Original Research Paper

Volume-8 | Issue-7 | July-2018 | PRINT ISSN No 2249-555X

Pharmaceutical

APPLICATION OF QUALITY BY DESIGN: DEVELOPMENT OF GENERIC MODIFIED RELEASE NOVEL DIVIDABLE MATRIX TABLET OF GLICLAZIDE

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ABSTRACT The purpose of this study was to develop and optimize the matrix based generic dividable modified release formulations of Gliclazide through quality by design approaches. The quality target product profile was decided and critical quality attributes were identified for whole and halved tablet. Two formulation variables: the content of HPMC K100LV (X1), and the content of HPMC K4M (X2) added in extragranular phase were optimized using the design of experiments. 3 level 2 factor (3^2)factorial design was used considering in vitro drug release of the drug after 2, 4, 6, 8, 10 and 12 hours as responses. Response surface plots and contour plots were drawn, and optimum formulations were elected by feasibility and grid searches. The *p* values were statistically significant (<0.5) for all models generated for different responses. The predicted and observed values were closely matched. Matrix tablet exhibited Korsmeyer–Peppas demonstrated that diffusion along with erosion could be the mechanism of release, as the value of release rate exponent (n) varied between 0.9102 and 0.9890, resulting in regulated and complete release until 12 hours. Validation of optimization study, performed using 9 confirmatory runs, indicated a very high degree of prognostic ability of response surface methodology, with mean percentage error (± SD)as 0.2775 ± 4.249. Matrix tablets have essentially similar drug release as the reference product in multimedia and can be divided into equal doses by hands. Response surface methodology is an efficient tool in the optimization experiments.

KEYWORDS : Gliclazide, Modified Release, Dividable Tablet, Breakability Testing, Design Of Experiment, 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 market which is capable of being divided but maintaining the desired dissolution profile., such as a scored tablet, which has deep break lines on both sides (top and bottom) of tablet faces at each line of division, allowing for easy breakage and getting the split of this dosage form with equal amount of fractions containing equal quantum of the Gliclazide, An increase in surface area, upon division does not alter in vitro drug release rates for the Gliclazide half tablets. Divisible tablet have identical in-vitro dissolution profile as the whole tablet for a period of 12 hours.

The purpose of this research is to design a consistent quality product with its reproducible manufacturing process to consistently deliver the intended performance upto the shelf life of drug product. Complete development of product covers from generation of an idea to complete dossier filing. Checklist for formulation development, in brief, is illustrated in Figure 1.

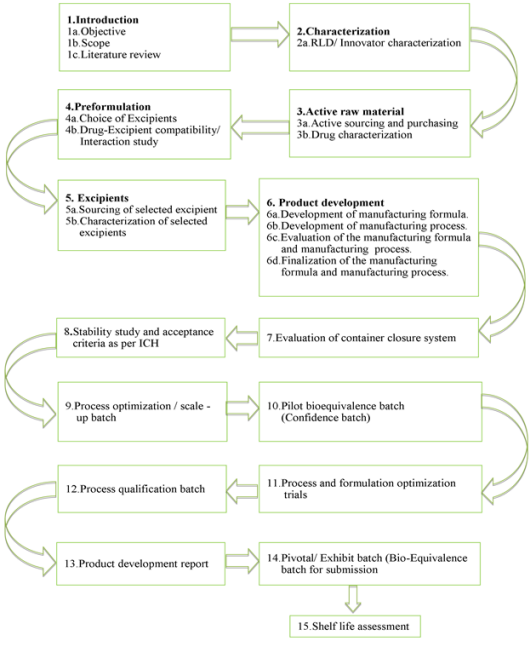

Figure 1. Comprehensive checklist for formulation development

The design of experiments (DoE) bridge relationships between critical process parameters (CPPs) and critical to quality attributes (CQAs) and also helps to fix working range of process parameters which effects [14, 15, 18]. The quality target product profile (QTPP) and CQA of the drug product are given below.

Target product profile Summary

1. To develop modified release tablet formulation similar to Diamicron MR.
2. Target drug product should have similar dissolution profile as that of innovator product in multimedia.
3. The formulation must have adequate stability to meet ICH requirements for stability of new drug product.

Summary of CQA of product.

1. Appearance
2. Weight
3. Hardness
4. Friability
5. Assay
6. Content uniformity
7. Dissolution profile in multimedia

Response surface methodology (RSM) is used from the design of experiments to generate the model that describes the optimum relationship between the process variables and responses for the development of the dividable matrix tablet using 2^3full factorial design. True response surface can model easily with a factorial experimental design with excellent precision and at a minimum cost of the experiment. Response surface methodology (RSM) techniques improve the performance or response of a process or product [13, 19–23].

Silent Feature

Gliclazide modified release tablet 60 mg is a dividable dosage form, which has a deep scoring line on both faces to split tablet with an accurate weight of fractions containing equal amounts of the drug. Dissolution of whole and halved tablet of these two formulations (test and reference sustained release tablet) have been performed in 4 dissolution medium to check the behavior of product from in acidic and intestinal pH. In vitro ethanol dose dumping studies were performed on test whole and halved tablets using 0 %, 5 %, 20 % and 40 % ethanol with pH 7.4 phosphate buffer. The investigators found that the studied formulation enables the prolonged and reproducible release of Gliclazide, the release being insensitive to variations in the pH of the dissolution medium for a period of 12 hours after the beginning of dissolution and maintain their extended release performance in alcohol (intact and broken) which clearly concludes that an increase in surface area, after splitting does not alter in vitro dissolution for the Gliclazide halved tablets and that ensures regular and continuous blood levels after absorption of the matrix tablet by the oral route and the generic halved and whole tablet with marketed formulation had similar release patterns and followed Hixson-Crowell mechanism by super case II transport.

2. Materials & methods

2.1. Materials

The detailed list of the excipients/raw materials used in the preparation of Gliclazide 60 mg, prolonged drug release tablet is given in Table 1. Diamicron modified release tablet 60 mg, RLD procured from Servier laboratories Ireland. Analytical grade reagents and solvents are used in the study.

Table 1: List of drug and excipient used in the formulation development

Excipient	Function	Purchased/Procured from
Gliclazide Ph.Eur	Active drug substance	Indoco Remedies Limited, Mumbai, India
Hypromellose As Hydroxy Propyl methyl cellulose (Methocel K 100 LV) 100 cps Ph.Eur	Release retardant	Colorcon, India
Hypromellose As Hydroxy Propyl methyl cellulose (Methocel K 4 CR) 4000 cps Ph.Eur	Release retardant	Colorcon, India
Lactose Monohydrate (Pharmatose 200 M) Ph.Eur	Diluent	DFE Pharma
Magnesium Stearate Ph.Eur	Lubricant	Peter greven, Germany.

