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Alginate-based bipolymeric-nanobioceramic composite matrices for sustained drug release

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ABSTRACT

Alginate-based bipolymeric–nanobioceramic composite matrices for sustained drug release were developed through incorporation of nano-hydroxyapatite [nHAp] powders within ionotropically-gelled calcium ion-induced alginate-poly (vinyl pyrrolidone) blends polymeric systems. nHAp powders were synthesized by precipitation technique using calcium hydroxide [$Ca(OH)_2$] and orthophosphoric acid [H_3PO_4] as raw materials. The average particle size of these was synthesized. nHAp powders was found as 19.04 nm and used to prepare nHAp-alginate-PVP beads containing DS. These beads exhibited drug entrapment efficiency (%) of 65.82 ± 1.88 to 94.45 ± 3.72% and average bead sizes of 0.98 ± 0.07 to 1.23 ± 0.15 mm. These beads were characterized by scanning electron microscopy (SEM) and Fourier transform-infra red (FTIR) spectroscopy analyses. Various nHAp-alginate-PVP beads containing DS exhibited prolonged sustained drug release and followed the Koresmeyer–Peppas model of drug release ($R^2 = 0.9908–0.9978$) with non-Fickian release (anomalous transport) mechanism ($n = 0.73–0.84$) for drug release over 8 h.

1. Introduction

Recently, the development of novel biopolymer-inorganic composites as drug delivery matrices has attracted much attention owing to their unique properties such as biodegradability and biocompatibility [1–4]. The synergistic effect of biopolymers and inorganic materials could improve the mechanical properties, drug entrapment and sustained drug release behavior [4]. In addition, these properties could be further tailored by altering the type and content of inorganic materials [4].

Alginates are referred to as a family of polyanionic copolymers derived from marine kelp, mainly the brown sea algae [5]. Alginates consist of two basic-building blocks, ∞-L-guluronic acid (G) and β-D-mannuronic acid (M) residues, linearly linked together by 1–4 linkages. Sodium alginate (SA), the sodium salt of alginic acid is soluble in water forming solutions of considerable viscosity [1]. Due to its suitable rheological property, it has long been used in pharmaceutical applications [6–8]. SA undergoes a sol–gel transformation in response to multivalent metal cations like Ca^{2+}, Zn^{2+}, Ba^{2+}, Al^{3+}, *etc.* and the aqueous solution of SA immediately forms cured gel matrices in the presence of these divalent cations due to ionotropic-gelation [5,9]. The gelation phenomenon of SA can be explained by the 'Egg-box Model' in which these multivalent cations bind to carboxyl groups on the adjacent alginate molecules [10,11]. These ionotropically-gelled alginate beads have been investigated for encapsulation of various therapeutic agents like drugs, enzymes, proteins, *etc.* [5,11–14]. Unfortunately, low entrapment efficiency of water soluble drugs in the ionotropically-gelled alginate beads remain a serious problem for developing sustained-release drug delivery systems. This occurs due to the leakage of drug molecules from the wet beads during cross-linking process [15]. Other major disadvantage of ionotropically-gelled alginate beads is the fast disintegration in intestinal fluid, which results a rapid drug release [16,17]. So, several modifications of ionotropical-gelled alginate beads as drug releasing matrices have

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been investigated and reported by various research groups, which are evidenced in previous literatures [16,18–23].

Poly (vinyl pyrrolidone) (PVP) is a water soluble polymer with suitable viscosity and biocompatibility, which has been used in the biomedical and pharmaceutical applications [24–27]. In previous literature, ionotropically-gelled beads using SA–PVP polymer-blends were also reported for sustained-release drug delivery [17,28]. The characterization of these beads revealed a possibility of intermolecular hydrogen bonding formed between —C═O groups of PVP and —OH groups of alginate chains, which might facilitate high drug entrapment and more sustained release of entrapped drugs [17,29].

Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$; HAp] is one of the ideal materials for the preparation of drug-releasing scaffolds because of its excellent properties such as the ability to adsorb a variety of chemical species and biocompatibility [30–33]. In the previous literature, several HAp-biopolymer composites as drug-release matrices have been reported by various research groups [1,4,34,35]. The present work reports a simple strategy for the development of HAp-alginate-PVP beads as sustained drug-release matrices through incorporation of synthetic nano-HAp (nHAp) powders within ionotropically-gelled calcium-ion induced alginate-PVP K30 blends-based polymeric systems. The commonly used diclofenac sodium (DS) was used as model drug in this work.

