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Preparation and Release Characteristics of Polymer-Reinforced and Coated Alginate Beads

Beom-Jin Lee and Geun-Hong Min

College of Pharmacy, Kangwon National University, Chuncheon 200-701, Korea

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Polymeric reinforcement and coatings of alginate beads were carried out to control the release rate of drug from alginate beads. A poorly water-soluble ibuprofen (IPF) was selected as a model drug. A commercially available Eudragit® RS100 was also used as a polymer. Effects of polymeric contents, the presence of plasticizers and amount of drug loading on the release rate of drug were investigated. The release rate of drug from alginate beads in the simulated gastric fluid did not occur within 2 h but released immediately when dissolution media were switched to the simulated intestinal fluid. No significant difference of release rate from polymer-reinforced alginate bead without plasticizers was observed when compared to plain (simple) beads. However, the release rate of drug from polymer-reinforced alginate beads was further sustained and retarded when aluminium tristearate (AT) as a plasticizer was added to polymer. However, polyethylene glycol 400 (PEG400) did not change the release rate of drug from alginate beads although PEG400 was used to improve dispersion of polymer and sodium alginate, and plasticize Eudragit® RS100 polymer. The presence of plasticizer was crucial to reinforce alginate gel matrices using a polymer. As the amount of drug loading increased, the release rate of drug increased as a result of decreasing effects of polymer contents in matrices. The significantly sustained release of drug from polymer-coated alginate beads occurred as the amount of polymer increased because the thickness of coated membrane increased so that cracks and pores of the outer surface of alginate beads could be reduced. The sustained and retarded action of polymer-reinforced and coated beads may result from the disturbance of swelling and erosion (disintegration) of alginate beads. From these findings, polymeric-reinforcement and coatings of alginate gel beads can provide an advanced delivery system by retarding the release rate of various drugs.

Key words : Alginate beads, Matrices, Polymeric-reinforced, Eudragit® RS100, Coating, Plasticizer, Release rate, Swelling, Erosion

INTRODUCTION

Alginic acid is a naturally occurring linear polysaccharide consisting of β-(1-4)-D-mannuronic acid and α-(1-4)-L-gluronic acid (Haug and Larsen, 1962). Alginate is used as an antacid adjuvant because it has a protective effect on the mucus layer. Alginate has been used in pharmaceutical formulation technology as tablet binder, disintegrant, gastric emptying time delaying substance, gelling agent, and sustained release matrix, and also in food additives as a stabilizer and viscosifier (Koji *et al.*, 1981; Bodmeier and Paeratakul, 1989; Hwang *et al.*, 1993; Sugawara *et al.*, 1994). A major property of alginic acid and its salt is to form the gel via a single-step process in the presence of calcium and other multivalent cations. Recently, alginate gel beads have been widely utilized as a vehicle for the controlled delivery of low molecules or macromolecules including cells and immobilizing enzymes (Kim and Lee, 1992; Lin and Ayres, 1992; Hwang *et al.*, 1993; Tomida *et al.*, 1993; Sugawara *et al.*, 1994). In pharmaceutical aspects, alginate gel beads have various useful properties in that they are easy to produce, stable in low pH, easy to form gel and reswell, and nontoxic when taken orally (Haug *et al.*, 1963; Yotsuyanagi *et al.*, 1987; Hwang *et al.*, 1993; Tomida *et al.*, 1993). However, the usefulness of alginate beads as a controlled delivery system has been complicated because the physical characteristics of alginate gel beads are influenced by concentration and viscosity grades of alginate, molecular size, calcium concentration, gelling time, size of

Correspondence to: Beom-Jin Lee, College of Pharmacy, Kangwon National University, 192-1, Hyoja-2-Dong, Chuncheon 200-701, Korea

beads and formulations (Kim and Lee, 1992; Ostberg *et al.*, 1993; Sugawara *et al.*, 1994). Although polymer-coated alginate beads for colonic delivery of drug and chitosan for reinforcing alginate gel matrix were reported (Lin and Ayres, 1992; Murata *et al.*, 1993), little information is available on the polymer-reinforced and coated alginate gel beads for the controlled delivery of drug.

