



## Formulation and Evaluation of Floating Alginate Beads of an Anti Ulcer Drug

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### ABSTRACT

The present study deals with the formulation and evaluation of floating beads of an anti-ulcer drug. Sodium alginate, a polysaccharide forms a bio-adhesive and stable gel with divalent cations such as  $\text{Ca}^{2+}$  which has enabled its suitability for sustained release of drugs. The present research work was focused on the development of a multiple unit floating formulation using natural polymers and gas-forming agents by employing ionotropic gelation method with Esomeprazole as a model drug. Beads with a combination of natural polymers such as sodium alginate and Xanthan gum with sodium bicarbonate as a gas forming agent were formulated. Drug and polymers were subjected for compatibility studies using FTIR. The formulated beads were characterized for particle size, percentage drug entrapment efficiency, *in-vitro* buoyancy and *in-vitro* drug release. The optical microscopic studies revealed that mean particle size of all the formulations was found in the range of  $1337.28 \pm 223.26$  to  $1902.61 \pm 138.02$   $\mu\text{m}$ . Percentage drug entrapment was between 52.5% - 87.5 % and buoyancy was found to be between 84% - 98%. The *in-vitro* drug release results indicated that increasing the concentration of sodium alginate with respect to the drug resulted in further retarding the drug release. The results obtained from this work suggested that a calcium alginate multiple unit floating drug delivery system can be successfully designed by the use of natural polymers and gas forming agents and the drug release can be sustained by making suitable modifications in the combination of sodium alginate with xanthan gum and sodium bicarbonate.

**Keywords:** Esomeprazole, Ionotropic gelation, Multiple unit floating drug delivery system, Sodium alginate, Sodium bicarbonate, Xanthan gum.

### INTRODUCTION

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action.<sup>1</sup> But oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine. To overcome these limitations, several controlled oral drug delivery systems with prolonged gastric residence times have been reported recently such as: floating drug dosage systems (FDDS), swelling or expanding systems, mucoadhesive systems, modified-shape systems, high density systems and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used.<sup>2</sup>

Floating drug delivery systems are among the several approaches that have been developed in order to increase the gastric residence time of the dosage forms. The multiple unit system has been developed to identify the merit over a single unit dosage form because the single unit floating systems are more popular but have a disadvantage of high variability of the gastrointestinal transit time, still the multiple unit dosage forms may be better suited because they are claimed to reduce the inter subject variability in absorption and lower the probability of dose dumping. Such a dosage form can be widely distributed throughout the gastrointestinal tract (GIT), which afforded the possibility of a longer lasting

retention and more reliable release of the drug from the dosage form.<sup>3</sup>

Lately, a wide variety of both natural and synthetic hydrophilic polyionic systems like alginates have been investigated for preparation of multiple-unit floating dosage forms.<sup>4</sup> Natural biodegradable polysaccharides like pectin, guar gum, chitosan, carrageenans, sodium alginate and gellan gum have been used in controlled drug delivery. Multiparticulate systems obtained by ionotropic crosslinking of these polymers have been used to develop floating drug delivery. Various approaches to induce buoyancy in crosslinked gel beads, some of which include freeze-drying, entrapment of gas or gas forming agents, use of volatile oils or fixed oils, have been used. The oil containing beads have limitations of coalescence of oil droplets yielding beads of greater particle size distribution, volatilization or leaching of oil. The floating dosage forms with carbonate salts as buoyancy imparting agent are simple to prepare as compared to other techniques. Their floating property is based on the evolution of carbon dioxide when in contact with acidic environment. The gel beads are multiple-unit systems which avoid "all or none" emptying from the stomach during migrating myoelectric complex (MMC) motility of the stomach, hence they are more advantageous than single-unit systems.<sup>5</sup>

Esomeprazole used as a model drug here is a proton pump inhibitor and S-enantiomer of omeprazole. The significant pharmacological action of esomeprazole is dose dependent suppression of gastric acid secretion;



without anticholinergic or H<sub>2</sub> blocking action. It is a powerful inhibitor of gastric acid: can totally abolish HCl secretion, both resting as well as stimulated by any of the secretagogues, without much effect on pepsin, intrinsic factor, juice volume and gastric motility.<sup>6</sup>

Sodium alginate, a natural polysaccharide forms a bio-adhesive and stable gel with divalent cations such as Ca<sup>2+</sup> which has enabled its widespread use for sustained release of drugs. It can be used for floating drug delivery since alginate beads are stable in acidic media thereby impeding the degradation of drug in the harsh acidic environment of the stomach.

