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Biphasic Release Characteristics of Dual Drug-loaded Alginate Beads

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The dual drug-loaded alginate beads simultaneously containing drug in inner and outer layers were prepared by dropping plain (single-layered) alginate beads into $CaCl_2$ solution. The release characteristics were evaluated in simulated gastric fluid for 2 h followed by intestinal fluids thereafter for 12 h. The surface morphology and cross section of dual drug-loaded alginate beads was also investigated using scanning electron microscope (SEM). The poorly water-soluble ibuprofen was chosen as a model drug. The surface of single-layered and dual drug-loaded alginate beads showed very crude and roughness, showing aggregated particles, surface cracks and rough crystals. The thickness of dual drug-loaded alginate beads surrounded by outer layer was ranged from about 57 to 329 μm. The distinct chasm between inner and outer layers was also observed. In case of single-layered alginate beads, the drug was not released in gastric fluid but was largely released in intestinal fluid. However, the release rate decreased as the reinforcing Eudragit® polymer contents increased. When the plasticizers were added into polymer, the release rate largely decreased. The release rate of dual drug-loaded alginate beads was stable in gastric fluid for 2 h but largely increased when switched in intestinal fluid. The drug linearly released for 4 h followed by another linear release thereafter, showing a distinct biphasic release characteristics. There was a difference in the release profiles between single-layered and dual drug-loaded alginate beads due to their structural shape. However, this biphasic release profiles were modified by varying formulation compositions of inner and outer layer of alginate beads. The release rate of dual drug-loaded alginate beads slightly decreased when the outer layer was reinforced with Eudragit® RS100 polymers. In case of dual drug-loaded alginate beads with polymer-reinforced outer layer only, the initial amount of drug released was low but the initial release rate (slope) was higher due to more swellable inner cores when compared to polymer-reinforced inner cores. The current dual drug-loaded alginate beads may be used to deliver the drugs in a time dependent manner.

Key words : Dual drug-loaded alginate beads, Scanning electron microscope, Biphasic release, Polymer-reinforced

INTRODUCTION

Various types of sustained release preparations that permit constant plasma concentration have been well-recognised. However, the sustained release is not always the optimal choice because nearly all functions of the body, including pharmacokinetics and pharmacodynamics in clinical situations displays significant daily variation and biological rhythms (Lemmer, 1991; Lamberg, 1991; Giunchedi *et al.*, 1991; Lin *et al.*, 1996). For these reasons, an intelligent drug delivery system can be designed which delivers not only in a controlled release but also in a circadian rhythmic pattern so that pharmacotherapy must be optimised by adapting the drug release to therapeutic needs or biological rhythms (Narisawa *et al.*, 1995; Lin *et al.*, 1996). The pharmaceutical dosage forms that mimic biological rhythms in the body have been widely investigated, including sigmoidal release system, pulsatile release tablet, time-controlled explosion system and pulsincap (Giunchedi *et al.*, 1991; Narisawa *et al.*, 1995). Recently, we investigated biphasic release characteristics of dual drug-loaded hydroxypropylmethylcellulose matrix tablet using drug-containing aqueous polymeric coatings to deliver the melatonin in a time dependent manner (Lee and Ryu, 1997). It implies that the dual drug-loaded preparations simultaneously contain drug in inner and outer layers.

Sodium alginate, a polysaccharide salt, is gelled when contacted with calcium and multivalent cations (Lee *et al.*, 1996). Alginate xero-gels are stable in low pH

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solution but swelled in weak basic solution followed by disintegration and erosion. The alginate beads have been investigated as a drug carrier and vehicle for the controlled delivery of low molecules or macromolecules (Lin and Ayres, 1992; Kim and Lee, 1992; Tomida *et al.*, 1993; Sugawara *et al.*, 1994; Lee and Min, 1996; Shin *et al.*, 1996). The gelling strength and release fashion of alginate beads may be closely dependent on the type and concentration of gel-inducing ions and alginate grades, gelling time, curing time, release testing medium, drug selected, size of beads and formulation compositions (Yotsuyanagi *et al.*, 1987; Kim and Lee, 1992; Ostberg *et al.*, 1994; Hwang *et al.*, 1995; Lee and Min, 1995; Lee *et al.*, 1996; Lee and Min, 1996; Shin *et al.*, 1996).

