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# Enhanced entrapment efficiency and modulated drug release of alginate beads loaded with drug–clay intercalated complexes as microreservoirs

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ABSTRACT

Calcium alginate (CA) beads loaded with intercalated complexes of propranolol HCl (PPN) and magnesium aluminum silicate (MAS), which serve as microreservoirs, were prepared using an ionotropic gelation method. The surface and matrix morphology, drug entrapment efficiency, thermal behavior, mechanical properties, and PPN release of the CA beads were characterized. The results showed that the molecular interaction of MAS with PPN and sodium alginate (SA) resulted in PPN–MAS intercalated complex particles as microservoirs and denser matrix structure formation in the CA beads. The small particles of the PPN–MAS complexes were embedded on the surface and in the matrix of the CA beads, which was revealed using SEM and EDX. The PPN entrapment efficiency of the PPN–MAS complex-loaded CA beads was significantly higher than that of the PPN-loaded CA beads. Increased MAS content caused an increase in PPN entrapment efficiency, thermal stability, and the strength of the CA beads. Moreover, the PPN–MAS complexes in the CA beads could remarkably reduce the initial burst of PPN release as well as its release rate in both 0.1 M HCl and phosphate buffer at pH 6.8, depending on the MAS content added. Additionally, the PPN–MAS complex-loaded CA beads also produced a sustained release pattern of PPN in simulated gastro-intestinal conditions. In conclusion, the CA beads containing drug–clay intercalated complexes as microreservoirs could enhance drug entrapment efficiency, reduce initial burst release and modulate drug release. Furthermore, these beads represent a promising oral drug delivery system for highly water-soluble cationic drugs.

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## 1. Introduction

In oral drug delivery systems, the dosing of drugs in multiple-units has been found to have advantages over single-unit dosage forms (Bechgaard & Nielsen, 1978). Multiple-unit dosage forms are often composed of numerous particles that are contained in a tablet or a capsule. The small particles are mixed with the contents of the gastro-intestinal (GI) tract and are distributed over a large area. Therefore, high local concentrations of the drug are avoided, and the risk of local irritations is reduced. Additionally, multiple-units are less variable and less dependent on gastric transit time, which results in a reproducible bioavailability of the drug.

Small beads have been used as drug carriers to prepare oral multiple-unit capsules intended for sustained release dosage forms (Takada & Yoshikawa, 1999). These beads can be prepared using an ionotropic gelation method, where polysaccharides are cross-linked to form an insoluble gel bead. Sodium alginate (SA), which is a naturally occurring non-toxic polysaccharide found in marine brown algae, is one of the polysaccharides employed to fabricate small beads. Gelation of SA occurs when uronic acids (α-L-guluronic and β-D-mannuronic acids) are cross-linked with divalent cations, such as calcium ions (Draget, 2000). Gelation occurs when the extended chain sequences of these acids adopt a regular twofold conformation and dimerize by chelating calcium, forming the so-called 'egg-box' structure (Grant, Morris, Rees, Smith, & Thom, 1973). Each calcium ion takes part in nine coordination bonds with each oxygen atom, resulting in a three-dimensional network of calcium alginate (CA). This phenomenon has been applied to the preparation of CA beads for use as a drug delivery system, by dropping the drug-containing SA dispersion into a calcium chloride bath (Østberg, Lund, & Graffner, 1994; Sugawara, Imai, & Otagiri, 1994). The CA beads could protect an acid-sensitive drug from gastric juice, and the drug was consequently released from the beads in the intestine (Fernández-Hervás, Holgado, Fini, & Fell, 1998; Hwang, Rhee, Lee, Oh, & Kim, 1995).

A low entrapment efficiency of water-soluble drugs in the CA beads is a problem for developing CA beads as a drug delivery system (Lee, Min, & Cui, 1999). This is largely due to the leakage of drug molecules from the wet beads during the cross-linking process. To solve this problem, the incorporation of water-soluble polymers, such as chondroitin sulfate (Murata, Miyamoto, & Kawashima, 1996), konjac glucomannan (Wang & He, 2002), gelatin (Almeida

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& Almeida, 2004), sodium starch glycolate (Puttipipatkhachorn, Pongjanyakul, & Priprem, 2005), and xanthan gum (Pongjanyakul & Puttipipatkhachorn, 2007a), have been used to improve drug entrapment efficiency by reinforcing CA beads due to complex formation of SA with such water-soluble polymers. An alternative approach involves the use of water insoluble materials for reinforcement of the CA beads. Due to the formation of a complex between the carboxyl groups of SA and the amino groups of chitin, water insoluble chitin has previously been added to the beads to retard drug release (Murata, Tsumoto, Kofuji, & Kawashima, 2003). Furthermore, complexes formed between an amine drug and a synthetic cation exchange resin have been applied as a drug carrier in the CA beads (Halder, Maiti, & Sa, 2005).

