*International Journal Of*

**Recent Scientific Research**

**ISSN: 0976-3031**

**Volume: 7(2) February -2016**

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THE OFFICIAL PUBLICATION OF
INTERNATIONAL JOURNAL OF RECENT SCIENTIFIC RESEARCH (IJRSR)
http://www.recentscientific.com/ recentscientific@gmail.com

ISSN: 0976-3031

Available Online at http://www.recentscientific.com

*International Journal of Recent Scientific Research*
*Vol. 7, Issue, 2, pp. 8889-8892, February, 2016*

*International Journal of Recent Scientific Research*

**RESEARCH ARTICLE**

# DEVELOPMENT & EVALUATION OF GLIPIZIDE FLOATING BEADS FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM

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**ARTICLE INFO**

***Article History:***

Received 15th November, 2015
Received in revised form 21st December, 2015
Accepted 06th January, 2016
Published online 28th February, 2016

***Keywords:***

Diabetes, Gastroretentive drug delivery, Mechanism of glipizide, Sulfonyl urea receptor, Glipizide floating beads, Drug entrapment efficiency, Swelling index.

**ABSTRACT**

Gastroretentive drug delivery system is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine. This have a bulk density less than gastric fluid & the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) & a better control of the fluctuation in plasma drug concentration.

Here, we use glipizide as the candidate drug which a second generation sulfonyl urea used as an anti-diabetic drug. It undergoes enterohepatic circulation. It acts on sulfonyl urea receptor. It produces action by blocking potassium channel in β-cell of islet of langerhans by which calcium channel get activated & increase more insulin release from individual β-cell. Gellan gum, magnesium stearate are used for the formulation of this glipizide microbeads. Here, we detect the sizes, densities, percentages of swelling of glipizide beads & percentages of drug entrapment efficiency to show that it may affect release time of active ingredient in tablet but not reduce the overall bioavailability of candidate drug.



## INTRODUCTION

Diabetes [1] is a defect in the body's ability to convert glucose (sugar) to energy. Glucose is the main source of fuel for our body. When food is digested it is changed into fats, protein, or carbohydrates. Foods that affect blood sugars are called carbohydrates. Carbohydrates, when digested, change to glucose. Examples of some carbohydrates are bread, rice, pasta, potatoes, corn, fruit & milk products. Individuals with diabetes should eat carbohydrates but must do so in moderation. Glucose is then transferred to the blood & is used by the cells for energy. In order for glucose to be transferred from the blood into the cells, the hormone-insulin is needed. Insulin is produced by the beta cells in the pancreas (the organ that produces insulin). Type 1 diabetes occurs most frequently in children & young adults, although it can occur at any age. Type 1 diabetes accounts for 5-10% of all diabetes in the United States. There does appear to be a genetic component to Type 1 diabetes, but the cause has yet to be identified.

Type 2 diabetes is much more common & accounts for 90-95% of all diabetes. Type 2 diabetes primarily affects adults, however recently Type 2 has begun developing in children. There is a strong correlation between Type 2 diabetes, physical inactivity & obesity.

The diagnosis of diabetes is made by a simple blood test measuring your blood glucose level. Usually these tests are repeated on a subsequent day to confirm the diagnosis. A diagnosis of diabetes is a frightening & bewildering experience because there is so much information to take in & the diagnosis may come as a shock.

| | NORMAL | DIABETES |
|---|---|---|
| Fasting blood sugar | 80-99 mg/dl | 126 mg/dl and above |
| Random blood sugar | 80-139 mg/dl | 200 mg/dl and above |
| 2 hour glucose tolerance test | 80-139 mg/dl | 200 mg/dl and above |

**Table 1** Various ranges of different diabetes conditions [1]

Numbness or tingling in hands or feet symptoms may occur rapidly with Type 1 diabetes; however, with Type 2 diabetes

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the onset is more insidious & may not be noticed. The following symptoms of diabetes are Blurred vision, Unusual thirst, Frequent urination, Slow-healing cuts, Unexplained tiredness, Rapid weight loss (Type 1 diabetes), Erectile dysfunction.