The purpose of present work was to prepare single-layered and dual drug-loaded alginate beads and to evaluate release characteristics of drug in simulated gastric fluid followed by intestinal fluids as a preliminary study. The poorly water-soluble ibuprofen was chosen as a model drug. The surface morphology and cross section of dual drug-loaded alginate beads were also investigated using SEM.

MATERIALS AND METHODS

Materials

Sodium alginate was purchased from Junsei (Tokyo, Japan). The ibuprofen as a model drug was obtained from Chong Kun Dang (Seoul, Korea). Eudragit® RS 100 and S100 were kindly supplied by courtesy of Ducwoo (Seoul, Korea). Aluminium tristearate (AT) and polyethylene glycol 400 (PEG 400) were purchased from Katayama (Osaka, Japan). Methanol was purchased from EM (New Jersey, USA). All other chemicals were of reagent grade and used without further purification.

Preparation of single-layered and dual drug-loaded alginate beads

Sodium alginate (1 g) was completely dispersed in deionized water (50 ml). The drug (1 g) and/or excipients such as polymers, AT and PEG400 were added into above alginate solution and mixed for 2 h. The AT and PEG400 were added into polymer as plasticizers to improve the dispersion and elasticity as reported previously (Lee and Min, 1995; 1996). The resulting mixtures were dropped into each 0.2 M $CaCl_2$ solution using a pipette (10 ml) for 15 min and then further cured for 15 min. The prepared alginate beads were promptly rinsed twice with deionized water, and then dried in an oven at 50°C over 18 h. The dried alginate beads were then weighed.

For the preparation of dual drug-loaded alginate beads simultaneously containing drug in inner and outer layers, the single-layered alginate beads as an inner core were embedded in 50 ml of alginate solution containing drug. The excipients such as polymers, AT and PEG400 were added to drug-containing alginate solution when necessary. The dual drug-loaded alginate beads were formed by continuously dropping the bubble-free dispersions through a disposable syringe (19 gauge) into 0.2 M $CaCl_2$ for 15 min. The gelled beads were further cured for 15 min, filtered, washed twice with deionized water and dried at 50°C for 12 h. The detailed formulation compositions of single-layered and dual drug-loaded alginate beads are given in Table I.

Scanning electron microscope (SEM) of alginate beads

The dried samples were coated with gold using a Auto Coating Unit E5200 coater (London, England) for about 2 min to obtain about 200 Å of the coating thickness. Surface morphologies and cross sectional view of the uncoated and coated alginate beads were characterized. Micrographs were taken at an accelerating voltage of 20 kV with a Cambridge Stereo Scan 200 (London, England).

Determination of drug contents in alginate beads

About 70 mg of alginate beads were exactly weighted

Table I. Formulation compositions of single-layered and dual drug-loaded alginate beads

Composition (g)	Single-layered					Dual Drug-loaded					
	S1	S2	S3	S4	S5	D-1		D-2		D-3	
						O[a]	I[b]	O	I	O	I
Sodium alginate	1	1	1	1	1	1	1	1	1	1	1
Eudragit® S100	0	2	4	0	0	0	4	0	4	0	0
Eudragit® RS100	0	0	0	3	5	0	0	2	0	5	0
AT	0	0	0	0.1	0.25	0	0	0.1	0	0.25	0
PEG	0	0	0	10	10	0	0	10	0	10	0
Water	50	50	50	40	40	50	50	40	50	40	0
Drug	1	1	1	1	1	1	1	1	1	1	1

[a]The formulation composition of outer layer of dual drug-loaded alginate beads. [b]The formulation composition of inner core of dual drug-loaded alginate beads.

and completely dissolved in 500 ml of the phosphate buffer solution (pH 7.4). Thereafter, the resulting turbid solution was filtered through a 0.45 μm millipore membrane filter. The concentration of drug after the proper dilution was determined using UV/VIS spectrophotometer at the wavelength of 265 nm.

