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Effect of Alkaline Excipients on The Release Profile of Gliclazide Extended Release Tablets

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Abstract

The antidiabetic drug gliclazide has very poor aqueous solubility, which leads to variability in *in-vitro* dissolution profile, posing problem in design of extended release tablets. This research paper relates to a matrix tablet that enables the extended release of Gliclazide, the release being insensitive to variations in the pH of the dissolution medium. Gliclazide is a hydrophobic weak acid, insoluble in water and acidic pH and soluble towards neutral to alkaline pH. Variation in pH results in inconsistent and irregular release of drug from the dosage form, which is not a desirable feature.

Extended release dosage form comprises of drug Gliclazide. The dosage form also contains water swellable polymers such as Hydroxypropylmethyl cellulose (HPMC), a pH modifier selected from a wide range of alkaline compounds, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium carbonate and calcium carbonate. The diluents were selected from lactose monohydrate, microcrystalline cellulose or dibasic calcium phosphate. The formulation is made by conventional wet granulation method.

Therefore, the aim of the study was to increase the solubility of the drug by incorporating alkaline excipient along with the drug and the retarding polymer like hydroxypropylmethyl cellulose for designing oral extended release tablets. The variability in the dissolution profile gets reduced substantially by increasing the localized solubility of the drug by maintaining the pH of the formulation.

Key Words: Antidiabetic drug, Extended release tablets, Light magnesium carbonate, hydroxypropylmethyl cellulose.

INTRODUCTION

Sulfonylurea derivative Gliclazide is a second-generation hypoglycemic agent widely used in the treatment of non-insulin dependent diabetes mellitus. They act by increasing insulin release from the beta cells in the pancreas (1). Various sulfonylureas have different pharmacokinetics. The choice depends on the propensity of the patient to develop hypoglycemia – long acting sulfonylureas with active metabolites can induce hypoglycemia.

The tablets are most widely used dosage forms because of their convenience in terms of self -administration, compactness, ease of manufacturing and accurate dosing. They are generally dosed several times a day with food depending on the condition and severity of diabetes (2). The major drawback in the therapeutic application and efficacy of gliclazide as oral dosage form is its very low aqueous solubility. It is characterized by low dissolution rate in purified water. Because of these reasons, its in vitro dissolution profile shows intra tablet release variations, which ultimately leads to the inter-individual variations in its bioavailability and poses problems in design of extended release tablets.

Various techniques have been used to improve the dissolution profile variability. Extended release formulations are designed to allow at least a two fold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance when compared to a conventional immediate release dosage form (2). Amongst extended release formulations, matrix technology is most widely used drug delivery system due to many advantages such as desired release profile for wide therapeutic drug category, dose and solubility, simple and cost effective manufacturing process, robust formulation and ease of drug release profiles from polymeric systems. The matrix system involves the homogenous dispersion of drug particles in either a hydrophobic or hydrophilic polymer matrix; therefore the

physicochemical nature of the matrix controls the release rate of the drug and determines the release mechanism (3). Hydroxypropylmethyl cellulose is the first choice for formulation of hydrophilic matrix system, providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and method (4).

Several mathematical models have been published, to elucidate the water and drug transport processes and to predict the drug release kinetics. The mathematical description of the entire drug release process is rather difficult, because of the number of physical characteristics that must be taken into consideration. These include the diffusion of water into HPMC matrix, HPMC (polymer) swelling, drug diffusion from the device, polymer dissolution, changing matrix dimensions, porosity and composition. Each model makes certain assumptions; the applicability of the respective models is restricted to certain drug polymer systems (5).

The objective of this study was to prepare hydrophilic matrix tablets containing Gliclazide and HPMC as hydrophilic polymer to retard the drug release along with an alkaline excipient in order to reduce the intra tablet variation in the drug release profile. The Gliclazide content was 30 mg per tablet. The manufacturing method chosen was the conventional wet granulation method. The manufacturing process was validated against pre-defined acceptance criteria on three experimental batches. The batches were evaluated for stability under stress conditions. Additionally the objective of this work was also to evaluate drug release data using various kinetic models and to determine the mechanism of drug release.

