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Research Article

FORMULATION EVALUATION OF SUSTAINED RELEASE FLOATING BEADS OF METFORMIN HYDROCHLORIDE USING SODIUM ALGINATE

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ABSTRACT

The objective of this study was to prepare and characterize beads of Alginate for floating delivery of metformin hydrochloride (MH). The beads were evaluated for particle size, surface morphology, percent drug entrapment, percentage yield and *in-vitro* drug release. The formed beads were sufficiently hard and spherical in shape. Photomicrographs show that the surface was porous in nature. The average particle diameter of beads was found to be in the size range of 100-150 µm and percent entrapment was 66.7% to 88.8%. The beads demonstrated favorable in-vitro floating ability. Prepared formulations showed better controlled release behavior. It is concluded that beads of Alginate could be serve as an effective carrier for highly water-soluble anti-hyperglycaemic drugs like MH for the sustained release drug delivery.

Key words: Beads, Floating Drug Delivery, Alginate, Metformin HCl

INTRODUCTION

Diabetes is one of the major causes of death and disability in the world. The global figure of people with diabetes is set to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025. Most cases will be of type II diabetes, with a sedentary lifestyle and obesity (1). A plethora of antidiabetic drugs are used in clinic, of which metformin hydrochloride (MH) is a very widely accepted drug. MH has elimination half-life of 6.5 h (2). In spite of its favorable clinical response and lack of significant drawbacks, chronic therapy with MH suffers from certain specific problems of which the most prominent being the high dose (1.5–2.0 g/day), low bioavailability (60%) and high incidence of gastrointestinal (GI) side effects (30% cases). Therefore, there are continued efforts to improve the pharmaceutical formulation of MH in order to achieve an optimal therapy. These efforts mainly focus on controlled/slow release of the drug including the sophisticated gastroretentive systems (3).

Gastric floating drug delivery system (GFDDS) is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug (4). Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to

provide better availability of new products with new therapeutic possibilities and substantial benefits for patients (5–9). Jain *et al*. has discussed *in-vitro* and *in vivo* characterization of calcium silicate-based floating microspheres of repaglinide and orlistat. (6–8) They have also reported preparation and evaluation of calcium silicate-based floating granular delivery system of repaglinide and ranitidine hydrochloride (9,10).

The objective of the study was to prepare and characterize beads of Alginate for floating delivery of MH. The obtained beads were evaluated for size analysis, surface morphology, percent drug entrapment, percent yield and *in-vitro* drug release study.

MATERIALS AND METHODS

Materials

Metformin HCl was supplied as a gift sample by Vectra Pharmaceuticals. Sodium Alginate and Calcium chloride was purchased from S. D. Fine Chemical Ltd. (Mumbai, India). All other chemicals were of analytical reagent grade and were used as received.

Preparations of Beads

The floating beads were prepared by inotropic external gelation technique. Sodium alginate was dissolved in deionized water at a concentration of 1-3 % (w/v) using gentle heat and magnetic stirring. On complete dissolution, an accurately weighed quantity of Metformin HCl and HPMC was added and dispersed uniformly. The dispersions were sonicated for 30 min to remove any air bubbles that might have been formed during the stirring process. After sonication sodium bi carbonate was added in the solution.

The bubble free sodium alginate-drug dispersions (50ml) were added drop wise via 22-guage hypodermic needle fitted with a 10ml glass- syringe into 100ml of calcium chloride solution (5%w/v) & stirred at 20rpm and finally allowed to stand for 30min. The droplets of the dispersion instantaneously gelled into discrete matrices upon contact with the Ca^{++} ions.

The former drug loaded floating beads were further filtered, washed & dried for 0.5-3 h at 60^0C-65^0C in an oven.

Particle Size and Surface Morphology

The average particle size of beads was determined with a photomicroscope (QUASMO) fitted with micrometric tools (Winzoe) and calculated as the average size of 100 beads. Particle size and surface morphology of metformin HCl beads were determined by scanning electron microscopy (SEM), Model Quanta FEI 200F. The dried beans were coated with gold foil (100 A°) under an argon atmosphere in a gold coating unit and micrographs were obtained at both higher and lower resolutions.

Percent Drug Entrapment and Percent Yield

The drug entrapment studies were carried out using U.V. Spectrophotometer. The yielded beads were crushed in a pestle mortar and weight of beads equivalent to 100mg metformin HCl was dissolved in methanol and kept for 24 hours. It was then filtered and a dilution of 10µg/ml was prepared. The absorbance of the filtered content was compared with standard absorbance.

