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Alginate-Coated Alginate-Polyethyleneimine Beads for Prolonged Release of Furosemide in Simulated Intestinal Fluid

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ABSTRACT Furosemide-loaded calcium alginate (ALG), calcium alginate-polyethyleneimine (ALG-PEI) and alginate-coated ALG-PEI (ALG-PEI-ALG) beads were prepared by ionotropic/polyelectrolyte complexation method to achieve controlled release of the drug. Effects of several formulation factors on the characteristics of the beads were investigated. Although variation in formulation factors did not influence the drug-loading efficiency (DLE) of ALG beads, rapid release of the drug in simulated intestinal fluid (SIF) could not be prevented. PEI treatment of ALG beads, however, prolonged the drug release considerably. Ionic interaction, as appeared from FTIR studies, between alginate and PEI led to the formation of polyelectrolyte complex membrane, the thickness of which was dependent on the conditions of PEI treatment as demonstrated by scanning electron microscopy (SEM). The membrane acted as a physical barrier to drug release from ALG-PEI beads. Alginate coating of ALG-PEI beads further prolonged the release of the drug by increasing membrane thickness and reducing swelling of the beads possibly by blocking the surface pores. Differential scanning calorimetry (DSC) study indicated that drug was not degraded by PEI treatment. The release data from ALG-PEI beads showed a good fit in power law expression, whereas the release data from ALG-PEI-ALG beads were found to fit in modified power law expression, and the mechanism of drug release changed from super case II transport to nearly Fickian transport, depending on the degree of gelation and formation of polyelectrolyte complex membrane.

KEYWORDS Alginate, Polyethyleneimine, Beads, Furosemide, Drug release, Release kinetics

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INTRODUCTION

Compared with single-unit dosage forms, multiunit drug delivery systems avoid the variations in gastric emptying and different transit rates through the gastrointestinal tract (Beckett, 1980), release drugs in a more predictable manner (Follonier & Doelkar, 1992), and spread over a large area preventing exposure of the absorbing site to high drug concentration on chronic dosing (Davis et al., 1984). Several synthetic polymers have been used to formulate multiunit dosage forms. Recently, much research efforts have been concentrated to develop drug-loaded microparticles using sodium alginate, a natural polymer obtained from marine brown algae, because of simple, mild and eco-friendly preparative conditions.

Sodium alginate is composed of α-L-guluronic acid and β-D-mannuronic acid residues at varying proportions of GG-, MM-, and GM-blocks (Penman & Sanderson, 1972). Its unique property to form calcium alginate gel through interaction between Ca^{2+} ions and carboxylate residues of GG blocks of alginate has been used to formulate ALG beads of various drugs such as indomethacin (Shiraishi et al., 1993), nitrofurantoin (Hari et al., 1996), acetaminophen, and ketoconazole (Cui et al., 2001). However, major disadvantages of ALG beads are low drug entrapment efficiency and rapid release of the loaded drug especially in SIF. Low DLE of ALG beads is attributed to its gel porosity, which is large enough to cause leakage of the loaded drugs (Liu et al., 1997) and may also be due to drug diffusion to the $CaCl_2$ solution. Although ALG beads do not swell appreciably in acidic fluid (Yotsuyanagi et al., 1987), the beads swell and erode/disintegrate rapidly in SIF, leading to quick release of the loaded drugs (El-Kamael et al., 2003; Tomida et al., 1993).

In an attempt to modify DLE and release rates of drugs from ALG beads, chitosan has been used in combination with alginate (Pillay & Fassihi, 1999). Chitosan, a positively charged polymer, interacts with negatively charged alginate to form polyelectrolyte complex membrane and thereby reduces the swelling of the resultant alginate-chitosan beads (Polk et al., 1994). Several polycations, such as poly-L-lysine (PLL) and polyethyleneimine (PEI), are also capable of reducing the permeability and pore size of gel networks (Gugerli et al., 2002; Kim & Park, 2004) and have been widely used to retain the morphology and functionality of bioactive agents such as islets of Langerhans for longer period (Lim & Sun, 1980; O'Shea et al., 1984). Further development involved alginate coating of PLL-treated ALG beads, leading to the formation of ALG-PLL-ALG microcapsules, which successfully retarded the release of bioactive substrate for a longer period (Thu et al., 1996). However, to the best of our knowledge, studies on alginate-coated or -uncoated ALG beads stabilized with polycations, such as polyethyleneimine, for controlled drug delivery of low molecular weight therapeutic agents have not been reported.

The objective of the present work was, therefore, to study the feasibility of using PEI to provide prolonged release of furosemide in SIF from ALG beads. The initial part of this work involved systematic examination of the effect of various formulation variables on the characteristics of furosemide-loaded ALG beads. Subsequent study involved development and characterization of PEI-stabilized ALG (ALG-PEI) beads and alginate-coated alginate-polyethyleneimine (ALG-PEI-ALG) beads for prolonged release of furosemide. PEI has been reported to exhibit several advantageous properties such as hydrophylicity, biocompatibility, and thermal stability (Kim & Park, 2004). Furosemide has been used as a model water-insoluble drug.

