RESEARCH ARTICLE

A floating pulsatile drug delivery system based on hollow calcium pectinate beads

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The objective of the present work is to envisage and develop hollow calcium pectinate beads for floating pulsatile release of aceclofenac intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. The method used for the development of the beads was a simple process of acid-base reaction during ionotropic cross linking. The floating beads obtained were porous, hollow with a bulk density <1 and had an F_{t50} of 14-24 h. The floating beads showed a two-phase release pattern with initial lag phase during floating in an acidic medium followed by rapid pulse in phosphate buffer. The approach indicates the use of hollow calcium pectinate microparticles as a promising floating pulsatile drug delivery system for site- and time-specific release of drug acting as per chronotherapy of disease.

Key words: *Aceclofenac, calcium pectinate beads, chronopharmacotherapy, floating pulsatile drug delivery*

INTRODUCTION

Natural biodegradable polysaccharides like pectin, guar gum, Chitosan, carrageenans, sodium alginate and gellan gum and agar have been used in controlled drug delivery.[1-5] A multiparticulate system obtained by ionotropic cross-linking of these polymers have been used to develop floating drug buoyancy in cross-linked beads, some of which include freeze drying entrapment of gas or gas forming agents and use of volatile oil or fixed oil have been used.[6-8] These approaches are complicated as they require specific equipment and handling techniques with limited acceptance. The oil containing beads have a limitation of coalescence of the oil droplet yielding beads of wider particle size distribution volatilization or leaching of oil.[9] Comparatively, the floating dosage forms containing sodium bicarbonate as the buoyancy imparting agent are simple to produce, which have been already attempted.[10,11] Their floating property is based on the evolution of CO_2 when in contact with an acidic environment followed by the ability of the polymer gel to entrap it, which decreases their density below and, on the other hand, violent gas generation, disintegration of dosage form burst release, dose dumping and alkaline microenvironment[12] is a limitation of these dosage forms. Choi *et al*.[13] have developed porous alginate beads containing riboflavin where the CO_2 g as was allowed to generate during cross-linking only, followed by freeze drying to improve porosity. The beads obtained by freeze drying remained buoyant over 12 h whereas the air-dried beads remained submerged. The studies revealed the presence of air-filled hollow spaces, inside the freeze-dried beads, which was responsible for the floatation property of the beads. Chronopharmacotherapy, the drug regimen based on circadian rhythm, is recently gaining much attention world wide. Various diseases like asthma, hypertension, acidity and arthritis show circadian variation, which demands time-scheduled drug release for effective action, e.g. inflammation associated with morning body stiffness, asthma and heart attack in the early hours of the day. To follow this principle, one must have to design the dosage form such that it can be given at the convenient time, e. g. bed time for the above-mentioned diseases with the drug release in mornings compared with evenings and site-specific absorption from the small intestine. Drug pharmacokinetics show circadian variation for various antiinflammatory drugs like indomethacin, ketoprofen, aceclofenac and diclofenac sodium, which have a greater absorption in the morning as compared with the evening and site-specific absorption from the small intestine. Therefore, to develop dosage forms for chronopharmacotherapy, the designed drug release should be time-specific as well as site-specific. Also, the purpose of the present study was to produce hollow/porous floating beads of pectin by a process of evolution of CO_2 during cross-linking in an acidic environment. Aceclofenac, an acid-insoluble

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nonsteroidal antiinflammatory drug (NSAID) was used as a model drug. The obtained beads were evaluated for drug content, size analysis, porosity, mechanical strength, *in vitro* floating properties and drug release properties.

MATERIALS AND METHODS

Materials

Low-methoxy pectin was the generous gift of Krishna Pectin Pvt. Ltd., Jalgaon, India. Aceclofenac was received from IPCA Lab, Mumbai, India. Other materials used in the study were calcium chloride, sodium bicarbonate, sodium alginate, tween 80 and acetic acid glacial. All chemicals and reagents used were of analytical grade.