In vitro release studies of alginate beads

The *in vitro* dissolution test of drug from alginate beads formulated was performed in triplicate using the dissolution apparatus type I (Fine scientific DST 600A, Seoul, Korea) at the stirring speed of 100 rpm at 37±0.5°C in the 500 ml of enzyme-free simulated gastric fluids (pH 1.4±0.1, NaCl-HCl buffer solution) for 2 followed by 500 ml of enzyme-free simulated intestinal fluids (pH 7.4±0.1, phosphate buffer solution) for 12 h. The simulated gastric and intestinal fluids were prepared according to the method of Lee and Lee (1995). The dissolution samples (1 ml) were collected at a given interval with replacement of equal volume of dissolution media, and were filtered through a 0.45 μm millipore membrane filter. The concentration of drug released from alginate beads as a function of time was determined using a UV/VIS spectrophotometer as mentioned previously.

The release rate (%/h) of drug-loaded alginate beads was obtained from the linear portion of the percentages of drug released against time using linear regression analysis.

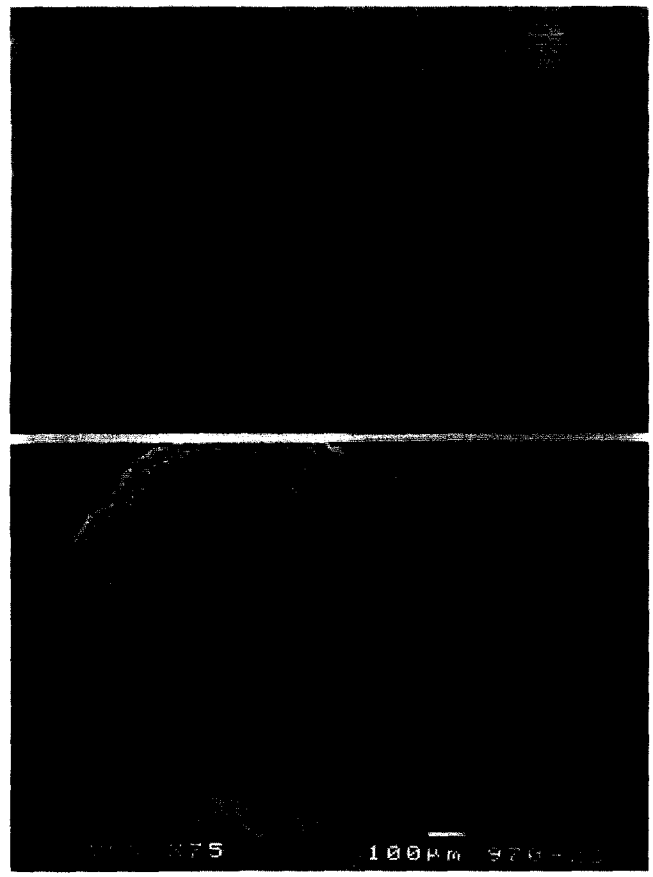

Fig. 1. Surface (top) and cross sectional view (bottom) of dual drug-loaded alginate beads using SEM.

RESULTS AND DISCUSSION

SEM of alginate beads

The surface morphology of single-layered alginate beads was previously reported (Lee and Min, 1996). The surface of single-layered alginate beads showed very crude and roughness as viewed at two different magnifications. The surface cracks and rough crystals of single-layered alginate beads were also visualized. On the other hand, the surface and cross sectional view of dual drug-loaded alginate beads using SEM is shown in Fig. 1. The surface of dual drug-loaded was also very crude and rough, showing in aggregated particles and crystals or pores. It was evident that the core beads were surrounded by the outer layers. The thickness of the dual drug-loaded alginate beads surrounded by outer layer was ranged from about 57 to 329 μm and was not uniform, maybe due to unequal distribution of the outer layer solution when dropped inner cores into $CaCl_2$ solution. The distinct chasm between inner and outer layers was also observed. It suggested that the chasm might be avoided by adding binders in the drug-containing alginate solution. The plasticization of the outer solution containing polymers could be also considered. The shape and formulation compositions of the inner and outer alginate beads appears to be important to modify the release rate.