2.2. Methods

2.2.1. *Experimental design*

During the trials as described above, it was observed that the excipients which mostly affect product quality are two different grades of Hypromellose in extragranular phase. Based on risk assessment outcomes, Design of Experiments (DoE) is applied to study the effect of extra-granular addition release retardant (Hypromellose) dissolution of the drug product. 2-factor 3-level Factorial Design was selected for the optimization purpose. The RSM was used to analyze the observed response [20, 36–39]. The studied independent factors were the amount of HPMC K100LV (X1, mg), and the amount of HPMC K4M (X2, mg). All other parameters (granulation time, speed of choppers and impellers, solvent addition rate and overall amount, FB drying temperature, time, air flow and % loss on drying, blending times and speed (pre-blending and final blending) were kept constant to minimize fluctuations. The actual and coded values of independent variables are shown in Table 2 along with their low and high levels, which were selected based on the results from preliminary experimentation. Two-dimensional (2D) contour plots and three-dimensional (3D) response plots resulting from the equations were constructed and the software employed for the said purpose was Design Expert® (Version-8.0.7.1, Stat-Ease Inc., Minneapolis, MN)

Table 2: Actual and coded value of variables along with their level in a 32 full factorial design

Independent variables	Level used, actual (coded)		
	Low, (-1)	Middle, (0)	High, (+1)
X1 = Amount of HPMC K100LV (mg)	10	30	50
X2 = Amount of HPMC K4M (mg)	5	20	35

2.2.2. *Preparation of matrix tablet*

Ten different formulations were prepared, by varying the quantum of release retardant and keeping the drug amount (18.75% w/w) and the total tablet weight constant, according to the experimental design matrix proposed by the Design-Expert® Software (Version-8.0.7.1, Stat-Ease Inc., Minneapolis). Tablets were prepared by wet granulation with purified water and compression (with a rotary tablet press at a force of 80-120 newtons) (N) of the components previously sieved i.e., Gliclazide, lactose monohydrate, HPMC K 100 LV and HPMC K 4 M (40 mesh) and mixed for 10 min in a rapid mixer granulator (RMG) (Bowman and Archer Pharma machines, Mumbai, India). Dry the granules in fluid bed dryer (FBD) (Retsch, Mumbai, India) at 60˚ C ± 5 to obtain Loss on drying (LOD) of Not more than (NMT) 1.5 %. Sieve of #20 is used for the sifting of dried granules and granules were charged in double cone blender. Add HPMC K 100 LV (#40) and HPMC K4 M (#40) to double cone blender having dried granules at 12 rotation per minute (RPM) for 15 minutes. Add previously sifted magnesium stearate (#60) to above granules and blend in double cone blender at 12 RPM for 5 minutes. The samples were withdrawn and checked for blend uniformity prior to compression and particle size distribution, bulk density, tapped density, Hausner ratio and compressibility index. Weight uniformity of the tablets was controlled (OHAUS CORPORATION USA, PAG413C) (C.V.±2%). The qualitative and quantitative composition of development batches is given in table 3.

Table 3: Qualitative and quantitative composition of the development batches

Ingredients	60 mg prolonged release tablet									
	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run 10
Intragranular										
Gliclazide	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0
Lactose Monohydrate	152.8	147.8	182.8	167.8	172.8	132.8	162.8	202.8	187.8	165.81
HPMC K 100 LV	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
HPMC K4 M	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0	19.0
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Extragranular										
HPMC K 100 LV	30.0	50.0	30.0	30.0	10.0	50.0	50.0	10.0	10.0	31.81

HPMC K4 M	35.0	20.0	5.0	20.0	35.0	35.0	5.0	5.0	20.0	20.18
Magnesium Stearate	3.20	3.20	3.20	3.20	3.20	3.20	3.20	3.20	3.20	3.20
Total weight of tablet	**320.0**	**320.0**	**320.0**	**320.0**	**320.0**	**320.0**	**320.0**	**320.0**	**320.0**	**320.0**

2.2.3. Measurement of flow of granules

2.2.3.1. Hausner ratio and Carr's compressibility index (CI): 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.

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

2.2.4. Physicochemical characterization of matrix tablet (Whole tablet and halved tablet)

2.2.4.1. Thickness: Vernier caliper is used for measuring the thickness of the tablets during initial middle and end of compression and results were reported for an average of 20 tablets.

2.2.4.2. Weight variation: 20 tablets from initial middle and end of compression were taken to check uniformity of weight, a four decimals digital electronic balance (METTLER-TOLEDO AJ150, Switzerland).

2.2.4.3. Resistance to crushing (Hardness): For each formulation batch (Run 1-10), the resistance to crushing (hardness) of 10 whole tablets, were determined using hardness tester (ERWEKA TBH-28, Germany). During compression, hardness was routinely checked at initial, middle and end during to control an acceptable range of tablet hardness.

2.2.4.4. Friability: For each formulation batch (Run 1-10) the tablets (equivalent to 6.5 gram (gm.) of weight) were brushed. The tablet sample was weighed and charged in the drum. Tablets were rotated for 100 times and removed. Any loose dust from the tablets was removed as before. Loss of mass is presented in percentage.

2.2.4.5. Uniformity of weight: Ten tablets of each formulation weighed individually. The 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 weighed 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 Polyvinylidene difluoride (PVDF) filter. The 5.0ml filtered solution was diluted to 50ml with diluent in a volumetric flask (About 100 microgram (µg)/ml of Gliclazide). The final samples were filtered through a 0.45 micron (µm) diameter membrane before injection into High-performance liquid chromatography (HPLC) system Ultraviolet (UV)/Photodiode Array (PDA) detector (Agilent 1200, USA) with the following chromatographic conditions: Mobile phase: mixture of 600ml mili-Q water, 400 ml acetonitrile , 1.0 ml of trifluoroacetic acid and 1.0ml of triethylamine, Zorbax Eclipse extra dense bonding (XDB) C8 Rapid resolution (150 x 4.6)millimeter (mm) 3.5G. or equivalent column), the mobile phase flow rate of 1.0 ml/minute at 25˚C ± 1˚C, the injection volume of 10.0 microliter (µl), and the UV detector set at a wavelength of λ = 220 nanometer (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 the 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 a 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), 900 ml of 0.1 N hydrochloric acid solution, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer for dissolution. 10 ml aliquots were collected from a dissolution medium of each vessel at specified time intervals (1, 2, 4, 6,8,10 and 12 hours) for the 12-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 was taken 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. Dissolution results of Gliclazide are presented as time curves versus percent drug release. Similarity factor (f2) is used to compare the similarity between the release of test and reference at different time intervals (FDA, 2000), as the following equation:

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

1.1.1.1. Fourier transform infrared (FTIR) spectroscopy study

The chemical structure of the Gliclazide, RLD, and the final blend of 60 mg of matrix tablet were analyzed using an FTIR spectrophotometer (FTIR-8400; Shimadzu, Singapore) using Potassium bromide (KBr) pellet technique. For that, the mixture is prepared using the sample to KBr in 1: 40 ratio and compressed using the manual press. The pellet was positioned in the sampler and spectral scanning was carried in the wavelength region between 4000-500 cm-1 with a scan speed of 1 cm/s.