The percentage yield was determined and calculated as the weight of the beads recovered from each batch divided by total weight of drug and polymer used in the preparation.

$$\% \text{ Percentage yield} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \text{ x } 100$$

In-vitro Release Study

The release kinetics of metformin hcl floating beads were determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (Basket method). The dissolution test was performed using 900 ml of pH 1.2 Hydrochloric acid buffer & Simulated gastric fluid at 37±0.5°C and 100 rpm. A 5 ml

of sample was withdrawn from the dissolution apparatus at different time intervals. The sample solutions were replaced with fresh dissolution medium of same quantity. Absorbance's of these solutions were measured at λmax of 233 nm using a Labtronics UV/Vis double beam spectrophotometer and cumulative percentage release of drug was calculated.

Comparison of dissolution profile:

Data obtained from the in- vitro release studies of metformin HCl floating bead formulations were fitted to various kinetic equations such as zero order, first order, Higuchi model and Korsmeyer- Pappas model.

Model Fitting of Release Study

Five kinetic models including the zero order (Eq. 1), first-order (Eq. 2), Higuchi matrix (Eq. 3) & Peppas–Korsmeyer (Eq. 4) release equations were applied to process the *in-vitro* release data to find the equation with the best fit using PCP Disso V 3.0 software (India) (11,12).

$$R = k_1 t \qquad \text{(Eq. 1)}$$

$$\log UR = \frac{k_2 t}{2.303} \qquad \text{(Eq. 2)}$$

$$R = k_3 t^{0.5} \qquad \text{(Eq. 3)}$$

$$R = k_4 t^n \quad \text{or} \quad \log R = \log k_4 + n \log t \qquad \text{(Eq. 4)}$$

Where R and UR are the released and unreleased percentages, respectively, at time (t); k_1, k_2, k_3 & k_4 are the rate constants of zero-order, first-order, Higuchi matrix, Peppas–Korsmeyer, respectively.

RESULT AND DISCUSSION

Preparations of Beads

In the present investigation, a multiparticulate delivery system of MH capable of providing controlled release was prepared using Alginate. Schematic Representation of preparation of beads is shown in Fig. 1. & Formulation charts Table I. The method of preparation of beads was found to be simple and reproducible.

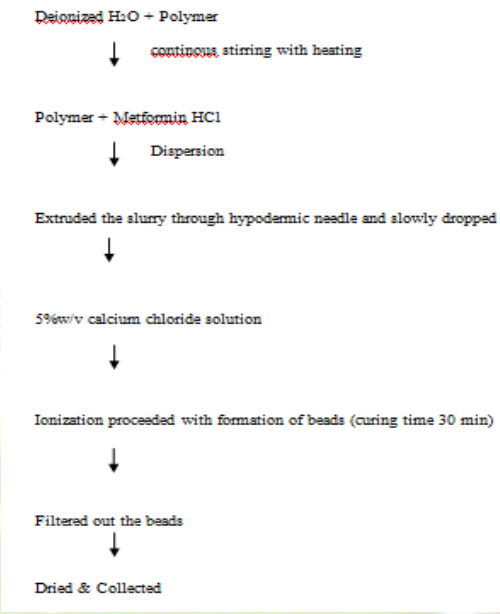

Fig. 1 Schematic presentation of method of preparation of Alginate beads of metformin HCl

Table I formulation Chart

Ingredients	Formulation Codes		
	F1	F2	F3
Metformin HCl	2gm	2gm	2gm
Sodium alginate	2gm	2.5gm	3gm
HPMC	0.5gm	0.5gm	0.5gm
Sodium bi carbonate	0.1gm	0.1gm	0.1gm
Calcium chloride	5%	5%	5%

Particle Size and Surface Morphology

The particle size determination was performed for all nine batches. Results were as shown in Table II. The mean bead size was found to be in the range of 100 – 250 µm.

Table II: Particle size for batch F_1 – F_3.