Preparation of the beads

The hollow porous beads were prepared by dissolving 275 mg of pectin and 100 mg of aceclofenac was dispersed in 10 ml of deionized water and various amounts of sodium bicarbonate were uniformly mixed, as shown in Table 1. The dispersion was sonicated for 30 min to remove any air bubbles. The resultant dispersion was dropped via a 23-gauge syringe needle (0.65 mm internal diameter) into 80 ml of 2% w/v calcium chloride solution containing 10% acetic acid. The content was stirred at 100 rpm using a magnetic stirrer for 15 min. The beads were filtered and washed three times with distilled water and subsequently oven dried at 50°C for 4 h.

Table 1: Formulation of the beads

Material	Formulation				
	A_1	A_2	A_3	A_4	A_5
Pectin (mg)	275	275	275	275	275
Drug (mg)	100	100	100	100	100
SBC (mg)	-	-	0.065	0.140	0.220
$CaCl_2$ (mg)	1.5	1.5	1.5	1.5	1.5
Acetic acid 10% (v/v)	-	6	6	6	6

Bead characterization

Drug content

Twenty-five milligram beads of each batch was placed in 100 ml phosphate buffer, pH 7.4, and mechanically agitated on a shaker at 200 rpm for 24 h. The resultant dispersion was filtered through a Whattman filter paper 41 and analyzed at 275 nm using a UV spectrophotometer (PharmaSpec UV-1700, Shimadzu Scientific Instruments, Kyoto, Japan). The encapsulation efficiency was determined by the following formula:

$$\text{Encapsulation efficiency}(\%) = \frac{AQ}{TQ} \times 100$$

where, AQ is the actual drug content of the beads and TQ is the theoretical quantity of drug present in the beads.

Size analysis

Randomly selected 20 beads were observed under a stereomicroscope (Carl Zeiss, Germany) attached with a digital camera. Biovis image plus software was used to analyze the image of the beads and then expressed in terms of different parameters such as diameter, roundness and circulatory factor.

Bead porosity and bulk density

The bead porosity was determined using a mercury porosimeter Quantachrome Instruments, Florida, USA.[10] The pressure was applied from 0 to 6000 psi. The mercury intrusion data were recorded and plotted against pressure. Standard values for contact angle and surface tension of mercury were used for calculations. The bulk density of the beads was also measured using the same mercury porosimeter.

Scanning electron microscopy

Beads and their cross-sections were coated with a thin gold palladium layer by a sputter-coater unit. The surface topography was analyzed by a scanning electron microscope (SEM) (Stereoscan S 250 MKIII, Cambridge, UK).

Buoyancy test

The obtained beads were studied for buoyancy and floating time using a USP XXIII type 2 (LABINDIA Disso 2000, LabIndia instruments Pvt Ltd. Thane India.) dissolution test apparatus. One hundred beads of each batch were placed in 900 ml 0.1 N hydrochloric acid (pH 1.2) containing 0.02% w/v tween 80 and alginate. The media was maintained at 37°C ± 0.5 and stirred at 100 rpm. The number of sinking beads was observed visually.

Dissolution studies

The dissolution studies of the beads equivalent to 100 mg of aceclofenac were performed using a USP XXIII type 2 dissolution test apparatus. The drug release study was carried out in 0.1 N hydrochloric acid initially for 2 or 6 h depending on the floating characteristic of the beads followed by dissolution in phosphate buffer of pH 7.4, each 900 ml maintained at 37°C ± 0.5 and agitated at 100 rpm. Periodically, samples were withdrawn and filtered through a Whattman filter paper 41 and the concentration of aceclofenac was measured spectrophotometrically at 271 and 275 nm for acidic and basic media, respectively.

RESULTS AND DISCUSSION

Many natural polymer like alginates, pectin and Chitosan have gained importance due to their biocompatibility and biodegradable, inexpensive and nontoxic nature. They form a multiparticulate system by simple ionotropic gelation, which can be formulated to provide various desired drug release patterns. Pectin is a heterogeneous anionic polysaccharide with an ability to produce water-insoluble complexes with a drug and has been used in novel drug delivery. Pectin is not digested by gastric enzymes and has minimum swelling, but pectin undergoes rapid swelling in an alkaline environment thus forming a very good base for colonic or intestinal drug delivery.

