



Formulation and Evaluation of Floating Gastro Retentive Glipizide Tablets



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Abstract

Glipizide, a BCS class II drug commonly prescribed for the type II diabetes, as an oral hypoglycaemic agent. But its insolubility in water leads to low oral bioavailability due to limiting dissolution rate. Therefore, the solubility of glipizide was increased by solid dispersion method followed by formulation of floating tablets using 32 full factorial designs. Solid dispersion of PEG 4000 and 6000 with glipizide at different ratio was prepared by fusion method. The floating tablets were prepared by direct compression method, using HPMC K4M, HPMC K15M and sodium bicarbonate was used to maintain buoyancy. The floating tablets were evaluated for various physiochemical properties and *in vitro* drug release studies.

The saturated solubility of pure glipizide was 7.9µg/ml which was enhanced to 204.3µg/ml, after preparation of solid dispersion, in 1:6 ratios with PEG 6000. The glipizide-PEG complex was confirmed by FT-IR spectroscopy and DSC thermo gram. All the formulations showed floating lag time 73-145 seconds, floating duration more than 24 hours and drug content was found in the range of 95.41 to 99.02%. Batch number F7 showed 61.48% of *in vitro* drug release in 8 hours hence, batch F7 was compared with marketed Glynase XL and showed 51.58% similarity factor. *In vitro* release kinetics of batch F7 followed the zero order release and super class II transport diffusion

Keywords: Glipizide; Solid dispersion; Factorial design; Floating tablets; Buoyancy; Floating time

Introduction

From past few decades' greater attention have been focused on development of sustained release (SR) or controlled release (CR) drug delivery systems due to Complications and expense involved in marketing of new drug entities [1]. The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time which over comes problem of gastric retention as in case of conventional oral delivery. Indeed, gastric drug retention is receiving significant interest now a day [2]. Gastro retentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs that are preferentially absorbed from upper GIT [3]. Various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating systems [4,5] and expanding systems bio adhesive systems, modified-shape system and

high-density systems [6]. The floating drug delivery systems, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be an effective and rational approach to the modulation of controlled oral drug delivery. These systems were useful for those drugs that act locally in the proximal part of gastrointestinal tract or are poorly absorbed in the intestine. These dosage forms have a bulk density lower than that of the gastric fluid. After oral administration, they can remain in the stomach and deliver drugs in a sustained release manner [7].

Solid dispersion technique was selected as it was utilized in limited number of researches to increase the solubility of glipizide. It has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs [8,9]. In solid dispersions, the particle size of the drugs was reduced, the wettability and the dispersibility were enhanced; therefore, drug dissolution was improved markedly [10]. Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes. Glipizide is

a weak acid (pKa=5.9) practically insoluble in water and acidic environment and highly permeable (class II) drugs according to the Biopharmaceutical Classification System (BCS) [11]. The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 2-4 hours. Glipizide is reported to have a short biological half-life (3.4±0.7 hours) requiring it to be administered in 2 to 3 doses of 2.5 to 10mg per day. SR formulations that would maintain plasma levels of drug for 8 to 12 hours might be sufficient for once a day dosing for glipizide. SR products are needed for glipizide to prolong its duration of action and to improve patient compliance [12].

Materials and Methods

Materials

Glipizide was generously gifted by USV, Ltd. Mumbai, India. HPMC (K4M, K15M) and microcrystalline cellulose were obtained from Signet, Pune, India. Sodium bicarbonate, magnesium stearate, PEG 4000, 6000 and talc were purchased from Thomas Baker, Mumbai.

Method

Preparation of the glipizide PEG complex: Solid dispersions (SDs) at various weight ratios 1:1, 1:2, 1:3, 1:4, 1:5, and 1:6 were prepared by melting method. Glipizide was added to the molten base comprising of PEG4000 and PEG 6000 respectively. The blend was heated 10 °C above the melting point

of each carrier for 5min with continuous stirring. The systems were placed 24 hours for drying. The mass was crushed, ground gently with a mortar and pestle and passed through sieve# 40.

Evaluation of Glipizide PEG complex Solubility measurements: Saturated solutions were prepared by adding the glipizide to 0.1 NHcl. It was performed by adding gradually amount of glipizide to the solution until undisclosed glipizide was present after 24h of stirring on a magnetic stirrer. The solutions were filtered using a cellulose acetate membrane (0.45µm). The concentrations of the glipizide were determined spectroscopically with UV/Vis Spectrophotometer at wavelength 276nm [13].

