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COMPARATIVE STUDY OF ALGINATE AND PECTIN SUSTAINED RELEASE FLOATING BEADS OF METFORMIN HYDROCHLORIDE

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ABSTRACT

The objective of this study was to prepare floating beads of Metformin HCl in six batches using sodium alginate alone and in combination with pectin polymer as drug release modifier in various proportions and investigated for physicochemical properties and drug release potential. All investigated properties showed satisfactory results as the increased concentration of sodium alginate and other polymeric dispersions increased sphericity, size distribution, flow properties and mean diameter of the floating beads. The obtained drug entrapment efficiencies were in the range of 50.6% - 88.8%.Increase in the concentration of calcium chloride significantly affected the mean diameter but no appreciable change in morphology and drug release behavior occurred. Resulted floating beads were encapsulated in HPMC shells and coated with eudragit S-100 polymer to achieve colon targeting.

Beads size determination of metformin HCl was carried out by scanning electron microscopy *[*SEM*]* which revealed that the mean particle diameter was in range of 100-250µm. Various physicochemical parameters of formulations were determined such as bulk density *[*0.475-0.566g/cc*]*, tapped density *[*0.511-0.757g/cc*]*, carr's index *[*24.84-7.76%*]*, angle of repose *[*13.13-14.99*]* & Hausner ratio *[*1.24-1.10*]*. In-vitro release study of each formulation was carried out on dissolution apparatus *[*TDT 06L, Electro lab*]* in buffer solutions and the results were ranging from 90.96%-79.16% while in simulated fluid it ranged from 94.41%-81.47%. The best drug release profile was seen with formulation F1 *[*metformin HCl*]* in simulated fluid *[*84.12%*]* respectively.

Accelerated stability testing results revealed that there were no physical and chemical changes in the beads during three months study.

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, a model drug for this study, is an oral antidiabetic drug. It 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*. *[*6–8*]* has discussed *in vitro* and *in vivo* characterization of calcium silicate-based floating microspheres of repaglinide and orlistat. 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, Pectin 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 ionotropic external gelation technique. Sodium alginate *[*with or without pectin*]* 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^{0}C-65^{0}C 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 beads 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 f loating 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*] [*23,24*]*.

$$R = k_1 t$$

$$\log \mathrm{UR} = \frac{k_2 t}{2.303}$$

$$R = k_3 t^{0.5}$$

$$R = k_4 t^n$$

or

$$\log R = \log k_4 + n \log t$$

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.

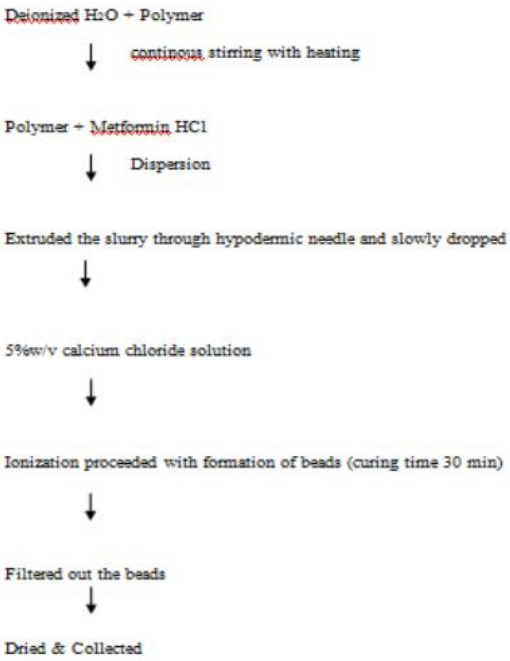

Fig. 1 Schematic presentation of method of preparation of Alginate beads of metformin HCl

Table I Formulation Chart

Ingredients	Formulation Codes		
	F1	F2	F3
Metformin HCl	2gm	2gm	2gm
Sodium alginate	2gm	2.5gm	3gm
Pectin	-	-	-
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 2. The mean bead size was found to be in the range of 100 – 250 µm.

Table 2: Particle size for batch F_1 – F_6.

Serial no.	Formulation code	Size *[µm]*
1	F_1	100± 5
2	F_2	120± 8
3	F_3	150± 4
4	F_4	160± 14
5	F_5	200± 9
6	F_6	250± 10

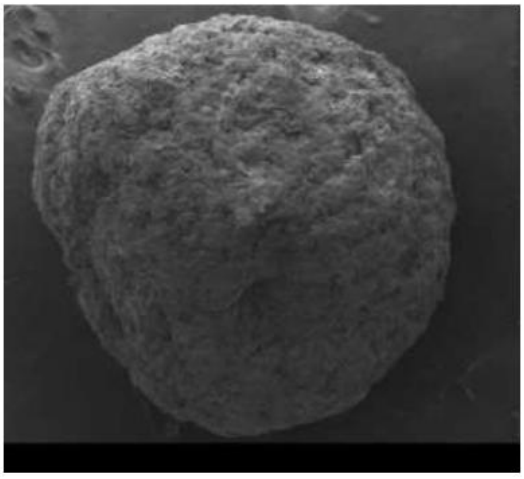

Fig. 2 Scanning electron photomicrograph

Percent Drug Entrapment and Percent Yield

The floating beads of batch F_2, F_3 and F_6 formulations showed entrapment efficiency of 79.7%, 88.8% & 78.7% respectively while formulations F_4 and F_5 exhibited lesser drug entrapments. It attributed to the permeation characteristics of each polymer.