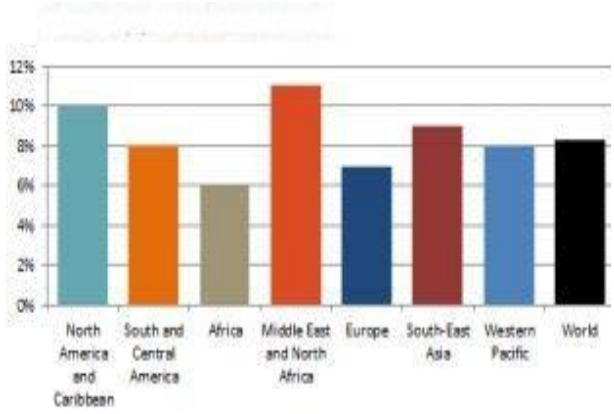


**Figure 1** Prevalence (%) of diabetes in adults, 2013 [1]

Oral administration is the most convenient & preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery has recently been gained huge potential in pharmaceutical field to achieved improved therapeutic advantage such as ease of dosing administration, patient compliance & flexibility in formulation. Drugs are easily absorbed from the gastrointestinal tract (G.I.T.) & have a short half lives are eliminated quickly from the systematic circulation. Frequently dosing of this drug is required to achieve a suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) & maintain an effective drug concentration. Gastroretentive drug delivery [1,2,3] is an approach to prolonged gastric residence time, thereby targeting site specific drug release in the upper gastrointestinal tract for local & systemic effect. Gastroretentive doses forms can remain in the gastric region for long periods & hence significantly prolonged gastric retention time of the prolonged. Over the last few decades several gastroretentive drug delivery approaches being designed & developed, including: high density (sinking) system that is retained in the bottom of the stomach [4], low density (floating) systems that causes buoyancy in gastric fluid [5,6], mucoadhesive systems that causes bio-adhesion to stomach mucosa, unfold able, extendible.

### *About the candidate drug*

Glipizide [7,8] is an oral hypoglycemic drug i.e. antidiabetic drug. It is oral short acting second generation sulfonyl urea drug that undergoes enterohepatic circulation. It is most potent in contrast to others of same group. It is whitish, odorless powder of $pK_a$ is about 5.9. It is insoluble in water & alcohol & soluble in 0.1 (N) NaOH & freely soluble in dimethyl formamide.

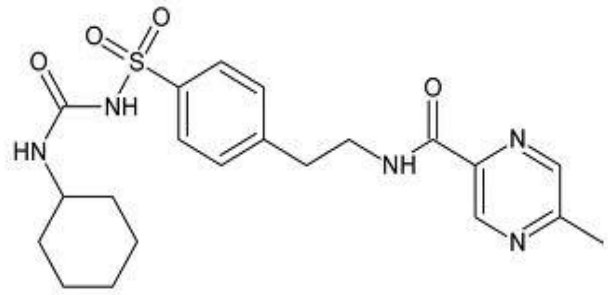


**Figure 2** Structure of glipizide [9]

***IUPAC name:*** 1-cyclohexylcarbomyl-3-[[P-[2-(5-methylpyrazine- carboxamido) ethyl] phenyl] sulfonyl] urea.

***Chemical formula:*** $C_{21}H_{27}N_5O_4S$

***Molecular weight:*** 445.55 Dalton.

***Pharmacokinetic:*** Glipizide are well absorbed orally & are 90% plasma protein bound & have low volume of distribution (0.2-0.4 L/kg). Some are primarily metabolized–produces active metabolite. It is excreted unchanged in urine.

***Pharmacodynamics:*** Sulfonyl urea drug act on Sulfonyl receptor of the β-cell surface where drug bind to receptor & blocks the ATP sensitivity potassium channel & then depolarization occur & calcium concentration increases & exocytosis of insulin occurs.

***Mechanism:*** Glipizide likely bind to ATP-sensitive potassium-channel Sulfonyl receptor on the pancreatic cell surface, reducing potassium conductance & causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage-sensitive calcium channels, raising intracellular concentrations of calcium ions, which induces the secretion, or exocytosis, of insulin.