Glipizide-PEG complex study

The infrared spectra of pure drug (glipizide) and drug-PEG complex (1:1) were recorded between 400 and 4000cm⁻¹ by FT-IR spectrometer (Jasco 4100 series) using KBr pellet technique. Similarly DSC thermo gram of above combination was recorded and interpreted [14].

Preparation of Tablets

All the tablets were prepared by direct compression method. All the ingredients (Table 1) were passed through sieveno. 40# and blend in an octagonal blender for 10min. Magnesium stearate was used to lubricate the blend. The lubricated blend was then compressed on 12 stations rotator tablets machine (CIPS machinery India) using single 8mm flat punches.

Table 1: Composition of glipizide floating tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide-PEG 6000 eq. to 10mg of glipizide	70	70	70	70	70	70	70	70	70
HPMC K4M	20	20	20	25	25	25	30	30	30
HPMCK15M	20	25	30	20	25	30	20	25	30
Sod.carbonate	20	20	20	20	20	20	20	20	20
MCC	66	61	56	61	56	51	56	51	46
Mg.Stearate	4	4	4	4	4	4	4	4	4
Total	200	200	200	200	200	200	200	200	200

Evaluation of Tablets

Floating lag time and buoyancy time: The tablets were placed in a 100ml beaker containing 100ml 0.1 NHcl. The time required for the tablet to rise to the surface and float was taken as the floating lag time. The time for which tablets kept floating was termed as 'buoyancy time' of the tablets which was determined for all the formulations [3].

Percentage of drug content: Twenty Tablets were weighed individually and the drug was extracted in 0.1 NHcl followed by filtration through 0.45µm. The solution was analysed by using spectrophotometer at 276mm.

Swelling study: Water uptake study of the dosage form is conducted by using USP dissolution apparatus-II in 900ml of distilled water which is maintained at 37±0.5 °C, rotated at 100rpm. At selected regular intervals, the tablet is withdrawn

and weighed. Percentage swelling of the tablet is expressed as percentage water uptake (%WU) or % Swelling index [2].

$$\% \text{ Swelling index} = \frac{W_t - W_o}{W_o} \times 100$$

W_t

Where,

W_t - weight of the swollen tablet,

W_o - initial weight of the tablet

In vitro Release Studies: Drug release studies of the prepared floating tablets as well as the commercially available Glynase XL 10mg (USV Ltd) tablets were performed, in triplicate, in a USP dissolution tester apparatus, type- II (Paddle method) at 37 °C ± 0.5 °C and 100 rpm. The tablets were placed into 900ml of 0.1NHcl solutions (pH 1.2). The drug content was determined spectrophotometrically at a wavelength of 276mm.

Kinetic modelling of drug release profiles: The drug release kinetics was studied by plotting the data obtained from the *in vitro* drug release in various kinetic models like zero order, first order, Higuchi, and Hixson-Crowell model. The model with the highest correlation coefficient was considered to be the best fitting one.

Factorial design: A 3² full factorial design was constructed to study the effect of the amount of HPMC K4M(X₁) and the amount of HPMC K15M(X₂) on the drug release from gastro retentive glipizide tablets (Table 2 & 3). The dependent variables chosen were % drug release and floating lag time (FLT). A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

Table 2: Independent variable for the experimental design.

Code	-1	0	1
X1 (HPMC K4M)	20	25	30
X2(HPMC K15M)	20	25	30

Table 3: Each tablet contains glipizide-PEG 6000 complex equivalent to 10mg of glipizide, Sodium bicarbonate 20mg, Magnesium stearate 4mg, MCC to make 200mg tablet. 32Factorial design batches.

Batch	X1	X2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where Y is the dependent variable, b₀ is the arithmetic mean response of the 9 runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X₁ and X₂) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X₁X₂) show how the response changes when 2 factors are changed simultaneously. The polynomial terms (X₁² and X₂²) are included to investigate nonlinearity [15-17].

