AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Design, Development and Evaluation of Multiple- Unit Beads of Gliclazide

Jadupati Malakar, Sujit Karmakar, Amites gangopadhyay Debajyoti Ghosh

1. Department of Pharmaceutics, Bengal College of Pharmaceutical Sciences and Research, Durgapur–713212, West Bengal, India

ABSTRACT

This present investigation deals with the design, development and evaluation of multiple unit beads containing gliclazide. The various gliclazide beads were prepared by ionotropic gelatin technique using sodium alginate, guargum and magnesium stearate in different ratios. These multiple unit beads were evaluated for size analysis, drug entrapment efficiency and *in vitro* drug release in simulated gastric fluids (pH 1.2) and phosphate buffer (pH 7.4). All these formulated showed sustained *in vitro* drug release in simulated gastric fluid over 6 hours. The gliclazide release was found to be more sustaining with the reduction of guargum content in the formulation .The drug release pattern of these multiple unit gliclazide beads (F-6 and F-7) were correlated well with first order model where F-1, F-4, F-5, F-8 and F-2 toF-3 was correlated well with Korsmeyer-Peppas model and Higuchi model with non-Fickian diffusion mechanism. All the experimental results showed that the gliclazide loaded beads successfully sustain the drug release along with improve the oral bioavailability of candidate drug.

Keywords: Multiple unit beads, gastroretentive, gliclazide, ionotropic-gelation.

*Corresponding Author Email: jadupati_pharma@yahoo.co.in

Received 8 June 2012, Accepted 20 June 2012

Please cite this article in press as: Malakar J *et al.*, Design, Development and Evaluation of Multiple-Unit Beads of Gliclazide. American Journal of PharmTech Research 2012.

INTRODUCTION

Gliclazide, a sulfonylurea antidiabetic, chemically is 1-(3-Azabicyclo [3.3.0] oct – 3yl-3-p-tolyl sulfonylurea that is also used in the management of type 2 diabetes mellitus. It is extensively absorbed from gastrointestinal tract.[1] The literature reviews demands that oral route is still considered most preferable and convenient route as it offers many advantages like patient acceptance, convenience and safe. [2] In recent years, various sustained or controlled drug delivery system have been developed to overcome the drawbacks relevant to conventional delivery like variable gastric emptying and rapid gastrointestinal transit time leads to inadequate drug release from the dosage form at absorption site in gastro-intestinal tract.[3] The gastroretentive drug delivery systems have been investigated and developed to assure prolong gastric residence and enhanced bioavailability of applied candidate drug. Various approaches of gastroretentive drug delivery system have been adopted for enhancement of gastroretention dosage forms like floatation [4], mucoadhesion [5,6], sedimentation [7], unfoldable, expandable, or swellable systems [8], superporous hydrogel systems [9], magnetic systems [10], etc. The single unit gastroretentive systems such as tablets or capsules may exhibit the all-or- none emptying phenomenon.[11]On the other hand, multiple-unit dosage forms may be an alternative since they have been shown to reduce the inter- and intra- subject variabilities in drug absorption as well as to lower the possibility of dose-dumping characteristics, *etc*.[12,13]

Now a day multiple unit systems for oral sustained or controlled delivery have been grown up as an emerging trend in pharmaceutical research as well as well accepted to pharmaceutical researcher. In the present investigation, we have formulated gliclazide multiple unit beads composed of sodium alginate as base material and guar gum and magnesium stearate as release modifiers by ionotropic gelation technique and evaluated them as size, drug entrapment efficiency and drug release.

MATERIALS AND METHODS

Materials

Gliclazide was purchased from B. S. Traders Pvt. Ltd India. Sodium alginate (Central drug house, India), guar gum (B. S. Traders Pvt. Ltd., India), magnesium stearate (Loba Chemie., India), aluminium chloride (Merck Ltd., India) were used. All other chemicals and reagents used were of analytical grade.

Methods

Preparation of beads containing gliclazide

The beads containing gliclazide was prepared by ionotropic -gelation method. Briefly, required amount of sodium alginate was dissolved in 100ml demineralised water with constant stirring. Required amount of guar gum and magnesium stearate, 100mg of gliclazide were added to sodium alginate solution. The final mixture containing sodium alginate, guar gum and magnesium stearate was stirred at 5000 rpm continuously for 30 min until the homogeneous and stable suspension was formed. Then, the suspension was dropped through 23G needle into 10 % (w/v) aluminum chloride solution (100 ml), and the added droplets were retained for 15 min in the aluminum chloride solution to complete the curing reaction. The prepared beads were filtered. The dried beads containing gliclazide were stored in desiccators until used.

Table 1: Composition of various gliclazide beads.