1.1.1.2. Optimization and validation of a model

A total of 9 runs were generated by the Design- Expert software for the 3^2 factorial design. Statistical validation of the equation was established using Analysis of variance (ANOVA). The Models were evaluated using statistically significant terms and R^2 value. An intensive grid search was conducted to find out the composition of the optimized formulation having a controlled drug release. One optimum checkpoint formulation was selected in order to evaluate optimization capabilities of the model generated using a 3 levels 2 factors (3^2) factorial design. Checkpoint Formulation (Run No. 10; Table 3) was prepared through optimal process variables and variables were examined for the responses. Prediction error was calculated from quantitative comparison of experimental value and predicted value. [18, 32, 33].

1.1.1. Physicochemical characterization of matrix tablet (Halved tablet)

The physicochemical characterization i.e., hardness, friability, content uniformity and dissolution were carried out on a halved tablet as per the method is given for characterization of the whole tablet (section 2.2.4).

2.1.6. Breakability test methods

2.1.6.1. Manual method

The tablet was held between the thumb and the index finger, division into two halves was done by breaking open the tablet at the score line side. Percent loss of mass was calculated after subtracting the weight of split portions from the weight of the whole tablet taken before splitting and the percentage was calculated.

2.1.6.2. Tablet-splitter

For this test tablet splitter, "Apex ultra-tablet cutter" was used. The

tablet splitter cover was lifted up and the tablet was placed into "V" shaped holder. To split the tablet the cover was firmly brought down and closed to split the tablet. Percent loss of mass was calculated after subtracting the weight of split portions from the weight of the whole tablet taken before splitting and a percentage was calculated.

3. *Results and discussion*

3.1. Statistical analysis of data

Using 3^2 factorial design, a total of nine runs was carried out for the preparation of matrix tablet and investigated the effects of two independent variables on the dependent variable (response) using factorial design. The responses were evaluated by cross-product contribution (2FI) and linear mathematical model (suggested) generated by statistical design.

$$Y = \beta_0 + \beta_1 A + \beta_2 B \quad \text{--- [2]}$$
$$Y = \beta_0 + \beta_1 A + \beta_2 B + \beta_{12} AB \quad \text{--- [3]}$$

Where β_0 is the intercept; β_1 to β_{12} is the estimated coefficient obtained from the observed experimental values of Y (response; drug release at different time interval); A and B are the coded levels of the factors. The coefficient corresponding interaction (AB) was determined from the results of the experiments. Detail composition of all the experiments carried out is summarized in Table 3.

A study showed that the formulation parameters had an influence on the drug release. The final equations in term of coded factors for the response are given below:

$$Y2 = 21 - 6.16A - 5.5B - 1.75AB \quad \text{--- [4]}$$
$$Y4 = 48.77 - 12.33A - 8.66B \quad \text{--- [5]}$$
$$Y6 = 65.77 - 10A - 9.5B - 4.25AB \quad \text{--- [6]}$$
$$Y8 = 82.66 - 8A - 8.66B \quad \text{--- [7]}$$
$$Y10 = 92.88 - 8.16A - 7.16B - 5.5AB \quad \text{--- [8]}$$
$$Y12 = 98.66 - 6.66A - 4.83B - 6.25AB \quad \text{--- [9]}$$

The equation represents the quantitative effects of factor (A, B & AB) upon the response (Y). The sign of the coefficient shows how the factor influences the response. Response increases (synergistic) with positive coefficient as factor moves from low (-1) to high (+1) level and if the coefficient is negative then inverse relationship/antagonist effect). The software generates Quadratic, cross-product contribution (2FI), cubic and linear models for the responses. The linear and cross-product contribution (2FI) model showed the best fit for the response. The ANOVA of the regression model demonstrated that the linear model and cross-product contribution (2FI) were highly significant (p-value, <0.0001, R^2> 0.8) indicating excellent goodness of fit. Main and interaction effects of the independent variables can be easily understood by 3D response surface plots while visual representation can be achieved through 2D contour plots. [60] To visualize the effect of independent variables on drug release, 3D response surface plots (Figure.2a) and 2D contour plots (Figure.2b) were constructed.