MATERIALS

Gliclazide was obtained from Bal Pharma, Chennai, India, dibasic calcium phosphate (Rhodia), lactose monohydrate (Supertab 30, HMV), microcrystalline cellulose (Avicel PH 102, FMC), Hydroxypropylmethyl cellulose (HPMC K 100 LV and HPMC K 4 M, Colorcon), colloidal anhydrous silica (Aerosil 200, Evonik), magnesium stearate (Ferro) and sodium hydrogen carbonate (Merck). All other excipients were of standard pharmaceutical grade.

METHODS

Formulation of oral extended release tablets

Extended release tablets containing 30 mg of Gliclazide were formulated with varied compositions as listed in Table 1, Gliclazide and excipients were mixed and passed through 40mesh screen. The blend was processed using conventional non aqueous granulation method by incorporating combination of hydroxypropylmethyl cellulose (HPMC 4000 cps and HPMC K100LV) as a sustained release matrix former, lactose monohydrate was used as the tablet filler, formulation with and without light magnesium carbonate and sodium hydrogen phosphate as alkaline excipient, colloidal silicon dioxide as glidant and magnesium stearate as lubricant.

Tablets were also formulated using dibasic calcium phosphate as the diluents, which is water insoluble and has alkaline pH.

TABLE 1 Formulations of Gliclazide extended release tablets

Ingredients (%)	1	2	3	4
Drug (Gliclazide)	15	15	15	15
HPMC K4M	7.5	7.5	7.5	7.5
HPMC K 100 LV	22	22	22	22
Light Magnesium carbonate	1.25	-	-	-
Lactose Monohydrate	23.75	25	-	-
Dibasic calcium phosphate	-	-	25	23.75
Maltodextrin	28.5	28.5	28.5	28.5
Sodium hydrogen carbonate	-	-	-	1.25

Evaluation of the tablets

The tablets were evaluated for weight variation, pH, friability, hardness, assay, related substances and in-vitro dissolution profile.

Weight variation:

Twenty tablets were selected at random and the average weight was determined. Then the individual tablets were compared with the average weight. The limit for weight variation was kept at ± 3%.

Hardness and Friability (United States Pharmacopoeia):

The hardness of the tablets was checked using Monsanto hardness tester. The friability test was done with a Friabilator (Electrolab, Mumbai, India). Ten tablets were weighed and subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolved at 25 rpm and dropped the tablets from a distance of 6 inches with each revolution. After 100 revolutions, the tablets were dusted and reweighed. The percentage friability was calculated from the loss in weight of intact tablets.

pH:

Ten tablets were selected and crushed in motor. The crushed material was transferred to a beaker and 25 ml purified water was added. It was sonicated for 10 minutes and pH of the resulting solution was checked using pH meter.

***In-vitro* dissolution studies:**

The drug release profile of the formulated tablets were studied using USP dissolution apparatus I (Electrolab, TDT- 08L). The paddle speed of 100 rpm was used for dissolution testing for selected modified release tablets. The media were pH 6.8 phosphate buffer solution and pH 7.4 phosphate buffer solution, 900 mL. Sample aliquots were withdrawn at predetermined time points at 1,2,4,6,8,10 hours, filtered through 0.45micron filter and were suitably diluted. The gliclazide content was estimated using a UV spectrophotometer (Shimadzu at the wavelength of 260 nm and 290 nm. The amount of the drug released was estimated from the calibration curve.

Process validation:

Experimental batches were validated to confirm the accuracy and reproducibility of physical and chemical characteristics. Mixing time was validated by performing content uniformity test for gliclazide in the blend at dry mixing stage and lubricated granules stages after 15 and 30 minutes. While compression, hardness, thickness and weight variation was evaluated and data was compared for all three batches. *In- vitro* release profile, assay and related substances results were also evaluated and compared with pre defined criteria.