EXPERIMENTAL

Materials

Furosemide IP (M/S Minichem Lab, Kolkata, India) was obtained as gift sample. Sodium alginate (SD Fine Chemicals, India; 1121cP of 2.5% w/v solution as determined in Brookfield viscometer, model no. DV-E at 25°C using spindle no. 2 at 20 rpm), calcium chloride dihydrate (Qualigens, India), polyethyleneimine (50% w/v, Sigma-Aldrich, USA) and all other analytical grade reagents were obtained commercially and used as received.

Preparation of Furosemide-Loaded Calcium Alginate Beads

In 30 mL of aqueous solution of sodium alginate (0.9, 1.8, and 2.7% w/v), required amount of furosemide (44 μm) was dispersed uniformly and homogenized for 5 min. Bubble-free dispersion was

dropped through a 16 bore glass syringe in a gently agitated calcium chloride solution. After incubating for predetermined times, the gelled beads were separated by filtration, washed with 3×100 mL deionized water, air dried overnight, and finally dried at 50°C for 4 h. The following experimental parameters were varied:

1. incubation time: 4, 8, and 24 h;
2. concentration of calcium chloride solution: 1, 3, and 6% w/v; and
3. amount of furosemide: 30, 50, and 70% w/w of the polymer.

Preparation of ALG-PEI Beads

Furosemide (50% w/w) was uniformly dispersed in 2.5% w/v sodium alginate solution and homogenized for 5 min. Bubble-free dispersion was dropped through 16 bore glass syringe in a slowly agitated 3% calcium chloride solution. After 30 min, the resultant beads were washed with 3×100 mL of deionized water. Following removal of surface moisture with tissue paper, ALG beads were incubated in 1 or 2% w/v PEI solution for 5 or 10 min. After blotting the excess surface liquid with tissue paper, beads were air dried for 24 h and then vacuum dried at 50°C for 4 h.

Preparation of ALG-PEI-ALG Beads

ALG-PEI beads were suspended in 0.2% w/v sodium alginate solution for 2 min with gentle stirring. Resulting ALG-PEI-ALG beads were incubated in 3% calcium chloride solution for 5 min. The beads were washed with deionized water, air dried for 24 h, and finally vacuum dried at 50°C for 4 h.

Scanning Electron Microscopy (SEM)

Dried beads were mounted onto stubs by using double-sided adhesive tape and vacuum coated with gold film using sputter coater (Edward S-150, UK). Coated particles were observed under scanning electron microscope (Jeol, ISM-5200, Japan) for surface characteristics. Cross sections of ALG-PEI beads and ALG-PEI-ALG beads were observed under SEM in the same way.

Drug-Loading Efficiency (DLE)

About 20 mg, accurately weighed, furosemide-loaded ALG, ALG-PEI, or ALG-PEI-ALG beads were dissolved in 250 mL of USP phosphate buffer solution (pH 7.4) by shaking on a mechanical shaker for 24 h. The solution was filtered through Whatman filter paper. An aliquot following suitable dilution was assayed spectrophotometrically (Hitachi, 200-20, Japan) for furosemide at 277 nm. To ascertain whether the polymers interfered with the estimation of furosemide at 277 nm, recovery analysis was conducted by using 20 mg of furosemide with or without sodium alginate or PEI solution at different dilutions. The recovery averaged $100.94 \pm 0.03\%$, indicating that the polymers did not interfere with the estimation of furosemide. Drug-loading efficiency was determined by using the following relationship:

$$\text{Drug loading efficiency (DLE)} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

Drug Release Study

In vitro release of furosemide from ALG, ALG-PEI, ALG-PEI-ALG beads were monitored by using 20-mg beads, accurately weighed, in 900 mL of SIF (USP phosphate buffer solution, pH 6.8) at 37 ± 0.5°C and 50 rpm using programmable dissolution tester [Paddle type, model TDT-06P, Electrolab, (USP), India]. Aliquots were withdrawn at predetermined intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions, were assayed spectrophotometrically at 277 nm.

Swelling Ratio-Time Profiles

Swelling ratios of dried beads with or without drug were determined gravimetrically in slightly agitated USP phosphate buffer solution (pH 6.8). The beads were removed periodically from the solution, blotted to remove excess surface liquid, and weighed on an electronic balance (Precisa, XB-600 MC, Switzerland).

Swelling ratio (% w/w) was determined from the following relationship and plotted against time.

$$\text{Swelling ratio} = (W_t - W_o)/W_o \times 100$$

where W_o and W_t are, respectively, initial weight of the beads and weight of the beads at time *t*.

FTIR Study

IR spectra for drug-free ALG and ALG-PEI beads were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR, 410 JASCO, Japan) with KBr pellets.

Differential Scanning Calorimetry (DSC)

DSC scans of about 5 mg, accurately weighed, furosemide, and ALG, and ALG-PEI beads containing almost the same amount of drug were performed in an atmosphere of nitrogen. The weighed amount of sample was kept in hermetically sealed aluminium pans and heated at a scanning rate of 10°C/min over a temperature range of 50–300°C in NETZSCH DSC 200 PC instrument.

Statistical Analysis

Each formulation was prepared in duplicate, and each analysis was duplicated. Effect of formulation variables on DLE and release parameter ($t_{50\%}$) were tested for significance by using analysis of variance (ANOVA: single factor) with the aid of Microsoft® Excel 2002. Difference was considered significant when $p<0.05$.

