Sodium Alginate Polymeric Floating Beads for the Delivery of Cefpodoxime Proxetil

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ABSTRACT: Sodium alginate (SA) floating beads containing cefpodoxime proxetil, a third-generation cephalosporin antibiotic, were prepared by precipitation method using calcium carbonate as gas generating agent. Hydroxypropyl methylcellulose (HPMC) was used in all the four formulations in different proportions (F1, F2, F3, and F4) as swelling agent to control the release of the drug. Gas generating agent forms pores on the surface of the beads because of the rapid escape of CO_2 during the curing process in precipitating media. Scanning electron microscopy confirmed their porous and grossly spherical structure, and the size of the beads were in the range of 700–1000 μm. The size of the beads increases with the increase in the concentration of gas-forming agent and decreases with the increase in the concentration SA. The drug entrapment efficiency was found to be in the range of 85.3–91.1%. F2 shows least entrapment, whereas F3 shows maximum entrapment. The percentage porosity was 82.1–89.1%, and the mean pore diameter was 0.41–0.52 μm. The porosity depends on the concentration of gas-forming agent. The mechanical strength of the beads was 591–1073 g. All the formulations showed good floating time. The *in vitro* release was performed in glycine dissolution media according to USP for about 12 h. The cumulative % drug release was found to be 67.5–87.3%. The *in vitro* dissolution study reveals that the concentration of the gas generating agent and SA affects the release rate. J Appl Polym Sci 114: 1921–1926, 2009

Key words: cefpodoxime proxetil; gastroretentive system; floating drug delivery system; floating SA beads; gas-forming agent

INTRODUCTION

Oral controlled release drug delivery formulations using bioacceptable polymers have limited utilization if the system cannot remain in the vicinity of the absorption site for a longer time. Thus, site- and time-specific oral drug delivery have recently been of great interest in the pharmaceutical field to achieve overall therapeutic efficacy.[1] A problem encountered with the conventional oral controlled release dosage forms is the inability to increase their residence time in the stomach and the proximal portion of the small intestine.[2] The most convenient route for drug delivery has historically been by oral ingestion.[3] However, the oral controlled drug delivery system is complicated by gastric residence times, which leads to incomplete drug release in the absorption zone and reduce the efficacy of the administered dose.

To overcome these problems several methods have been made recently to extend gastrointestinal transit time of the dosage forms. One such method is floating drug delivery systems. Such systems have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. Although the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. In this direction, polymeric hydrogels of natural origin were designed as floating drug delivery systems. The advantages of the hydrogels are that they are biocompatible and tailor made polymer network provides good stability for the encapsulated drug.[4,5]

In this investigation, it is intended to formulate and evaluate the floating sodium alginate (SA) beads for increasing the bioavailability of cefpodoxime proxetil (CP). SAs polysaccharides are known to be haemocompatible and do not accumulate in any organs of the human body and are used as hydrophilic polymers in the development of controlled release formulations for the delivery of drugs.

CP is an orally administered, extended spectrum, semisynthetic antibiotic of cephalosporin class. CP is a prodrug; its active metabolite is cefpodoxime. After oral administration, CP is absorbed from the

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TABLE I
Design of Different Formulations of Sodium Alginate Beads and Their Sizes

Formulation	Polymer % (w/v)		$CaCO_3$ % (w/v)	Cefpodoxime proxetil % (w/v)	Bead size (μm ± SD)	
	SA	HPMC			Wet	Dry
F1	3	0.3	1.5	1.5	3670 ± 0.8	966.33 ± 0.1
F2	3	0.3	3	1.5	3880 ± 0.3	988.67 ± 0.4
F3	4	0.36	1.5	1.5	2340 ± 0.7	842.86 ± 0.5
F4	4	0.36	3	1.5	2930 ± 0.5	938.17 ± 0.8

gastrointestinal tract and deesterifies to active metabolite cefpodoxime. Although the recommended dose range is between 100 and 400 mg, only 50% of administered cefpodoxime dose is absorbed systemically.[6]

EXPERIMENTAL

Materials

CP was procured from Biochem Pharmaceutical, Mumbai, India. Hydroxypropyl methylcellulose (HPMC) K4M was procured from Colorcon Asia, and SA was procured from Snap Naturals and SA Products, Mumbai, India. All other chemicals used were of analytical grade purchased from S.D. Fine Chemicals, Mumbai, India.

