



Formulation And Evaluation Of Sustained Release Matrix Tablets Of Glipizide

Dhanashri Fand^[1], Sumedha Alone^[2], Pragati Jadhav^[3], Harshad

Chandanshive^[4] Vishal Babar^[5]

Dattakala college of pharmacy, Bhigwan, Maharashtra

ABSTRACT

Glipizide is one of the most commonly used anti-diabetic drug for treatment of type 2 diabetic mellitus. It is effective and pancreatic secretion of insulin. Glipizide is used for patients with type 2 diabetes who have failed diet and exercise therapy and it appears to be the most effective in the first phase of insulin. Glipizide has a short biological half-life, i.e. 2 to 5 hrs, which is rapidly eliminated, so requiring to be administered in 2 to 3 doses of 2.5 to 15mg per day. Hence, once-daily sustained release matrix tablets of glipizide were developed. Many methods are used for the preparation of sustained release preparations of glipizide. The review article summarizes the research material in the field of sustained release tablets of glipizide.

KEYWORDS: sustained release Diabetes, Matrix tablet, Granulation method. β -cyclodextrin Microcrystalline Cellulose, dissolution study.

1. INTRODUCTION

Over recent years, cyclodextrin and their derivatives have received considerable interest in the pharmaceutical field due to their potential to form complexes with a variety of drug molecules. Sustained release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half-life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance. Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) drug delivery systems. Glipizide is a weak acid ($pK_a = 5.9$) practically insoluble in water and acidic environment and highly permeable (class II) drugs according to the Biopharmaceutical Classification System (BCS). Glipizide is widely used sulphonyl urea antidiabetic agent, for the treatment of patients with type II diabetes. Glipizide stimulates insulin secretion from the β cells of pancreatic islets tissue, increases the concentration of insulin in the pancreatic vein and may increase the number of insulin receptors. A rapidly absorbed drug having faster elimination. Rate with short half-life makes it a suitable candidate to be formulated for the sustained delivery. The objective of the present investigation is to design Glipizide matrix tablets with β -CD. The dissolution study of Glipizide β -CD

complex shows Significant increase in the drug release from Glipizide β - CD Complex than pure drug. The formation of the inclusion Compounds greatly modifies the physical and chemical properties Of the guest molecule, mostly in terms of water solubility. Glipizide with beta Cyclodextrin increase the solubility in Phosphate buffer and water also. Glipizide is widely prescribed and effective anti-diabetic drugs .Were selected for formulation into sustained release drug delivery System in the form of matrix tablets employing polymers namely Hydroxyl propyl methyl cellulose (HPMC), Carboxy methyl Cellulose sodium (NaCMC) and Microcrystalline cellulose (MCC).

2. Materials and methods

Glipizide was gift sample from Micro Labs Ltd. B-CD was Purchased from Signet Chemical Corporation. All other chemicals And reagents used were of analytical grade.

2.1 Preparation of matrix tablets

The matrix tablets of Glipizide / Glipizide- β -CD-complex were Prepared as per the formulae given in Table. The matrix tablets of Glipizide/glipizide beta cyclodextrin complex were prepared Employing HPMC K4 M as a matrix former by direct Compression method. The ingredients consisting of Glipizide / Glipizide- β -CD-complex, hydroxypropyl methyl cellulose, Sodium carboxy methyl cellulose, microcrystalline cellulose (Avicel) were passed through a sieve no. 60 separately and mixed For 30 min in a plastic bag to obtain a uniform blend. The blend Was lubricated with talc and magnesium stearate. The lubricated Blend was compressed in to matrix tablets. The compressed Matrix tablets were evaluated for the tablet properties using Official procedures.

2.2. Preparation of inclusion complex by kneading method

Glipizide and β -cyclodextrin in 1:1 M ratios were triturated in a Mortar with 10 ml of distilled water. The thick slurry was kneaded For 45 minutes and dried at 55 °C. The kneaded product was Passed through mesh no 100 and stored in dessicator.

2.3 Phase solubility analysis

Phase solubility studies were performed in triplicate according to The procedure reported by Zingone and Rubessa [15]. Excess Amounts of Glipizide (20 mg) was added to 20 ml of distilled Water containing various concentrations of β -cyclodextrin (0.3-1.5 mM) taken in a series of stoppered conical flasks. The Samples were shaken for 72 hours at room temperature on a rotary Flask shaker. After equilibrating for 72 hours aliquots of 2 ml Were withdrawn and suitably diluted. The diluted samples were Filtered using distilled water and assayed for Glipizide by Measuring the absorbance at 276 nm against distilled water as a Reagent blank. The phase solubility diagram was constructed by Plotting the concentration of β -cyclodextrin against the Concentration of Glipizide. The stability constant KC of Glipizide B-cyclodextrin complex was calculated using Higuchi and

Connor's equation [16].

$K_c = \text{slope} / S_o (1 - \text{slope})$ S_o = Intrinsic solubility of Glipizide in aqueous complexation Media. The slope was calculated from solubility diagram. Measuring the absorbance at 276 nm against distilled water as a Reagent blank. The phase solubility diagram was constructed by Plotting the concentration of β -cyclodextrin against the Concentration of Glipizide. The stability constant K_C of Glipizide B-cyclodextrin complex was calculated using Higuchi and Connor's equation [16]. $K_c = \text{slope} / S_o (1 - \text{slope})$ S_o = Intrinsic solubility of Glipizide in aqueous complexation Media. The slope was calculated from solubility diagram.