RESULTS AND DISCUSSION

Because the formulation of spherical beads primarily depends on the viscosity of sodium alginate solution, the concentration range within which drug-loaded spherical alginate beads could be prepared was determined by dropping sodium alginate solution containing 30% w/w furosemide in calcium chloride solution and incubating for 4 h. At 0.9% w/v sodium alginate concentration, the beads were elongated and at 2.7% w/v alginate concentration, most of the beads developed tails. Low viscosity of dilute sodium alginate solution produced spheroidal droplets, whereas highly viscous solution produced droplets with tails as the droplets ejected from the needle. Because of instant surface curing, the initial shape of the ejected droplets was maintained. The beads prepared above 0.9% and below 2.7% w/v alginate were spherical. Hence, further studies were carried out by using 1.8% w/v sodium alginate solution.

Loading Efficiency of ALG Beads

DLE of ALG beads varied from 97.16% to 100.49%, depending on the formulation factors such as incubation time, $CaCl_2$ concentration, and initial drug load with coefficient of variation being confined within 0.27–2.49%. Moreover, variation in each of the formulation factors did not produce any significant change ($p>0.05$) in DLE. The loading efficiency of various drugs such as nitrofurantoin (Hari et al., 1996) and indomethacin (Shiraishi et al., 1993) in ALG beads have been reported to be, respectively, 4% and 32%. Although gel porosity of ALG beads is responsible for low DLE (Liu et al., 1997), pH of cross-linking solution also appears to be important in achieving higher DLE. Lowering of pH of $CaCl_2$ solution considerably increased the loading of diclofenac-Na in ALG beads (Pillay & Fassihi, 1999). Moreover, DLE of alginate beads also depends on the incubation time, $CaCl_2$ concentration, and drug solubility (Lee et al., 1999). The greater the solubility of a drug in $CaCl_2$ solution, the lower is the DLE of alginate beads. The solubility of furosemide in $CaCl_2$ solution was found to be negligible and did not change with either time or increase in the concentration of $CaCl_2$. Consequently, the loading efficiency of furosemide in ALG beads was high and was not affected by either incubation time or $CaCl_2$ concentration.

Drug Release From ALG Beads

Release of furosemide from ALG beads in phosphate buffer solution of pH 6.8 (SIF) was rapid and complete in 2.5 h, irrespective of the variation in formulation factors. The drug release was accompanied with rapid swelling and erosion/disintegration of ALG beads and has been considered as a major disadvantage of ALG beads in sustaining drug release in SIF. It has been reported that Na^+ ions present in the dissolution medium interact with the gel-forming

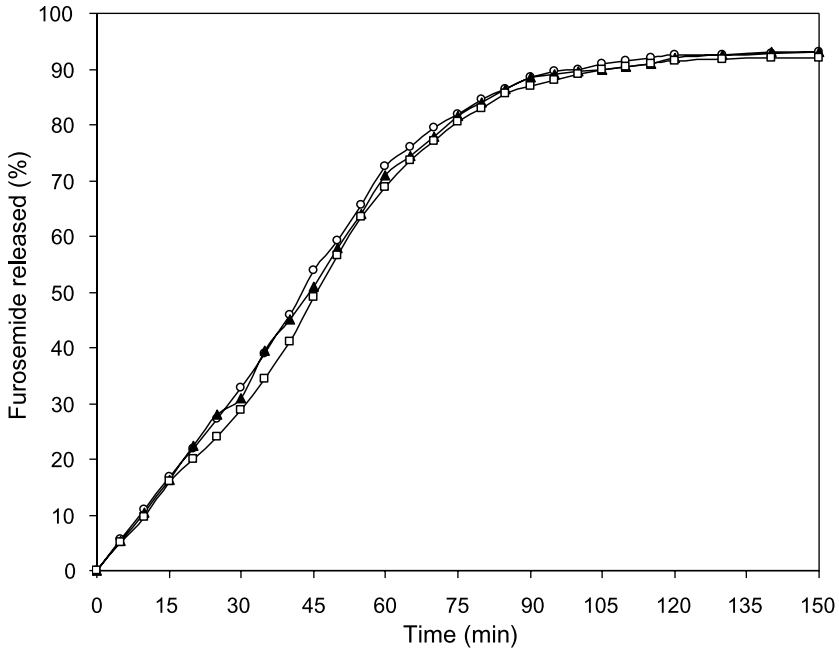

FIGURE 1 **Release Profiles of Furosemide From Calcium Alginate Beads Prepared Under Different Gelation Time. Gelation Time: (○) 4 h, (▲) 8 h, (□) 24 h. Maximum s.d. = ± 3.46% (n = 4).**

Ca^{2+} ions (Tomida et al., 1993), and as the Ca^{2+} ions are exchanged, electrostatic repulsion is developed between the ionized –COOH groups of alginates resulting in rapid swelling and erosion (Kikuchi et al., 1997). Release profiles of furosemide from ALG beads, which were prepared under different incubation times, appeared to be almost superimposable (Fig. 1). Increase in gelation time neither influenced the time required for 50% drug release ($t_{50\%}$) nor the dissolution efficiency parameter (defined as the area under the release profile curve upto certain time *t*, divided by the total area of 100% dissolution, and multiplied by 100) (Khan & Rhodes, 1972) significantly ($p > 0.05$). Similar observations were noted in case of drug release from ALG beads prepared by using increasing $CaCl_2$ concentration (1–6%) (Fig. 2). Although increase in

