle size distribution, density (table 14) and finally tablets were evaluated for drug release (table 15).

Table No. 14 – Effect of granulation time on physicochemical properties of Lubricated Blend

Final Blend	**B.No. #006B (Kneading Time-5min)**	**B.No. #007 (Kneading Time-8min)**
Bulk Density (gm/ml)	0.493	0.510
Tapped Density (gm/ml)	0.651	0.692
Carr's Index (%)	24.27	26.30
Haunser Ratio	1.32	1.35

Table No. 15 – Drug release of Gliclazide MR 30 mg Tablet in pH 7.4 Phosphate Buffer.

Gliclazide MR Tablets 30 mg, Batch No. #008C			
Media: pH 7.4 Phosphate Buffer, Apparatus : Paddle, RPM:100 Volume: 900ml			
% Cumulative Drug Release			
Time points [in Hours]	**RLD 143742**	**B.No. #006B**	**B.No. #007**
0	0	0	0
1	5.6	4.12	3.50
2	13.54	11.36	10.31
3	20.17	18.24	16.15
4	29.41	26.15	23.31

6	40.10	37.61	34.46
8	56.71	51.37	48.36
10	62.92	57.34	55.91
12	75.16	69.17	66.38
16	84.37	82.67	78.52
20	95.35	84.93	81.34
24	99.17	92.67	90.8
F2 value		**13.47**	**10.87**
F1 Value		**65.39**	**56.766**
Time Points Covered	**1,2,3,4,6,8 hours**		

Conclusion – The physical properties of blend reflect that there is impact of kneading time on drug release profile. Increased kneading time causes decrease in drug release. Hence granulation fixed with minimum required kneading time to get desired granule to meet the drug release of reference.

3.2.7.3 Pre – Lubrication time optimization

Extra-granular ingredients i.e., Hypromellose K 100 LV (Methocel K 100 LV) Ph.Eur and Hypromellose K4 M (Methocel K 4M) Ph.Eur were sifted through # 40 sieve and mixed with the dried granules in V-blender. Pre Lubrication was done in V-Blender at 20 ± 1 rpm for 10 minutes. In order to optimize the mixing time, sampling of pre-lubricated blend was done at 5, 10 and 15 minutes. The results of blend uniformity of the prelubricated blend were tabulated below in table 16

Table No. 16- Content uniformity (in %) of Gliclazide in the Prelubricated Blend

Gliclazide MR tablet 60 mg Batch No. #008C			
Sampling Location	**5min**	**10min**	**15min**
1	103.1	101.9	100
2	103.5	102.8	102.6
3	101.8	102.7	103.7
4	101.4	100.1	103.1
5	101.2	101.8	104.4
6	100	98	101.5
7	100.9	105.2	102.6
8	104.6	104.2	102
9	99.9	102.2	102.5
10	100.7	101.4	101.4
11	102.7	101	103.
Minimum	**99.9**	**98**	**100**
Maximum	**104.6**	**105.2**	**104.4**
Average	**101.8**	**101.9**	**102.4**
%RSD	**1.47**	**1.89**	**1.17**

Conclusion- After reviewing the above data, it was observed that % RSD at all the three time points i.e., 10, 15 and 20 minutes is coming less than 2%. Hence last time point i.e., 15 minutes (RSD ≥ 2) has been finalized and the content uniformity of pre-lubricated blend is within the acceptance criteria. Based on the result 15 min was recommended as optimum blending time and recommended for exhibit batch.

3.2.7.4 Lubrication:

Pre-lubricated blend was lubricated with Magnesium Stearate USP-NF (Vegetable Grade) (sifted through #60 sieves) for 5 minutes in V-blender at 20 ± 1 rpm. Sampling was carried out at 3 minutes and 5 minutes time points' interval to check the blend uniformity of Gliclazide. The results of blend uniformity obtained were tabulated in table 17:

Table No. 17- Content uniformity (in %) of Gliclazide in the Lubricated Blend

Gliclazide MR Tablets 30 mg Batch No. #008C		
Sampling Location	**3 Minutes**	**5 Minutes**
1	102.2	99.5
2	99.5	97.7
3	101.2	97.5
4	101.8	99.7
5	102.4	97.9
6	99.7	97.7
7	102.4	97.1
8	101.5	97.8
9	99.1	97.7
10	99.1	99.5
11	102.3	99.1
Minimum	**99.1**	**97.3**
Maximum	**102.4**	**99.9**
Average	**101.0**	**98.5**
%RSD	**1.37**	**0.96**

Conclusion- The content uniformity of lubricated blend carried out at 3 minutes and 5 minutes shown blend uniformity within the acceptance criteria. Based on the result 5 minutes was recommended as optimum lubrication time.