Formulation code	Drug (mg)	Sodium alginate (mg)	Guar gum (mg)	Mag. stearate (mg)
F-1	100	200	100	20
F-2	100	200	100	10
F-3	100	200	50	10
F-4	100	100	50	10
F-5	100	100	100	20
F-6	100	100	50	20
F-7	100	100	100	10
F-8	100	200	50	20

Determination of drug entrapment efficiency

Accurately weighed 100mg of prepared beads from each batch were taken separately and were crushed using pestle and mortar. The crushed powders were placed in 100ml of 0.1N HCl (pH 1.2) and 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–vis spectrophotometer (Thermo Spectronic UV-1, USA) by measuring absorbance at λ_{Max} of 226.5nm. 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 calipers (CD-6" CS, Mitutoyo Corporation, Japan) by inserting the beads in between the space of two metallic plates and 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 20 beads from each batch.

In vitro drug release studies

The *in vitro* release of prepared beads containing gliclazide was tested using dissolution apparatus type-II (Campbell Electronics, India). An equivalent weight of beads containing 100mg gliclazide was placed into 900ml of simulated gastric fluid (pH 1.2) for initial 2 hrs and 3 to 6 hrs in phosphate buffer (pH 7.4) maintained at 37±0.5°C and 50 rpm paddle speed. 5ml of aliquots was collected at regular time intervals, and same amount of fresh dissolution medium was replaced into dissolution vessel to maintain the sink condition throughout the experiment. The collected aliquots were filtered and further diluted suit ably to analyze using a UV–vis spectrophotometer (ThermoSpectronic UV-1, USA) by measuring absorbance at λ_{Max} of 226.5nm.

Analysis of *in vitro* drug release kinetics and mechanism

To analyze the mechanism of drug release from these gliclazide beads, the *in vitro* dissolution data were fitted to various mathematical models like zero order, first order, Higuchi, and Korsmeyer-Peppas models. [14-17]Zero-order Model: $F = K_0 t$, where F represents the fraction of drug released in time t, and K0 is the apparent release rate constant or zero-order release constant. First-order Model: $\ln (1-F) = - K_{1st} t$, where F represents the fraction of drug released in time t, and K_1 is the first–order release constant. Higuchi Model: $F = K_H t$, where F represents the fraction of drug released in time t, and K_H is the Higuchi dissolution constant. Korsmeyer-Peppas Model: $F = K_P t^n$, where F represents the fraction of drug released in time t, K_P is the rate constant and n is the release exponent, this indicates the drug release mechanism.

Again, the Korsmeyer-Peppas model has been employed in the *in vitro* drug release behavior analysis of various pharmaceutical formulations to distinguish between various release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (relaxation- controlled release). When, $n \leq 0.5$, it is Fickian release. The n value between 0.5 and 1.0 is defined as non-Fickian release. When, $n \geq 1.0$, it is case-II transport and this involves polymer dissolution and polymeric chain enlargement or relaxation. [17]

RESULTS AND DISCUSSION

The gliclazide beads containing sodium alginate, guar gum and magnesium stearate were prepared through cross-linking between sodium alginate with Al^{3+} in a suitable concentration range. The effect of used polymers and magnesium stearate as variables in multiple unit gliclazide loaded beads on responses like size analysis; DEE(%) and cumulative drug release(%) were evaluated.

Beads size

The average size of these formulated gliclazide beads were found in a range between 1.62 ± 0.14 to 1.78 ± 0.05 **(Table 2).**It has been investigated that the beads size increased on increment of amount of polymer i.e. sodium alginate and guargum that could be attributed due to increase of viscosity by addition of alginate in increasing ratio which causes enhancement of droplet size during addition of cross-linking agent.

Table 2: Results of average beads size, drug entrapment efficiency and drug release at 6 h for various gliclazide beads (n =3).

Formulation code	Size (Mean± S.D*)	DEE (Mean ± S.D*)	R_{6h} (Mean ± S.D*)
F-1	1.78 ± 0.05	72.69 ± 1.35	26.11 ± 2.12
F-2	1.75 ± 0.09	73.55 ± 2.11	26.39 ± 2.63
F-3	1.71 ± 0.07	70.45 ± 2.71	20.79 ± 2.05
F-4	1.62 ± 0.14	67.31 ± 2.41	24.60 ± 2.87
F-5	1.65 ± 0.11	67.82 ±2.31	27.17 ± 2.16
F-6	1.64 ± 0.06	66.88 ± 2.14	25.41 ± 2.81
F-7	1.66 ± 0.11	68.45 ± 1.55	25.77 ± 2.34
F-8	1.70 ± 0.12	69.56 ± 1.65	21.04 ± 2.24

*S.D. = Standard deviation, DEE = Drug entrapment efficiency, R_{6h} = % Drug release at 6h.