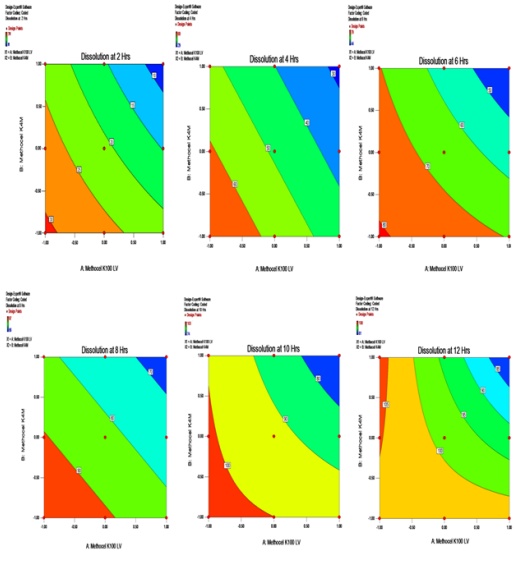

Figure 2a. 3 D response surface graphs

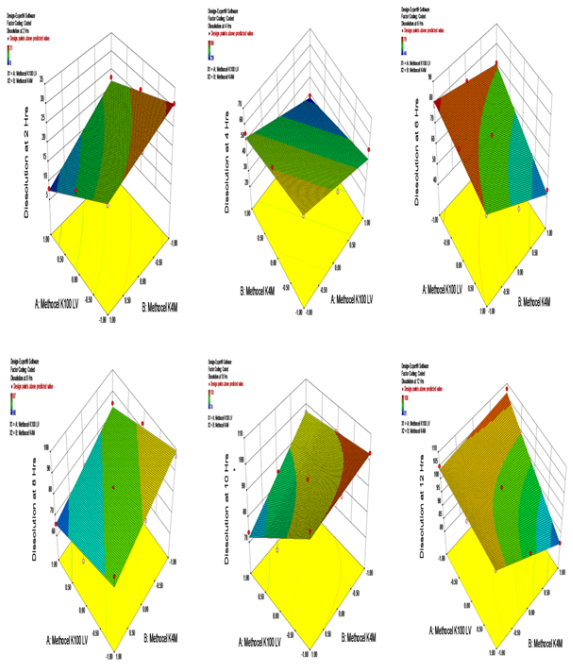

Figure 2b. 2D Contour plots

Table 4 showed the model summary statistics of responses. Data in Table 5 showed the p-values of each factor and coefficient estimate for the measured responses. Significant values indicated in bold faces. Most significant negative effect on the drug release from matrix tablet is the amount of HPMC K100LV and amount of HPMC K4M. All the points were selected and observed their experimental and predicted value to validate the model (Table 6) for the responses. The lower magnitudes of percentage prediction error (-14.08 to +11.55) were observed for the response. In current study robustness of the mathematical model and high prognostic ability of the RSM is indicated by the significant value of R2 and lower value of prediction error.

Table 4: Model summary statistics of responses Y1 = Drug release at 2 hours, Y2 = Drug release at 2 hours, Y3 = Drug release at 6hours, Y4 = Drug release at 8 hours, Y5 = Drug release at 10 hours, Y6 = Drug release at 12 hours

Response	Model	Std. Dev.	R^2	Adjusted R^2	Predicted R^2	PRESS	Significance
Y_1	Linear	1.84	0.95	0.93	0.86	56.11	
	2FI	1.27	0.98	0.96	0.94	25.34	Suggested
	Quadratic	1.01	0.99	0.98	0.91	36.40	
	Cubic	0.5	0.99	0.99	0.89	45.56	
Y_2	Linear	4.17	0.93	0.91	0.83	247.80	Suggested
	2FI	4.20	0.94	0.90	0.73	399.98	
	Quadratic	2.78	0.98	0.96	0.81	279.64	
	Cubic	0.67	1.00	1.00	0.94	81.00	
Y_3	Linear	4.20	0.91	0.89	0.75	306.93	
	2FI	2.60	0.97	0.96	0.89	136.37	Suggested
	Quadratic	3.17	0.98	0.94	0.72	345.80	
	Cubic	2.17	1.00	0.97	0.31	855.56	
Y_4	Linear	3.04	0.94	0.92	0.83	149.96	Suggested
	2FI	2.65	0.96	0.94	0.80	181.26	
	Quadratic	3.22	0.97	0.91	0.61	349.24	
	Cubic	2.50	0.99	0.94	-0.28	1139.06	
Y_5	Linear	5.11	0.82	0.76	0.45	473.72	
	2FI	2.67	0.96	0.93	0.81	162.57	Suggested
	Quadratic	3.10	0.97	0.91	0.66	298.03	
	Cubic	3.33	0.99	0.90	-1.34	2025.00	
Y_6	Linear	5.31	0.71	0.61	0.07	533.49	
	2FI	1.61	0.98	0.96	0.92	47.79	Suggested
	Quadratic	1.86	0.98	0.95	0.83	97.29	
	Cubic	2.50	0.99	0.91	-0.98	1139.06	

Table 5: Coefficient estimate and p-values of each factor for the measured responses Y_1 = dissolution at 2hours, Y_2 = dissolution at 4hours, Y_3= dissolution at 6hours, Y_4= dissolution at 8hours, Y5 = dissolution at 10hours and Y_6= dissolution at 12hours

Factors	Y_1		Y_2		Y_3		Y_4		Y_5		Y_6	
	Coefficient estimate	p- Value	Coefficient estimate	p-Value	Coefficient estimate	p-Value	Coefficient estimate	p-Value	Coefficient estimate	p-Value	Coefficient estimate	p-Value
A_1	-6.17	< 0.0001	-12.33	0.0004	-10	0.0002	-8.0	0.0007	-8.17	0.0007	-6.67	0.0002
B_2	-5.50	0.0001	-8.67	0.0022	-9.5	0.0003	-8.7	0.0004	-7.17	0.0012	-4.83	0.0007
A_1B_2	-1.75	0.0402	-	-	-4.25	0.0222	-	-	-5.50	0.0091	-6.25	0.0006
A_1^2	-	-	-	-	-	-	-	-	-	-	-	-
B_2^2	-	-	-	-	-	-	-	-	-	-	-	-

Table 6: The 32 design matrix (in coded level) along with optimized batch and experimental results with predicted value and % prediction error

Run	Independent variables		Drug release																					
	A (mg)	B (mg)	Experimental value[a]						Predicted value						Residual						% Prediction error[b]					
			Dissolution in hours						Dissolution in hours						Dissolution in hours						Dissolution in hours					
			2	4	6	8	10	12	2	4	6	8	10	12	2	4	6	8	10	12	2	4	6	8	10	12
1	-1	1	17.02	37.02	54.21	70.15	81.17	92.05	15.5	40.11	56.27	74	85.72	93.83	1.52	-3.09	-2.06	-3.85	-4.55	-1.78	8.93	-8.35	-3.80	-5.49	-5.61	-1.93
2	-1	-1	13.03	35.08	53.16	74.34	85.27	93.31	14.83	36.44	55.77	74.66	84.72	92	-1.8	-1.36	-2.61	-0.32	0.55	1.31	-13.81	-3.88	-4.91	-0.43	0.65	1.40
3	0	-1	27.13	53.12	78.30	93.36	100.41	102.18	26.5	57.44	75.27	91.33	100.05	103.5	0.63	-4.32	3.03	2.03	0.36	-1.32	2.32	-8.13	3.87	2.17	0.36	-1.29
4	1	-1	20.32	45.09	68.15	83.34	94.16	100.18	21	48.77	65.77	82.66	92.88	98.66	-0.68	-3.68	2.38	0.68	1.28	1.52	-3.35	-8.16	3.49	0.82	1.36	1.52
5	0	0	23.16	55.34	71.26	87.22	102.39	108.19	23.14	52.44	70.52	82	99.38	106.57	0.02	2.9	0.74	5.22	3.01	1.62	0.09	5.24	1.04	5.98	2.94	1.50
6	1	0	8.13	29.36	44.18	66.34	74.37	81.41	7.58	27.77	42.02	66	72.05	80.91	0.55	1.59	2.16	0.34	2.32	0.5	6.77	5.42	4.89	0.51	3.12	0.61
7	0	1	23.15	51.32	69.27	85.42	97.19	103.02	22.08	45.11	69.52	83.33	97.38	103.08	1.07	6.21	-0.25	2.09	-0.19	-0.06	4.62	12.10	-0.36	2.45	-0.20	-0.06
8	1	1	31.09	69.15	79.26	97.31	103.46	105.17	30.91	69.77	81.02	99.33	102.72	103.91	0.18	-0.62	-1.76	-2.02	0.74	1.26	0.58	-0.90	-2.22	-2.08	0.72	1.20
9	-1	0	27.31	65.26	76.29	89.31	100.31	104.24	27.16	61.11	75.77	90.66	101.05	105.33	0.15	4.15	0.52	-1.35	-0.74	-1.09	0.55	6.36	0.68	-1.51	-0.74	-1.05
10	0.09	0.01	19.18	45.09	62.39	79.18	91.42	98.31	19.02	45.85	62.41	78.70	90.87	97.99	0.16	-0.76	-0.02	0.48	0.55	0.32	0.83	-1.69	-0.03	0.61	0.60	0.33