The purpose of the present work was to prepare polymer-reinforced and coated alginate gel beads and to evaluate release characteristics of drug in the simulated gastric and intestinal fluid, varying the amount of polymer, plasticizers and drug loading. A poorly water-soluble ibuprofen (IPF) was selected as a model drug. Commercially available Eudragit® RS100 as a polymer and aluminium tristearate (AT) as a plasticizer were also used, respectivelye.

MATERIALS AND METHODS

Materials

Ibuprofen (IPF) was provided courtesy of Yuhan Corp. (Seoul, Korea). Sodium alginate was purchased from Junsei Chemical Co. (Tokyo, Japan). Eudragit® RS100 was obtained from Rohm Pharma (Darmstadt, Germany). Aluminium tristearate (AT), polyethylene glycol 400 (PEG400) and liquid paraffin were purchased from Katayama Chemical Co. (Osaka, Japan), Hayashi Pure Chemical Co. (Osaka, Japan) and Junsei Chemical Co., respectively. n-Hexane was purchased from Duksan Pharmaceutical Co. LTD. (Seoul, Korea). All other chemicals were of reagent grade and used without further purification.

Preparation of reinforced alginate beads

For the preparation of Eudragit® RS100-reinforced alginate beads, IPF and sodium alginate were mixed and completely suspended with deionized water. On the other hand, Eudragit® RS100 dissolved in PEG400 and AT were mixed and stirred for 1h. The resulting suspension was combined and completely mixed over 1 h using sonicator and stirrer. The final mixtures were gently dropped into 0.1M $CaCl_2$ (50 ml) using a pipette (10 ml) and stirred for 4h for the gelation and curing of beads. The beads formed were filtered, briefly rinsed with deionized water, and then dried in an oven at 50°C over 12 h. The plain (simple) and the polymer-reinforced alginate beads were characterized depending on the presence or the absence of Eudragit® RS100 in the matrix of alginate gel beads. The formulation compositions are shown in Table I. Formulation codes were designated as F1 to F13 depending on the content of polymer, presence of plasticizers and amount of drug loading. The ratio of polymer and AT was kept at 20 in case of F6-F13.

Table I. Formulation compositions for the preparation of polymer-reinforced alginate gel beads

Formulation cides	Drug (g)	Polymer (g)	PEG400 (g)	AT[a] (g)	Water (g)
F1	2	0	0	0	100
F2	2	4	0	0	100
F3	2	10	0	0	100
F4	2	0	20	0	80
F5	2	2	20	0	80
F6	2	2	20	0.1	80
F7	2	4	20	0.2	80
F8	2	6	20	0.3	80
F9	5	4	5	0.2	95
F10	5	4	10	0.2	90
F11	5	4	20	0.2	80
F12	5	2	20	0.1	80
F13	5	6	20	0.3	80

[a]Aluminium tristearate (AT) as a plasticizer of polymer (Eudragit® RS100). Sodium alginate (2 g) was invariably used. The ratio of polymer and AT was kept at 20 in case of F6-F 13.

Preparation of coated alginate beads

Eudragit® RS100-coated alginate beads were prepared for the purpose of sustained delivery of drug with a minor modification of Kawata *et al.* (1986). Plain alginate beads were coated with Eudragit® RS100 coating solution prepared as follows. Eudragit® RS100 (1. 0, 1.5, and 2g) as a polymer was added to 30 ml of acetone as a solvent in a glass vessel and completely dissolved with the stirring speed of 300 rpm in a water bath at 17°C. The constant amount of AT (0.1g) was then added to the mixture with additional stirring for 30 min. The plasticizer was used to prevent electrification and flocculation of particles. Plain alginate beads were added to the coating solution and then liquid paraffin (40 ml) was poured into the above mixture. The solution temperature was gradually increased to 40°C by 5°C interval with a simultaneous increase of stirring speed to 800 rpm by 50 rpm interval every 30 min. The coated alginate beads were finally formed as a result of evaporation of acetone. The coated alginate beads were filtered through a filter paper (diameter 110 mm), washed with n-hexane (50 ml) and then dried in an oven at 50°C for 30 min with further drying at room temperature. Formulation codes were also designated as F14, F15 and F16 when the

amount of polymer used was 1.0, 1.5 and 2.0 g in coating solutions, respectively.