Preparation of floating sodium alginate beads

Floating SA beads of CP were prepared as shown in Table I using different proportions of drug, SA, HPMC, and $CaCO_3$. The weighed quantity of SA and HPMC were mixed with water to form a gel, and then the drug was incorporated by triturating. Then, gas-forming agent $CaCO_3$ was added to the gel form.[7] The resulting gel form was dropped through a 26G syringe needle into 50 mL of calcium chloride solution (1% w/v) containing 10% v/v acetic acid. The solution containing beads were stirred using magnetic stirrer for about 10 min. The beads were allowed to remain in the same solution for 2 h to improve their mechanical strength. The formed beads were separated, washed initially with ethanol and subsequently with distilled water, and then air-dried.

Characterization of beads

Size analysis and morphology of the beads

The size of SA beads was measured by taking 5–10 beads on glass slide under polarized light.[8,9] The mean diameter was calculated by measuring the number of divisions covered by beads. The stage micrometer was previously calibrated using ocular micrometer.

Drug entrapment efficiency of the SA beads or determination of entrapment efficiency

Beads (10 mg) were dissolved in 100 mL of glycine dissolution media (USP) by shaking in a flask, if necessary sonicated.[10] The solution was filtered and after sufficient dilution with glycine dissolution media, the solution was analyzed spectroscopically at 259 nm. The entrapment efficiency (EE) was calculated using following equation:

$$EE = (\text{Actual drug content in the beads} / \text{theoretical drug content}) \times 100.$$

Bead porosity and mean pore diameter

The bead porosity was measured using porosimetry.[11] The pressure was applied from 0 to 6000 psi. The mercury intrusion data were recorded. Standard values for the contact angle and surface tension of mercury were used for calculations.

Mechanical strength of beads

Ten beads of identical size were selected from each batch, and the crushing strength of each bead was determined using mercury load cell method.[11]

In vitro floating property study

The time taken for dosage form to emerge on the surface of the medium is called the buoyancy lag time, and the duration of time by which the dosage form constantly emerges on the surface of the medium is called the total floating time (TFT).[12] Initially, weighed amount from each formulation batch was placed in USP Type II dissolution apparatus containing 900 mL acidic buffer (pH 1.2), using paddle at a rotational speed of 75 rpm. The temperature of medium was maintained at 37°C ± 2°C. Initially, all the beads start floating with zero floating lag time. Then the TFT of the beads was determined.

In vitro release study

Dissolution of the SA beads of each batch was carried out using USP Type-II apparatus using paddle.[12,13] The glycine dissolution media of 900 mL

was filled in a dissolution apparatus, and the temperature of the medium was set at 37°C ± 2°C. SA beads equivalent to 50 mg drug were placed in each dissolution vessel, and the rotational speed of paddle was set at 75 rpm. The sample (5 ml) was withdrawn at predetermined time interval for 12 h and the same volume of fresh medium was replaced. The samples were analyzed for drug content against glycine dissolution media as a blank at 259.0 nm using double-beam UV–visible spectrophotometer. The content of drug was calculated using the equation generated from the standard curve. Then the cumulative % drug release was calculated.

Stability studies

The accelerated stability studies were conducted for selected formulation as per the ICH guidelines.[14,15]

Long-term testing: 25°C ± 2°C/ 60% ± 5%RH for 12 months.

Accelerated testing: 40°C ± 2°C/ 75% ± 5%RH for 6 months.

The selected formulations were analyzed for the drug's physical appearance, EE, floating ability, and *in vitro* release study.