The objective of the present study was to formulate and evaluate calcium alginate beads of esomeprazole by ionotropic gelation technique using natural polymers such as sodium alginate and xanthan gum along with gas forming agent such as sodium bicarbonate.

## MATERIALS AND METHODS

### Materials used

Esomeprazole (Yarrow Chem products, Mumbai), Sodium alginate (HiMedia Laboratories Pvt. Ltd., Mumbai), Xanthan gum (HiMedia Laboratories Pvt. Ltd., Mumbai), Sodium bicarbonate (Ranbaxy Fine Chemicals, New Delhi), Calcium chloride (RFCL Limited, New Delhi), Acetic acid (Merck Specialities Private Ltd., Mumbai), Glutaraldehyde (S.D. Fine Chemicals Ltd., Boisar)

### Methods

#### Preformulation Studies

#### Drug Excipient Compatibility Studies

##### FTIR Study

The drug and polymer interactions were studied by Fourier Transform Infrared Spectroscopy by KBr disc method. FTIR spectra help to confirm the identity of the drug and to detect the interaction of the drug with the excipients. FTIR spectrum of the samples (esomeprazole, sodium alginate, xanthan gum, physical mixture of esomeprazole and sodium alginate, physical mixture of esomeprazole and xanthan gum) were recorded on a FTIR 8400 (Shimadzu, Japan).

*Method:* In this technique, a solid sample of approximately 2-3 mg is allowed to mix with about 0.5- 1 g of KBr (which is transparent to IR) and then the mixture is subjected to thorough grinding in a mortar, and then the mixture is pressed in a pellet die manually and placed in a Fourier transform infrared spectrophotometer (FTIR) (Shimadzu Corporation 8400 S, Japan).

### Experimental methods

#### I. Calibration curve of Esomeprazole

The standard calibration curve of Esomeprazole was plotted using methanol as solvent. The absorption maxima ( $\lambda_{max}$ ) were determined using UV-visible spectrophotometer and the graph was plotted for

absorbance versus concentration of Esomeprazole. The absorbance of each concentration was measured separately, using distilled water as a blank at  $\lambda_{max}$  of the drug using Shimadzu UV/Visible 1601 Spectrophotometer.

#### II. Formulation of calcium alginate beads

Calcium alginate beads containing Esomeprazole were prepared by ionotropic gelation method. Initially, required quantity of sodium alginate was accurately weighed and dissolved in distilled water using mechanical stirrer. To this solution, xanthan gum was added. After some time, to this solution drug and sodium bicarbonate were added. The above solution was mixed thoroughly by means of mechanical stirrer. Then the solution was sonicated for about 30 min so as to remove air bubbles. After sonication, the solution was kept aside for 30 min. The resultant solution was dropped via a 23-gauge syringe needle (0.65 mm internal diameter) into 80 ml of 2% w/v calcium chloride (CaCl<sub>2</sub>) solution containing 10% v/v acetic acid. Beads formed were washed with distilled water for 3 times. These beads were then placed in aqueous solution of 1 % glutaraldehyde for about 1 h. Glutaraldehyde was used as a hardening agent. Finally, beads were filtered and dried at room temperature.

**Table 1:** Formulation of calcium alginate beads of Esomeprazole

Ingredients (mg)	FB-1	FB-2	FB-3	FB-4
Esomeprazole	40	40	40	40
Sodium alginate	80	100	120	140
Xanthan gum	40	40	40	40
Sodium bicarbonate	40	40	40	100

#### III. Evaluation of Beads

**Yield of calcium alginate beads:** The percentage yield of calcium alginate beads was calculated by the following formula;

$$\% \text{ yield} = \frac{\text{actual weight of product}}{\text{total weight of drug and polymer}} \times 100$$

#### Particle size analysis

**Optical microscopy:** Calcium alginate beads were observed under 4X magnification in an optical microscope (Olympus LITE image) and an average of 100 particles were counted.