[a]Standard deviation was calculated from three independent samples
[b] Percent prediction error was calculated using the formula (Experimental value – predicted value)/experimental value × 100

3.2. Measurement of flow of granules

Bulk density and Tapped density was found to be uniform among different batches of the granules and ranged from 0.439 gm/mL to 0.526 gm/mL and 0.586 gm/mL to 0.678 gm/ml. The Hausner ratio and Compressibility index of the granules of all batches ranged from 1.28 to 1.33 and 22.41 to 25.33, respectively (Table 7). The flow of the granules is found to be passable as per Hausner ratio.

Table 7: Measurement of flow of granules

Physical properties	Number of Runs									
	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run10
Bulk density (g/ml)	0.469	0.456	0.503	0.483	0.498	0.439	0.486	0.526	0.512	0.493
Tapped density (g/ml)	0.627	0.602	0.649	0.638	0.667	0.586	0.639	0.678	0.674	0.651
CI	25.19	24.25	22.49	24.29	25.33	25.08	23.94	22.41	24.03	24.27
HR	1.33	1.32	1.29	1.32	1.33	1.33	1.31	1.28	1.31	1.32

3.3. Physicochemical Characteristics of matrix tablet (whole tablet)
3.3.1.Physicochemical characterization

The produced tablets (Formulations 1–10, Table 10); had a thickness ranged from 3.61 mm to 4.50 mm. Weight variation of produced tablet ranged from 319.5 mg to 322.1 mg. The resistance to crushing and percentage friability of the tablets of all batches ranged from 70 N to 160 N and 0.11% to 0.35%, respectively. The results of drug content for a tablet containing Gliclazide are summarized in Table 8 and ranged from 98.94% to 103.11 %. The results of content uniformity studies for whole tablets containing Gliclazide are summarized in Table 9 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, RUN 10. 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., the content uniformity of active substance expressed as a percentage of the declared content should be within the limits of 85-115 and RSD 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 8: Physiochemical characterization for Matrix tablets.

Compression parameters	Batch Number									
	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9	Run 10
Average weight (mg)	320.6	320.9	320.5	321.6	321.6	319.7	321.6	318.9	320.9	320.9

Thickness (mm)	3.78-4.20	4.10-4.41	3.75-4.00	3.80-4.10	3.81-3.96	4.23-4.50	3.91-4.32	3.61-3.82	3.71-3.92	3.80-4.15
Resistance to crushing (N)	100-140	80-110	110-150	100-140	100-135	70-100	80-120	120-160	110-140	100-140
Friability (%) at 100 rev	0.24	0.31	0.18	0.20	0.27	0.35	0.23	0.11	0.24	0.22
Uniformity of weight (mg)	320.9 (319.4-320.4)	320.6 (318.9-323.4)	322.1 (319-1-323.2)	321.7 (318.5-330.1)	319.5 (317-323.1)	321.5 (319.6-323.4)	319.6 (317.9-322.8)	319.6 (318.7-321.6)	320.8 (318.6-322.4)	321.8 (320.5-323.1)
Assay (Drug content) %	103.11	99.8	98.94	100.5	101.8	100.02	102.7	100.5	100.3	99.87
Punch dimension (mm)	15.0 X 7.5 mm, concave, oval shaped with deep breakline on both the punches with embossing 60 on both sides on upper punch and plain lower punches.									
Length (mm)	15.06	15.04	15.1	15.05	15.08	15.06	15.1	15.1	15.1	15.03
Width (mm)	7.49	7.51	7.52	7.48	7.49	7.49	7.51	7.51	7.5	7.51

Table 9: Comparative uniformity of dosage units (by content uniformity) for whole and halved tablet of optimized trial.

Run 10 Whole tablet		Run 10 Halved Tablet	
Units	**% Drug**	**Units**	**% Drug**
1.	98.2	1.	98.1
2.	99.1	2.	100.3
3.	96.2	3.	98.8
4.	101.1	4.	97.6
5.	99.0	5.	96.6
6.	99.7	6.	99.5
7.	100.2	7.	99.9
8.	97.0	8.	99.0
9.	99.5	9.	99.3
10.	98.9	10.	99.6
Average	**98.9**	**Average**	**98.9**
SD	**1.41**	**SD**	**1.13**
K	**2.4**	**K**	**2.4**
Acceptance value	**1.65**	**Acceptance value**	**2.11**

3.3.2. In-vitro drug release

The dissolution profile comparison in pH 7.4 phosphate buffer clearly distinguishes the dissolution profile of other formulations. The dissolution profile of optimized formulation (Run 10) was found to be most comparable to reference listed drug Diamicron MR 60 mg tablet with the highest F2 value of 82.10 in pH 7.4 phosphate buffer amongst all the other studied batches. But other formulations don't show the desired dissolution pattern. Some are showing faster dissolution than Diamicron MR 60 mg tablet where others showing slower dissolution except Run 4, which shows essentially similar dissolution profile when compared with RLD, the F2 value is 78.57. Drug release in pH 7.4 buffer of development batches and optimized (halved and whole tablet) in comparison to RLD is presented through Figure. 3. Drug release in 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer of optimized Tablet (halved and whole tablet) in comparison to RLD is presented in Figure. 4, 4 and 6. Incomplete drug release from Diamicron MR 60 mg tablet and optimized formulation (Run 10) (Approximately 14 % and 13 %) of Gliclazide was observed in 0.1 N HCl and (Approximately 52 % and 55 %) in pH 4.5 acetate buffer. Complete drug release achieved in pH 6.8 phosphate buffer i.e.100 % in 12 hours, similarity factor, F2 is 72.47 where dissimilarity factor, F1 is below 15 i.e. 7.47 when compared with Reference listed drug.