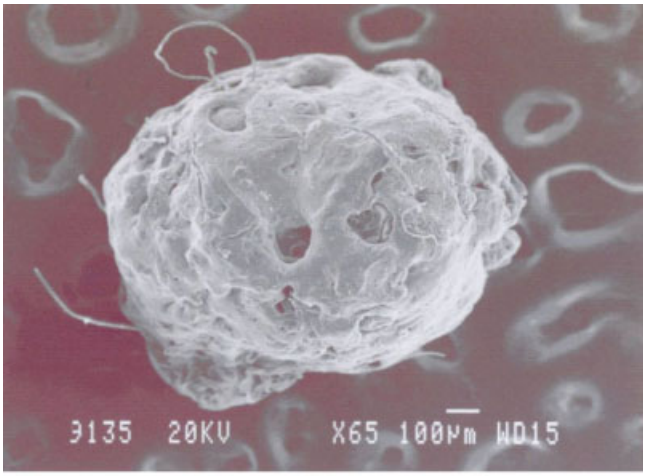
Data analysis

The matrix systems were reported to follow the zero-order release rate and the diffusion mechanism for the release of the drug.[16] To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained were fitted in to zero order, first order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the *r*-values obtained, the best-fit model was selected.

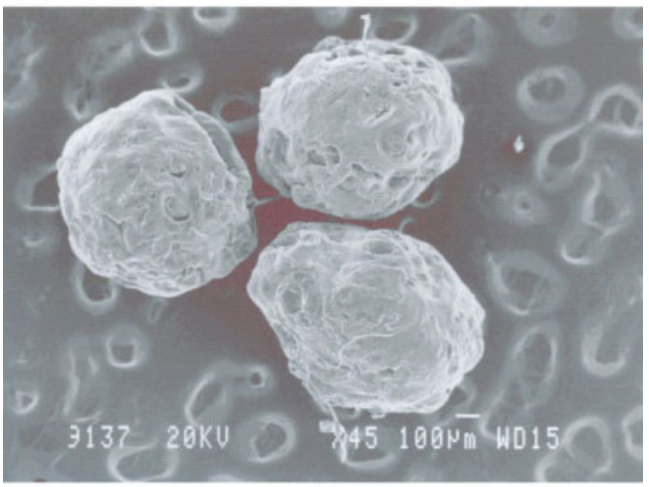
RESULTS AND DISCUSSION

Formulation of floating sodium alginate beads

Floating SA beads were successfully prepared for the delivery of CP to enhance absorption and bioavailability by increasing the gastric retention time. In concern to this approach, the primary necessity is to float the beads in gastric environment. In this study, four formulations were prepared. In each formulation, the SA concentration and gas-forming agent concentration were varied. The detailed composition of each formulation is given in Table I. The method used to prepare the SA beads was by dripping method using 26G needle into the 1% calcium chloride solution containing 10% v/v acetic acid. The beads were formed due to the crosslinking of the SA with divalent calcium ions of the $CaCl_2$ solution.



(a)



(b)

Figure 1 Scanning electron microphotographs of formulation F1 (a) and F3 (b). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

This mechanism is called ionotropic gelation. Thus the prepared SA beads were dried in air after washing with distilled water.

Characterization of floating beads

Size analysis and morphology of the beads

The scanning electron photomicrographs of the formulation are shown in Figure 1. The beads of the drug of all batches are almost grossly spherical. The scanning electron microscope images of beads illustrate the spherical shape with thin and incomplete calcium surface coating. The beads with higher gas-forming agent concentration for F2 and F4 were porous, rough, and grossly spherical. The surface topography reveals that the beads were highly porous because of the rapid escape of the carbon dioxide during formulation. Inward dents were observed for formulations F2 and F4 probably because of the collapse of the walls of the beads during the *in situ* drying

TABLE II
Results of Drug Entrapment Efficiency and Physical Properties of SA Beads

Formulation code	Drug entrapment efficiency (%)	Average mean pore diameter μm ± SD	Porosity average (%) ± SD	Mechanical strength of beads (g)
F1	87.97	0.41 ± 0.003	84.89 ± 0.32	707 ± 0.03
F2	85.30	0.50 ± 0.14	89.10 ± 0.99	591 ± 0.14
F3	91.12	0.45 ± 0.38	82.1 ± 1.79	1073 ± 0.38
F4	89.60	0.52 ± 0.33	87.93 ± 0.95	905 ± 0.83

process. The number of observed pores appears to be directly related to the amount of gas-forming agent.