Release characteristics of alginate beads

The pharmacological and pharmacokinetic activity of many drugs are highly dependent on the time of day, showing circadian variation of activity. A proposed circadian variation of pharmacological activity or response as a function of time of day is drawn in Fig. 2. In case of drug with circadian rhythmic variations, the release rate must be modified to simulate the pharmacological activity or response assuming that the continuous absorption of drug through gastrointestinal tract and *in vitro*/*in vivo* characteristics are correlated (Lemmer, 1991; Lamberg, 1991). The idealised release profiles of drugs with circadian rhythms as a function of time of day is also drawn in Fig. 3. For example, the release rate of drug with maximal activity during the daytime needs to be reduced to coincide with *in vivo* characteristics when compared to night time and vice versa.

Release profiles of single-layered alginate beads in the simulated gastric fluid followed by the intestinal fluid are given in Fig. 4. Unlike the melatonin, the

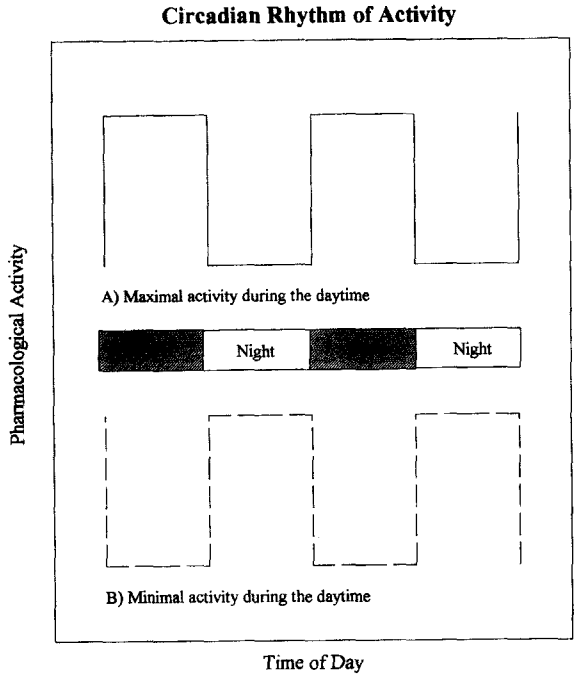

Fig. 2. A proposed circadian variation of pharmacological activity or response as a function of time of day.

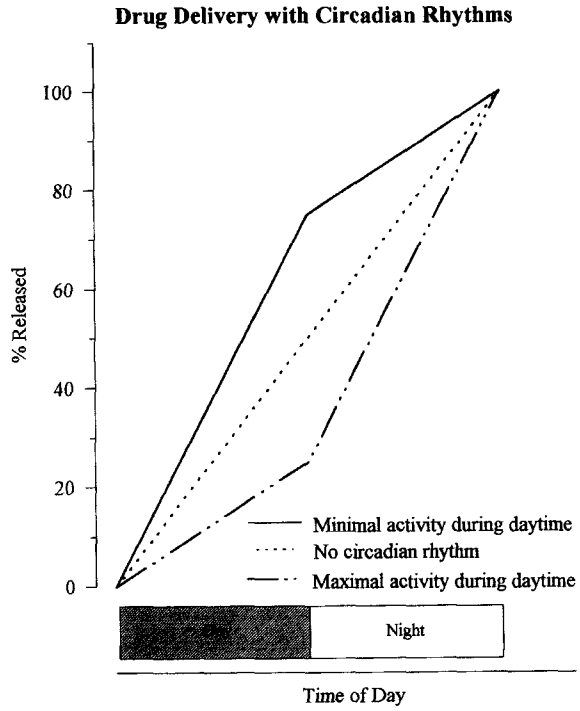

Fig. 3. The idealised release profiles of drugs with circadian rhythms as a function of time of day.