Drug release kinetics:

To analyze the *in - vitro* release data various kinetic models were used to describe the release kinetics. The drug release profile obtained in dissolution test were plotted in different models such as zero order rate kinetics (Eq. 1) which describes the system where the drug release rate is independent of concentration and plotted as amount of drug release vs. time (6). The first order (Eq. 2), which describes the release from system where release rate is concentration dependent and shows the log cumulative percentage of drug remaining in insoluble matrix as a square root of a time dependent process. Higuchi square root kinetics, describes the release of drug from insoluble matrix as a square root of time dependent process based on Fickian diffusion equation (eq. 3) and Korsmeyer-peppas model which is log cumulative % drug release vs. log time which is used to find out the mechanism of drug release (7). Slope of the appropriate plots and regression coefficient (r) were determined.

The release of drugs from the matrix tablets can be analyzed by release kinetics theory as follows (8):

Zero order kinetics: $C=K_0t$ (1)

Where K_0 is the zero order rate constant expressed in units of concentration/ time and t is the time in hours (9).

First order kinetics:

$\log C = \log C_0 - kt/2.303$ (2)

Where K is the first order constant reflecting the design variables of the system and t is the time in hours (10).

Higuchi model :$Q=Kt^{½}$ (3)

Where Q is the percentage of drug release at time t and K_1 is Higuchi release rate constant that reflects the shape and the internal structure of the matrix as well as the drug concentration and solubility.

Korsmeyer-peppas model:$Q=K_2 t^n$ (4)

Where K_2 is a constant incorporating the structural and geometric characteristics of the matrix tablets and n is the release exponent indicating the drug release mechanism (11). This model is usually used to analyze the drug release when the mechanism is not known or when more than one type of release process is involved.

The following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (Higuchi model); log cumulative % drug release vs. log time (Korsmeyer model).

To compare the differences in dissolution profiles between commercial product and the experimental formulations, the similarity factor f_2 is applied and defined by (eq.5)

$f_2 = 501\ g\ \{[\ 1 + 1/n \square\ Wt\ (R1-T1)2] -0.5\ X\ 100\}$ (5)

Where n is the number of dissolution sample times and R1 and T1 are the individual percentages dissolved at each time points, t for the reference and test dissolution profiles respectively.

Stability studies

Matrix extended release tablets were packed in alu/alu blister pack and subjected to the stability studies as per the ICH guidelines - 25^0C/60% RH, 30^0C/ 65% RH and 40^0C/75% RH. The tablets were analyzed for all the above given evaluation and mainly for the drug release, assay and related substances and were tested after 1,2, 3 and 6 months of storage time points.

RESULTS AND DISCUSSION

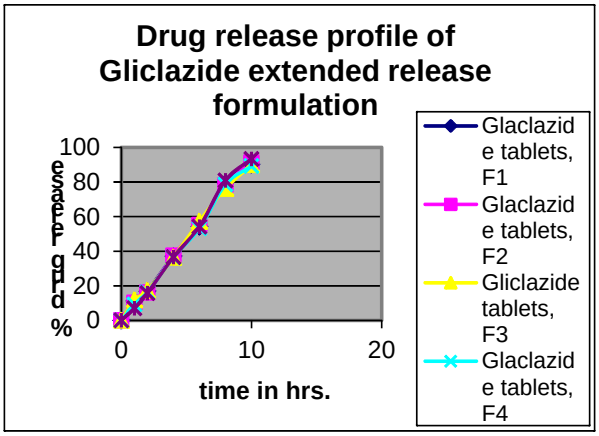
Several batches of tablet formulations from 1 to 4 containing a dose of 30 mg of gliclazide were made using HPMC as the extended release matrix forming polymer with and without pH modifier, light magnesium carbonate and sodium hydrogen phosphate as indicated in Table 1. The drug Gliclazide is used as the micronized material with an average particle size of less than about 30 microns. Formulation 1 contains 29.5% of combination of different viscosity grades of HPMC along with light magnesium carbonate. Formulation 2 is the similar to 1 without light magnesium carbonate. Formulation 3 is made with an alkaline excipient dibasic calcium phosphate as the diluent that makes the major portion of the tablet, with similar concentration of the rate controlling polymer. Formulation 4 contains sodium hydrogen carbonate as an alkaline excipient, which has a pH of 8.3 to give overall alkalinity to the tablets. The tablets were formulated by conventional non-aqueous granulation method. All the formulations were compressed into tablet using 7.00 mm circular shallow concave punches at a hardness of about 40-50 Newtons. The physical attributes of the tablet were found to be satisfactory. Friability of the tablet was within the acceptable range of 1% (Table 2). The assay was well within the limit of 90-110%. The duration of drug release ranged from about 10-12 hours for all the formulations. The dissolution profile of Gliclazide from the innovator product (Diamicron tablets from Servier, France) and experimental formulations 1, 2, 3 and 4 is illustrated in Figure 1.