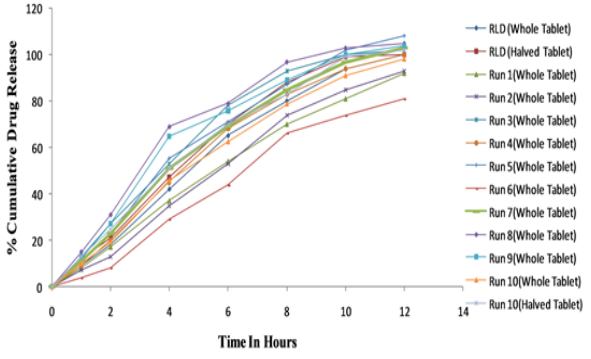

Figure 3. Cumulative drug release of RLD full and half tablet with Run 01-10 full tablet and Run 10 half tablet in pH 7.4 phosphate buffer, 900ml, paddle at 100 rpm.

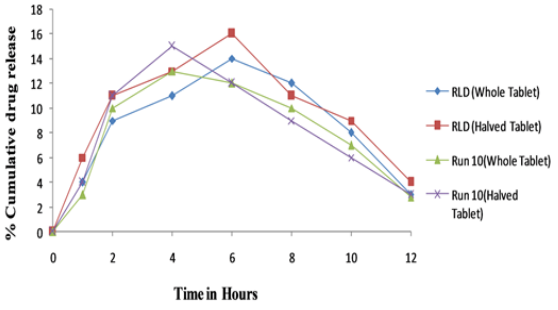

Figure 4. Cumulative drug release between RLD full and half tablet with Run 10 full and half tablet in 0.1 N HCL, 900ml, paddle at 100 rpm.

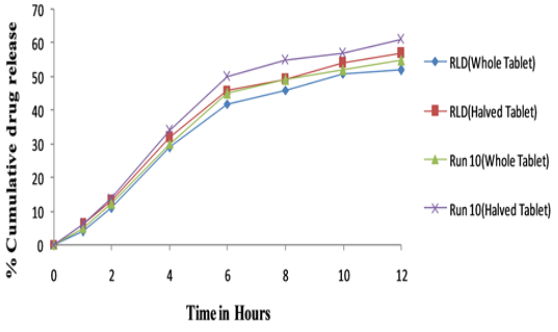

Figure 5. Cumulative drug release between RLD full and half tablet with Run 10 full and half tablet in pH 4.5 Acetate buffer, 900ml, paddle at 100 rpm.

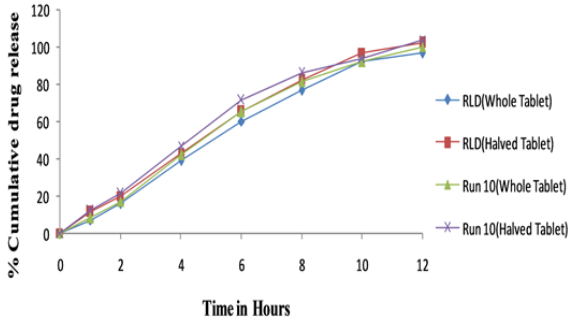

Figure 6. Cumulative drug release between RLD full and half tablet with Run 10 full and half tablet in pH 6.8 phosphate buffer, 900ml, paddle at 100 rpm.

3.3.3. FTIR spectroscopy study

The FTIR spectra of materials (Fig. 7) were obtained in order to analyze the prepared matrix tablet. The characteristic peaks of Gliclazide, are remained very close in the FTIR spectra of Gliclazide matrix tablet (run-10) [Tablet and blend], indicating no existence of the different association form of the Gliclazide with excipients. The FTIR analysis confirmed the compatibility of the Gliclazide with formulation excipients.

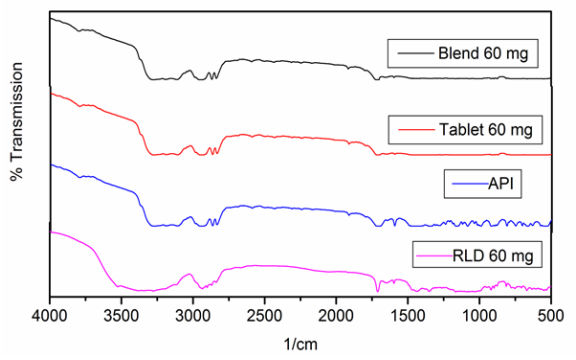

Figure 7. FTIR for Diamicron MR 60 mg tablet, Active pharmaceutical ingredient, Gliclazide MR 60 mg tablet and Blend (ready for compression) of gliclazide MR 60 mg tablet.

3.3.4. X-ray powder diffraction (XRD)

Respective portions of powdered samples of Active Gliclazide, Diamicron MR 60 mg tablet, Gliclazide MR 60 mg tablet and Final blend (ready for Compression) of Gliclazide MR 60 mg tablet were compared for XRD (Figure 8). The tablet contains significant levels of crystalline phases, with only minor peaks corresponds to active Gliclazide. The diffraction peaks for all four products are closely matched in both angle and intensity, indicating that crystallinity of active can be seen clearly, there is no transformation of active from one form to other.

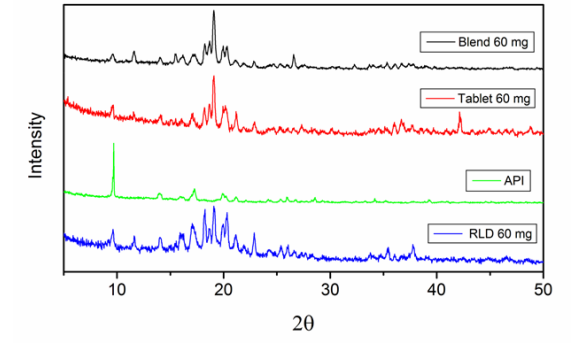

Figure 8. XRD for Diamicron MR 60 mg tablet, Active pharmaceutical ingredient, Gliclazide MR 60 mg tablet and Blend (ready for compression) of gliclazide MR 60 mg tablet.