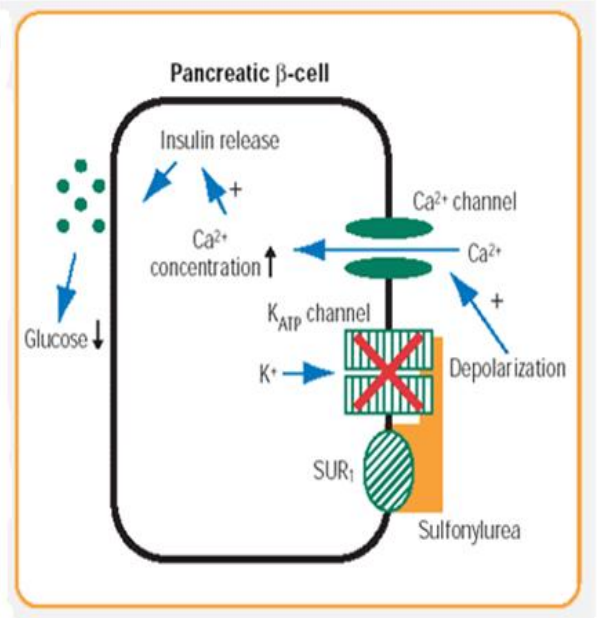


**Figure 3** Mechanism of glipizide [9]

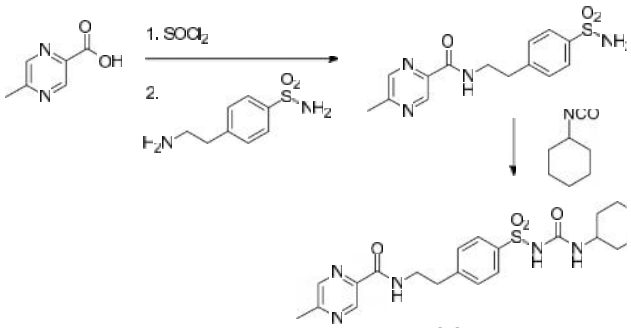

**Figure 4** Synthesis of glipizide [10]

## MATERIALS

Glipizide was purchased from B. S. Traders Pvt. Ltd India. Gellan gum (Loba Chemie, India), Magnesium stearate (Loba Chemie, India), Maleic acid (Merck Ltd, India) were used.

## METHODOLOGY

***Preparation of glipizide floating beads***

The beads containing glipizide was prepared by ionotropic-gelation method. Briefly, required amount of gellan gum was dissolved in 10 ml demineralised water with constant stirring. Required amount of magnesium stearate, 50 mg of were added to gellan dispersion. The final mixture containing gellan & magnesium stearate was stirred at 5000 rpm continuously for 30 min until the homogeneous & stable suspension was formed. Then, the suspension was dropped through 23G needle into 5 % (w/v) maleic acid (20 ml), & the added droplets were retained for 15 minutes in the maleic acid solution to complete the curing reaction. The prepared beads were filtered. The dried beads containing glipizide were stored in desiccators until used.

**Table 2** Composition of various glipizide floating beads

| Formulation Code | Drug(mg) | Gellan gum(mg) | Magnesium stearate (mg) | Maleic acid (% w/v) |
|---|---|---|---|---|
| F-1 | 50 | 130 | 50 | 5 |
| F-2 | 50 | 130 | 25 | 5 |
| F-3 | 50 | 130 | 0 | 5 |
| F-4 | 50 | 115 | 50 | 5 |
| F-5 | 50 | 115 | 25 | 5 |
| F-6 | 50 | 115 | 0 | 5 |
| F-7 | 50 | 145 | 50 | 5 |
| F-8 | 50 | 145 | 25 | 5 |
| F-9 | 50 | 145 | 0 | 5 |

***Determination of drug entrapment efficiency***

Accurately weighed 100 mg of prepared beads from each batch were taken separately & were crushed using pestle & mortar. The crushed powders were placed in 100 ml of 0.1 N HCl (pH 1.2) & kept for 24h with occasionally shaking at 37±0.5°C. After the stipulated time, the mixture was stirred at 500 rpm for 15min on a magnetic stirrer. The polymer debris formed after disintegration of bead was removed by filtering through Whatman® filter paper (No. 40). Then, the drug content in the filtrate samples were determined using a UV–spectrophotometer (Thermo Spectronic UV-1, USA) by measuring absorbance at $\lambda_{Max}$ of 223 nm. The % DEE of beads was calculated using this following formula

% DEE = (actual drug content in beads/ theoretical drug content in beads) × 100

***Determination of bead size***

Diameters of dried beads were measured using digital slide callipers (CD-6" CS, Mitutoyo Corporation, Japan) by inserting the beads in between the space of two metallic plates & diameter of resultant beads were displayed in the digital screen of the previously calibrated equipment. The average size was then calculated by measuring the diameter of 3 sets of 6 beads from each batch.

