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Research paper

Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery

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Abstract

The purpose of this work was to develop hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium 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. To overcome limitations of various approaches for imparting buoyancy, hollow/porous beads were prepared by simple process of acid-base reaction during ionotropic crosslinking. The floating beads obtained were porous (34% porosity), hollow with bulk density <1 and had $F_{t50\%}$ of 14–24 h. In vivo studies by gamma scintigraphy determined on rabbits showed gastroretention of beads up to 5 h. The floating beads provided expected two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. This approach suggested the use of hollow calcium pectinate microparticles as promising floating-pulsatile drug delivery system for site- and time-specific release of drugs acting as per chronotherapy of diseases.

Keywords: Floating-pulsatile drug delivery; Calcium pectinate beads; Diclofenac sodium; Hollow beads; Gamma scintigraphy; Chronotherapy

1. Introduction

Natural biodegradable polysaccharides like pectin, guar gum, chitosan, carrageenans, sodium alginate and gellan gum have been used in controlled drug delivery [1–5]. Multiparticulate systems obtained by ionotropic crosslinking of these polymers have been used to develop floating drug delivery. Various approaches to induce buoyancy in crosslinked beads, some of which include freeze-drying, entrapment of gas or gas forming agents, use of volatile oils or fixed oils, 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 limitations of coalescence of oil droplets yielding beads of wider particle size distribution, volatilization or leaching of oil [9]. Comparatively, the floating dosage forms containing sodium bicarbonate as buoyancy imparting agent are simple to produce which have been already attempted [10,11]. Their floating property is based on the evolution of carbon dioxide when in contact with acidic environment followed by the ability of polymer gel to entrap it which decreases their density below one. On the other hand, violent gas generation, disintegration of dosage form, burst release, dose dumping and alkaline microenvironment [12] are limitations of these dosage forms. Choi et al. [13] have developed porous alginate beads containing riboflavin where the carbon dioxide gas was allowed to generate during crosslinking only, followed by freeze-drying to improve porosity. Talukder and Fassihi [14] developed a floatable multiparticulate system by crosslinking low methoxylated pectin and sodium alginate. The beads obtained by freeze-drying remained buoyant over 12 h, whereas the air-dried beads remained submerged. The study revealed the presence of air-filled hollow spaces

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inside the freeze-dried beads, which was responsible for the flotation property of the beads. Sriamornsak et al. [15] developed floating calcium pectinate beads by emulsion-gelation method. Such technique can be considered as alternative to overcome limitations of sodium bicarbonate containing floating drug delivery systems. Chronopharmacotherapy, the drug regime based on circadian rhythm, is recently gaining much attention worldwide. Various diseases like asthma, hypertension, acidity, and arthritis show circadian variation, that demands time-scheduled drug release for effective drug action, e.g., inflammations associated with morning body stiffness, asthma, and heart attack in early hours of the day [16]. 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 the morning. Drug pharmacokinetics too show circadian variation for various anti-inflammatory drugs like indomethacin, ketoprofen and diclofenac sodium which have greater absorption in morning as compared to evening [17], and site-specific absorption from small intestine [18,19]. Therefore, to develop dosage form for chronopharmacotherapy the desired 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 carbon dioxide during crosslinking in acidic environment. Diclofenac sodium, an acid-insoluble NSAID, was used as model drug. The obtained beads were evaluated for drug content, size analysis, porosity, mechanical strength, in vitro and in vivo floating properties and in vitro drug release.

2. Materials and methods

2.1. Materials

Low methoxy pectin, GENU®LM-104As, was the generous gift of C P Kelco (Denmark). Diclofenac sodium was received from Emcure Pharmaceuticals, Pune (India). Other materials used in the study were calcium chloride dihydrate (Sisco Research Lab. Pvt. Ltd., Mumbai, India), sodium bicarbonate (Loba Chemie, Mumbai, India), acetic acid, glacial (100%) (E Merck, Mumbai, India), stannous chloride (E Merck, Mumbai, India), and technicium −99m (as pertechnate) $TC^{99}O_4^-$. All chemical reagents used were of analytical grade.

2.2. Preparation of beads

Three hundred milligrams of pectin was dissolved in 10 ml of deionized water, 150 mg diclofenac sodium and various amounts of sodium bicarbonate were uniformly mixed, as shown in Table 1. The dispersion was sonicated for 30 min. (Ultrasonicator, Toshcon, Ajmer, India) 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 ($CaCl_2$) solution containing 10% acetic acid. The content was stirred at 100 rpm using magnetic stirrer for 15 min. The beads were then filtered, washed three times with distilled water and subsequently oven-dried at 50 °C for 4 h.

2.3. Drug content

20 mg beads of each batch were placed in100 ml phosphate buffer, pH 7.4, and mechanically agitated on shaker (Steelmet Industries, Pune, India) at 200 rpm for 24 h. The resultant dispersions were filtered and analyzed at 277 nm using UV spectrophotometer (JASCO-V500, Kyoto, Japan). The encapsulation efficiency was determined by the following formula:

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

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

2.4. Bead characterization

2.4.1. Infrared spectroscopy

The infrared spectra of diclofenac sodium, calcium pectinate beads (without drug, sodium bicarbonate and acetic acid) and drug-loaded porous calcium pectinate beads were recorded on FTIR (JASCO-FTIR 5300). The samples were prepared on KBr press (Spectra Lab, Mumbai, India).

2.4.2. Size analysis

Randomly selected 20 beads were observed under a stereomicroscope (Carl Zeiss, Germany) attached with a digital camera (Watec, WAT-202, Japan). Biovis image plus

Table 1
Composition, percent yield and encapsulation efficiency profiles of calcium pectinate beads

Batch No.	A1	A2	A3	A4	A5
Amount of pectin (mg)	300	300	300	300	300
Amount of drug (mg)	150	150	150	150	150
SBC (mg)[a]	–	–	0.075	0.150	0.225
Amount of $CaCl_2$ (g)	1.6	1.6	1.6	1.6	1.6
Acetic acid 10% (v/v) (ml)	–	8	8	8	8
% encapsulation efficiency	63.78 ± 1.92	77.86 ± 2.29	71.48 ± 1.10	76.66 ± 2.66	80.53 ± 1.81
% yield	92.86 ± 1.07	93.55 ± 1.05	90.03 ± 1.03	92.83 ± 1.40	88.55 ± 1.23

[a] SBC: Sodium bicarbonate.