Preparation of the beads

Preparation of the beads was performed by keeping the amount of pectin constant and by varying the amount of sodium bicarbonate. The beads were prepared in the ratio of 0.25:1, 0.5:1, 0.75:1 and 1:1, respectively. The first two formulations were prepared without sodium bicarbonate to observe the effect of acid and alkali. The first two formulations showed a higher level of density. It may be due to the fact that no base is available to react with acidified calcium chloride and thus there is no production of gas, which decreases its density. Formulations A_3-A_6 were prepared as per the above ratio. Formulation A_6 yielded irregular-shaped beads of poor mechanical strength. This may be due to excess liberation of gas, which made the matrix weak and the beads failed to retain the shape after drying. Calcium pectinate beads showed greater strength than alginate. Therefore, pectinate was selected for preparation of the beads.

Bead characterization

Drug content

Formulation A_1 showed the least encapsulation efficiency, which may be due to the insolubility of drug in the acid medium. Further, formulation A_2 showed an increase in the encapsulation efficiency due to an increased amount of acidic cross-linking.

The formulation A_3 showed a decreased encapsulation efficiency because sodium bi carbonate (SBC) was added. In further formulations A_3-A_5, the encapsulation efficiency increased with an increasing amount of SBC. This might be attributed to the alkaline microenvironment that is created by the SBC inside the beads. In the formulation A_3 batch, the amount of SBC acted individually causing scattered microchannels leading to drug loss. This is then supported by the fact that the bulk density was highest for formulations A_4 and A_5 and that collective action exerted by the released amount of SBC leads to the formation of a prominent hollow structure due to entrapment of the generated gas. This entrapment leads to the coalescence of gas bubbles, which pushed the internal matrix toward the periphery, forming thick boundaries and minimizing drug leaching.

Size analysis

Drug-loaded beads of A_1 and A_2 were comparatively the comparative spherical shape. Other formulations showed a decrease in the roundness, which can be attributed to the amount of SBC. Presence of SBC may be responsible for softening of pectin beads and, subsequently, deformation due to agitation. The particle size increased with the increase in the amount of SBC in the polymer matrix and due to the presence of entrapped gas bubbles. Increase in porosity was also observed, as presented in Table 2.

Scanning electron microscopy

The drug-loaded beads with and without SBC were studied under an SEM. The overdried beads of formulation A_2 were small and dense with a wrinkled circumference due to gradual water loss. The surface of formulation A_5 prepared using highest SBC was very rough and porous. The cross-section of beads of the A_5 formulation showed an either hollow core or multiple small packets in the matrix.

Table 2: Bead characterization

Formulation	Diameter (mm)	Roundness	Porosity (%)	Bulk density (g/cm²)
A_1	1.42 ± 0.05	0.75 ± 0.06	-	0.11 ± 0.01
A_2	1.46 ± 0.06	0.74 ± 0.06	-	1.88 ± 0.11
A_3	1.68 ± 0.06	0.66 ± 0.08	-	1.28 ± 0.12
A_4	1.83 ± 0.09	0.75 ± 0.07	26.28	0.87 ± 0.13
A_5	1.99 ± 0.10	0.77 ± 0.07	32.46	0.88 ± 0.07

The thick boundaries in the beads may be due to the coalescence of the gas bubbles that pushed the internal matrix toward the periphery forming thick boundaries. The precipitated drug crystals can be seen embedded in the matrix [Figure 1].

Bead porosity and bulk density

The bulk density of earlier formulations A_1-A_3 was high due to the absence of a less amount of SBC. Decrease in the bulk density was observed with increase in size and porosity [Table 2].

