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Trivalent ion cross-linked pH sensitive alginate-methyl cellulose blend hydrogel beads from aqueous template

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ABSTRACT

pH sensitive alginate-methyl cellulose blend hydrogel beads were prepared by single water-in-water (w/w) emulsion gelation method in a complete aqueous environment. The influence of different variables like total polymer concentration, gelation time and crosslinker content on *in vitro* physico-chemical characteristics and drug release rate in different medium were investigated. Drug loaded beads were evaluated through Fourier Transform Infra-red (FTIR), X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC) analysis. Scanning electron microscopy (SEM) picture of the dried beads suggested the formation of hemispherical particles. FTIR analysis indicated the stable nature of the drug in the blend hydrogel beads. DSC and XRD analysis revealed amorphous state of drug after encapsulation. The drug release profile in acidic medium was considerably less in compared in alkaline media. Formulations showed non-Fickian type transport mechanism. This trivalent ion crosslinked beads not only improves drug encapsulation efficiency but also enhances drug release in alkaline media.

1. Introduction

Over the last few years, a great deal of attention has been paid to the development of polysaccharide-based hydrogel beads through ionotropic gelation technique useful as potential carriers in controlled drug delivery [1]. One of the advantages of this technique is that the drug encapsulation in the beads could be achieved in an eco-friendly aqueous environment [2]. In addition, multiunit systems avoid the vagaries of gastric emptying and different transit rates through the gastrointestinal tract, thereby, drugs release more uniformly and prevent exposure to a high drug concentration, when compared to single unit dosage form on chronic dosing [3,4].

Methyl cellulose (MC) is a natural carbohydrate polymer and freely soluble in water. It forms aqueous solutions and demonstrates a unique property to form reversible physical gels due to hydrophobic interactions when heated above a particular temperature [5]. Drug release from matrices can be controlled and enhanced by the addition of such water-soluble or water swellable carbohydrate polymer [6].

Sodium alginate (SAL), a hydrophilic anionic biopolymer [7–9] obtained from brown sea weeds, is a polysaccharide composed of varying proportions of D-mannuronic acid (M) and L-guluronic acid (G) residues which are arranged in MM or GG blocks interspersed with MG blocks [10]. Its unique property of forming water insoluble calcium alginate gel through ionotropic gelation with divalent calcium (Ca^{2+}) ions in a simple and mild condition has made possible to encapsulate both macromolecular agent [11] and low molecular weight therapeutic agent [12] in calcium alginate beads. However in physiological environment, calcium alginate beads tend to have poor mechanical stability and erode rapidly in simulated intestinal fluids leading to quick release of the loaded drugs [13]. Further, the gel strength of alginate beads was improved by the formation of polyelectrolyte complex for the controlled delivery of drugs. But the results were not so encouraging. To overcome this limitation, the concept of smart polymer as well as the use of blend hydrogel beads containing carbohydrate polymers is getting the favor of scientist regarded in the design of pH-sensitive drug delivery systems [14].

Simultaneously, it has been reported earlier [15] that due to higher valency, the cross-linking rate for trivalent aluminum (Al^{3+}) ions were faster than divalent Ca^{2+} ions. Furthermore, the beads cross-linked with Al^{3+} ions released the protein over a longer duration in simulated intestinal fluid, than those cross-linked with Ca^{2+} ions. Thus, the faster cross-linking rates with Al^{3+} ions could be very useful to load higher percentage of drug into the beads. This

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is why in this study trivalent Al^{3+} ion was used instead of Ca^{2+} ion for the preparation of blend hydrogel network beads for prolonged intestinal specific delivery of an anti-nociceptive drug, diclofenac sodium (DS).

DS is clinically used as a strong antinociceptive agent and used in the treatment of inflammation induced pain like arthritis. The biological half-life of diclofenac sodium is about 1.2–2.0 h; therefore it requires multiple dosing to maintain therapeutic drug-blood level. It causes gastric ulceration, if present in large doses in gastrointestinal tract. It is poorly soluble in an acidic pH [16] and rapidly soluble in alkaline pH [17]. Hence, the attempt to formulate a retard release form of diclofenac sodium can eliminate the need for multiple dosing with improved patient compliance and decreased side effects in the gastric environment.

Earlier the preparation of sodium alginate–methylcellulose (SAL-MC) blend microspheres for the controlled release of nifedipine was reported by single water-in-oil (w/o) emulsion crosslinking method using glutaraldehyde as a crosslinker in the presence of a strong acid to generate a hydrogel with moderate drug encapsulation efficiency [18] but in this paper we have described the formation of drug-loaded sodium alginate (SAL)–methyl cellulose (MC) blend hydrogel beads in presence of trivalent metal ion as a crosslinker by single water-in-water (w/w) emulsion gelation method in a complete aqueous environment by avoiding the hazards of using corrosive and toxic solvents with improved drug encapsulation efficiency. Hence, we formulated trivalent Al^{3+} ion-induced SAL–MC blend hydrogel beads by varying the total polymer concentration (2–3% w/v), gelation time (15–30 min) and cross-linker content (1–5% w/v) as well as evaluated their physicochemical properties by various evaluation parameters such as drug–polymer interaction study through Fourier transform infrared (FTIR) spectroscopy, the physical state of drug in the blend hydrogel matrix through differential scanning calorimetry (DSC) analysis and X-ray diffraction (XRD) analysis and the morphology of the blend hydrogel beads were evaluated by Scanning electron microscopy (SEM).