2.4 Evaluation of tablets

I. Weight variation test

All prepared matrix tablets were evaluated for weight variation as Per USP monograph. Twenty tablets were weighed collectively And individually using an electronic balance. The average weight Was calculated and percent variation of each tablet was calculated. The percent deviation was calculated using the following formula. Percentage weight variation = $(\text{Individual weight} - \text{Average Weight} / \text{Average weight}) \times 100$

II. Friability

Friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_o) or a sample of tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again .Percentage friability was calculated from the loss in Weight as given in equation as below .The weight loss should not Be more than 1% w/w. %Friability = $(W_o - W) / W_o \times 100$

III. Drug content.

Ten tablets were weighed and grounded in a mortar to get fine Powder; powder equivalent to the mass of one tablet extracted With pH 7.4 phosphate buffer and filtered through 0.45 μ Membrane filter paper. The Glipizide content was determined Spectrophotometrically at 276nm using an UV- spectrophotometer After suitable dilution

IV. Weight Variation Test

To study weight variation, 20 tablets of each formulation were Weighed using an electronic balance, and the test was performed According to the official method

V. Hardness

Hardness of the tablets was determined using a hardness testing Apparatus.

2.5 Drug release study on glipizide matrix tablets

Dissolution study of matrix tablet performed in triplicate Employing USP XXII dissolution test apparatus type II using Phosphate buffer pH 7.4 as a dissolution media. The matrix tablet Was loaded into a basket of dissolution apparatus; stirrer at 75 Rpm and 37°C ± 0.5C. The sample (5 ml) taken at each sampling Time was replaced with fresh dissolution medium (5 ml). The Samples were analyzed spectrophotometrically at 276 nm using Phosphate buffer pH 7.4 as blank. The raw dissolution data was Analyzed for calculating the amount of drug released and Percentage cumulative drug released at different time intervals.

3. Stability studies

To assess the drug and formulation stability, stability studies were Done according to ICH guidelines. The formulation (F12) was Selected for stability study on the basis of in vitro drug dissolution Studies .In the present study, stability studies were carried out at 40°C/75% RH in closed high density polyethylene bottles for 3 Months. The samples were withdrawn after periods of 1 month, 2 Month and 3 month and evaluated for physical changes, hardness, Friability, drug content, during the stability studies.

Table 1: Composition of matrix tablets of Glipizide (Thretical weight of each table

| Formulation Code | Glipizide | Glipizide β-CD complex | HPMC | NaCMC | Avicel | Mg sterate | Talc | |
|------------------|-----------|------------------------|------|-------|--------|------------|------|--|
| F1 | 10 | | 20 | 20 | 144 | 04 | 02 | |
| F2 | 10 | | 40 | 25 | 109 | 04 | 02 | |
| F3 | 10 | | 60 | 50 | 74 | 04 | 02 | |
| F4 | 10 | | 80 | – | 104 | 04 | 02 | |
| F5 | 10 | | 100 | – | 84 | 04 | 02 | |
| F6 | 10 | | 120 | – | 64 | 04 | 02 | |
| F7 | – | 70 | 20 | 20 | 84 | 04 | 02 | |
| F8 | – | 70 | 40 | 25 | 49 | 04 | 02 | |
| F9 | – | 70 | 60 | 50 | 14 | 04 | 02 | |
| F10 | – | 70 | 80 | – | 44 | 04 | 02 | |
| F11 | – | 70 | 100 | – | 24 | 04 | 02 | |
| F12 | – | 70 | 120 | – | 4 | 04 | 02 | |

3.1 Drug Release Characteristics of Glipizide Matrix Tablets

Glipizide release from the matrix tablets formulated was slow and Sustained over 24 hrs and depended on the drug form used in the Matrix tablets and the polymer used. The formulations F1 to F12 Employing Hydroxy propyl methyl cellulose K4M, Carboxy Methyl cellulose Sodium as matrix forming polymer (Table 1 and 2). Thus with matrix forming polymers, Glipizide release from The matrix tablets, was high, sustained and complete in 24 hrs When Glipizide- β -CD complexes were used. The F12 has shown 96.32 ± 2.320 release in 24 hrs is compared with matrix tablets Formulated employing Glipizide alone, was very slow with all the Polymers concentration. Glipizide release rates were much higher In the case of matrix tablets containing Glipizide β -CD complexes (Figure1, 2 and 3). Analysis of release data as per zero order Kinetics model indicated that the zero order kinetic model is Applicable to describe the release data. The correlation coefficient value is 0.996 zero order kinetic model.

3.2 Results and discussion

Matrix tablets were formulated employing Glipizide alone and Their β -CD complexes with an objective of evaluating the Feasibility of employing drug- β -CD complexes in the design of Sustained release tablet formulations for obtaining slow, sustained And complete drug release in 24 hrs. All the matrix tablets were Found to be non disintegrating in water, acidic (pH 1.2) and Alkaline (pH 7.4) fluids. As such, the formulated matrix tablets Were of good quality with regard to drug content, hardness and Friability.

4. Acknowledgments

The authors are thankful to the management Doon Valley Institute of Pharmacy and Medicine, Karnal, (Haryana), India for Carrying out project work.

5. Conclusion

Glipizide release from the matrix tablets formulated was slow and sustained 24 h and depended on the drug form used in the matrix tablets and the polymer used. In each case matrix tablets were prepared by dried compression method employing Hydroxy propyl methyl cellulose K4M (HPMC), as matrix formers at various concentrations in the formula. All the matrix tablets

prepared were evaluated for drug content, drug release kinetics. The F12 has shown release is 96.32 ± 2.320 in 24 hrs is compared with matrix tablets formulated employing Glipizide alone, was very slow with all the polymers concentration. Glipizide release rates were much higher in the case of matrix tablets containing Glipizide β -CD complexes. Hence complexation with β cyclodextrin (β -CD) is recommended (i) to enhance the solubility and dissolution rate of glipizide (ii) in the formulation of controlled release products of glipizide to achieve slow, controlled and complete drug release in 24 hrs for once a day administration.

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