Determination of drug contents in alginate beads

About 0.7g of alginate beads were ground in a pestle. The ground powder (500 mg) was exactly weighed and completely dissolved in 500 ml of phosphate buffer (pH 7.4) by stirring for 7-8 h. The resulting solution was filtered through a millipore membrane (pore size 0.2 μm, diameter 25 mm). The concentration of drug was determined using an UV-VIS spectrophotometer (Pharmacia LKB Ultrospec, Cambridge, England) at the wavelength of 265 nm.

Dissolution studies

The in vitro dissolution of drug from alginate gel beads was performed in triplicate using the dissolution apparatus type I (Fine Scientific DST600A, Seoul, Korea) at the stirring speed of 100 rpm at 37±0.5°C. Dissolution media for the first 2 h was 500 ml of enzyme-free simulated gastric juice (pH 1.4±0.1) followed by enzyme-free simulated intestinal fluid (pH 7.4±0.1). The simulated gastric and intestinal fluid were prepared according to Lee and Lee (1995). The dissolution samples (3 ml) were collected at a given interval with replacement of equal volume of temperature-equilibrated media, and were filtered through a millipore membrane. The concentration of drug released as a function of time was determined using an UV-VIS spectrophotometer as mentioned previously. Ethanol (1 ml) was added in gastric sample for analysis but not in intestinal sample.

RESULTS AND DISCUSSION

It has been known that alginate gel beads are stable in low acidic pH but swell and disintegrate in intestinal pH (Yotsuyanagi *et al.*, 1987; Kim and Lee 1992). It is necessary to retard the rate of swelling and disintegration (erosion) for the sustained delivery of drug over a long period, otherwise, most drugs would be released in the intestinal fluid within a few hours. Although many works have been carried out on alginate gel beads as a vehicle, little attempt has been made on the reinforcement of alginate bead matrices or the reduction of pores and cracks on the outer surface using polymeric materials for the controlled delivery of drug. The release rate of drug would be fast if alginate beads have cracks and pores on the surface.

A commercially available Eudragit® RS100, a copolymer synthesized from acrylic and methacrylic acid esters with low content of quaternary ammonium groups, was used for the reinforcement of alginate gel matrices and coating. Eudragit® RS100 has pH-independent solubility and low water penetration (Lehmann, 1989).

Effects of the content of polymer without plasticizers on the release rate of drug from polymer-reinforced alginate beads are shown in Fig. 1. The drug release of a poorly water-soluble drug in the simulated gastric fluid did not occur within 2 h. It is well-known that alginate beads is very stable in acidic environment without swelling and disintegration. Therefore, gastric-labile drugs and enzymes can be entrapped in alginate gel matrices (Yotsuyanagi *et al.*, 1987; Hwang *et al.*, 1993). However, when dissolution medium was switched to the simulated intestinal fluid, the release of drug occurred immediately. No significant difference of release rate from polymer-reinforced alginate bead (F2 and F3) without plasticizers was observed when compared to plain alginate beads (F1). However, the release rate of drug from polymer-reinforced alginate beads was further sustained and retarded when plasticizer (AT with a constant amount of PEG400) was added to polymer (Fig. 2). The plasticizer was useful to improve flexibility and reduce brittleness of polymers. The softening effect of plasticizer on the polymeric particles results in effective film formation during coating by decreasing film-forming temperature (Lehmann, 1989).