**Scanning electron microscopy:** The surface morphology and internal structure of the beads were observed by scanning electron microscopy using JEOL JSM-T scanning electron microscope (Japan).

#### Drug entrapment efficiency

Accurately weighed quantity of calcium alginate beads equivalent to 40 mg of Esomeprazole was triturated and the triturate was taken in 100 ml volumetric flask containing small quantity of methanol. The content was

dissolved by sonication for about 15 min and the volume was made up to 100 ml with methanol. From the above solution 10 ml was withdrawn and transferred into 50 ml volumetric flask and the volume was made up to the mark with distilled water. From the above solution 5 ml was withdrawn and transferred into 25 ml volumetric flask and the volume was made up to the mark with distilled water. The absorbance of the resulting solution was measured at 301 nm, using distilled water as blank. All the analysis was carried out in triplicate. The percentage drug entrapment was determined using the following equation,

$$\% \text{ Drug entrapment efficiency} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug loaded expected}} \times 100$$

### **In-vitro buoyancy**

*In-vitro* buoyancy studies were done using dissolution test apparatus USP type II (rotating paddle). 50 calcium alginate beads containing Esomeprazole were taken and added to the dissolution flask containing 0.1 N HCl as medium (900 ml). Temperature was maintained at 37°C ± 0.5°C for 12 h. Paddle was maintained at 50 rpm. The floating and the settled portion of beads were recovered separately. Buoyancy percentage was calculated as the ratio of the number of beads that remained floating to the total number of beads taken.<sup>7</sup>

### **In-vitro drug release**

*In-vitro* drug release studies were carried out with LAB INDIA DISSO 8000 using USP dissolution rate testing apparatus II method (rotating paddle method). The drug loaded calcium alginate beads equivalent to 40 mg of Esomeprazole were introduced into dissolution flasks containing 900ml of 0.1N HCl. The temperature was maintained at 37±0.5°C and paddle rotating speed at 50 rpm. 5ml of aliquot was withdrawn at regular predetermined intervals and sink conditions were maintained throughout the study by replacing equal volume of fresh dissolution medium. The samples taken were diluted to 25 ml with distilled water and analyzed spectrophotometrically at 301 nm using distilled water as blank. All the analysis was carried out in triplicate.

### **In-vitro drug release kinetics**

Data obtained from *in vitro* drug release studies were fitted to various kinetic models like zero-order, 1<sup>st</sup> order, Higuchi, Korsmeyer peppas and Hixon crowell model using PCP Disso V3 to predict the drug release mechanism.

## **RESULTS AND DISCUSSION**

### **Calibration curve of Esomeprazole**

The  $\lambda_{\text{max}}$  of Esomeprazole at 10 µg/ml concentration was found to be 301 nm. The standard calibration curve was found to be linear in the range of 4-20 µg/ml.

## **Preformulation Studies**

### **FTIR study**

The IR spectrum of pure Esomeprazole as shown in Figure 1(a) demonstrated characteristic peak at 1058.85 cm<sup>-1</sup> corresponding to S=O stretching. The peak at 1446.51 cm<sup>-1</sup> and 1543.91 cm<sup>-1</sup> indicated C=C stretch. Peaks at 3018.39 cm<sup>-1</sup> and 3095.54 cm<sup>-1</sup> indicated aromatic C-H stretching. The peak at 3499.05 cm<sup>-1</sup> indicated aliphatic N-H stretching. Also the peak at 2891.10 cm<sup>-1</sup> indicated C-H alkane stretching confirming the drug as Esomeprazole.

The study of IR spectra of sodium alginate as shown in Figure-1(b) demonstrated the characteristic absorption bands for Hydrogen bonded OH stretch at 2910.38 cm<sup>-1</sup>; C-H stretch at 2898.81 cm<sup>-1</sup> and 2923.88 cm<sup>-1</sup>; C-OH stretch from glycosidic bonds at 1087.78, 1058.85, 1029.92, 1072.35 cm<sup>-1</sup>; Carboxylate ion 2 bands at 1604, 1612 and 1413 cm<sup>-1</sup> and stretching vibration of C-O-C at 946 cm<sup>-1</sup> and 896 cm<sup>-1</sup>.