3.2.7.5 Tablet Compression Process Development

The risk of the compression step to impact Uniformity of dosage units and drug release of the tablets was identified as high. Process variables that could potentially impact these two drug product CQAs were identified and their associated risk was evaluated.Compression was carried out using 15 Station, single rotatory Chamunda compression machine. The tablet press run at Low and High speed to check uniformity of weight and Hardness adjusted at Low and High Hardness to check impact on drug release.

Table18summarize the physical parameters of the tablet compressed at different tablet hardness for all four strength and Table19summarize the drug release of the tablet compressed at different hardness for all four strength.

Table No. 18: Physical Parameters of Tablets – Effect of Hardness

Gliclazide MR Tablets 30 mg, Batch No. #008C						
Parameters	**Low Hardness**		**Optimum Hardness**		**High Hardness**	
	Minimum	**Maximum**	**Minimum**	**Maximum**	**Minimum**	**Maximum**
Uniformity of Weight (mg)	157.55	161.5	158.45	160.35	159.3	161.85
Thickness (mm)	3.21	3.15	3.15	3.05	2.80	3.10
Hardness (N)	40	60	60	80	100	140
Friability (%)	0.04		0.03		0.01	

Table No 19– Dissolution in pH 7.4 Phosphate Buffer – Effect of Hardness

Gliclazide MR Tablets 30 mg, Batch No. #008C				
Media: pH 7.4 Phosphate Buffer, Apparatus : Paddle, RPM:100 Volume: 900ml				
% Cumulative Drug Release				
Time points [in Hours]	**RLD 143742**	**#008**		
		#008A (40-60N)	**#008B (60-100N)**	**#008C (100-140N)**
0	0	0	0	0
1	5.6	3.50	4.12	5.50
2	13.54	10.31	11.36	13.64
3	20.17	16.15	18.24	19.13
4	29.41	23.31	26.15	28.17
6	40.10	34.46	37.61	39.51
8	56.71	48.36	51.37	53.61
10	62.92	55.91	57.34	59.27
12	75.16	66.38	69.17	69.79
16	84.37	78.52	82.67	78.38
20	95.35	81.34	84.93	94.39
24	99.17	90.8	92.67	99.37
F2 value		**10.87**	**13.47**	**5.46**
F1 Value		**56.766**	**65.39**	**73.90**
Time Points Covered	**1,2,3,4,6,8 hours**			

4.0 Control Strategy

Based upon the satisfactory and acceptable results summarized above, control strategy was proposed for submission batches of the Gliclazide MR tablets is presented in table 20.

Table No. 20- Control Strategy for Generic Gliclazide MR Tablets 30mg

Factor	Attributes and Parameter	Ranges Studies (Lab Scale)	Actual data for the	Proposed Range For Commercial Scale	Purpose of Control
Gliclazide Attributes					
Gliclazide Particle Size Distribution	D(0.9)	Between 35 µm -60 µm	51.25 µm	Between 35 µm -60 µm	To ensure in-vitro Drug Release, in vivo performance and batch-to-batch consistency.
	D(0.5)	Less Than 20 µm	15.15 µm	Less Than 20 µm	
	D(0.1)	Less Than 5 µm	3.5 µm	Less Than 5 µm	
Dry Mixing					
RMG Dry mixing	Dry Mixing Time	5 minutes to 8 minutes	5 minutes	5 minutes	To ensure content uniformity is met consistently.
Wet Granulation					
RMG (Granulation end point)	Amperage reading	Impeller 44A	Impeller 48A	Impeller 35-48A	To ensure desired granules PSD, uniformity, density and flowability achieved consistently and batch to batch consistency
Drying Process					
Drying	LOD (At 1050 C for 5 minutes)	1-2%	NMT 1.5 %	NMT 1.5 %	To ensure desired granules PSD, uniformity, density and flowability achieved consistently, and batch to batch consistency
Sifting and Milling					
Sifting and Milling	Sieve size	#30 ASTM	#20ASTM	#20ASTM	To ensure granules PSD, uniformity and flowability are achieved consistently, and batch to batch consistency.
	Mill Screen Orifice Size	1.0 mm, 0.8 mm,	1.0 mm, 0.8 mm,	1.0 mm, 0.8 mm,	
Prelubrication					
Prelubrication Blending	Blending Time	10 minutes to 20 minutes	10 minutes	10 minutes	To ensure consistent uniform mixing of granules with Extragranular material except magnesium stearate.
Lubrication					
Lubrication	Blending Time	3 minutes to 5 minutes	5 minutes	5 minutes	To ensure consistent uniform mixing of prelubricated blend with magnesium stearate.