The effect of PEG400 on the release rate of drug

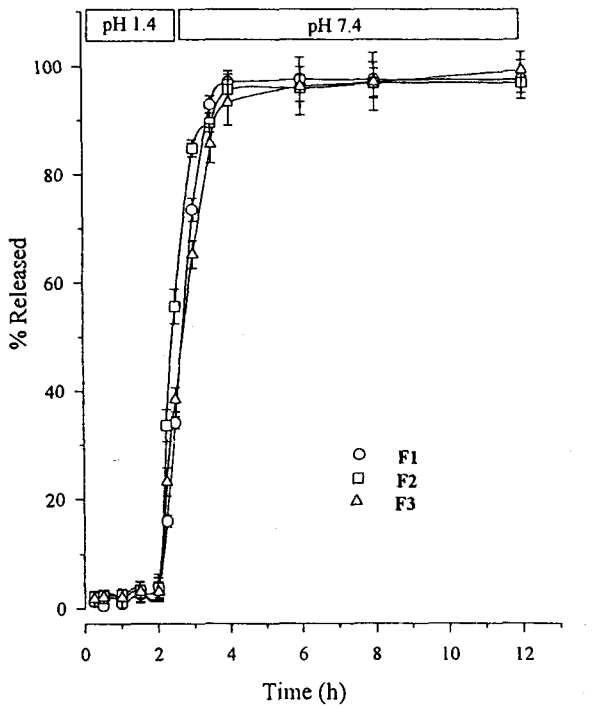

Fig. 1. Effects of the content of polymer without plasticizers on the release rate of drug from polymer-reinforced alginate beads in the simulated gastric (pH 1.4) and intestinal fluid (ph 7.4).

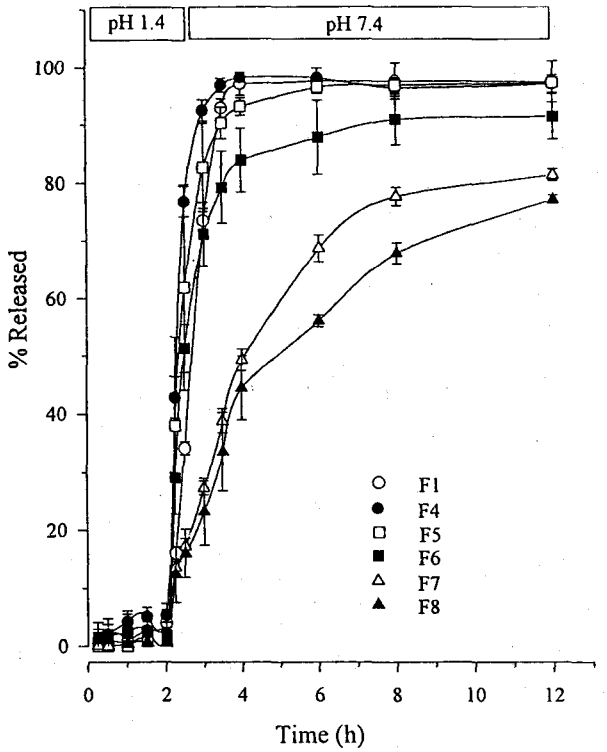

Fig. 2. Effects of the content of polymer with plasticizers on the release rate of drug from polymer-reinforced alginate beads in the simulated gastric (pH 1.4) and intestinal fluid (pH 7.4)

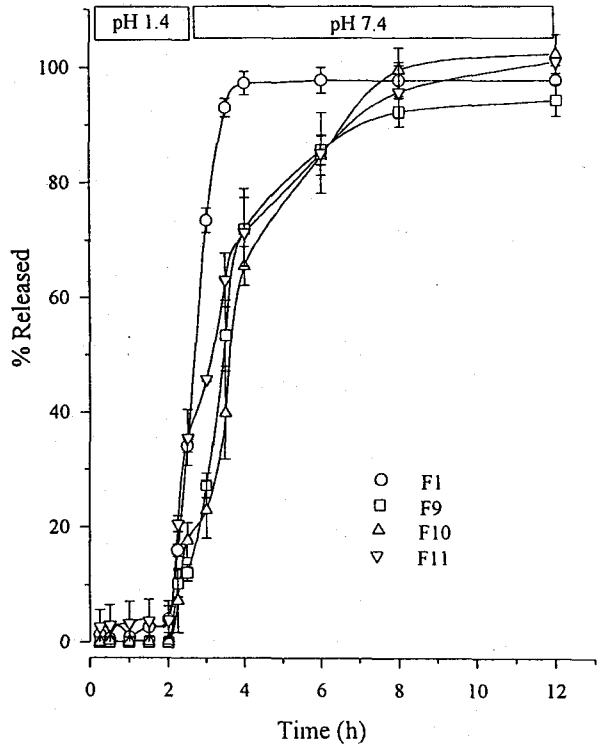

Fig. 3. Effect of PEG400 on the release rate of drug from polymer-reinforced alginate beads in the simulated gastric (pH 1.4) and intestinal fluid (pH 7.4)