3.3.5. Optimization and validation of RSM

Drug release of optimized formulation corresponding to the predicted values of the amount of HPMC K100LVand HPMC K4M was determined to access the reliability of the developed mathematical model; Based on controlled drug release pattern from the formulation the optimized formulation was selected. The desirable range of the drug release obtained was restricted to $10 \leq Y2hour \leq 30$, $30 \leq Y4hour \leq 50$, $50 \leq Y6hour \leq 70$, $70 \leq Y8hour \leq 90$, for 10 and 12 hours NLT 90%. Maximum requisite of an optimum formulation with controlled drug release from the matrix tablet is fulfilled by the formulation composition with the HPMC K100LV level, (coded) 0.09 mg, and the level of HPMC K4M, 0.01 mg was found to fulfill the qualitative and quantitative composition of the optimized batch of Gliclazide MR 60 mg tablet is given in Figure 9.

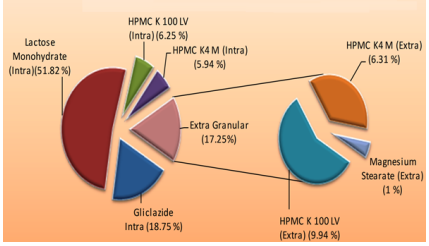

Figure 9. Pie chart for Qualitative and Quantitative composition of Gliclazide MR 60 mg tablet optimized formulation.

Desirable regression ranges for optimal formulation and process variable is indicated by desirability plot (Figure. 10a) and region of optimal formulation and process variables is indicated by overlay plot (Figure. 10b. Optimized formulation (run 10; Table 3) was evaluated for drug release from matrix tablet. The optimized formulation of Gliclazide MR 60 mg showed controlled drug release of 98.31 ± 0.005 with small error value (0.33) in 12 hours. The high prognostic ability of the factorial design is proved through results of the present investigation.

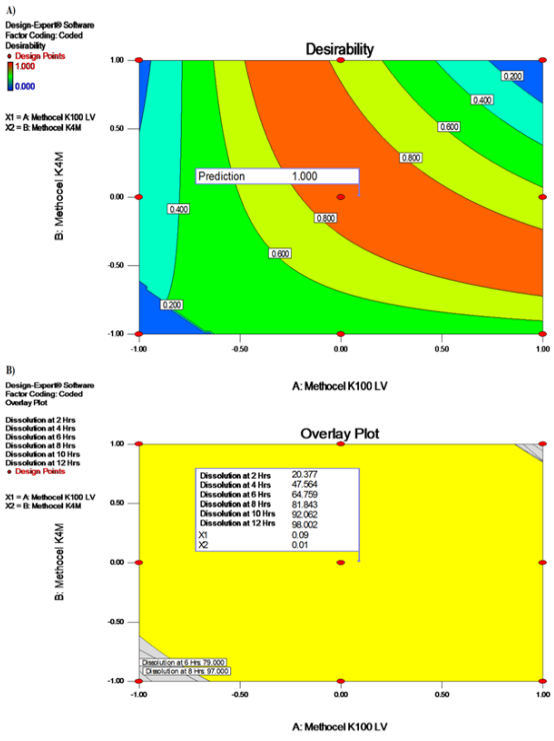

Figure 10a. Desirability Plot & **Figure 10b**. Overlay Plot.

3.3.6. In vitro drug release kinetic studies

The in vitro drug release studies of the experimental run 10 were performed in phosphate buffer (pH-7.4) for 12 hours. 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 $10 \leq Y2hour \leq 30$, $30 \leq Y4hour \leq 50$, $50 \leq Y6hour \leq 70$, $70 \leq Y8hour \leq 90$, for 10 and 12 hours NLT 90%. Release mechanism was evaluated with different kinetic models. The release kinetic model having a value of regression coefficient R2>0.75. The data were fitted into Korsmeyer-Peppas model. Linearity (R2: 0.9890) with a value of the slope (n) ≥ 0.43 is achieved from the sample. This n value, however, appears to indicate that anomalous transport is the leading mechanism of drug release from Gliclazide MR 60 mg tablet which indicates that polymer has a complex matrix like network and drug was completely entrapped in it and released by diffusion then erosion mechanism.

3.4.Physicochemical Characteristics of matrix tablet (halved tablet)

The results of resistance to crushing of tablets and friability testing for the optimized batch are presented in Table-10. Acceptable values of friability NMT 1.0% were obtained in tablets of the optimized batch with good hardness values, confirms superior mechanical properties that are able to resist handling. The results of loss of mass per breakability test method are presented in Table 11, Table 12 (expressed as % of tablet weight). A regulatory requirement for the maximum loss of mass upon breaking is 3.0 % w/w. In view of the results reported for loss of mass on breaking as per breakability and nomenclature guideline of USFDA and in line with Ph. Eur. requirements on friability, we consider a loss of mass 3.0 % acceptable and friability not more than 1.0 % for a halved tablet. Loss of mass by the manual method and tablet splitter method for Run 10 is 0.59 % and 0.69 % respectively which clearly indicated that formulation meet this requirement.

Table 10: Resistance to crushing of tablets and friability testing for Optimized formulation Run 10

No of samples	Resistance to crushing of Whole tablets (N)	Resistance to crushing of Halved tablets (N)
	Run 10	**Run 10**
Sample 1	120	80
Sample 2	121	85
Sample 3	128	78
Sample 4	127	81
Sample 5	119	89
Sample 6	118	76
Sample 7	124	72
Sample 8	122	81
Sample 9	120	85
Sample 10	123	84
Sample 11	124	83
Sample 12	131	78
Sample 13	119	82
Sample 14	126	84
Sample 15	117	80
Sample 16	129	85
Sample 17	131	84
Sample 18	121	78
Sample 19	123	77
Sample 20	130	79
AVERAGE	**123.65**	81.05
S.D	**4.45**	3.96
R.S.D	**3.6**	4.88
Minimum	**117**	72
Maximum	**131**	89
Weight equivalent to 6.5 gms taken for friability. NMT 1.0 %	**% Friablity**	
	Run 10	**Run 10**
	0.22 %	**0.37 %**

Table 11: Breakability losses obtained from breaking tablets of optimized formulation Run 10 using manual method at optimum hardness.