The FTIR spectra of the pure xanthan gum [Figure 1(c)] showed a broad absorption peak at 3353.02 cm<sup>-1</sup> indicating the hydrogen bonded OH groups, 2872.77 cm<sup>-1</sup> indicating C-H aromatic stretch, 1279.68 cm<sup>-1</sup> indicating an C-O-C stretch, 1607.56 cm<sup>-1</sup> indicating C=O stretch.

The IR spectra of physical mixture of drug and polymers [Figure 1(d) and 1(e)] showed neither shift nor disappearance of characteristic drug peaks, suggesting that there is no interaction between drug and polymers. The characteristic absorption peaks of Esomeprazole were also found in physical mixture of drug and polymers.

### **Particle size analysis**

#### **Optical microscopy**

The mean particle size of all the formulations was found to be in the range of 1337.28 ± 223.26 to 1902.61 ± 138.02 µm (Table 3), which was found to be a bit larger than expected and it was observed that the size increased with the increase in the concentration of sodium alginate in the drug: sodium alginate ratio.

#### **Scanning electron microscopy**

The surface morphology of calcium alginate beads was captured by Scanning Electron Microscopy (SEM). SEM photographs of the samples along with optical microphotographs revealed that the floating beads were nearly spherical with porous surface. SEM photographs of beads are shown in Figure 2.

### **Yield of calcium alginate beads**

The percentage yields of all the formulations were calculated and the yield was found to be in the range of 64 - 72.72 % (Table 2).

### **Drug entrapment efficiency**

The percentage drug entrapment efficiency of beads in all the formulations was found to be in the range of 52.5% - 87.5 %. The formulation FB-4 which showed better *in-*

*in vitro* results also showed maximum drug entrapment efficiency of 87.5%. The % drug entrapment efficiency was more when the concentration of sodium alginate was increased in the drug: sodium alginate ratio.

**Table 2:** Data of percentage yield and drug entrapment of the formulations

Formulation Code	% yield	% Drug entrapment
FB-1	64	52.5
FB-2	72.72	63.75
FB-3	69.16	78.75
FB-4	65.62	87.5