Buoyancy test

By observing the buoyancy and time required for sinking all the beads, the floating property of all the beads was studied. Surface tension of the human gastric juice (35-50 N/m²)[10] was simulated by adding a surfactant. Beads of formulations A_1 and A_2 sunk immediately while most of the beads of the A_3 formulation sunk to the bottom. Beads of formulations A_4 and A_5 showed satisfactory buoyancy and remained floating for 7-12 h, respectively. F_{t50}, the time required to sink 50% of the beads assuring linear approaches of sinking, was presumed up to 16 h [Figure 2].

Dissolution study

The beads of formulations A_1, A_2 and A_3 were not studied for dissolution because they were not floating and it was assumed that they would remain in the stomach for about 2 h only, whereas beads of A_4 and A_5 were floated and assumed that they will remain in the stomach for about 6 h. All the beads released only 3-4% of the drug in the acidic medium irrespective of time. The low drug release at gastric pH is also advantageous to reduce gastric irritation of NSAID. After this lag time, it follows pulsatile release in phosphate buffer within 30-40 min [Figure 3]. The porous/hollow beads showed excellent lag in drug release at acidic pH, which may be due to insolubility of the drug and pectin. In acidic pH, calcium pectinate exists in a protonated form, having reduced swelling, while pulsed release in phosphate buffer can be attributed to rapid swelling and gel relaxation of calcium pectinate gel in alkaline pH. Secondly, at pH > 6.8, aceclofenac sodium is freely soluble, which resulted in rapid drug release.