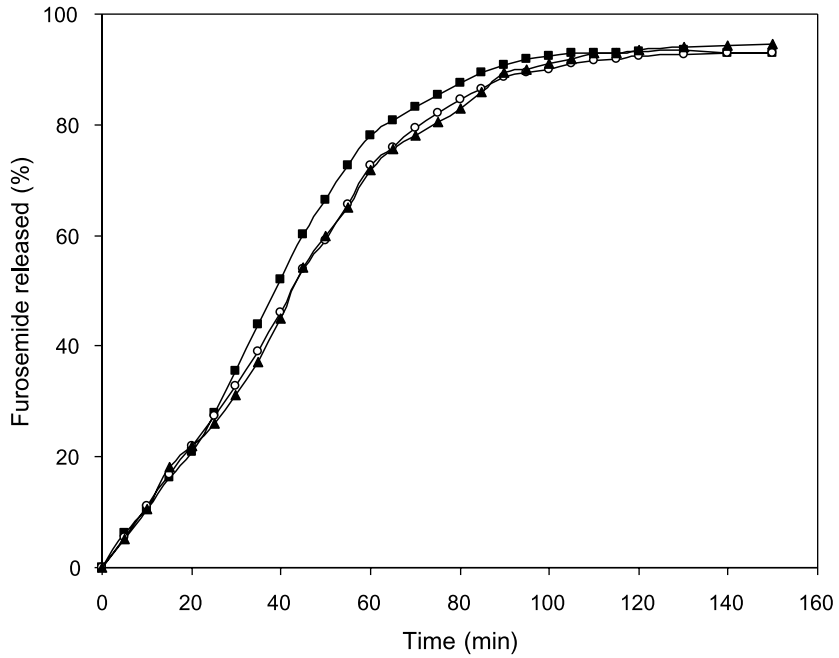

FIGURE 2 **Release Profiles of Furosemide From Calcium Alginate Beads Prepared with Different Concentrations of $CaCl_2$: (■) 1%, (○) 3%, (▲) 24 h. Maximum s.d. = ± 1.24% (n = 4).**

TABLE 1 **Effect of Polyethyleneimine (PEI) Treatment and Alginate Coating on Furosemide Loading Efficiency (DLE) of ALG Beads**

Concentration of PEI (% w/v)	Exposure time (min) in PEI solution	DLE (%) of ALG-PEI beads mean (±s.d, n=4)	DLE (%) of ALG-PEI-ALG beads mean (±s.d, n=4)
1	5	89.5 (±0.30)	85.7 (±2.02)
	10	85.1 (±1.27)	83.4 (±1.29)
2	5	85.5 (±1.22)	79.9 (±1.47)
	10	81.3 (±1.64)	77.7 (±1.04)

gelation time and $CaCl_2$ concentration increases the thickness of gel membrane (Blandino et al., 1999), rapid swelling and breakdown of gel structure of ALG beads at pH 6.8 resulted in rapid release of the drug.

Increase in initial drug loading from 30 to 70%, however, tended to increase the release of the drug as evident from the decrease in time required for 50% release ($t_{50\%}$) from 43 to 31 min. Increase in drug loading decreases the polymer concentration to a threshold disentanglement value and thus, the gel microstructure weakens (Lee & Peppas, 1987). Moreover, incorporation of furosemide might have interfered with the ionotropic gelation of alginate. When the swelling studies of ALG beads were conducted by using empty beads and beads containing 70% furosemide (see Fig. 6), the drug-loaded beads swelled and collapsed rapidly in comparison with the empty beads. This confirms that incorporation of furosemide in alginate beads not only causes matrix disentanglement but also interferes with the ionotropic gelation and hence the matrix disintegrates leading to rapid release of the drugs.

Drug-Loading Efficiency of ALG-PEI Beads

In an attempt to sustain the release of the drug in SIF, furosemide-loaded ALG beads were treated with different concentrations of PEI solution for different periods of time. Treatment of ALG beads with PEI solution, however, affected DLE. Increase in both PEI concentration and exposure time decreased DLE (Table 1). Higher pH (10.3) of PEI solution, which diffused inwardly into the beads, was responsible to dissolve the drug, which then diffused out of the beads, leading to decrease in DLE. Similar decrease in DLE of acetaminophen and ketoconazole in PLL-stabilized ALG beads has been reported (Cui et al., 2001).