Magnesium aluminum silicate (MAS) is a mixture of natural smectite clays, specifically montmorillonite and saponite (Kibbe, 2000; Viseras, Aguzzi, Cerezo, & Lopez-Galindo, 2007). MAS has a layered silicate structure, and the surface of the silicate layer contains numerous silanol groups (SiOH), which are able to form hydrogen bonds with other substances (Gupta, Vanwert, & Bogner, 2003). The separation of the layered structures occurs when these clays are hydrated in water, and the weakly positively charged edges and the negatively charged faces of MAS are presented. Due to the interaction of the silanol groups of MAS with the carboxyl groups of SA, MAS has been used to improve the physical properties of CA beads (Puttipipatkhachorn et al., 2005). Recently, MAS was used as an adsorbent for amine drugs to form drug-MAS complexes. A simultaneous formation of small particle drug-MAS complexes occurred when a MAS dispersion and a drug solution were mixed, due to electrostatic interactions between these materials (Rojtanatanya & Pongjanyakul, 2010; Suksri & Pongjanyakul, 2008). Thus, the drug-MAS complexes obtained provided a sustained release pattern of the drug (Pongjanyakul, Khunawattanakul, & Puttipipatkhachorn, 2009; Rojtanatanya & Pongjanyakul, 2010). Therefore, it is possible that the drug-MAS complexes can be added to a SA dispersion before the cross-linking process to prepare CA beads that contain drug-MAS complexes, which serve as drug microreservoirs. The resulting complexes may enhance drug entrapment efficiency and modulate drug release.

Propranolol HCl (PPN), a secondary amine compound with high water solubility, was the first β-adrenoceptor-blocking drug to achieve wide therapeutic use for the treatment of angina and hypertension (Dollery, 1991). Due to the short half-life of PPN (3.9 h) (Dollery, 1991), PPN has been selected as a drug candidate for developing multiple-unit sustained release dosage forms (Paker-Leggs & Neau, 2009). Moreover, PPN has previously been reported to form small particle complexes with MAS (Rojtanatanya & Pongjanyakul, 2010). Therefore, the aim of this study was to prepare and investigate CA beads loaded with PPN–MAS complexes that serve as microreservoirs. The SA dispersions containing PPN–MAS complexes formed with different MAS concentrations were prepared and characterized according to particle size, zeta potential, and the amount of PPN adsorbed prior to cross-linking using different concentrations of calcium chloride. The surface and matrix morphology of the PPN–MAS complex-loaded CA beads were investigated using a scanning electron microscopy and energy dispersive X-ray analysis. Moreover, PPN entrapment efficiency, thermal behavior, mechanical properties, and PPN release of the beads were examined.

## 2. Materials and methods

### 2.1. Materials

MAS (Veegum®HV, Lot No. V-GHV-5H-367) and PPN (Batch No. M080115) were purchased from the R.T. Vanderbilt Company, Inc. (Norwalk, CT, USA) and Changzhou Yabang Pharmaceutical Co., Ltd. (Jiangsu, China), respectively. SA (Manugel®DMF, Batch No. 991131) was obtained from ISP Thailand Ltd. (Bangkok, Thailand). All other reagents used were of analytical grade and used as received.

### 2.2. Preparation of PPN–MAS complex dispersions

A 4% (w/v) MAS suspension was prepared using hot water and cooled to room temperature prior to use. Next, the 4% (w/v) MAS suspension in 4.7, 9.4 or 18.8-ml volumes were mixed with 25 ml of the 1% w/v PPN deionized water solution in a beaker, and then the PPN–MAS dispersions were adjusted to a final volume of 50 ml to yield MAS concentrations of 0.38, 0.75, or 1.5% (w/v), respectively. The pH of all dispersions was approximately 7.6, which was measured using a pH meter (Ion Analyzer 250, Corning, USA). Next, the dispersions were incubated at 25 °C for 24 h to allow PPN adsorption onto the MAS particles to equilibrate and obtain complete formation of the PPN–MAS complexes. The PPN–MAS complex dispersions were investigated as described in Section 2.4.

### 2.3. Preparation of SA dispersions with PPN–MAS complexes

SA (0.75 g) was gently added to the PPN–MAS complex dispersions, which had been incubated at 25 °C for 24 h. The SA dispersions with PPN–MAS complexes were incubated again at 25 °C for 24 h. Then, the dispersions obtained were characterized and used to prepare the CA beads.

### 2.4. Characterization of PPN–MAS complex dispersions

#### 2.4.1. Microscopic morphology studies

The morphology of the PPN–MAS complexes in the dispersions was investigated using an inverted microscope (Eclipse TS100, Nikon, Japan) and imaged using a digital camera (Coolpix 4500, Nikon, Japan).

#### 2.4.2. Particle size determination

The sizes of the MAS particles and the PPN–MAS complexes in the dispersions were measured using a laser diffraction particle size analyzer (Mastersizer2000 Model Hydro2000SM, Malvern Instrument Ltd., UK). The samples were dispersed in 70 ml of deionized water in a small volume sample dispersion unit and stirred at a rate of 50 Hz for 30 s prior to measurement. The particle sizes in terms of volume weighted mean diameter were then recorded.

#### 2.4.3. Zeta potential measurement

The zeta potential of the MAS particles and the PPN–MAS complexes in the dispersions were measured using a laser Doppler electrophoresis analyzer (Zetasizer Model ZEN 2600, Malvern Instrument Ltd., UK). The samples were kept at 25 °C, and the dispersions were diluted using deionized water to obtain the appropriate concentrations (count rates >20,000 counts per second) prior to measurement.

#### 2.4.4. Determination of PPN adsorbed onto MAS

The clear supernatants of the dispersions were collected, diluted with deionized water, and then filtered through a 0.45-μm cellulose acetate membrane. The amount of PPN in the supernatants was analyzed using an UV–vis spectrophotometer (Shimadzu UV1201, Japan) at a wavelength of 289 nm. The amount of PPN adsorbed onto the MAS was calculated as the difference between the amount of PPN added and the amount of PPN in the supernatant.

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