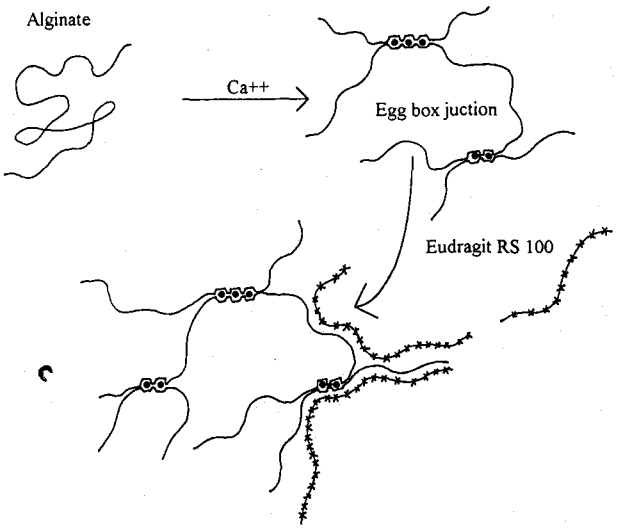

Fig. 4. Schematic diagram of the formation of polymer-reinforced alginate gel beads

from polymer-reinforced alginate beads (F9, F10 and F11) is shown in Fig. 3. It suggested that PEG400 did not change the release rate of drug from alginate beads although PEG400 was used to improve the dispersion of polymer and sodium alginate, and plasticize Eudragit® RS100 polymer. However, it was obvious that as the amount of AT increased, the release rate of drug from polymer-reinforced alginate beads decreased. The retarding effect of AT from polymer-reinforced alginate beads was more significant when compared to PEG400 (see also Fig. 2).

The retarding effect of polymer with plasticizer resulted from polymeric reinforcement of alginate gel matrices. The schematic diagram of mechanism of polymer-reinforced alginate beads is shown in Fig. 4. Murata *et al.* (1993) previously used chitosan to reinforce alginate gel matrix and investigate effects of chitosan on gel matrix erosion. Likewise, Eudragit® RS 100 could be sited within the alginate gel matrices so that drug release was hindered as a result of protecting effects from swelling and disintegration. In this study, the release from the polymer-reinforced alginate matrix beads is mainly due to swelling forces because the erosion from the polymer-reinforced alginate beads was not found in the simulated intestinal fluid. The more alginate beads swell, the greater the diffusion.

On the other hand, the effect of amount of drug loading on the release rate of drug from polymer-reinforced alginate beads is also studied in Fig. 5. As the amount of drug loaded increased, the release rate of drug increased as a result of decreasing effect of polymer content in the alginate beads. The reinforcing effect of polymer in alginate gel matrices was reduced as drug contents increased in alginate beads. It

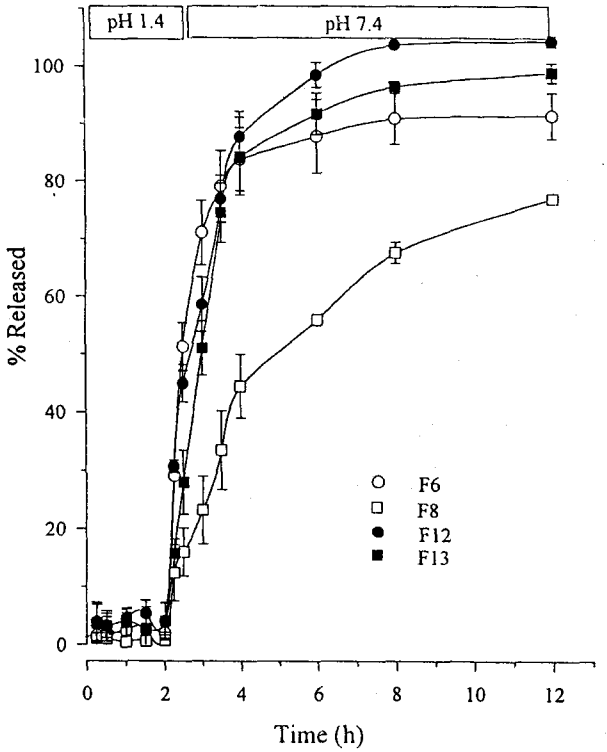

Fig. 5. Effects of the amount of drug loading on the release rate of drug from polymer-reinforced alginate beads in the simulated gastric (pH 1.4) and intestinal fluid (pH 7.4).