TABLE 2 Physico-chemical parameters of formulated gliclazide tablets

Weight variation n=20	Thickness (mm) n=20	Friability (%) n=10	Hardness (N) n=20	Drug content (%) n= 20
Mean =1.625 mg Max 1.648 mg Min 1.552 mg	Mean = 3.2mm ± 0.2 mm	0.057	Mean= 55 Newtons ± 3% S.D= 2.541	Mean = 99.5% S.D= 2.1542

n - No. of tablets

Figure 1 Drug release profile of Gliclazide extended release formulations.



The dissolution was tested on 12 tablets of each formulation. The RSD for formulation 1 is 5%, which indicated that the drug release variability within the tablets is much less whereas for the formulation 2 without light magnesium carbonate the RSD is above 10% at each time point. RSD is calculated which represents the difference in the release profile within the tablets. The formulation 3 with dibasic calcium phosphate as the diluent and formulation 4 with sodium hydrogen phosphate also show the RSD well within the limit of 5%. (Tables 3 and 4).

The pH as illustrated in Table 5, show pH difference in tablets with light magnesium carbonate, which leads to the uniform drug release profile.

TABLE 5 pH of the tablets

Formulations	1	2	3	4
pH of the tablet	7.02	5.9	7.2	7.1

Gliclazide being hydrophobic weak acid is insoluble in purified water and acidic pH and soluble towards neutral to alkaline pH of 6-8. Its solubility increases with increase in pH. For the modified release tablets as drug action is for at least 10 hrs, the tablet remains in the acidic medium for 1-2 hrs. where solubility of drug is very low around 5-7% and when it reaches the alkaline pH the solubility of gliclazide increases and causes variation in the drug release profile due to difference in the pH of the tablet and the dissolution medium. The solubility of gliclazide is pH dependent increasing almost 3 fold from pH 7.0 to pH 8.3.

TABLE 3 Dissolution profile in pH 6.8 Phosphate buffer

Time in hours	Formulation 1 (% drug Release)	RSD (%)	Formulation 2 (% drug Release)	RSD (%)
1	5.6 - 7.2	17.68	4.5 – 11.8	63.34
4	32.5 -33.8	2.77	28.97 – 38.95	20.78
6	69.8 -71.3	1.5	66.9 – 79.5	12.17
10	89.5 - 91.6	1.64	79.5- 89.6	8.45

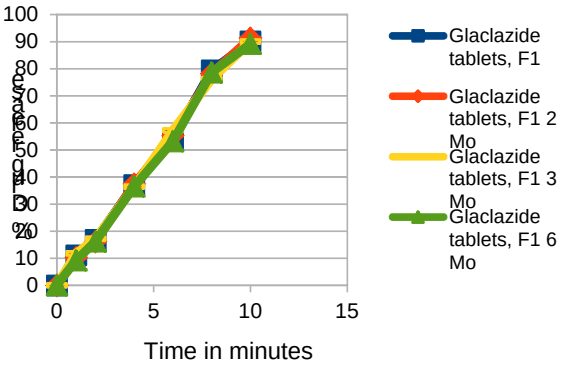
TABLE 4 Dissolution profile in pH 7.4 Phosphate buffer

Time in hours	Formulation 1 (% drug release)	RSD (%)	Formulation 2 (% drug Release)	RSD (%)
1	6.9 – 9.4	21.69	5.4-11.2	50.12
4	38.5 – 40.4	3.41	34.5 – 42.5	25.1
6	70.4 – 74.3	3.81	68.2 – 78.3	12.71
10	89.6-92.5	2.25	82.98 – 96.45	10.62