Release of Drug From ALG-PEI Beads

Release of furosemide from ALG-PEI beads was prolonged considerably compared with that from ALG beads. Figure 3 shows that the release of the

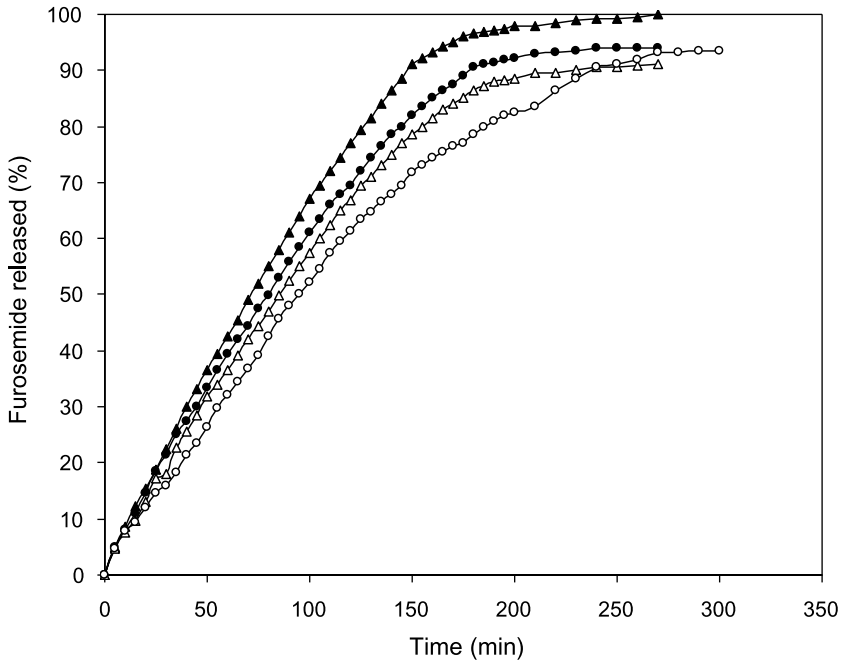

FIGURE 3 **Effect of PEI Concentration and Exposure Time on the Release of Furosemide from ALG-PEI Beads. 1% PEI: 5 min (▲), 10 min (△); 2% PEI: 5 min (●), 10 min (○). Maximum s.d.=±3.12% (n=4).**

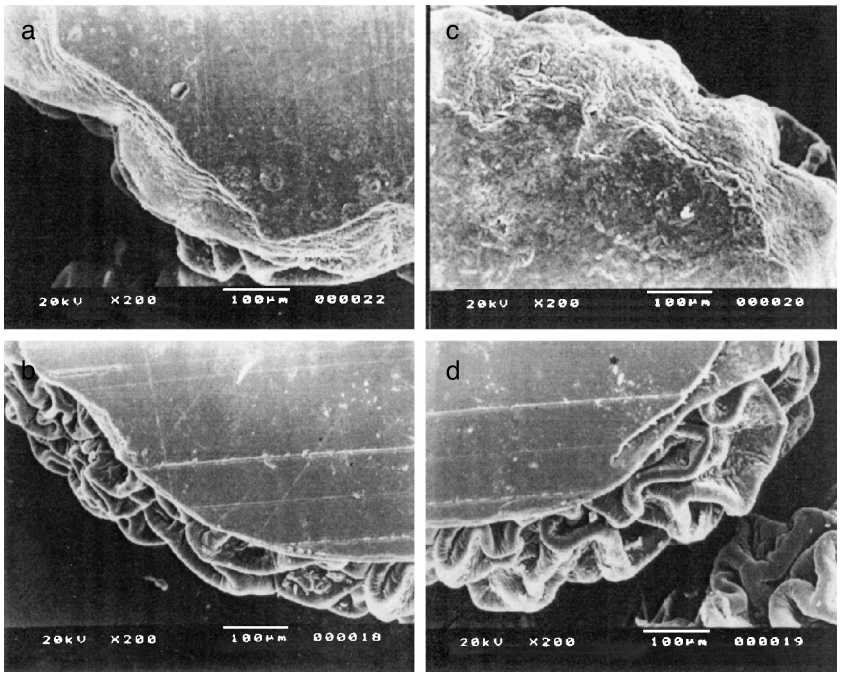

FIGURE 4 **Scanning Electron Micrographs of Cross Section of Drug-Loaded Alginate Beads Showing Polyelectrolyte Complex Membrane Formed by PEI Treatment: (a) 1% w/v, 5 min; (b) 1% w/v, 10 min; (c) 2% w/v, 5 min; and (d) 2% w/v, 10 min.**

drug was extended at different rates depending on the condition of PEI treatment. The higher the concentration of PEI and exposure time, the slower was the drug release from ALG-PEI beads. PEI is a highly branched molecule having branched sites separated by many secondary amine groups. The branching distribution provides many charged nitrogen atoms and makes the molecule cationic (Kim & Park, 2004). PEI is, therefore, expected to react with anionic alginate polymer to form a complex membrane. Cross-sectional view under SEM indeed demonstrated the formation of a complex membrane around the beads. PEI solution diffused through the formed membrane into the core of the beads with time as well as due to the concentration gradient and, thus, increased the thickness of the membrane. It is evident from Fig. 4 that thickness of the membrane increased with increase in both PEI concentration and exposure time. FTIR spectra of sodium alginate showed the characteristic bands of –OH, symmetrical and asymmetrical $-COO^-$ groups, respectively, at 3446.17 cm^{-1}, 1609.31 cm^{-1}, and 1415.49 cm^{-1}. The respective band positions in ALG-PEI beads shifted, respectively, to 3419.17 cm^{-1}, 1606.41 cm^{-1}, and 1417.42 cm^{-1} (Fig. 5). Although inconclusive without further investigation, it appeared that PEI reacted with alginate molecules through ionic interaction to form polyelectrolyte complex membrane. Swelling studies also demonstrated that ALG-PEI beads exhibited lower swelling ratios than ALG beads (Fig. 6). Moreover, the swelling ratios of both empty and drug-loaded ALG-PEI beads were almost similar. This indicates that in contrast to drug-loaded ALG-PEI beads, the collapse of the gel microstructure of ALG-PEI beads due to incorporation of drug was prevented by PEI treatment. It has been reported that strong ionic interaction between PEI and acrylic acid leads to the formation of interpenetrating polymer network structure. The tight network structure and high molecular entanglement developed because of the presence of highly branched PEI molecules reduced the pore size and water absorption of the network

