The Thai Journal of Pharmaceutical Sciences

Volume 36
Issue 0 *supplement issue*

Article 31

1-1-2012

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DEVELOPMENT OF CALCIUM ALGINATE FLOATING BEADS PREPARED BY IONOTROPIC GELATION TECHNIQUE

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KEYWORDS: Calcium alginate floating beads, Alginate, Floating properties, Sustained drug release, Ionotropic gelation

INTRODUCTION

The drug bioavailability of pharmaceutical dosage forms is influenced by various factors. One of the important factors is the gastric residence time (GRT) of these dosage forms[1]. Short GRT can result in incomplete drug release from the drug delivery system (DDS) in the absorption zone (stomach and upper part of small intestine), leading to a diminished efficacy of the administered dose[2]. Therefore, different approaches have been proposed to retain the dosage form in the stomach. Floating drug delivery system (FDDS) is one of gastroretentive dosage forms which could prolong GRT to obtain sufficient drug bioavailability[2, 3]. The system basically floats in the gastric fluid because of its lower bulk density compared to that of the aqueous medium. FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine[4]. It is also useful for drugs that act locally in the proximal part of gastrointestinal (GI) tract such as antibiotic administration for *Helicobacter pylori* eradication in the treatment of peptic ulcer[5] and for drugs that are poorly soluble or unstable in the intestinal fluid[6]. Sodium alginate (SA) is a sodium salt of alginic acid, a naturally occurring non-toxic polysaccharide found in brown algae. Alginate has been widely used as food and pharmaceutical additives, such as tablet disintegrant and gelling agent. It contains varying amounts of (1–4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues, and is composed of homopolymeric blocks and blocks with an alternating sequence[7, 8]. Gelation occurs by cross-linking of the uronic acids with divalent cations, such as Ca^{2+}. This phenomenon has been used to prepare an alginate bead for drug delivery system. The formation of calcium alginate beads by ionotropic gelation was achieved by dropping the drug-containing SA dispersion into a calcium chloride bath[9]. In this study, calcium alginate floating beads prepared by ionotropic gelation technique was developed for gastroretentive drug delivery systems. The obtained beads were evaluated for bead size, entrapment efficiency, floating properties and drug release based on formulation variables such as alginate type, drug type and size of needle.

MATERIALS AND METHODS

Materials

Two types of sodium alginate with different M/G ratios (Manucol® DMF (MCDMF), Batch No. 631254, and Manugel® DMB (MGDMB), Batch No. 771131, IPS Technologies, USA) were used. Anhydrous theophylline (Lianyungang Foreign Trade Corp., China), metronidazole HCl (P.C. Drug Center, Bangkok, Thailand), calcium chloride dihydrate (Merck, Germany), and glutaraldehyde (Ajax Finechem, Australia) were used as received. Light mineral oil and all other chemicals were standard pharmaceutical grade.

Preparation of calcium alginate floating beads

The calcium alginate floating beads were prepared by ionotropic gelation method. Two grams of sodium alginate were dissolved in water with agitation. Ten grams of light mineral oil were added to the solution to make 100-g mixtures and homogenized using a high speed homogenizer (IKA®-Werke, Yellowline DI25 basic, GmbH & Co.KG, Germany) , at 8000 rpm for 5 min. The drugs (2 g) were dispersed in an emulsion of oil and sodium alginate mixture. The dispersion was then extruded, using a needle, into 0.34M calcium chloride which was gentle stirred at room temperature. The distance from the needle to the surface of calcium chloride solution was fixed to 5 cm. The gel beads formed were allowed to stand in the solution for 20 min before being separated and washed with distilled water. The beads were dried at 40 °C for 12 h.

Evaluation of calcium alginate floating beads

1. Particle size of gel beads

The mean diameter of 20 dried beads was determined by optical microscopy (BH-2, Olympus. Japan). The microscope eyepiece was fitted with a micrometer by which the size of the beads could be determined.

2. Floating properties of the gel beads

Floating properties of the gel beads was studied at 37 ± 0.5 °C by soaking 50 beads in 150 mL of 0.1 N HCl solution (pH 1.2). Each vessel was shaken at 100 rpm using an Environmental Shaker-Incubator (ES-20, BiOSAN, Gibthai Co. Ltd., Thailand) The percentage of floating samples was measured by visual observation.