Serial no.	Formulation code	Size (µm)
1	F_1	100± 5
2	F_2	120± 8
3	F_3	150± 4

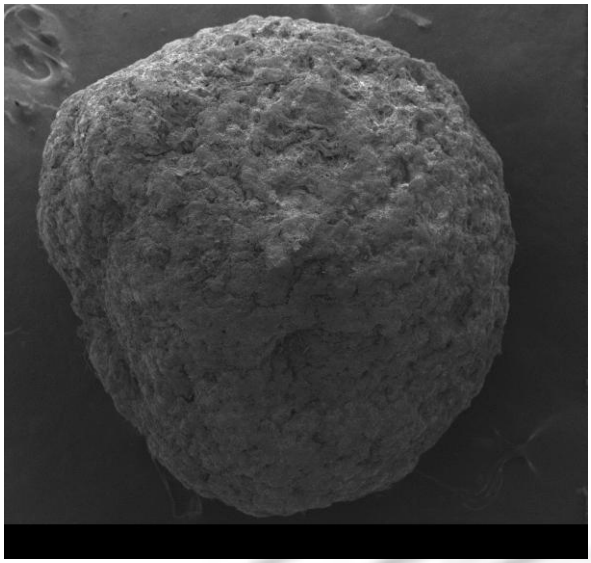

Fig. 2 Scanning electron photomicrograph

Percent Drug Entrapment and Percent Yield

The floating beads of batch F_3 formulation showed entrapment efficiency of 88.8%. It attributed to the permeation characteristics of each polymer.

Table III: Percentage Entrapment efficiency for batch $F_1 – F_3$.

Formulation Code	% Entrapment
F_1	66.7
F_2	79.4
F_3	88.8

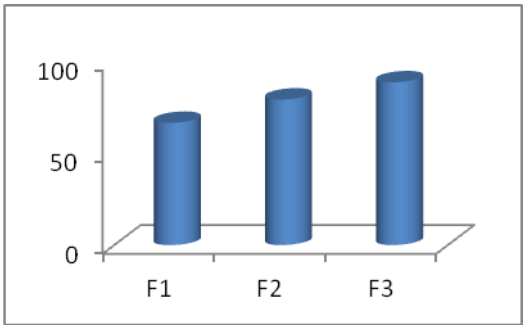

Fig. 3**: % Entrapment of Formulation F_1-F_3**

Percentage Yield:

The maximum % yield was found to be 90.26% with batch F_2 and minimum of 72.70% with F_1 batch.

Table no.4.5: Percentage Yield for batch $F_1 – F_3$.

Formulation	Theoratical Yield (mg)	Practical Yield (mg)	Percentage Yield (%)
F_1	4000	2240.0	72.70
F_2	4500	2500.0	90.26
F_3	5000	3220.0	87.50

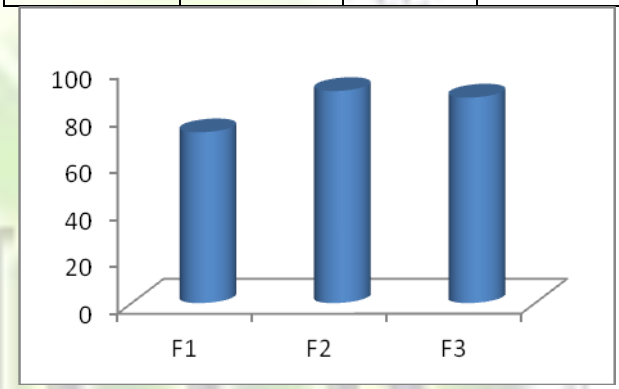

Fig. 4**: % Yield of Formulation F_1-F_6**

***In-vitro* Release Study**

The *in-vitro* drug release profiles of floating beads of MH were evaluated in SGF. The release of MH from different prepared formulations as represented (Fig. 5). It was found that approximately 85-90% drug released after 12 h. The pattern provides an idea about the effect of concentration of Alginate on drug release from beads, i.e., the higher the Alginate content, better the controlled drug release.

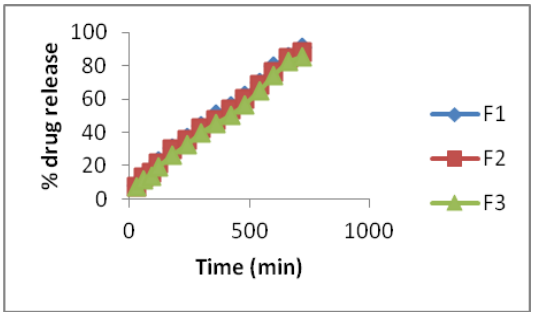

Fig. 5: Comparative graph of drug release study of $F_1 – F_3$

CONCLUSION

It is concluded that the method of preparation of beads was found to be simple, reproducible, and provides good yield. The *in-vitro* data obtained for floating beads of metformin HCl showed excellent buoyancy ability. Prepared formulation showed better controlled release behavior when compared with its conventional dosage form and comparable release profile with marketed sustained release product of metformin HCl. Thus, Alginate can be considered as an effective carrier for the design of a gastroretentive multiparticulate drug delivery system of highly water-soluble antihyperglycemic drugs like metformin HCl for the effective management of type 2 diabetes mellitus.

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