***Determination of density***

The mean weights & diameters of the beads were measured & used to calculate densities of beads using the following equations:

$\rho = M/V$, & $V=4/3\pi r^3$

Where ρ, *M*, *V*, & *r* are the density (g/cm3), weight (g), volume (cm3), radius (cm) of the beads, respectively.

***Swelling Study***

Weigh accurately amount of drug loaded floating beads were taken in a 500 ml beaker containing 0.1 N HCl as swelling medium. Weights of swelled glipizide floating beads were taken at 1 hour interval for 7 hours & calculate percentages of swelling of prepared beads.

## RESULTS AND DISCUSSION

**Table 3** Various studied parameters for glipizide floating beads

| Formulation Code | Size (mm) Mean±S.D(n=6) | Density (gm/cm$^3$) | Swelling (%) | Floating time (hours) | Drug entrapment efficiency (%) |
|---|---|---|---|---|---|
| F-1 | 0.797±0.069 | 0.825 | 110 | >22 | 69.63 |
| F-2 | 0.795±0.224 | 0.915 | 133 | >22 | 67.35 |
| F-3 | 0.675±0.0.113 | 0.947 | 145 | >22 | 63.25 |
| F-4 | 0.618±0.073 | 0.812 | 111 | >22 | 60.15 |
| F-5 | 0.656±0.099 | 0.845 | 121 | >22 | 70.25 |
| F-6 | 0.743±0.083 | 0.887 | 131 | >22 | 63.39 |
| F-7 | 0.783±0.052 | 0.883 | 126 | >22 | 68.85 |
| F-8 | 0.755±0.065 | 0.882 | 139 | >22 | 71.12 |
| F-9 | 0.683±0.042 | 0.956 | 147 | >22 | 72.25 |

***Bead Size***

The size of beads made up of gellan gum, magnesium stearate entrapped beads containing glipizide measured by using digital size caliper. The average size of these dried beads ranged from 0.675±0.073 to 0.797±0.069 mm (Table 3). Increasing beads size us due increasing proportion of gellan gum into formulation. This could be attributed due to increase in viscosity of emulsion with incorporation of gellan gum in increasing ratio that in turn increased the droplet size.

***Density***

Density values of various gellan beads containing glipizide ranged from 0.812 to 0.956 gm/cm$^3$ (Table 3). All the beads density are less than 1, due to magnesium stearate entrapped gellan beads containing glipizide due to increase in drug to polymer ratio due to entrapped polymeric systems are in line with results reported in previous literature.

***Swelling index***

The in vitro swelling studies of various gellan beads containing glipizide in stimulated gastric fluid (pH 1.2) are presented in table 3. The swelling depends upon the amount of magnesium stearate, as it is lipophilic in nature. The range of swelling percentage ranges from 110 to 147 that means in formulation F-1 has high percentage of magnesium stearate than in F-9.

***Drug entrapment efficiency***

The range of drug entrapment efficiencyranges has high percentage in formulation code of F-9 as shown in table 3.

**Figure 5** Prepared glipizide beads

## CONCLUSION

Gastroretentive glipizide beads were prepared using gellan gum; maleic acid & magnesium stearate to control delivery of glipizide as well as it impart a sustained release effect. The results of current study clearly indicate a promising potential of these gastroretentive beads containing glipizide can be a good alternative to the sustained release dosage of candidate drug. In this study we concluded that beads size increase due to gellan gum as it is viscous in nature when mixed with water. The density of glipizide beads was less than 1 as gellan gum & magnesium stearate has low density.

The swelling index depends upon the amount of magnesium stearate in formulation decrease the swelling property of beads due to its lipophilicity. This delivery was found to be simple, reproducible, easily controllable & easily available.

**Acknowledgements**

Authors gratefully thank to the Principal Prof. (Dr.) Arkendu Chatterjee, Bengal College of Pharmaceutical Sciences & Research, Bidhannagar, Durgapur-713212.

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**How to cite this article:**

Ratnamala Dutta., Raj Biswas., Somenath Bhattacharya and Sonia Auddy.2016, Development & Evaluation of Glipizide Floating Beads For Gastroretentive Drug Delivery System. *Int J Recent Sci Res.* 7(2), pp. 8889-8892.

TSSN 0976-3031