Result and Discussion

The solubility of glipizide was increased as a linear function of carrier concentration. Solid dispersion prepared by PEG 6000 (1:6 ratio), showed 204.3 ppm solubility which is 25 times more than solubility of pure glipizide. The FT-IR spectrum of glipizide showed principle functional groups wave number at 1688.37, 1649.8, 1529.27, 1159.01, 1034.62 and 904.45cm⁻¹ (Figure 1). In the glipizide-PEG 6000 complex spectra principle wave number peak was diminished which indicates the formation of glipizide-PEG 6000 complex (Figure 2). DSC of pure glipizide showed the peak at the 218.0 Celsius while only one peak at 62.3 Celsius of

excipients observed for glipizide-PEG complex which confirms the formation of glipizide-PEG complex (Figure3).

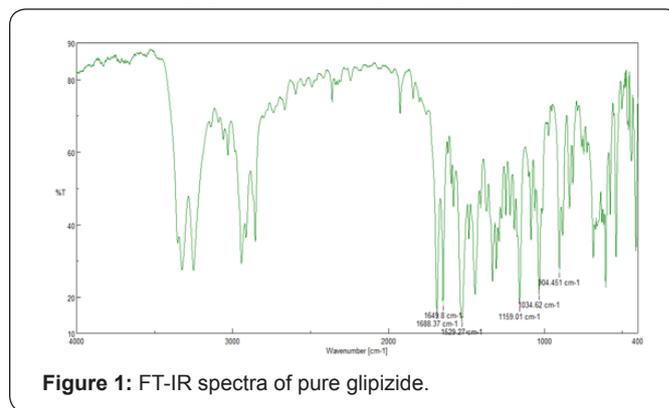


Figure 1: FT-IR spectra of pure glipizide.

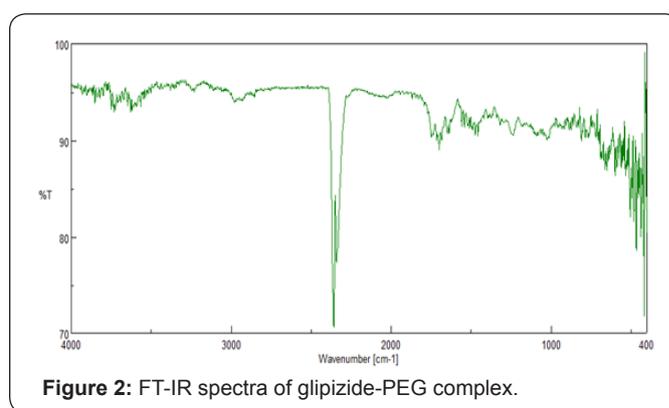


Figure 2: FT-IR spectra of glipizide-PEG complex.

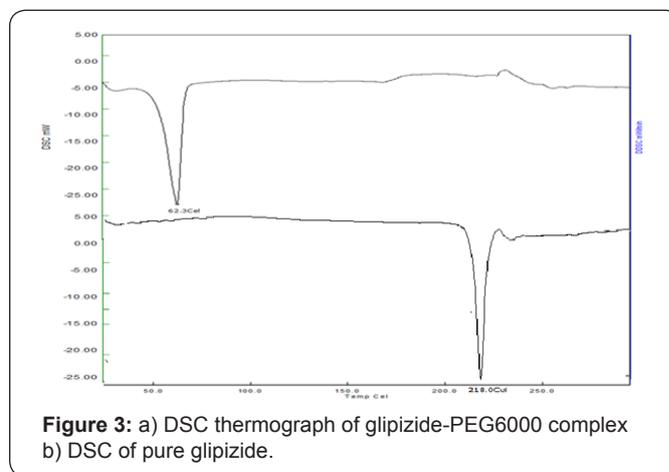


Figure 3: a) DSC thermograph of glipizide-PEG6000 complex b) DSC of pure glipizide.

The *in vitro* testing revealed the ability of all the tablets to maintain buoyant more than 24h (Table 4). This indicates that the gel layers, formed by the HPMC, enabled efficient entrapment of the generated gas bubbles. The possible increase in tablet porosity made it float on the test medium (0.1NHcl) for this extended period of time. The formulations with HPMC K4M and HPMC K15M showed significant swelling and good tablet integrity. The formulations with HPMC K15M showed higher swelling compared to formulations with K4M. Drug uniformity results were found to be good among all batches; the percentage of drug content ranged from 95.41% to 99.78% (Table 5).

Table 4: Evaluation of floating tablets.