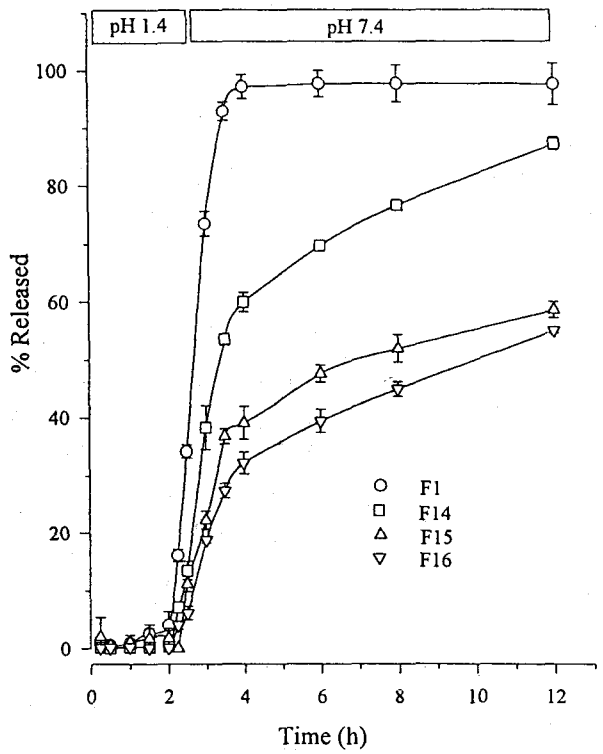

Fig. 6. The release profiles of drug from polmer-coated alginate beads in the simulated gastric (pH 1.4) and intestinal fluid (pH 7.4). Formulation codes were designated as F14, F15 and F16 when the amount of polymer used was 1.0, 1.5 and 2.0 g with a constant amount of AT (0.1 g), respectively.

was also observed that the release rate of drug was retarded when the amount of polymer plasticized with AT increased (F8 vs F13 compared to F6 vs F12).

The plain alginate beads were further coated with Eudragit® RS100 polymer to efficiently control the release rate of drug. Although polymer-reinforced alginate beads retard drug release by reducing swelling and erosion, coated alginate beads may be useful not only to retard swelling and erosion but also to overcome the possible defects of the outer surface of alginate beads such as cracks and pores. The porosity and any structural defect of alginate beads give a fast release and a low efficiency of incorporating drug (Kim and Lee, 1992). Eudragit polymer was used as a coating material for sustained delivery of drug (Lehmann, 1989; Lin and Ayres, 1992)

The release profiles of drug from polymer-coated alginate beads as a function of polymer contents are given in Fig. 6. Like the plain and polymer-reinforced alginate beads, the coated beads were stable in gastric juice but released drug in the simulated intestinal fluid. The significantly sustained release of drug occurred from coated alginate beads as the polymer contents increased. As polymer contents increased, the thickness of coated membrane increased so that cracks and pores on the surface of alginate beads could be reduced. Therefore, swelling and erosion of alginate beads were further disturbed, resulting in the decrease of drug release. However, slightly fast release within the initial 1 h in the simulated intestinal fluid followed by a zero order release was observed. It was not clear why the drug was initially quickly released from coated alginate beads. The surface and integrity of coated alginate beads must be evaluated using scanning electron microscopy to explain the diffusional behavior of drug from alginate gel matrices. Detailed release mechanism of drug from alginate beads is under investigation.

In conclusion, the retarding effect of drug from polymer-reinforced alginate beads was observed. However, the presence of plasticizer was crucial to reinforce alginate gel matrices using a Eudragit® RS100 polymer. AT was useful to impart retarded action of Eudragit® RS100 polymer in alginate beads. However, PEG400 did not change the release rate of drug from polymer-reinforced alginate beads. The release rate of drug from polymer-reinforced alginate beads increased as the amount of drug loaded increased as a result of decreasing effect of polymer in the matrices. The drug release from alginate beads coated with Eudragit® RS100 polymer was further retarded as po-

lymer contents increased due to the reduction of pores and cracks on the outer surface of alginate beads. The sustained and retarded action of polymer-reinforced and coated alginate beads mainly result from the disturbance of swelling and erosion (disintegration) of alginate beads. From these findings, polymeric reinforcement and coatings of alginate gel beads can provide an advanced delivery system by retarding the release rate of various drugs.

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