DS is a non-steroidal anti-inflammatory drug (NSAID), which is widely used clinically as strong analgesic [36–38]. It is used in the treatment of rheumatoid arthritis and osteoarthritis [36,38]. The biological half-life of it is about 1–2 h; therefore, it requires multiple dosing to maintain therapeutic drug-blood level [39]. It is poorly soluble in acidic pH and rapidly soluble in alkaline pH [40]. The common adverse effects of DS are gastritis and peptic ulceration [41]. Hence, the formulation of sustained-release dosage form of DS can eliminate the need for multiple dosing with improved patient compliance. In the light of the above discussion, the attempt was made to develop novel nanoceramic–biopolymeric composite matrices in the form of nHAp-alginate-PVP beads containing DS for sustained release of DS by ionotropic-gelation method using $CaCl_2$ as cross-linking agent.

2. Materials and methods

2.1. Materials

DS (Techno Remedies, India), SA (Central Drug House, India), PVP (PVP K30, Loba Chemie, India), calcium chloride ($CaCl_2$; Merck Ltd., India), calcium hydroxide ([$Ca(OH)_2$]; Qualigens Fine Chemicals, India) and orthophosphoric acid (H_3PO_4; Qualigens Fine Chemicals, India) were used. All other chemicals and reagents were commercially available and of analytical grade.

2.2. Synthesis of nHAp by precipitation technique

In brief, 50 mL of aqueous suspension of 0.5 M $Ca(OH)_2$ was prepared and vigorously stirred for 10 min. Then, 50 ml of 0.3 M H_3PO_4 was slowly added into the $Ca(OH)_2$ suspension. pH of the synthesis system was carefully adjusted to 10.3–10.5 by 1 M NH_4OH. The suspensions were well stirred (300 rpm) using magnetic stirrer for 45 min and aged overnight at room temperature. Precipitates were subjected to vacuum filtering using Büchner funnel, repeatedly washed with deionized water and filtered again. The precipitates were collected by centrifugation and then lyophilized (Eyela FDU 1200) to obtain dried nHAp and stored in a desiccator.

2.3. Particle size determination of nHAp

Synthesized nHAp powders were dispersed into 10 ml phosphate buffer, pH 7.4 and sonicated for 5 min before size measurement. The obtained homogeneous suspensions were examined for particle size using a laser scattering particle size analyzer (MALVERN ZETASIZER, MAL500999, UK).

2.4. Preparation nHAp-alginate-PVP beads containing DS

nHAp-alginate-PVP beads containing DS were prepared using $CaCl_2$ as cross-linking agent by ionotropic-gelation method. Briefly, SA and PVP K30 dispersions were prepared separately in deionized water by 1000 rpm stirring for 10 min using a magnetic stirrer (Remi Motors, Mumbai). Afterwards, both the dispersions were well mixed and synthesized nano-HAp powders were added to the dispersion mixtures and homogenized for 10 min at 1000 rpm using a homogenizer (Remi Motors, Mumbai). Then, DS was added to the dispersion mixtures maintaining drug to polymer ratio, 1:2 and homogenized again for 10 min at 1000 rpm. The resulting dispersions were then added via an 18 G needle into agitated $CaCl_2$ aqueous solutions containing 0.08% (w/v) Tween 80. The added droplets were retained in $CaCl_2$ solutions for 15 min to complete curing reaction and to produce spherical, rigid beads. The formed beads were then collected by filtration and washed with deionized water twice before drying in air for 24 h and dried beads were stored in a desiccator. Formulation variables of different nHAp-alginate-PVP beads containing DS are enlisted in Table 1.

2.5. Determination of drug entrapment efficiency

Accurately weighed, 100 mg of beads were crushed using pestle and mortar. The crushed powders of drug containing beads were placed in 500 ml of phosphate buffer, pH 7.4 and kept for 24 h with occasionally shaking at $37 \pm 0.5\,^{\circ}C$. After the stipulated time, the mixture was stirred at 500 rpm for 15 min on a magnetic stirrer. The polymer debris formed after disintegration of bead was removed filtering through Whatman® filter paper (No. 40). The drug content in the filtrate was determined spectrophotometrically using a UV–vis spectrophotometer (Shimadzu, Japan) at 276 nm. The drug entrapment efficiency of beads was calculated by using this following formula:

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Actual drug content in beads}}{\text{Theoretical drug content in beads}} \times 100$$

2.6. Bead size measurement

The diameters of dried beads were measured using digital slide calipers (CD-6″ CS, Mitutoyo Corporation, Japan) by inserting the beads in between the space of two metallic plates and diameter of resultant beads were displayed in the digital screen of the previously calibrated equipment. The average size was then calculated by measuring the diameter of 3 sets of 20 beads from each batch.

2.7. Scanning electron microscopy (SEM) analyses

The gold-coated beads were photographed under a scanning electron microscope (JEOL JSM-6360, JEOL Ltd., Japan) at an acceleration voltage of 5 kV.

2.8. Fourier transform-infrared (FTIR) spectroscopy analyses

Samples were reduced to powder and analyzed as KBr pellets by using a Fourier transform-infrared (FTIR) spectroscope (Shimadzu, Japan). The pellet was placed in the sample holder. Spectral