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Xanthan–alginate composite gel beads: Molecular interaction and in vitro characterization

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Abstract

Xanthan gum (XG), a trisaccharide branched polymer, was applied to reinforce calcium alginate beads in this study. Composite beads consisting of XG and sodium alginate (SA) were prepared using ionotropic gelation method. Diclofenac calcium-alginate (DCA) beads incorporated with different amounts of XG were produced as well. Molecular interaction between SA and XG in the composite beads and the XG–DCA beads was investigated using FTIR spectroscopy. Physical properties of the XG–DCA beads such as entrapment efficiency of diclofenac sodium (DS), thermal property, water uptake, swelling and DS release in various media were examined. XG could form intermolecular hydrogen bonding with SA in the composite beads with or without DS. Differential scanning calorimetric study indicated that XG did not affect thermal property of the DCA beads. The DS entrapment efficiency of the DCA beads increased with increasing amount of XG added. The XG–DCA beads showed higher water uptake and swelling in pH 6.8 phosphate buffer and distilled water than the DCA beads. A longer lag time and a higher DS release rate of the XG–DCA beads in pH 6.8 phosphate buffer were found. In contrast, the 0.3%XG–DCA beads could retard the drug release in distilled water because interaction between XG and SA gave higher tortuosity of the bead matrix. However, higher content of XG in the DCA beads increased the release rate of DS. This can be attributed to erosion of small aggregates of XG on the surface of the DCA beads. This finding suggested that XG could modulate physicochemical properties and drug release of the DCA beads, which based on the existence of molecular interaction between XG and SA.

Keywords: Molecular interaction; Calcium alginate bead; Xanthan gum; Diclofenac sodium

1. Introduction

Sodium alginate (SA) is a sodium salt of alginic acid, a naturally occurring non-toxic polysaccharide found in marine brown algae. Alginate has been widely used as food and pharmaceutical additives, such as a tablet disintegrant, a thickening and a suspending agent. It contains two uronic acids, α-L-guluronic and β-D-mannuronic acids, and is composed of homopolymeric blocks and blocks with an alternating sequence (Draget, 2000). Gelation occurs by cross-linking of the uronic acids with divalent cations, such as Ca^{2+}. The primary mechanism of this gelation involves extended chain sequences which adapt a regular two-fold conformation and dimerize with specific chelation of Ca^{2+}, the so-called 'egg-box' structure (Grant et al., 1973). Each Ca^{2+} ion takes part in nine co-ordination link with an oxygen atom, resulting in three-dimensional network of calcium alginate. This phenomenon has been applied for preparing an alginate bead employed as a drug delivery system by dropping the drug-containing SA dispersion into a calcium chloride bath (Østberg et al., 1994; Sugawara et al., 1994). The calcium alginate beads could protect an acid-sensitive drugs from gastric juice, and the drug was consequently released from the beads in the intestine (Hwang et al., 1995; Fernández-Hervás et al., 1998). Thus, drug-loaded alginate beads are suitable for nonsteroidal anti-inflammatory drugs, which caused gastric irritation. Moreover, the alginate beads also exhibited a potential for a pulsatile release system of macromolecular drugs (Kikuchi et al., 1997).

Incorporation of some substances could modify physical properties of calcium-alginate beads. Insoluble substances, such as wax particles (Kim et al., 2005; Pongjanyakul et al., 2006)

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and magnesium aluminum silicate (Puttipipatkhachorn et al., 2005), could improve drug entrapment efficiency and retard drug release from the beads due to an increase in hydrophobic property and an interaction of silanol groups of magnesium aluminum silicate with carboxyl groups of alginate, respectively. Chitin, water-insoluble polymer, was added into the beads so as to retard drug release in pH 6.8 dissolution medium. This was owing to the formation of a complex between the carboxyl groups of alginate and the amino groups of chitin (Murata et al., 2002). Additionally, water-soluble polymers, such as chondroitin sulfate (Murata et al., 1996), konjac glucomannan (Wang and He, 2002), gelatin (Almeida and Almeida, 2004), and sodium starch glycolate (Puttipipatkhachorn et al., 2005), have been also used to reinforce calcium alginate beads because of complex formation of alginate with such water-soluble polymers.