#### ***In-vitro* buoyancy**

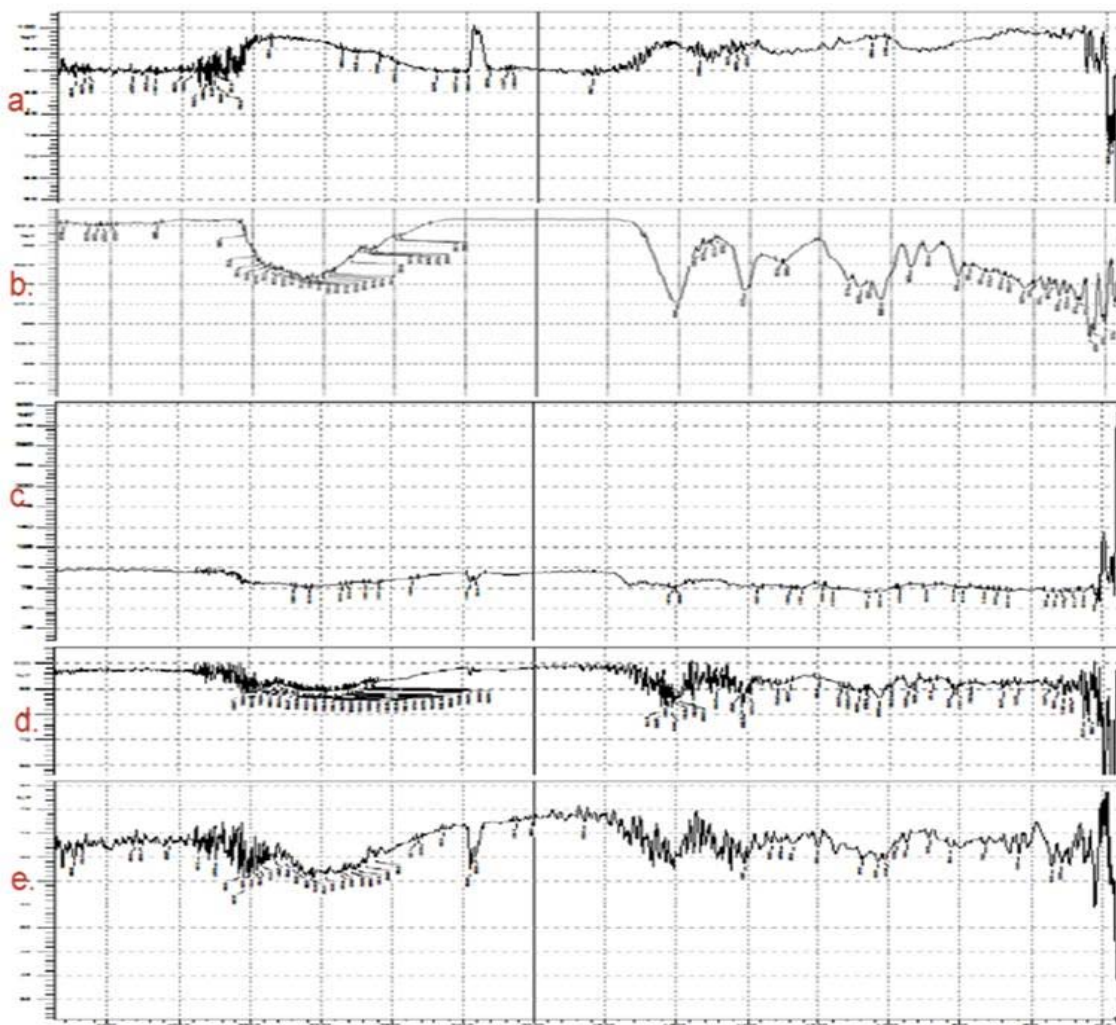
The *in-vitro* buoyancy studies showed that all the formulations floated for more than 8 h but the formulation FB-4 with the highest concentration of sodium bicarbonate showed better buoyancy compared to other formulations.

#### ***In-vitro* drug release**

The *in-vitro* drug release studies revealed that the formulation FB-4 containing maximum concentration of sodium alginate showed a slow and sustained drug release of 60.74 % at the end of 8 h. The results indicated that increasing the concentration of sodium alginate with respect to the drug resulted in further decrease in the drug release (as shown in Figure 3).

#### ***In-vitro* drug release kinetics**

The drug release data when fitted into various kinetic equations, showed Peppas release pattern for formulation FB-1 with  $R^2$  value of 0.9830 while for formulation FB-2 the best fit model was Hixon-Crowell with  $R^2$  value of 0.9924. Formulations FB-3 and FB-4 showed zero order release pattern with  $R^2$  value of 0.9978 and 0.9879 respectively. The drug release kinetics data revealed that the mechanism of drug release followed by formulation FB-1 was Fickian diffusion while the formulations FB-2 and FB-4 followed anomalous transport mechanism (Non-Fickian diffusion) and formulation FB-3 followed Super Case-II transport mechanism.



**Figure 1:** a) I.R. spectra of Eesomeprazole; b) I.R. spectra of sodium alginate; c) I.R. spectra of xanthan gum; d) I.R. spectra of physical mixture of Eesomeprazole and sodium alginate; e) I.R. spectra of physical mixture of Eesomeprazole and xanthan gum.

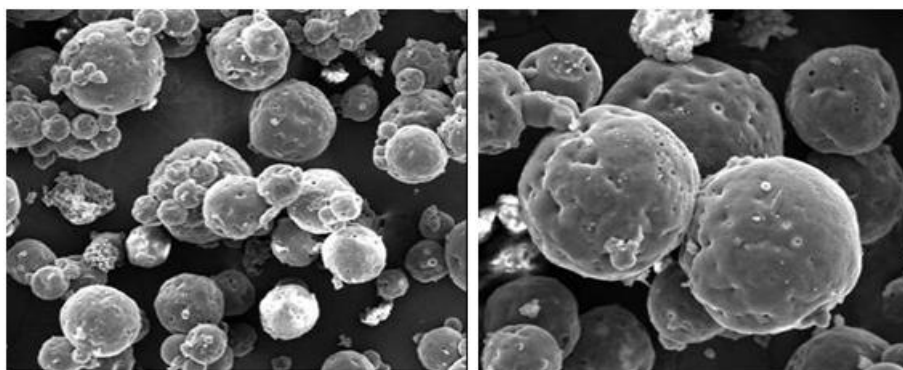


Figure 2: Scanning electron microscopy images of Esomeprazole-sodium alginate beads