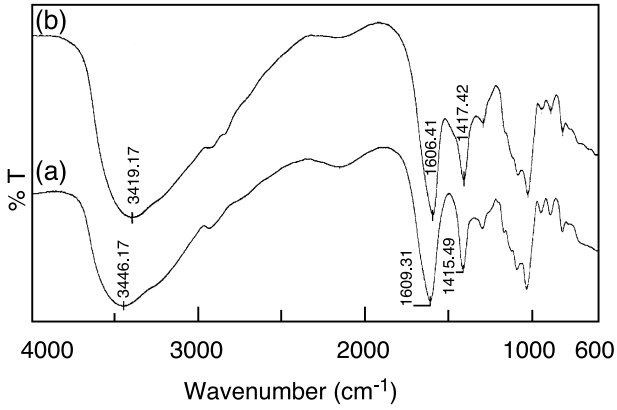

FIGURE 5 **FTIR Spectra of Sodium Alginate (a) and PEI-Treated Alginate (ALG-PEI) Beads (b).**

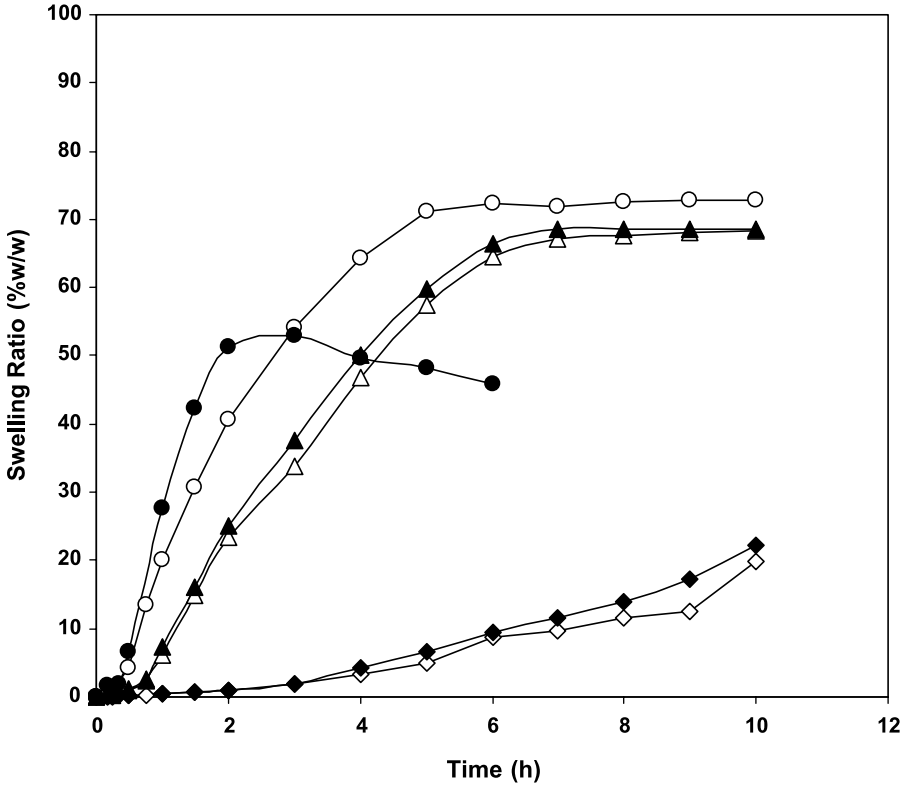

FIGURE 6 Swelling Ratio-Time Profiles of Calcium Alginate (ALG) Beads (○, ●), PEI-Treated Alginate (PEI-ALG) Beads (△, ▲), and Alginate Coated ALG-PEI (ALG-PEI-ALG) Beads (◇, ◆). Open Symbols: Drug-Free Beads; Closed Symbols: Drug-Loaded Beads.