Drug entrapment efficiency

The DEE of formulated gliclazide beads ranged from 66.82 ± 2.14 to 72.69 ± 1.35 (Table 2). The DEE study concluded that drug entrapment was directly proportional to amount of the polymer used in formulation and high entrapment was found in these beads with comparatively high alginate and guar gum content. This could be happened due to physical interaction of candidate drug with alginate or entanglement of higher amount of drug inside intricate cross-linked aluminium alginate gel network.

In vitro drug release study

The *in vitro* drug release studies for all formulated gliclazide beads were carried out in dissolution apparatus type-II using simulated gastric fluid (pH 1.2) for initial 2 hrs and 3 to 6 hrs in phosphate buffer (pH 7.4). All beads showed prolonged sustained release of gliclazide over 6h (Figure 1).The cumulative drug released from these beads containing gliclazide in 6h (R_{6h} %) was within the range of 20.79±2.05 to 27.17±2.16% (Table 2). It was observed that the cumulative drug release increased with the increasing of guargum content that could be the hydrophilicity of the guargum and may undergo hydrolysis in presence of buffer medium. In other hands sodium alginate has the ability to remain intact or unionized in acidic medium that favors sustain release whereas it swells in phosphate buffer and another materials magnesium

stearate which made a lipophilic barrier upon the surface that also sustained the drug release too some extent.

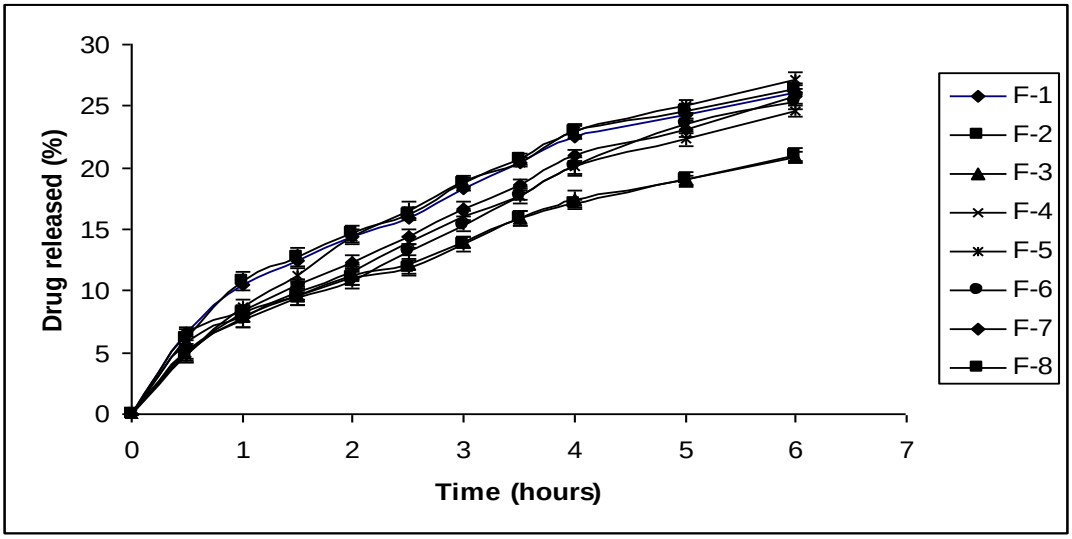

Figure 1: *In vitro* drug release from Gliclazide loaded beads in simulated gastric fluid, pH 1.2.

To analyze the mechanism of drug release from these gliclazide beads, the *in vitro* dissolution data were fitted to various mathematical models like Zero order, First order, Higuchi, and Korsmeyer-Peppas models. The results of the curve fitting into these above mentioned mathematical models are given in **Table 3.** The drug release pattern of gliclazide beads of formulation F-6 and F-7 were correlated well with first order model (R^2 = 0.992 and 0.993) over a period of 6 hours. Whereas F-1, F-4, F-5 and F-8 was correlated with Korsmeyer-Peppas model (R^2 = 0.994, 0.997, 0.992 and 0.990) over a period of 6 hours and F-2 to F-3 was correlated well with Higuchi model (R^2 = 0.991 to 0.992, respectively) when their respective correlation coefficients in simulated gastric fluids were compared.

Table 3: Results of curve fitting of the in vitro gliclazide release data from different gliclazide beads in simulated gastric fluid, pH 1.2.