Table 3: Characterization of the formulations

Formulation Code	Mean particle size (µm)	Buoyancy after 8 h (%)	Drug release (%)
FB-1	1348.53 ± 68.83	92	75.34
FB-2	1771.47 ± 86.96	96	70.88
FB-3	1337.28 ± 223.26	84	54.49
FB-4	1902.61 ± 138.02	98	60.74

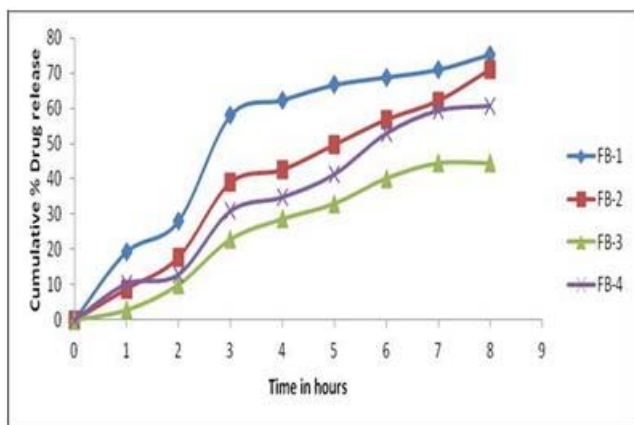


Figure 3: Comparative *in vitro* dissolution profile

**CONCLUSION**

The results obtained in this work suggested that a calcium alginate multiple unit floating drug delivery system can be successfully designed by the use of natural polymers and gas forming agents. The formulation was found to be stable and compatible throughout the experimental investigation of its efficacy. All the parameters were within the acceptable range and the drug release was sustained by making suitable modifications in the combination of sodium alginate with xanthan gum and

sodium bicarbonate as gas forming agent. Thus the sustained delivery of different categories of drugs could be achieved by employing selected natural and synthetic polymers along with suitable concentration of gas forming agent to induce the required buoyancy in turn to prolong the gastric emptying time.

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**REFERENCES**

1. Patel SS, Ray S, Thakur RS, Formulation and evaluation of floating drug delivery system containing Clarithromycin for *Helicobacter pylori*, Acta Poloniae Pharmaceutica-Drug Research, 63, 2006, 53-61.
2. Choi BY, Park HJ, Hwang SJ, Park JB, Preparation of alginate beads for floating drug delivery system: effects of CO<sub>2</sub> gas forming agents, International Journal of Pharmaceutics, 239, 2002, 81-91.
3. Sarkar BK, Tanwar SS, Soni P, Jain P, Formulation, characterization and *in-vitro* evaluation of floating microspheres of esomeprazole, International Journal of Bioassays, 01, 2012, 11-12.
4. Patel RP, Baria AH, Pandya NB, Stomach-specific drug delivery of famotidine using floating alginate beads, International Journal of Pharm Tech Research, 01, 2009, 288-291.
5. Jagdale SC, Kurhe PA, Kuchekar BS, Chabukswar AR, Development of gastroretentive calcium pectinate beads for floating drug delivery of famotidine using pectin and carbonate salts, International Journal of Novel Drug Delivery Technology, 01, 2011, 122-129.
6. Kulkarni S, Tripathi S, Mehta PD, Lodhi NS, Sengar NPS, Esomeprazole in the treatment of acidic disorder: an overview, Asian Journal of Biochemical and Pharmaceutical Research, 01, 2011, 562-566.
7. Fursule RA, Patra CH, Patil GB, Kosalge SB, Patil PO, Deshmukh PK, Study of multiparticulate floating drug delivery system prepared by emulsion gelation technique, International Journal of ChemTech Research, 01, 2009, 162-167.

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