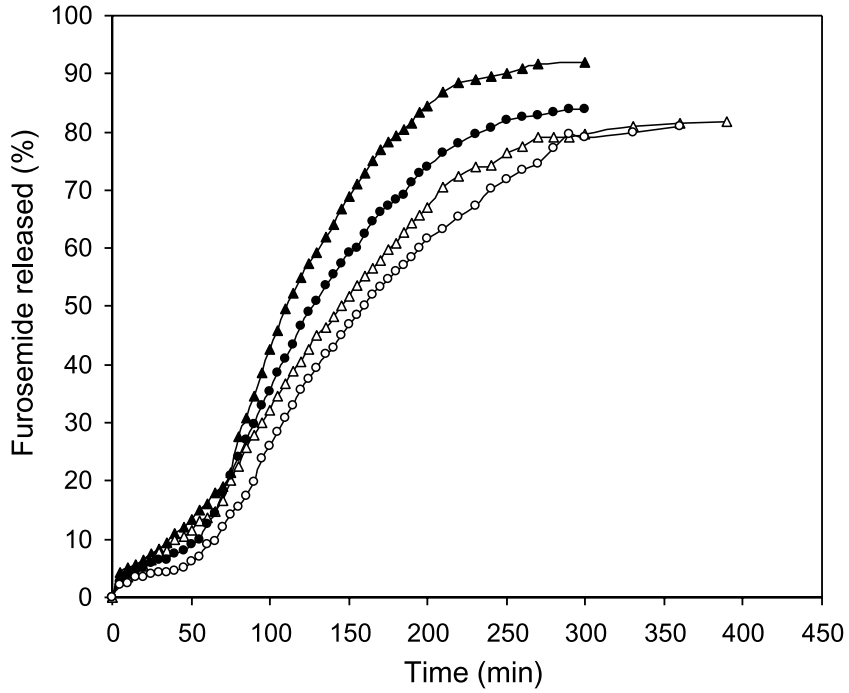

FIGURE 7 Release Profiles of Furosemide From Alginate Coated ALG-PEI (ALG-PEI-ALG) Beads. Key: Coating Time: 1% w/v: 5 min (▲), 10 min (△); 2% w/v: 5 min (●), 10 min (○). Maximum s.d.=±2.24% (n=4).

structure (Kim & Park, 2004). Formation of tight polyelectrolyte complex membrane through interaction between PEI and alginate, and having reduced swelling behavior and possibly reduced pore size, served as a physical barrier to drug diffusion resulting in decrease in drug release.

Release of Drug From ALG-PEI-ALG Beads

With an intention to further prolong the drug release at pH 6.8, ALG-PEI beads were coated with alginate membrane. DLE of the resulting ALG-PEI-ALG beads was found to decrease by 2–5% in comparison to ALG-PEI-ALG beads (Table 1). Coating of ALG-PEI beads with alginate increases the weight of beads and, consequently, the amount of drug present per unit weight of beads decreases. This led to decrease in the drug content of ALG-PEI-ALG beads in comparison with that of ALG-PEI beads. Release of furosemide from ALG-PEI-ALG beads was found to be further prolonged (Fig. 7). Because the time of coating and concentration coating solution were kept constant, decrease in drug release from ALG-PEI-ALG beads followed the same rank order in decrease as that from ALG-PEI beads. The additional coating of alginate around ALG-PEI beads may be responsible for the decrease in drug release. However, a cross-sectional view of the ALG-PEI-ALG beads could not demonstrate the formation of separate alginate coating around the ALG-PEI beads. Instead, the polyelectrolyte complex membrane appeared qualitatively thicker to some extent. Following the explanation of Thu et al. (1996) regarding the formation of ALG-PLL-ALG beads, unreacted PEI present at the surface of ALG-PEI beads reacted with sodium alginate to form additional membrane. Formation of such a membrane might have increased the thickness of the barrier membrane, plugged the surface pores of ALG-PEI beads, and led to the decrease in swelling ratios of ALG-PEI-ALG beads compared with that of ALG-PEI beads (Fig. 6). In addition, incorporation of drug did not collapse the ALG-PEI-ALG beads due to same reasons as for ALG-PEI beads. Consequently, the

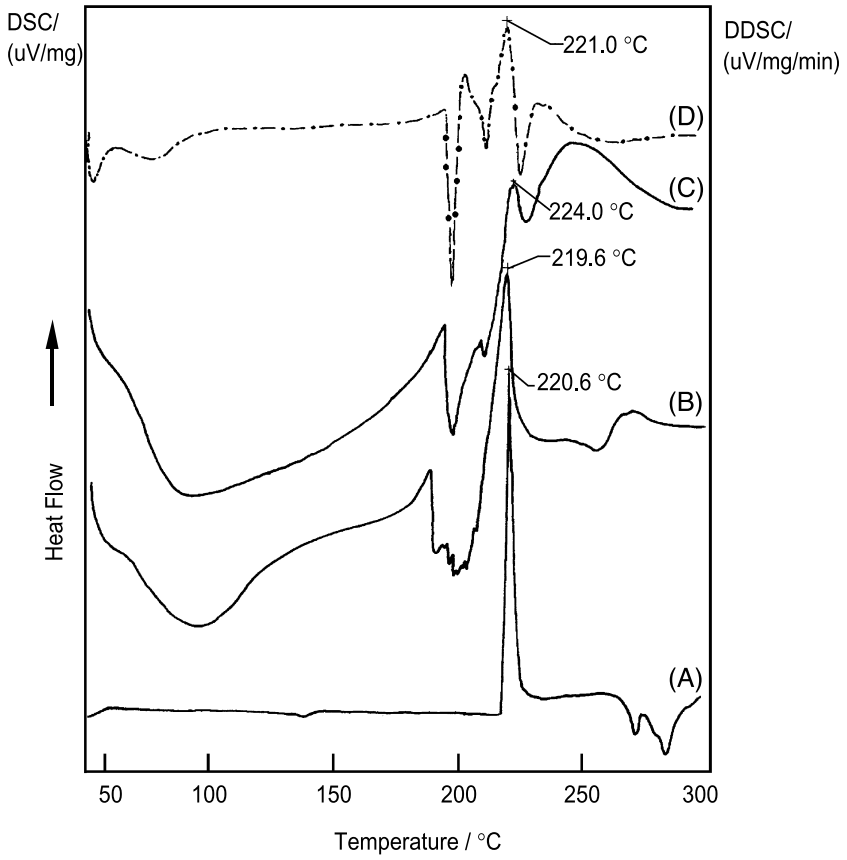

FIGURE 8 **DSC Thermograms of (A) Furosemide, (B) Furosemide-Loaded ALG Beads, (C) ALG-PEI Beads, and (D) Thermogram of Derivative DSC of Thermogram (C).**

drug release from ALG-PEI-ALG beads was considerably prolonged.