poorly water-soluble ibuprofen was not released in the gastric fluid because of low solubility and stability of alginate beads in acidic environment as reported previously (Lee and Min, 1995; 1996). The release rate was then highly increased in the intestinal fluid due to the solubility of model drug, and the increased

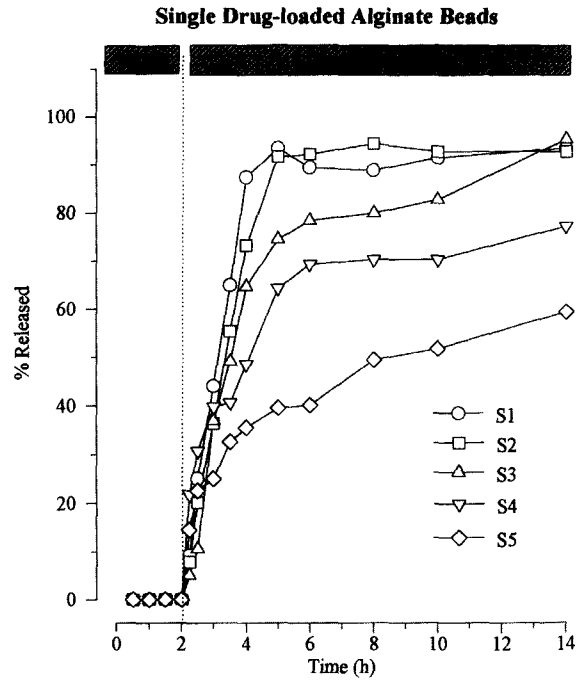

Fig. 4. Release profiles of single-layered alginate beads in the simulated gastric fluid for 2 h followed by the intestinal fluid (n=3).

swelling and erosion rate of the beads. However, the release rate decreased as the reinforcing Eudragit® polymer contents increased. When the AT and PEG 400 as plasticizers were added into polymer, the release rate largely decreased. It is known that the swelling and disintegration of alginate beads can be changed by the physicochemical properties of sodium alginate and drug, dissolution medium, affinity of calcium to phosphate and sodium/calcium exchange or excipients added (Ostberg *et al.*, 1994; Lee and Min, 1995; Hwang *et al.*, 1995; Shin *et al.*, 1996; Lee and Min, 1996).

Due to the swelling and erosion behaviors of alginate beads, the release rate can be modified by changing the formulation compositions and shape of the beads. Recently, the dual walled beads containing stearyl alcohol microspheres using sodium alginate or chitosan were prepared to modify the release rate (Lee *et al.*, in press). In addition, we investigated biphasic release characteristics of dual drug-loaded HPMC matrix tablet using drug-containing aqueous polymeric coatings to deliver the drug in a time-dependent manner (Lee and Ryu, 1997). Likewise, the dual drug-loaded alginate beads simultaneously containing drug in inner and outer layers of the alginate beads were prepared by dropping alginate beads embedded in drug-containing sodium alginate dispersion into $CaCl_2$ solution. Release profiles of dual drug-loaded alginate beads in the simulated gastric fluid followed by the intestinal fluid are given in Fig. 5. Like the single-layered alginate