Batch No Run 10	1 / 2 tablet mass (mg)	2 / 2 tablet mass (mg)	Whole tablet mass (mg)	Difference	Loss of mass %
Sample 1	160.1	158.6	320.8	2.1	0.65
Sample 2	161.5	160.4	321.4	1.5	0.46
Sample 3	159.4	161.2	322.4	1.8	0.55
Sample 4	160.2	158.9	320.5	1.4	0.43
Sample 5	162	160.1	324.1	2	0.61
Sample 6	160.9	161.8	324.2	1.5	0.46
Sample 7	158.6	159.7	320.6	2.3	0.71
Sample 8	159.2	161.3	322.4	1.9	0.58
Sample 9	160.5	160.8	322.9	1.6	0.49
Sample 10	161.4	160.9	324.6	2.3	0.7
Sample 11	162.5	159.2	323.6	1.9	0.58
Sample 12	162.8	158.9	324.1	2.4	0.74
Sample 13	161.2	160.3	323.6	2.1	0.64
Sample 14	160.8	159.7	322.4	1.9	0.58
Sample 15	159.6	160.3	321.9	2	0.62
AVERAGE	**160.71**	**160.14**	**322.63**	**1.91**	**0.59**
S.D	**1.22**	**0.97**	**1.38**	**0.31**	**0.10**

Table 12: Breakability losses obtained from breaking tablets of optimized formulation Run 10 using "Tablet Splitter Method" at optimum hardness.

Batch No Run 10	1 / 2 tablet mass (mg)	2 / 2 tablet mass (mg)	Whole tablet mass (mg)	Difference	Loss of mass %
Sample 1	158.6	157.9	319.4	2.9	0.91
Sample 2	159.6	159.7	321.6	2.3	0.72
Sample 3	160.3	160.9	322.4	1.2	0.37
Sample 4	160.2	162.4	324.1	1.5	0.46
Sample 5	159.7	160.3	323.4	3.4	1.05
Sample 6	161.3	158.8	322.9	2.8	0.87
Sample 7	162.1	159.2	323	1.7	0.53
Sample 8	162.8	159.9	324.5	1.8	0.55
Sample 9	159.8	162.1	323.9	2	0.62
Sample 10	157.9	161.1	321.8	2.8	0.87
Sample 11	162.7	160.7	326.1	2.7	0.83
Sample 12	161.9	160.9	324.3	1.5	0.46
Sample 13	160.3	161.9	325.1	2.9	0.89
Sample 14	160.9	160.8	323.5	1.8	0.56
Sample 15	160.4	161.5	324.1	2.2	0.68
AVERAGE	**160.57**	**160.54**	**323.34**	**2.23**	**0.69**
S.D	**1.41**	**1.26**	**1.62**	**0.65**	**0.20**

The results of content uniformity studies (Table 9) for whole tablets and a halved tablet containing Gliclazide, which shows the percentage of drug present in each tablet (n=3), S.D and A.V for optimized formulation batch, RUN 10. The contents of Gliclazide in each tablet fulfilled pharmacopeia requirements. The results of content uniformity studies for both halved tablets containing Gliclazide 30 mg in both halves supposed to contain 100 % in both halves.

Content uniformity of Gliclazide is carried out by HPLC method, determined on halved tablets of final batch. The procedure was performed on ten whole tablets and ten halves separately. According to the Ph.Eur. (Reference), the content uniformity of active substance expressed as a percentage of the declared content should be within the limits of 85-115 and R.S.D should be equal or smaller than 6. The results of the content uniformity analysis for halved tablets were: 98.9 % with A.V of 2.11(NMT 15) which fulfills Pharmacopoeial requirements. Scored tablets bring added value to solid dosage forms, both with respect to their possibility for flexibility of dosing and for cost savings of medication. Based on the dissolution behavior in pH 7.4 phosphate buffer (Figure 3) the halved tablet of optimized formulation Run 10 was found to be essentially same when compared with the whole tablet of Run 10 and a halved portion of Diamicron MR 60 mg tablet, Similarity factor (F2 value) is 58.79 and 64.88 and, dissimilarity factor (F1 value) is 11.50 and 9.24 respectively. The similarity factor of the whole versus halved tablet of the optimized batch run 10 in pH 6.8 phosphate buffer was found to be similar, F2 value of 65.23 and dissimilarity factor 11.27. F2 value is not calculated in pH 4.5 acetate buffer and 0.1 N HCl due to incomplete drug release from Gliclazide modified release tablet, halved tablet lies within the specification (range) of drug release criteria set for the whole tablet. The result for Content uniformity and assay is given in Table 9. The detail observation of physicochemical characterization (hardness, friability) of a halved tablet is given in Table 10. Loss of mass obtained from breaking of the whole tablet for the optimized formulation using manual method and tablet splitter method is given in Table 11 & 12. Dissolution of a halved tablet in pH 7.4 phosphate buffer, 0.1 N hydrochloric acid, pH 4.5 acetate buffer and pH 6.8 phosphate buffer were carried out and reported through figure 3, 4, 5, and 6.

4.Conclusions

Based on the results obtained from dissolution profile of Gliclazide MR tablet 60 mg tablet in multimedia we may conclude that Gliclazide MR tablet 60 mg tablet shows a similar dissolution profile in pH 1.2, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer, However, incomplete release (approx. 10% and 50 %) due to degradation of Gliclazide was observed in 0.1 N HCl and pH 4.5 acetate buffer. It is also evident from breakability study that halved tablet and the whole tablet has a similar dissolution profile in pH 7.4 phosphate buffer (release media). According to the results obtained, we may conclude that tablets from Run 10 satisfy Pharmacopoeial requirements concerning crushing strength and friability. Application of two breaking method used showed little differences in loss of mass, i.e. 0.59 through the manual method and 0.69 through tablet cutter. The results of content uniformity studies for halved tablets containing Gliclazide contain 98.9 % of drug content with Acceptance value of 2.11. From above study, we can conclude that the results obtained in this study support tablet splitting option, which is very important for obtaining the required dosage when a dosage form of the required strength is unavailable, and for better individualization of the therapy. With reference to the entire tablet, based on the comparison of average tablet mass, dimension, appearance, FTIR, XRD study, dissolution and breakability, the Gliclazide MR 60 mg, and Diamicron MR 60 mg tablets are found to be essentially similar.

In the current research work, both processes and formulations are challenged and optimized to make sure that the drug product can be

manufactured from a robust and competent procedure according to DOE concepts. Quality attributes are consistently met for validation during routine manufacturing because critical parameters are established and verified with appropriate control during scale up. Manufacturing efficiency and consistency can be improved through a focus on optimization of process ranges and robustness within a continuous improvement process.

Acknowledgment

Authors are very much thankful to director and research guide for providing valuable assistance to carry out this research work. The authors gratefully acknowledge the respective vendors of excipients for providing the gift sample.

Declaration of interest

The authors report no conflicts of interest.

References

[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 the 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 a 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 optimization 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. Korsmeyer, 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. Gurney, 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.