The sizes of SA beads of all the four batches are also shown in Table I. The size of the beads was found to be 966.33, 988.67, 842.86, and 938.17 μm for F1–F4 batches, respectively. By keeping other factors constant, the bead size was found to increase with the increase in the concentration of gas-forming agent, which may be due to the pore formation and decrease in the concentration of SA; however, the former showed major effect. Thus, the beads of F2 is larger than F1 similarly F4 is larger than F3 because of the higher amount of gas-forming agent, and also F3 and F4 are smaller than F1 and F2 because of the high concentration of SA.

Drug entrapment efficiency of the sodium alginate beads

The values of total % incorporation efficiency of the drug are shown in Table II. The high incorporation efficiencies are seen with lower concentrations of gas-forming agent like F1 and F3 as gas-forming agent shows increased porosity and pore diameter, which is unable to retain the drug more effectively as seen with the formulations F2 and F4. The drug EE is also increased with the increase in the concentration of polymer, which may be due to highly dense internal structure of SA matrix and increased bonding and encapsulation of particles in beads. Thus, drug EE is higher for the formulation F3 than F4.

Mechanical strength of beads

Mechanical strength testing was performed to study the effect of gas-forming agent and polymer concentration on gel strength of SA beads. The high proportion of gas-forming agent made the beads highly fragile and porous as in F2 and F4 and hence showed lower crushing strength than other formulations containing lower concentration of gas-forming agent F1 and F3. The beads prepared by using 3% (w/v) SA solutions F1 and F2 showed crushing strength of 707 and 591 g, respectively. However, 4% (w/v) SA solutions F3 and F4 showed 1073 and 905 g, respectively, probably due to greater bonding of increased strength with increase in SA concentration. Higher mechanical strength of beads is important for avoiding breaking and distortion of beads during normal handling. The results of mechanical strength are given in the Table II.

TABLE III
Results of Floating Ability of SA Beads in Acidic Buffer pH 1.2 of Formulations F1–F4

Formulation code	Floatation property	Duration of floatation (h)
F1	++	More than 12 h
F2	++	More than 12 h
F3	−+	More than 12 h
F4	−+	More than 12 h

Porosity and mean pore diameter of beads

Porosity and mean pore diameter was studied to determine the effects of gas-forming agent on pore structure of floating beads. The % porosity for the formulations of F1, F2, F3, and F4 was 84.59, 89.10, 82.11, and 87.93%, respectively. By increasing the ratio of gas-forming agent as in F2 and F4, the % porosity and pore diameter of the beads were increased, but it does not depend on the concentration of polymer and hence no significant change appears in the porosity and pore diameter among F3 and F4 as shown in Table II.

In vitro buoyancy studies

The floating ability of the prepared beads was evaluated in acidic buffer (pH 1.2). The wet beads had

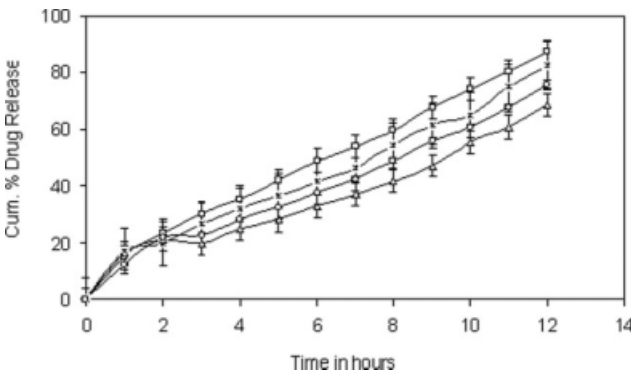


Figure 2 *In vitro* drug release profile for formulations F1(x), F2 (□), F3 (Δ) and F4 (○).

