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
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 5 min with continuous stirring. The systems were placed for 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 N HCl. It was performed by adding gradually amount of glipizide to the solution until undisclosed glipizide was present after 24 h of stirring on a magnetic stirrer. The solutions were filtered using a cellulose acetate membrane (0.45 µm). The concentrations of the glipizide were determined spectroscopically with UV/Vis Spectrophotometer at wavelength 276 nm.

Glipizide-PEG complex study

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

Preparation of Tablets

All the tablets were prepared by direct compression method. All the ingredients (Table 1) were passed through sieves numbered 40 and blended in an octagonal blender for 10 min. 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 8 mm flat punches.

Table 1: Composition of glipizide floating tablets.

| Ingredients          | F1  | F2  | F3  | F4  | F5  | F6  | F7  | F8  | F9  |
|----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glipizide (6000 eq. to 10 mg 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  |
| Soda 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 100 ml beaker containing 100 ml 0.1 N HCl. 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.

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

Swelling study: Water uptake study of the dosage form is conducted by using USP dissolution apparatus-II in 900 ml of distilled water which is maintained at 37±0.5 °C, rotated at 100 rpm. 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 [% WU] = [Wt - Wo] × 100

Where,

Wt - weight of the swollen tablet,
Wo - 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 10 mg (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 900 ml of 0.1 N HCl solutions (pH 1.2). The drug content was determined spectrophotometrically at a wavelength of 276 nm.
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 | X₁ (HPMC K4M) | X₂ (HPMC K15M) |
|------|---------------|-----------------|
| -1   | 20            | 20              |
| 0    | 25            | 25              |
| 1    | 30            | 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 = b₀ + b₁X₁ + b₂X₂ + b₁₁X₁² + b₂₂X₂²

Where Y is the dependent variable, b₀ is the arithmetic mean response of the 9 runs, and bi is the estimated coefficient for the factor Xi. 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 904.45 cm⁻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).

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 (0.1N HCl) 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/cm²) | Avg. Weight (mg) | Friability (%) | Tablet thickness (mm) | Tablet diameter (mm) |
|------------------|-------------------|-----------------|----------------|-----------------------|----------------------|
| F1               | 6.1±0.15          | 201.6±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          | 197.6±2.8       | 0.37±0.05      | 4.0±0.01              | 7.88±0.03            |
| F5               | 6.3±0.15          | 200.3±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          | 199.3±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          | 198.6±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 [(1+ (Rt-Tt)*1/n)-0.5]. Similarity factor was found to be 51.58%, more than 50% value is acceptable.

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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