Stability of Drug in ALG-PEI Beads

DSC thermograms of furosemide, furosemide-loaded ALG, and ALG-PEI beads are presented in Fig. 8. Furosemide exhibited a sharp endothermic peak at 220.6°C. The endothermic peak of the drug from ALG beads was found at 219.6°C, which was almost the same of that of the pure drug. The endothermic peak of the drug from ALG-PEI beads, however, shifted to 224°C. A small shift of the peak toward higher temperature may be attributed to the rigidity induced by ALG-PEI complex membrane. Furthermore, the thermogram (D), which is the derivative DSC (DDSC) of the thermogram (C), showed an endothermic peak at 221°C. The results ensured the stability of the drug in ALG-PEI beads.

Kinetics of Drug Release

Drug release from a swellable matrix primarily depends on the degree of gelation, hydration, chain relaxation, and erosion of the polymer and follows the classical power law expression (Ritger & Peppas, 1987)

$$M_t/M_\infty = K\,t^n$$

where M_t and M_∞ are, respectively, the amount of drug released at time t and at infinite time, K represents a constant incorporating structural and geometrical characteristics of the dosage forms, n denotes the diffusion exponent indicative of the mechanism of drug release. Values of n ranging from 0.45 to 0.5 indicate Fickian or diffusion controlled release; values of n ranging from 0.5 to 0.89 indicate non-Fickian or anomalous release, and values of n ranging from 0.89 to 1 indicate case II or zero order. If a time lag is observed in the early phase of drug release due to highly cross-linked polymer, the above

TABLE 2 Effect of Formulation Variables on Furosemide Release Kinetics Data from ALG, ALG-PEI, and ALG-PEI-ALG Beads

Formulations/variables	n	K	Correlation coefficient (r^2)
ALG beads			
Gelation time (h)			
4	1.034	0.010	0.9988
8	1.038	0.009	0.9987
24	1.047	0.008	0.9939
$CaCl_2$ concentration (% w/v)			
1	1.071	0.009	0.9895
3	1.034	0.010	0.9988
6	1.052	0.009	0.9949
Drug load (% w/w)			
30%	1.034	0.010	0.9988
50%	0.925	0.018	0.9913
70%	0.932	0.019	0.9967
ALG-PEI beads			
1% PEI			
5 min	0.885	0.011	0.9992
10 min	0.879	0.009	0.9971
2% PEI			
5 min	0.861	0.011	0.9985
10 min	0.852	0.009	0.9915
ALG-PEI-ALG beads			
1% PEI			
5 min	0.497	0.074	0.9854
10 min	0.504	0.053	0.9852
2% PEI			
5 min	0.536	0.051	0.9877
10 min	0.441	0.072	0.9853

expression has been modified (Pillay & Fassihi, 1999) as follows:

$$M_t/M_\infty = K\ (t - t_l)^n$$

where t_l represents time lag in drug release. The release data (up to 70%) of furosemide obtained from various ALG beads were found to fit in the classical power law expression, and the values of n were around 1 (Table 2). This indicates that drug release from ALG beads followed super case II transport mechanism due to rapid swelling and erosion of the beads. The drug release data from ALG-PEI beads also fitted well in the power law expression, and the values of n decreased below 1. The formation of polyelectrolyte complex membrane reduced the initial swelling and erosion of the beads and shifted the drug release mechanism toward anomalous transport or non-Fickian kinetics, indicating that drug was diffusing out through the beads with simultaneous polymer relaxation. Because the release of the drug from ALG-PEI-ALG beads exhibited a small time lag in initial release, the release data were fitted in the modified power law expression, and excellent linearity was noted. Because the alginate coating was increased, the release mechanism leaned more toward Fickian transport. As discussed earlier, alginate coating of ALG-PEI beads increased the coating thickness or plug the surface pores, resulting in delay in initial hydration and reduced swelling of the beads. Consequently, the mechanism of drug release leans more toward Fickian transport.

CONCLUSION

This study revealed that rapid drug release in SIF, a major problem associated with ALG beads, can be reduced considerably by treating the drug-loaded ALG beads with PEI. Release of furosemide was extended over different periods of time, depending on the conditions of PEI treatment, which formed polyelectrolyte complex membrane with alginates having various thickness offering resistance to the release of the drug to different degree. Alginate coating of ALG-PEI beads further prolonged the release of furosemide in SIF by forming thicker membrane, reducing the swelling of the beads and possibly by plugging the surface pores; thus, ALG-PEI-ALG beads can be used as a controlled release dosage form of furosemide.

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