Table 3: Percentage Entrapment efficiency for batch F_1 – F_6.

Formulation Code	% Entrapment
F_1	66.7
F_2	79.4
F_3	88.8
F_4	50.6
F_5	56.2
F_6	78.7

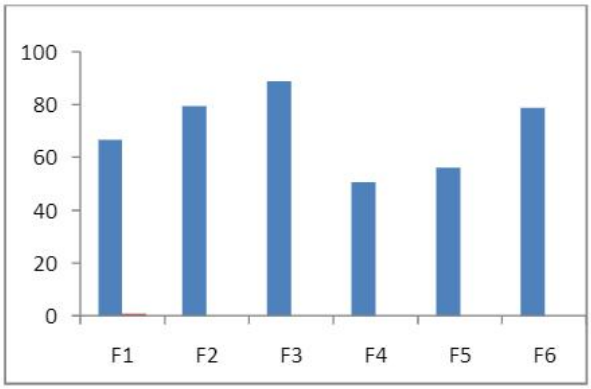

Fig 3: % Entrapment of Formulation F_1-F_6

Percentage Yield:

The maximum % yield was found to be 90.26% with batch F_2 and minimum of 60.70% with F_6 batch.

Table 4: Percentage Yield for batch F_1– F_6.

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
F_4	4000	3550.0	89.00
F_5	5000	4000.0	79.66
F_6	6000	4150.0	60.70

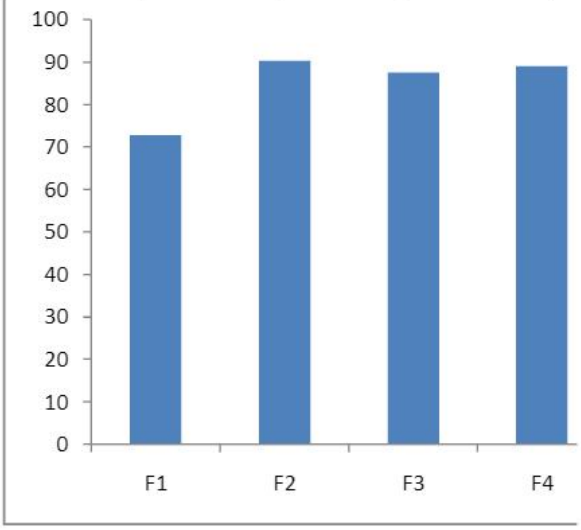

Fig 4: % Yield of Formulation F_1-F_6

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. 5,6*]*. 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.

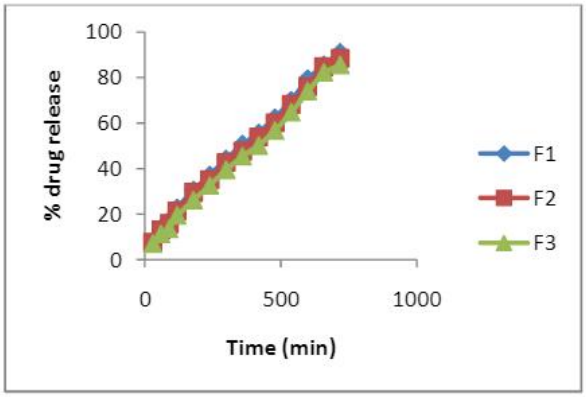

Fig. 5 Comparative graph of drug release study of F_1 – F_3

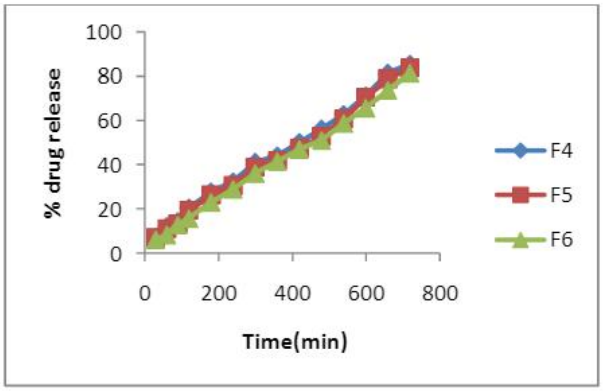

Fig. 6 Comparative graph of drug release study of F_4 – F_6

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 & Pectin 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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