2. Experimental

2.1. Materials

DS was obtained from Yarrow Chemicals Products, Mumbai, India. SAL (F_{MG} = 0.17, M_W = 165 kDa, viscosity of 1% w/v solution at 25 °C is 5.5 ± 2 cps), MC (M_W = 1000–4000 kDa, viscosity of 2% w/v solution at 20 °C is 3000–5000 mPa s) and aluminum chloride hexahydrate ($AlCl_3{\cdot}6H_2O$) were purchased from Hi-Media Laboratories Private Limited, Mumbai, India. Tween 80 was supplied by SD Fine Chemicals Private Limited, Mumbai, India. $BaCl_2{\cdot}2H_2O$, $ZnCl_2{\cdot}2H_2O$, $FeCl_3{\cdot}6H_2O$ and $CaCl_2{\cdot}2H_2O$ were procured from Merck Specialties Private Limited, Mumbai, India. All other reagents were purchased commercially and used as received without further purification.

2.2. Preparation of blank SAL–MC blend hydrogel beads

SAL and MC blend hydrogel was prepared and the resulting gum solution (pH 7.0) was added drop wise through a 21-gauge flat-tipped hypodermic needle into slightly agitated 100 ml of aqueous metallic salt solutions containing 0.08% (w/v) Tween 80. Different metallic salts were used in different concentrations (w/v): $CaCl_2{\cdot}2H_2O$ (5% w/v), $BaCl_2{\cdot}2H_2O$ (5% w/v), $ZnCl_2{\cdot}2H_2O$ (5% w/v), $FeCl_3{\cdot}6H_2O$ (5% w/v) and $AlCl_3{\cdot}6H_2O$ (1% and 5% w/v). Gelation of the hydogel beads were carried out at two different periods of time (15–30 min). The ability of different salt solutions to form isolatable, self-standing gelled beads was examined. The beads were formed instantaneously in the presence of trivalent Al^{3+} ions at all concentrations. The beads were, then isolated by filtration, washed with double distilled water (2× 100 ml) and dried at 37 °C in a hot air oven to constant weight and kept in vacuum desiccators at room temperature until used.

2.3. Preparation of drug-loaded SAL–MC blend hydrogel beads

SAL–MC blend hydrogel beads containing DS were prepared by single w/w emulsion gelation method from an aqueous template containing MC as an emulsion stabilizer. Briefly, required amount of DS (30% w/w) was homogeneously dispersed in an aqueous solution of SAL–MC blend hydogel. The dispersion was added drop wise through a 21-gauze flat-tipped hypodermic needle into slightly agitated 100 ml of aqueous $AlCl_3$ solution containing 0.08% (w/v) Tween 80. Following a different incubation period of time (15–30 min), the beads were isolated by filtration, washed with double distilled water (2× 100 ml) and dried at 37 °C in a hot air oven and kept in vacuum desiccators until used. The blended hydrogel beads were prepared using the following variables:

1) The total polymer concentration varied from 2 to 3% w/v (SAL to MC weight ratio 1:1% w/v and 1.5:1.5% w/v respectively).
2) Concentration of $AlCl_3$ solution varied from 1 to 5% w/v.
3) The gelation time varied from 15 to 30 min.

The composition of SAL–MC blend hydrogel beads was shown in Table 1.

2.4. Surface morphology analysis

Dried placebo and drug-loaded SAL–MC blend hydrogel beads were examined under a SEM (JEOL-JSM-6360, JEOL Datum Ltd, Tokyo, Japan). SEM photographs were taken at an acceleration voltage of 18 kV and at a chamber pressure of 1.0 mm Hg. The samples were just placed on NEM TAPE (Nisshinem. Co. Ltd., Tokyo, Japan) adhesive paper and photographs were taken.

2.5. Bead size analysis

The size of dried drug loaded hydrogel beads was measured using an optical microscope (Olympus Model HB, India). A standard stage micrometer was used to calibrate the eyepiece micrometer. Dried beads were placed on a glass slide and the number of divisions of the calibrated eye piece was counted. A hundred beads were randomly selected from each formulation and the individual particle volume mean diameter was calculated based on this formula:

$$1\ \text{eyepiece division} = \left[\left(\frac{\text{No of stage micrometer divisions}}{\text{no of eyepiece micrometer division}}\right) \times 10\,\text{mm}\right]. \quad (1)$$

2.6. Drug–polymer interaction analysis

FTIR spectra of SAL, MC, pure drug (DS), blank beads and drug-loaded beads were recorded in a Shimadzu FTIR Spectrophotometer (Model FTIR-8400s, Shimadzu, Japan). Each sample was mixed with potassium bromide at a ratio of 1:9 and converted into pellet at 100 kg pressure using a hydraulic press pellet technique in the wave region of 400–4000 cm^{-1}.