3. Determination of entrapment efficiency (EE) and drug release

Weighed calcium alginate floating beads were immersed and dispersed in 100 ml of 2%w/v sodium citrate for 12 h. The solution was then filtered, and the drug content was assayed by UV spectrophotometer (Varian, Australia) in the medium at 270.00 and 277.00 nm for theophylline and metronidazole HCl, respectively. The determinations were made in triplicate. The ratio of the actual drug content in the beads to the theoretical drug content was termed the entrapment efficiency (EE). The drug release studies were carried out using USP dissolution apparatus II (Vankel Model VK-7000, Vankel, USA) equipped with paddles which was operated at the speed of 50 rpm. Nine hundred milliliters of 0.1 N HCl (pH 1.2), as the dissolution medium, was placed in the glass vessel, assembled the apparatus, and equilibrated the dissolution medium to 37±0.5 °C. The amount of drug release was measured at predetermined time intervals and was then assayed with UV spectrophotometer using a 1.0 cm quartz cell. Each in vitro release study was performed in triplicate.

RESULTS

The calcium alginate floating beads prepared by ionotropic gelation technique was developed for gastroretentive drug delivery systems. The effects of formulation variables such as alginate type, drug type and size of needle were investigated. Alginate type did not affect bead size significantly (Table 1). However, the beads prepared by MGDMB alginate showed lower drug entrapment efficiency (Table 1) and slower drug release (Figure 1) comparing to those prepared by using MCDMF alginate. The beads containing theophylline as a model drug had slightly bigger bead size with higher entrapment efficiency and slower drug release than those containing metronidazole HCl as shown in Table 1 and Figure 2. Increasing needle size increased bead size, drug entrapment efficiency and decreased drug release (Table 1 and Figure 3). All formulations with 2%w/w sodium alginate, 2%w/w drug and 10%w/w light mineral oil showed immediate floating and maintained the buoyancy over a period of 12 hours.

Table 1 Mean diameter (n = 20) and entrapment efficiency (n = 3) of the calcium alginate floating beads at different formulation variables.

Variables	Mean diameter (mm±SD)	EE (%±SD)
MCDMF		
Metronidazole HCl		
Needle no. 18 (1.2 mm)	1.62 ± 0.06	45.24 ± 0.14
Theophylline		
Needle no. 18 (1.2 mm)	1.76 ± 0.06	115.48 ± 0.29
Needle no. 22 (0.7 mm)	1.34 ± 0.04	39.03 ± 1.81
MGDMB		
Metronidazole HCl		
Needle no. 18 (1.2 mm)	1.61 ± 0.04	37.96 ± 1.15
Theophylline		
Needle no. 18 (1.2 mm)	1.70 ± 0.08	101.04 ± 0.37
Needle no. 22 (0.7 mm)	1.32 ± 0.06	29.77 ± 1.11

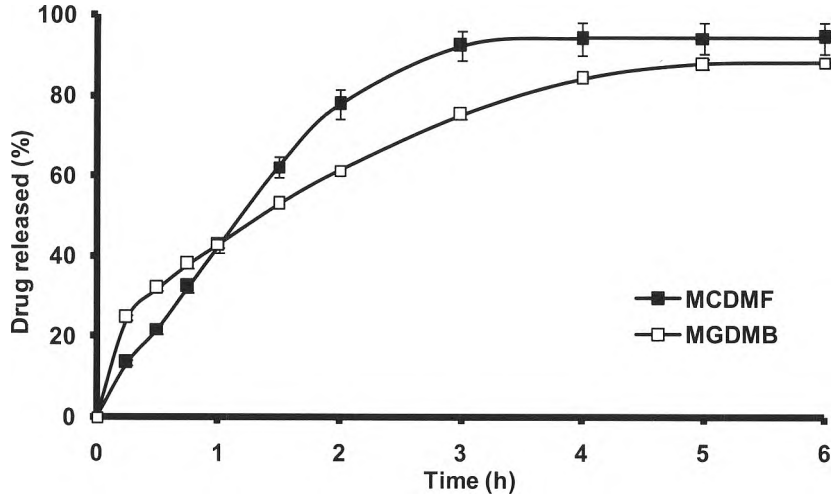

Figure 1 Effect of polymer type on theophylline release of calcium alginate floating beads (needle no. 18).