Formulation Code	Hardness (Kg/cm ²)	Avg. Weight (mg)	Friability (%)	Tablet thickness (mm)	Tablet diameter (mm)
F1	6.1±0.15	201.66±1.6	0.22±0.04	4.0±0.01	8.0±0.01
F2	6.4±0.16	199.0±1.9	0.23±0.03	3.98±0.01	8.0±0.01
F3	6.2±0.22	200.0±1.1	0.30±0.02	4.02±0.03	8.04±0.02
F4	6.0±0.09	197.66±2.8	0.37±0.05	4.0±0.01	7.88±0.03
F5	6.3±0.15	200.33±1.2	0.34±0.03	4.0±0.02	8.0±0.02
F6	6.5±0.14	199.0±1.6	0.26±0.01	4.0±0.01	7.88±0.03
F7	6.5±0.16	199.33±1.6	0.16±0.01	3.96±0.01	8.02±0.02
F8	6.6±0.10	200.0±1.4	0.19±0.05	4.0±0.02	8.04±0.02
F9	6.1±0.17	198.66±2.5	0.11±0.01	4.0±0.01	8.0±0.01

Table 5: *In vitro* evaluation of floating tablets.

Formulation Code	Floating lag time In (Sec)	Floating duration (hours)	Swelling index In%	Drug content %	% Drug release
F1	95±2.5	>24	245.0±1.5	98.91±2.80	26.19±1.1
F2	103±3.1	>24	247.0±2.1	95.41±1.80	24.28±2.9
F3	94±2.2	>24	256.0±1.1	97.36±1.64	22.24±1.4
F4	97±3.1	>24	250.5±2.4	98.46±2.1	25.28±2.2
F5	88±4.3	>24	254.0±2.4	96.39±3.4	25.39±1.6
F6	98±3.6	>24	266.5±2.2	98.10±2.2	23.40±1.5
F7	81±4.2	>24	255.0±1.4	98.91±2.80	62.12±2.2
F8	131±3.4	>24	268.5±1.6	96.44±1.6	24.3±1.6
F9	145±2.5	>24	274.5±1.3	97.45±2.6	19.38±2.6

Optimized batch F7 and marketed preparation (Glynase XL) were selected for the similarity factor study. The percentage of glipizide released from batch F7 and Glynase XL in 8 hours found to be 61.48% and 55.64 % respectively (Figure 4). Similarity factor was calculated using formula $50 + \log \left[\frac{1 + (R_t - T_t) \cdot 1/n}{0.5} \right]$. Similarity factor was found to be 51.58%, more than 50% value is acceptable.

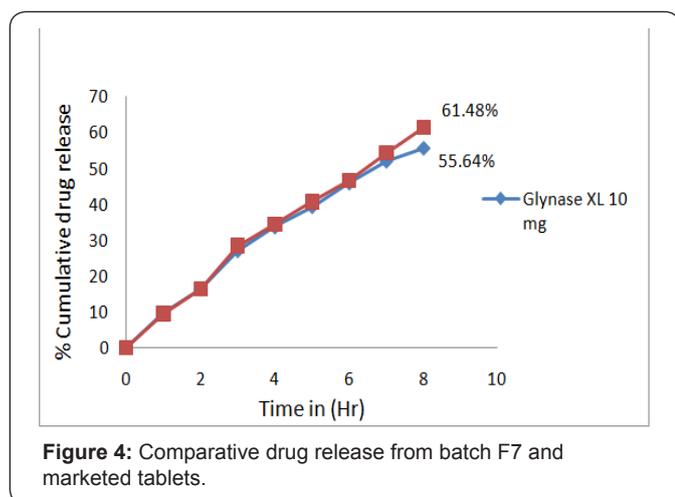


Figure 4: Comparative drug release from batch F7 and marketed tablets.

In the release kinetics study, data obtained from the dissolution studies was fitted in different models like zero order, first order, Higuchi, and Hixson-Crowell model. The model with the highest correlation coefficient was considered to be the best

fitting one [18-20]. The release mechanism was super case II transport as n value was 1.153. The best fitting model for F7 batch was zero order kinetics. This relationship can be used to describe the drug dissolution of several types of modified release dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs.

Conclusion

From this study, it may be concluded that floating tablets of glipizide can be formulated as a sustained released formulation. This approach can increase the gastric residence time and thereby improve its bioavailability. Reproducibility in formulation indicates easy scale up of formulation at large scale.

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