Light magnesium carbonate is also basic with a pH of 7.5 as tabulated in tables 3 & 4. Thus the pH of the tablet with light magnesium carbonate is 7.0, which is very close to the pH of the dissolution medium. The compounding is also easier with a pH modifier such as light magnesium carbonate, less water is needed and the granulation is denser with increased binding. The amount of pH modifier be in the range of 1-5%. When employing such carbonate compound as pH modifier, the formulation is not sensitive to the pH environment as in the basic pH drug has maximum solubility and pH is maintained both in tablets as well as the in the dissolution medium. This results in the uniform drug release and thus reduces the variability.

The drug release profiles of the extended release of formulation 1 shows no significant difference of drug release over 6 Months storage as given in Figure 2. Therefore a long shelf life can be obtained for the formulation.

Figure 2 Storage stability of Gliclazide extended release tablets in pH 6.8 phosphate buffer initial, 2,3,6 months under stress conditions: 40°C/75% RH.



The release kinetics data for zero order, first order, Higuchi and Korsmeyer peppas models is tabulated in Table 6.

The gliclazide extended release formulation, which is a matrix tablet comprising of hydrophobic drug with hydrophilic polymer, the release should follow three steps: First step is the penetration of the dissolution medium in the tablet matrix (hydration), second step is the swelling with concomitant or subsequent dissolution or erosion of the matrix and third step is the transport of the dissolved drug, either through the hydrated matrix or from the parts of the eroded tablet, to the surrounding dissolution medium (12). The percentage of gliclazide released at 2,4 and 10 hours was 15-30, 35-60 and more than 80% respectively for all the formulations. For predictive completion of release the drug release data of gliclazide for the formulation 1, obtained from dissolution is plotted as concentration (mg/ml) vs. time (hours). The straight line indicates zero order in accordance with equation 1, linear regression analysis of the data yields the equation of best line as r^2 0.995 (Table 6) and fig. 3.

But when the data was fitted to the other models such as First order, Higuchi and Korsmeyer- peppas r^2 was only 0.931, 0.973 & 0.944 respectively as depicted in the fig. 4,5, & 6. Hence according to equation 1 the slope of line corresponds to zero order rate constant as given in fig. 3.

The drug release data fitted zero order equation well. A good fitness to the zero order equation indicated that the release of the drug is independent of time and the release can be attributed to more than one factor that is diffusion coupled with erosion.

TABLE 6 The similarity factor f2 and the release kinetics of the commercial product and experimental formulations

Formulations	Zero order	First order	Higuchi model	Korsmeyer-peppas model	f2
Commercial product	0.991	0.925	0.984	0.933	-
F1	0.995	0.931	0.973	0.944	78.65
F2	0.988	0.093	0.977	0.935	61.5
F3	0.991	0.942	0.956	0.926	65.2
F4	0.989	0.944	0.954	0.925	62.2

Figure 3 Zero order Kinetics for formulation 1 :

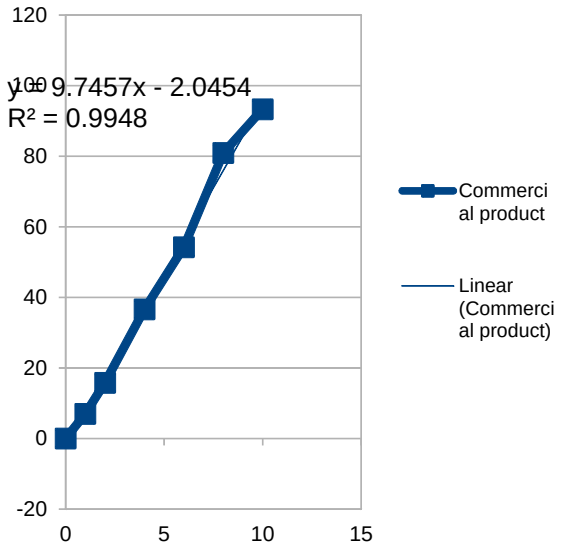


Figure 4 Higuchi Model for formulation 1:

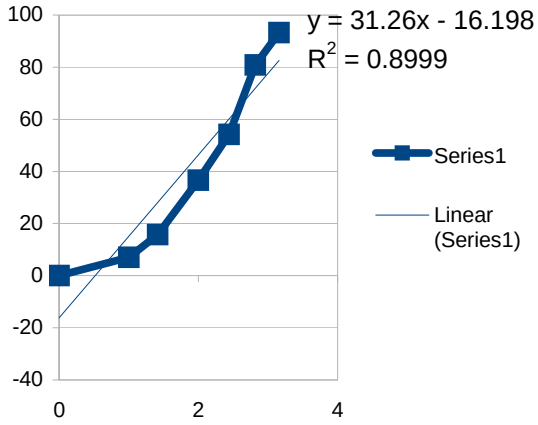


Figure 5 First order Kinetics for formulation 1:

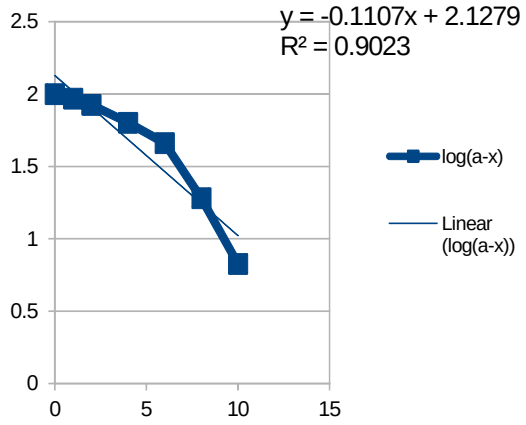
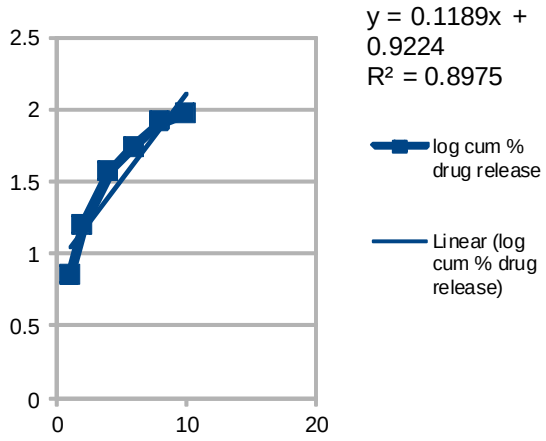


Figure 6 Korsmeyer's equation for formulation 1:



Process validation

Content uniformity for all the three batches was found within acceptable limits (95-105%). Drug content was measured as 96%, 99% and 100.2%, where it was noted that no significant difference was found in drug content at 85%and 100% for all the three batches indicating that adequate mixing was achieved at 54 min (85%) and further mixing may be omitted. Weight variation was found comparable for three batches, average weight of 20 tablets was observed at 1.624 gm, 1.659 gm and 1.632gm. The RSD for variation among different batches was only 5%. Reproducibility was also confirmed by comparing drug release profile for all the three batches. Dissolution profile was further verified and it confirmed the accuracy and reproducibility of drug release for 10 hours.

CONCLUSION

In this study, Gliclazide extended release matrix tablets were successfully prepared using a simple and economical method with the inclusion of alkaline excipient in the tablet. The tablet so made were found to be stable at accelerated storage conditions and acts favorably in the local pH in the microenvironment within and in the vicinity of the gelled tablet while being eroded, increasing the local solubility of the active compound thus facilitating the release of the active ingredient. The formulation is not sensitive to acidic environment and travels

through the gastric environment to the intestines where it is slowly dissolved and absorbed. Other drug substances, which show variability in the *in-vitro* dissolution can also be subjected to this technique of maintaining the pH of the microenvironment and reduce variability. The drug release kinetics of this formulation correspond best to zero order model in which drug release is through swelling and erosion.

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