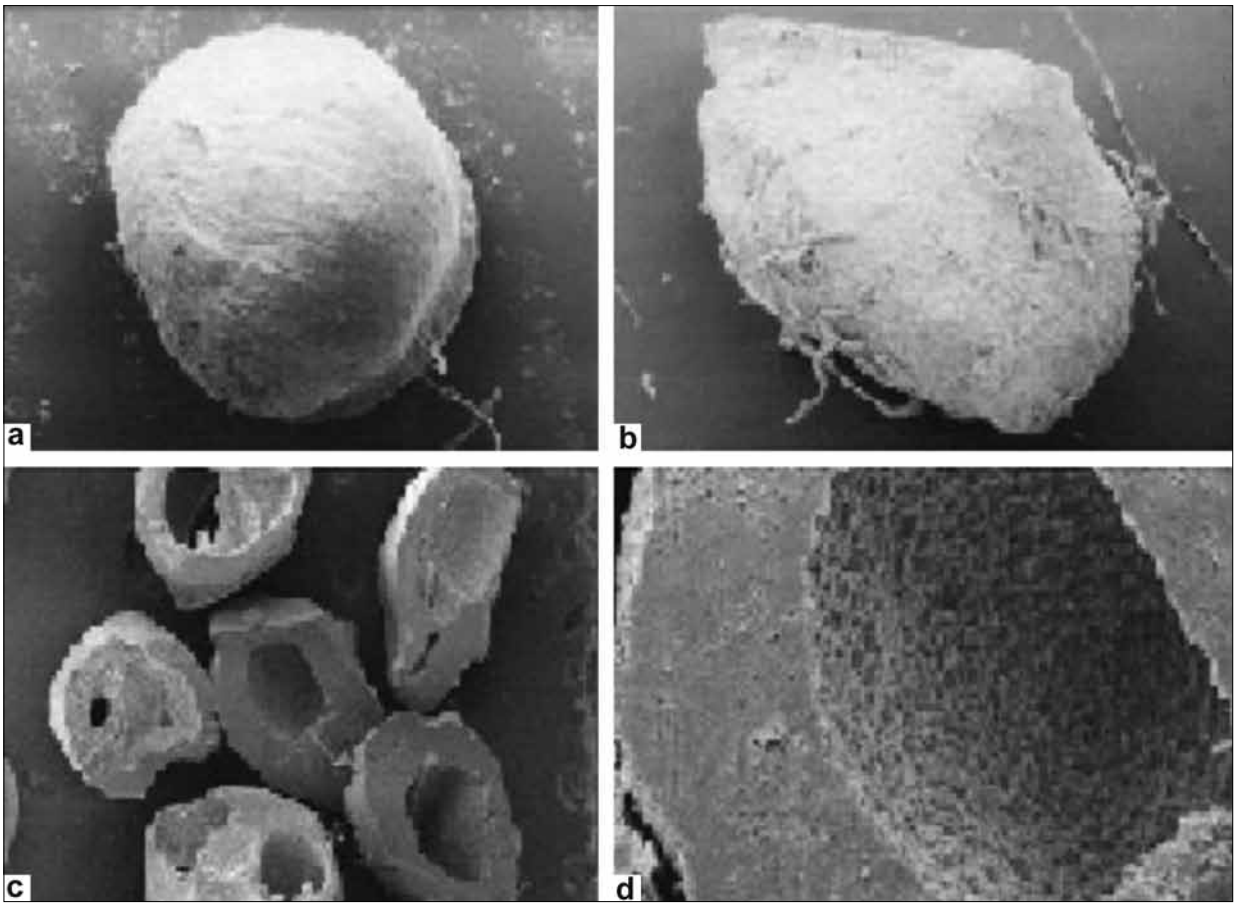

Figure 1: Scanning electron microscope of aceclofenac loaded calcium pectinate beads; (a) formulation A2 (×60.6); (b) formulation A5 (×62); (c) cross-section of formulation A5 (×100); (d) cross-section of formulation A5 (×500)

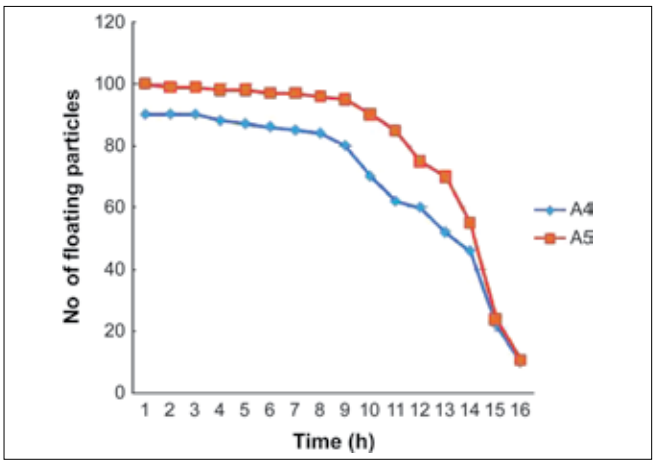

Figure 2: Floating profile of aceclofenac beads

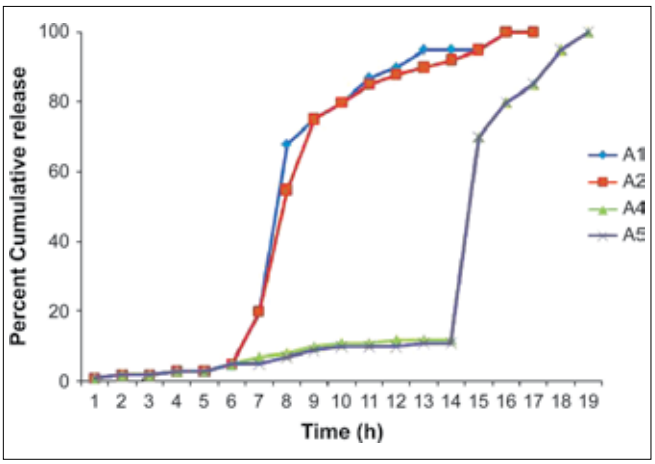

Figure 3: Cumulative drug release profile

CONCLUSION

Novel hollow calcium pectinate beads containing aceclofenac were prepared by a simple ionotropic gelation technique with *in situ* action of buoyancy imparting agent during formation. Overall, buoyant beads provided lag phase in the acidic medium while a pulsatile drug release in the alkaline pH that would be useful for rheumatoid and osteoarthritis. This can be extended for the time-scheduled drug having low solubility, poor absorption or degradation in the lower gastrointestinal tract.

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