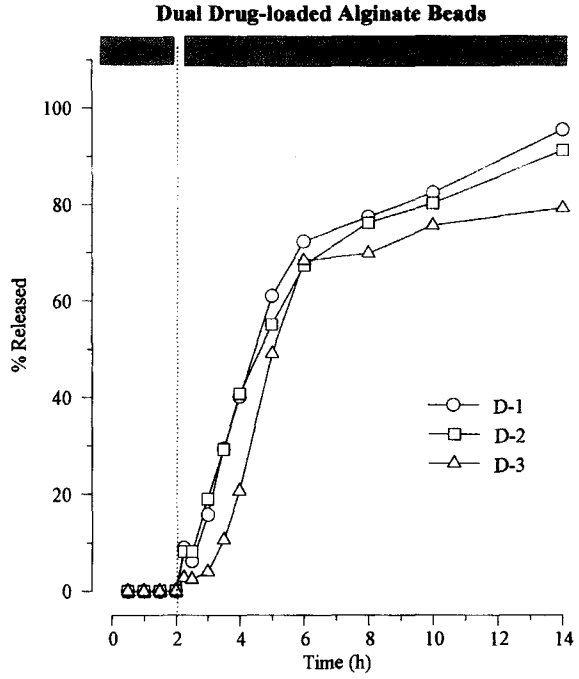

Fig. 5. Release profiles of dual drug-loaded alginate beads in the simulated gastric fluid for 2 h followed by the intestinal fluid (n=3).

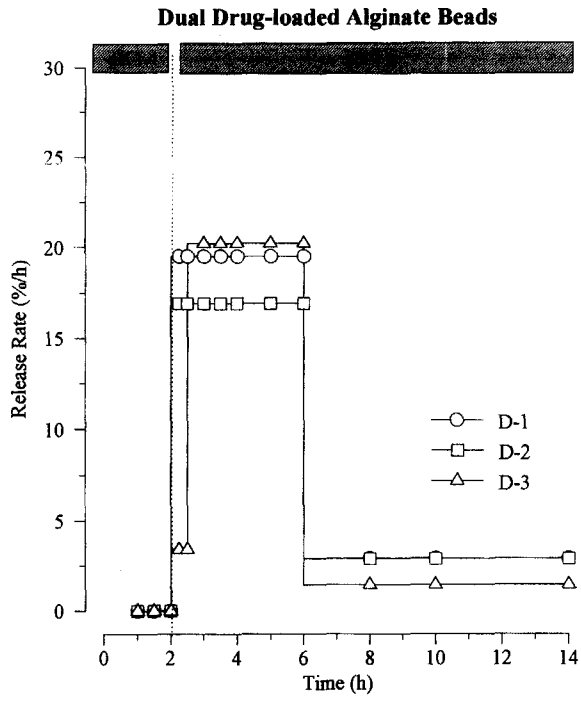

Fig. 6. The calculated release rate of dual drug-loaded alginate beads in the simulated gastric fluid for 2 h followed by the intestinal fluid (n=3).

beads, the release rate of dual drug-loaded alginate beads was stable in gastric fluid for 2 h but largely increased when switched in intestinal fluid. The drug linearly released for 4 h in the intestinal fluid followed by another linear release thereafter, showing a distinct biphasic release characteristics. There was a difference in the release profiles between single-layered and dual drug-loaded alginate beads due to their structural shape. However, the biphasic release profiles were modified by varying formulation compositions of inner and outer layer. The calculated release rate of dual drug-loaded alginate beads in the simulated gastric fluid followed by the intestinal fluid from the release profiles (Fig. 5) is also given in Fig. 6. In case of D-1 and D-2 formulations of dual drug-loaded alginate beads with the same inner core but the different outer layers, the initial release rate of D-2 slightly decreased because the outer layer was reinforced with Eudragit® RS100 polymers as reported previously (Lee and Min, 1996). In case of D-3 with Eudragit® RS100 polymer-reinforced outer layer but no polymer in inner cores, the initial amount of drug released was low because the outer layer was reinforced with high amount of Eudragit® RS100 polymers. However, the release rate (slope) was highly increased in intestinal fluid and then decreased thereafter when compared to D-1 and D-2 due to more swellable inner cores in intestinal fluid and then decreased thereafter. The drug dis- tribution and gelling strength of the dual drug-loaded alginate beads might be changed due to different structural shape and formulation compositions of inner and outer layers, resulting in change of the release rate and solute or solvent migration. However, in this study, dual drug-loaded alginate beads with initially slow release followed by fast release could not be obtained. The application of coating techniques to alginate beads may provide the more diversified release profiles in the future.

In conclusion, the release profiles were highly changed depending on the formulation compositions of inner and outer layers, and the structural shape of alginate beads. The current dual drug-loaded alginate beads simultaneously containing drug in inner and outer layers may be used to deliver the drugs in a time dependent manner.

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