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyar-Pepas R^2	n
F-1	0.787	0.974	0.993	**0.994**	0.555
F-2	0.787	0.967	**0.991**	0.989	0.576
F-3	0.796	0.985	**0.992**	0.991	0.524
F-4	0.903	0.988	.0969	**0.997**	0.658
F-5	0.877	0.970	0.972	**0.992**	0.701
F-6	0.938	**0.992**	0.946	0.989	0.989
F-7	0.880	**0.993**	0.975	0.984	0.585
F-8	0.825	0.981	0.988	**0.990**	0.574

Here, the Korsmeyer-Peppas model has been also applied to analyze the *in vitro* drug release behavior of different pharmaceutical formulations to distinguish between various competing release mechanisms: Fickian release (diffusion-controlled release), non Fickian release (anomalous transport), and case-II transport (swelling- controlled release). The value of release exponent (n) determined from *in vitro* gliclazide release data of various multiple unit beads ranged from 0.524 to 0.989 in simulated gastric fluid and phosphate buffer (**Table 3),** where all the formulations were followed the anomalous (non-Fickian) diffusion that could be high water uptake followed higher swelling of these beads supported the anomalous release mechanism of gliclazide.

CONCLUSION

Multiple unit beads for the gastroretentive delivery of gliclazide were successfully developed using calcium alginate, guargum and magnesium stearate as excipients by ionotropic gelation method. The *in vitro* results indicate that they are potentially useful and shown excellent drug entrapment as well as prolonged drug release pattern could possibly be advantageous in terms of increased bioavailability of gliclazide. The multiple unit beads delivery system were found to be simple, reproducible and economical where excipients used also were cheap and readily available. Finally, this delivery system may be an alternative in management type II diabetis mellitus.

ACKNOWLEDGMENT

The authors are thankful to the Principal and Management of Bengal College of Pharmaceutical Sciences and Research, Durgapur, India for their kind permission and help in conducting this research work.

REFERENCE

1. Martindale: The complete drug reference. 34th ed., London: pharmaceutical press; 2005: 332.
2. Sungthongjeen S. Paeratakul O, Limmatvapirat S and Puttipipatkhachorn S. Preparation and *in vitro* evaluation of a multiple-unit floating drug delivery system based on gas Formation Technique. Int J Pharm2006; 324:136–143.
3. Nayak AK, Malakar J and Sen KK: Gastroretentive drug delivery technologies: current approaches and future potential. J Pharm Edu Res 2010; 1:1–12.
4. Malakar J, Nayak AK and Pal DK. Development of cloxacillin loaded multiple-unit alginate-based floating system by emulsion–gelation method. Int J Biolog Macromol

2011; 50: 138-147.

5. Ponchel G, Irache JM. Specific and non-specific bioadhesive particulate system for oral delivery to the gastrointestinal tract. Adv Drug Del Rev1998; 34 191–219.
6. Nayak AK, Hasnain MS, Beg S, Alam MI: Mucoadhesive beads of glycalzide: design, development and evaluation. Sci Asia 2010; 36: 319–325.
7. Rouge N, Allemann E, Gex-Fabry M, Balant L, Cole ET, Buri P, Doelker E: comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol. Pharm Acta Helbetiae 1998; 73: 81-87.
8. Klausner EA. Lavy E, Friedman M and Hoffman A: Expandable gastroretentive dosage forms. J Control Rel *2003*; 90:143–162.
9. Chen J, Blevins WE, Park H and Park K: Gastric Retention Properties of Superporous Hydrogel Composites. J Control Rel 2000; 65: 73-82.
10. Fujimori J, Machida Y, Nagai T. Preparation of a magnetically responsive tablet and configuration of its gastric residence in beagle dogs. STP Pharm Sci 1994; 4: 425-430.
11. Kanivva N, Aoyagi N, Ogata H and Ejima A. Gastric emptying of enteric coated drug preparations. II. Effect of size and density of enteric coated drug preparations and food on gastric emptying rates in humans. J Pharmacobiodyn. 1988; 11: 571–575.
12. Ishak RAH, Awad GAS, Mortada ND and Nour SAK. Preparation, *in vitro* and *in vivo* evaluation of stomach specific metronidazole-loaded alginate beads as local anti-*Helicobacter pylori* therapy. J Control Rel 2007; 119: 207–214.
13. Elmowafy EM, Awad GAS, Mansour S and El-Shamy AE-HA. Ionotropically emulsion gelled polysaccharide beads: preparation, *in vitro* and *in vivo* evaluation. Carbohydrate Pol Sci 2009; 75:135–142.
14. Varelas CG, Dixon DG and Steiner C. Zero-order release from biphasic polymer hydrogels. J of Control Rel 1995; 34: 185-92.
15. Mulye NV, Turco ST. An examination of assumptions underlying the first order kinetic model for release of water soluble drugs from di-calcium phosphate dehydrate matrices. Drug Del of Indrust Pharm 1996; 22: 673-679.
16. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharm Sci 1961; 50: 874–75.
17. Korsmeyer RW et al: Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15: 25-35.