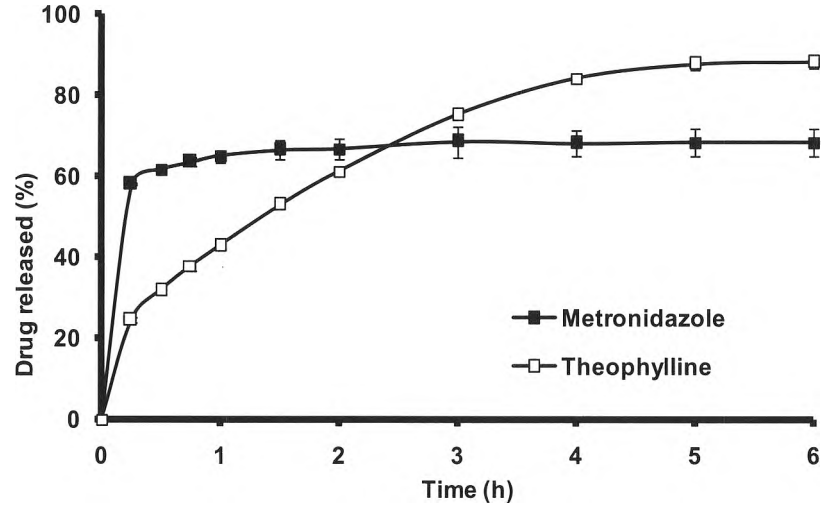

Figure 2 Effect of drug type on drug release of calcium alginate floating beads (MGDMB, needle no. 18).

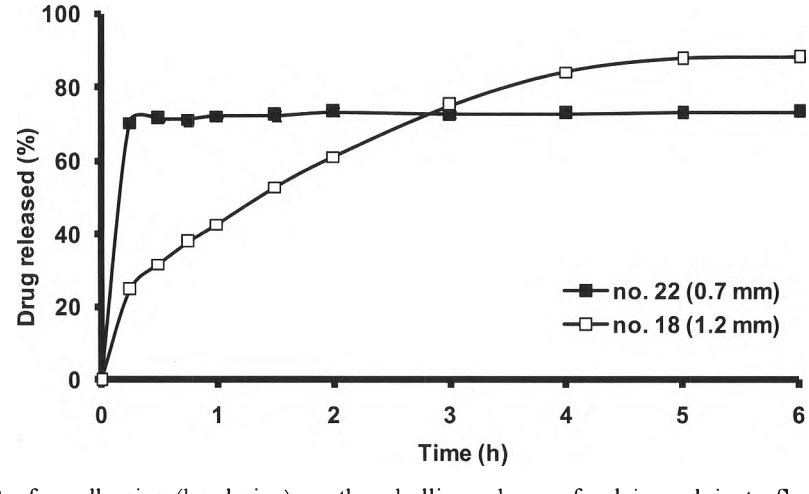

Figure 3 Effect of needle size (bead size) on theophylline release of calcium alginate floating beads (MGDMB, needle no. 18).

DISCUSSION

The calcium alginate floating beads prepared by ionotropic gelation technique was developed for gastroretentive drug delivery systems. An aqueous solution or dispersion of alginate was extruded into calcium chloride solutions and gel beads were formed instantaneously by ionotropic gelation in which intermolecular cross-links were formed between the divalent calcium ions and the negatively charged carboxyl groups of alginate molecules. The effects of formulation variables such as alginate type, drug type and size of needle were investigated. Alginate type did not affect bead size significantly. However, the beads prepared by MGDMB alginate showed lower drug entrapment efficiency and slower drug release comparing to those prepared by using MCDMF alginate. The possible explanation is MGDMB alginate can form higher gel strength with calcium ion because it has higher fraction of G blocks which is a key structural feature contributing to gel strength [10]. The beads containing theophylline as a model drug had slightly bigger bead size with higher entrapment efficiency and slower drug release than those containing metronidazole HCl because of the lower solubility of theophylline. Increasing needle size increased bead size, drug entrapment efficiency and decreased drug release. The smaller bead size led to the higher surface area and resulted in increasing drug release. The calcium alginate beads developed in this study showed immediate floating and were able to maintain buoyancy over a period of 12 hours with sustained drug release. The results suggested that this floating bead is a promising candidate for a gastroretentive drug delivery system which would be advantageous for drugs with an absorption window in the stomach or in the upper small intestine, as well as for drugs acting locally in the proximal part of the GI tract and poorly soluble or unstable drugs in the intestinal fluids.

CONCLUSION

The calcium alginate floating bead prepared by ionotropic gelation technique was developed. The formulation variables affected the size, entrapment efficiency and drug release of the system. The system exhibited immediate floating with maintained buoyancy over a period of 12 hours as well as a sustained release behavior. The results suggested that the calcium alginate floating bead developed in this study is a promising candidate for a gastroretentive drug delivery system.

ACKNOWLEDGMENTS

This work was financially supported by Research Funds from Yearly Budget, Naresuan University (R2555B006), Thailand.

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