Conclusions

Based on the results obtained from dissolution profile of RLD Diamicron MR tablet 30 mg tablet in multimedia we may conclude that Gliclazide MR tablet 30 mg tablet shows a similar dissolution profile in pH 5.5 phosphate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer, Dissolution in ethanol also confirms that ethanol has no effect on drug release pattern, no burst effect has been observed with different, higher to low concentrations of ethanol in release media. According to the results obtained, we may conclude that tablets from Trial 008C satisfy Pharmacopoeial requirements concerning crushing strength and friability. The results of content uniformity studies for halved tablets containing Gliclazide contain 98.42 % of drug content with Acceptance value of 3.02. Results of blending time conclude that 10min blending in octagonal blender will be finalized due to low RSD value of 1.62 and high mean drug content of 99.50 where as 15 minutes blending shows high RSD of 9.99 % with average content of 92.90. Also effect of lubrication time on assay was studied through content uniformity and results revels that 3 minute lubrication time (mean-97.77, RSD-2.52) in octagonal blender gives higher RSD values as compared to 5 minutes lubrication time (mean-97.60, RSD-1.96). Impact of Active particle size was studied in trails #004 and #005 and results revels that there is no significant impact of PSD on drug release. Higher kneading time (8min) is not optimum for this formulation as drug release significantly reduced as compared to RLD, F2 value is 51.76 but kneading time of 5 minutes gives drug release similar to RLD, F2 value 67.82. Dissolution results of trial #008A, #008B and #008C clearly revels the impact of Hardness on drug release of tablets. Similarity factor f2 value of trial #008A, #008B and #008C are 56.66, 65.39 and 73.90 respectively. From above study, we can conclude that the 5 minutes kneading time, 10 minutes blending time, 5 minute lubrication time and compression at hardness range of 100-140 N is best suited for this formulation. Discriminatory trial (negative batch - #009) successful to show discriminatory power of dissolution method, i.e. any small change in formulation or process parameter can be easily reflected in dissolution results. With reference to the entire tablet, based on the comparison of average tablet mass, dimension, appearance, Dissolution, alcohol induced dose dumping the Gliclazide MR 30 mg and Diamicron MR 30 mg tablets are found to be essentially similar.

In the current research work, formulations and processes are challenged and optimized to ensure that the drug product can be manufactured from a robust and efficient process. During scale-up critical parameters are established and verified with appropriate control strategies to ensure that quality attributes are consistently met for validation during routine manufacturing. Besides dedication to quality we should focus on optimization of process ranges and robustness in order to improve manufacturing efficiency and reliability within a continuous improvement process. Control strategy is finalized and fixed to commercialize this product.

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Declaration of interest

The authors report no conflicts of interest.

Reference:

[1] Wild Sarah, Roglic Gojka, Green Anders, Sicree Richard, K. Hilary, Global Prevalence of Diabetes: Estimates for the year 2000 and projection for 2030, Diabetes Care. 27 (2004) 1047–1053.

[2] V. Doničová, J. Brož, I. Sorin, Health care provision for people with diabetes and postgraduate training of diabetes specialists in eastern European countries., J. Diabetes Sci. Technol. 5 (2011) 1124–36.

[3] M. Bartnik, L. Rydén, R. Ferrari, K. Malmberg, K. Pyörälä, M. Simoons, E. Standl, J. Soler-Soler, J. Ohrvik, Euro Heart Survey Investigators, The prevalence of abnormal glucose regulation in patients with coronary artery disease. The Euro Heart Survey on diabetes and the heart, Eur. Heart J. 25 (2004) 1880–1890.

[4] H. King, R.E. Aubert, W.H. Herman, Global burden of diabetes, 1995-2025: Prevalence, numerical estimates, and projections, Diabetes Care. 21 (1998) 1414–1431.

[5] Parvez M Arayne M Zaman M Sultana N IUCr, Gliclazide, (1999) 74–75.

[6] Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12:413–420.

[7] P. Delrat, M. Paraire, R. Jochemsen, Complete bioavailability and lack of food-effect on pharmacokinetics of gliclazide 30 mg modified release in healthy volunteers., Biopharm. Drug Dispos. 23 (2002) 151–7.

[8] P. Jeyaprabha, T. Sudhamani, H. Mahendra, V. Ganesan, S.P. Senthil, I. Dec, P. Jeyaprabha, formulation and evaluation of gliclazide modified release tablets using hydroxypropyl cellulose, IRJP 1 (1) Dec 2010, 1 (2010) 282–287.

[9] Diamicron MR 60mg - Summary of Product Characteristics (SPC), (n.d.).

[10] W. He, M. Wu, S. Huang, L. Yin, Matrix tablets for sustained release of repaglinide: Preparation, pharmacokinetics and hypoglycemic activity in beagle dogs, Int. J. Pharm. 478 (2015) 297–307.

[11] C. Maderuelo, A. Zarzuelo, J.M. Lanao, Critical factors in the release of drugs from sustained release hydrophilic matrices, J. Control. Release. 154 (2011) 2–19.