TABLE IV
Model Fitting Release Profile of Formulations F1–F4

Formulation code	Mathematical models (kinetics)					Best-fit model
	Zero order (R)	First order (R)	Higuchi matrix (R)	Peppas model (R)	Hixson Crowell (R)	
F1	0.9713	0.9496	0.9566	0.9724	0.9708	Peppas
F2	0.9538	0.8754	0.9096	0.9395	0.9169	Zero order
F3	0.7750	0.9071	0.9744	0.9504	0.8711	Higuchi matrix
F4	0.9581	0.9395	0.9309	0.9593	0.9540	Peppas

better floating ability than dry beads. The floating ability of SA beads is directly related to the gas content of the polymer matrix, which depends on the concentration of the gas-forming agent. As the concentration of the gas-forming agent increases, the number of air trapped pores in beads increases, which makes the beads to float. Wet beads contain a greater proportion of CO_2 gas than the dry ones and are thus more buoyant. The floating results were not affected by the stirring speed of the paddle. The floating abilities persisted until disintegration of the beads began. The results of *in vitro* buoyancy studies are given in Table III.

Buoyancy of the beads is directly related to the concentration of gas-forming agent. Instantaneous *in vitro* floating behavior was observed for beads of all batches, which may be due to the low apparent density provided by the porous nature of beads. The floating time of SA beads increases with the increase in the concentration of gas-forming agent and decrease with the increase in the concentration of SA due to nonporous, denser solid component. Thus, F1 and F2 batches showed excellent floating time than F3 and F4.

In vitro drug release studies

Dissolution studies on all the four formulations of SA beads of CP were carried out using a USP XXIII Type II, i.e., paddle-type dissolution apparatus up to 12 h. The cum. % drug release in 12 h was found to be 80.46, 87.26, 67.85, and 72.61 for the formulations F1–F4 respectively. The cum. % drug release versus time graph for all the formulations is shown in Figure 2. F2 is the best formulation selected among all on the basis of maximum release. The maximum release of the drug may be due to the lower concentration of SA and higher concentration of gas generating agent, which increases the pore formation and thereby increases the floating percentage, and from which drug releases easily from the SA matrix.

TABLE V
Stability Studies for F2 Formulation Stored at Different Conditions

Tested after time (days)	Percent drug entrapment	Floating ability	Cum % drug release
At 25°C/60%RH			
10	84.1	++	84.945
20	83.89	++	85.463
30	83.50	++	86.432
At 40°C/75%RH			
10	82.19	++	85.945
20	81.89	++	86.963
30	82.50	++	83.432

Data analysis

The curve-fitting results of the release rate profile of the designed formulations gave an idea on the release rate profile and the mechanism of the drug release. Fitting of the release rate data to the various models revealed that formulations such as F1 and F4 follows the Peppas model. Formulations F2 follows the zero-order release and F3 follows the Higuchi matrix as shown in Table IV.

Stability studies

A stability study was conducted for the prepared beads, of formulation F2 at 25°C and 40°C with a relative humidity of 60% and 75%, respectively, for a period of 30 days. However, the stability testing of beads at various pH values was not studied. The sample after exposing to extreme conditions were analyzed for physical appearance, EE, drug release studies, and floating behavior of the SA beads at the end of 30 days.

There was no significant change observed in the physical appearance, EE, floating ability of beads, release characteristics of the beads, and floating behavior as conducted at an interval of 10 days. The results of stability studies are given in Table V.

CONCLUSIONS

This present study has been a satisfactory attempt to formulate the floating SA beads of CP, an orally administered extended spectrum semisynthetic cephalosporin antibiotic, with a view of improving its oral bioavailability and giving a controlled/sustained release of the drug. The SA beads were prepared by dripping method using 26G needle. Biocompatible, biodegradable polymer like SA can

be used to formulate a floating bead system. HPMC K_4M can be used along with the SA as a swellable polymer for sustained release of the drug from the beads. Good percentage EEs and practical yields were obtained with SA. The size of SA bead was found to decrease with the increase in the concentration of SA. The size of SA bead was found to increase with the increase in the concentration of gas-forming agent. The floating beads of drug with high concentration of gas-forming agent were more porous and buoyant, whereas those with less amount of gas-forming agent are less buoyant. Thus, the formulated floating beads seems to be a potential candidate as an oral gastroretentive controlled drug delivery system in this era of patenting of novel and controlled drug delivery systems.

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