Xanthan gum (XG) is an extracellular polysaccharide secreted by the microorganism *Xanthomonas campestris*. It is complex polysaccharide consisted of a primary chain of β-D-(1,4)-glucose backbone, which has a branching trisaccharide side chain comprised of β-D-(1,2)-mannose, attached to β-D-(1,4)-glucuronic acid, which terminates in a final β-D-mannose (Gruber, 1999). XG has been widely used in oral and topical formulations as a suspending and stabilizing agent (Wade and Weller, 1994), and a release sustaining agent in hydrophilic matrix tablets (Talukdar and Kinget, 1995; Sujja-areevath et al., 1996) and pellets (Santos et al., 2005). Elçin (1995) reported the combination of XG and SA to form spheres for entrapping enzyme in calcium chloride solution. An increase in XG content affected the water uptake of the spheres and this system could still retain the enzyme activity entrapped. However, no data reported about other physicochemical properties of this system. Recently, XG has been also used to combine with SA and zinc acetate in matrix tablets to enhance viscosity of swollen alginate matrix so that zinc ions could interact with alginate to form zinc alginate, resulting in retarding drug release (Zeng, 2004).

In the present study, we intended to prepare composite beads consisting of SA and XG, and diclofenac calcium alginate (DCA) beads reinforced with different amounts of XG by using ionotropic gelation method and using calcium ion as a cross-linking agent. Molecular interaction of XG and SA in the beads was investigated using FTIR spectroscopy. Moreover, physicochemical properties of the XG-DCA beads, such as entrapment efficiency of diclofenac sodium (DS), thermal behavior, water uptake, swelling, and drug release in various dissolution media were investigated as well.

2. Materials and methods

2.1. Materials

Diclofenac sodium (DS) was a gift from Biogena Ltd. (Limassol, Cyprus). Sodium alginate NF17 and xanthan gum were purchased from Srichand United Dispensary Co., Ltd. (Bangkok, Thailand) and Nam Siang Co., Ltd. (Bangkok, Thailand). All other reagents used in this study were of analytical grade and used as received.

2.2. Bead preparation

SA (1.5%, w/v) and XG (0.3, 0.5 and 1.0%, w/v) were dispersed in distilled water. XG–SA dispersion (80 ml) was dropped through a 1.2 mm inner diameter needle, from hypodermic syringe into 0.45 M calcium chloride solution (200 ml). The composite gel beads were cured in this solution for 1 h, then filtered, and rinsed several times with distilled water. The beads were dried at room temperature for 48 h, followed at 45 °C for 12–16 h. To prepare the DCA beads, DS (1%, w/v) was added into the dispersion and completely dissolved with a homogenizer for 5 min before cross-linking process, and then the preparation was proceeded as described above.

2.3. Rheological studies of composite dispersions

Rheological properties and viscosity of SA and XG–SA dispersions at the concentration used in Section 2.2 was studied using small sample adapter of Brookfield Digital Rheometer (Model DV-III, Brookfield Engineering Labs. Inc., Stoughton, MA) at 32 ± 1 °C. A rheogram of the samples was obtained by plotting between shear rate and shear stress from various revolution rates when a spindle (no. 34) was used. To characterize the type of flow of the samples, the following exponential formula was used (Martin, 1993):

$$F^N = \eta G \quad (1)$$

$$\log G = N \log F - \log \eta \quad (2)$$

where F, G, N, and η are shear stress, shear rate, exponential constant and viscosity coefficient, respectively. Rheological properties of 1% (w/v) XG dispersion could not be characterized by using this condition because it had too high viscosity.

2.4. Fourier transformed infrared (FTIR) spectroscopy

FTIR spectra of DS, SA, XG, calcium alginate beads and DCA beads were recorded with a FTIR spectrophotometer (Spectrum One, Perkin Elmer, Norwalk, CT) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1:100 and then pressed using a hydrostatic press at a pressure of 10 tons for 5 min. The disc was placed in the sample holder and scanned from 4000 to 450 cm^{-1} at a resolution of 4 cm^{-1}.

2.5. Particle size determination

Particle size of the DCA beads was determined using an optical microscope (Nikon, Japan). Two hundreds fifty beads were randomized and their Feret's diameters were measured and the mean diameters were calculated.

2.6. Drug content determination

Weighed DCA beads were immersed and dispersed in 100 ml of 0.067 M phosphate buffer at pH 6.8 for 12 h. Then, the solution was filtered, and the DS content was assayed by a