[12] O. Rosenzweig, E. Lavy, I. Gati, R. Kohen, M. Friedman, Development and in vitro characterization of floating sustained-release drug delivery systems of polyphenols, Drug Deliv. 20 (2013) 180–189.

[13] T. Puchert, C. V. Holzhauer, J.C. Menezes, D. Lochmann, G. Reich, A new PAT/QbD approach for the determination of blend homogeneity: Combination of on-line NIRS analysis with PC Scores Distance Analysis (PC-SDA), Eur. J. Pharm. Biopharm. 78 (2011) 173–182.

[14] H. Wu, M. White, M.A. Khan, Quality-by-Design (QbD): An integrated process analytical technology (PAT) approach for a dynamic pharmaceutical co-precipitation process characterization and process design space development ☆, Int. J. Pharm. 405 (2011) 63–78.

[15] V. Louren'o, D. Lochmann, G. Reich, J.C. Menezes, T. Herdling, J. Schewitz, A quality by design study applied to an industrial pharmaceutical fluid bed granulation, Eur. J. Pharm. Biopharm. 81 (2012) 438–447. doi:10.1016/j.ejpb.2012.03.003.

[16] J.B. Naik, R.K. Deshmukh, V. V Kamble, Development of Sustained Released Microparticles of Diclofenac Sodium Using Polymer Complex by Spray Drier, Am. J. PharmTech Res. 3 (2013) 892–904.

[17] R.K. Deshmukh, J.B. Naik, Aceclofenac microspheres: Quality by design approach, Mater. Sci. Eng. C. 36 (2014) 320–328.

[18] N.A. Charoo, A.A.A. Shamsher, A.S. Zidan, Z. Rahman, Quality by design approach for formulation development: A case study of dispersible tablets, Int. J. Pharm. 423 (2012) 167–178.

[19] J. Malakar, A. Kumar, Formulation and statistical optimization of multiple-unit ibuprofen-loaded buoyant system using 2 3 -factorial design, Chem. Eng. Res. Des. (2012) 1–13.

[20] R.K. Deshmukh, J.B. Naik, Optimization of sustained release aceclofenac microspheres using response surface methodology, Mater. Sci. Eng. C. 48 (2015) 197–204.

[21] R.K. Deshmukh, J.B. Naik, Diclofenac Sodium-Loaded Eudragit® Microspheres: Optimization Using Statistical Experimental Design, J. Pharm. Innov. 8 (2013) 276–287.

[22] A. Ahad, M. Aqil, K. Kohli, Y. Sultana, M. Mujeeb, A. Ali, Formulation and optimization of nanotransfersomes using experimental design technique for accentuated transdermal delivery of valsartan, Nanomedicine Nanotechnology, Biol. Med. 8 (2012) 237–249.

[23] D.C. Montgomery, Introduction to statistical quality control, Wiley, 1991. http://books.google.co.in/books/about/Introduction_to_statistical_quality_control.(accessed January 9, 2014).

[24] P. Balasubramani, R. Viswanathan, M. Vairamani, Response surface optimisation of process variables for microencapsulation of garlic (Allium sativum L .) oleoresin by spray drying, Biosyst. Eng. 114 (2012) 205–213.

[25] Y. Rhee, S. Chang, C. Park, S. Chi, E. Park, Optimization of ibuprofen gel formulations using experimental design technique for enhanced transdermal penetration, 364 (2008) 14–20.

[26] M. Gibaldi, S. Feldman, Establishment of sink conditions in dissolution rate determinations. Theoretical considerations and application to nondisintegrating dosage forms, J. Pharm. Sci. 56 (1967) 1238–1242.

[27] T. Higuchi, Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52 (1963) 1145–1149.

[28] T. Higuchi, Rate of release of medicaments from ointment bases containing drugs in suspension, J. Pharm. Sci. 50 (1961) 874–875.

[29] R.W. Korsmqer, R. Gumy, E. Doelker, P. Buri, N.A. Peppas, Mechanisms of solute release from porous hydrophilic polymers, 15 (1983) 25–35.

[30] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N.A. Peppas, Mechanisms of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35.

[31] A.W. Hixson, J.H. Crowell, Dependence of Reaction Velocity upon surface and Agitation, Ind. Eng. Chem. 23 (1931) 923–931.

[32] C. Carbone, B. Tomasello, B. Ruozi, M. Renis, G. Puglisi, Preparation and optimization of PIT solid lipid nanoparticles via statistical factorial design., Eur. J. Med. Chem. 49 (2012) 110–7.

[33] A. Mujtaba, M. Ali, K. Kohli, Statistical optimization and characterization of pH-independent extended-release drug delivery of cefpodoxime proxetil using Box – Behnken design, Chem. Eng. Res. Des. (2013) 1–10.