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Entrapment efficiency and release characteristics of polyethyleneimine-treated or -untreated calcium alginate beads loaded with propranolol–resin complex

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Abstract

Propranolol–HCl-loaded calcium alginate (ALG) beads, propranolol–resin complex (resinate)-loaded calcium alginate (RALG) beads and polyethyleneimine (PEI)-treated RALG (RALG–PEI) beads were prepared by ionotropic gelation/polyelectrolyte complexation method. The beads were evaluated and compared in respect of drug entrapment efficiency (DEE) and release characteristics in simulated gastric fluid (SGF, 0.1(N) HCl, pH 1.2) and simulated intestinal fluid (SIF, phosphate buffer, pH 6.8). DEE of RALG beads was considerably higher than that of ALG beads containing unresinated drug. However, DEE of RALG beads decreased with increase in both gelation time and concentration of the gel forming Ca^{2+} ions due to drug displacement from resinate. PEI treatment of RALG beads further decreased DEE as the polycation also displaced the drug from the resinate. The release of drug from all the beads was slow and incomplete in SGF owing to considerably less swelling of the beads and the decrease in drug release from the beads followed the order: RALG–PEI < RALG < ALG. In contrast to rapid discharge of the drug by ALG beads in SIF, RALG beads provided marginal prolongation in drug release as both ALG and RALG beads swelled and eroded rapidly although at different rates. On the other hand, drug release from RALG–PEI beads in SIF was considerably prolonged for different periods of time depending upon the conditions of PEI treatment. Interaction of the polycation with alginate resulted in the formation of polyelectrolyte complex membrane as evident from scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and fourier-transform infrared spectroscopy (FTIR) studies. The membrane having reduced swelling and erosion properties behaved as a physical barrier to drug release. Kinetics of the drug release also confirmed the formation of physical barrier as anomalous transport type of release associated with. RALG beads tended to shift towards Fickian transport in case of RALG–PEI beads.

Keywords: Propranolol; Cation-exchange resin; Calcium alginate; Polyethyleneimine; Drug release

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1. Introduction

Multi-unit controlled release dosage forms pass through the gut as if a solution avoiding the vagaries of gastric emptying and different transit rates (Beckett, 1980) and release drugs more uniformly in a predictable manner (Follonier and Doelkar, 1992). Various synthetic polymers have been used to develop multi-unit dosage forms using emulsion solvent evaporation methods. These techniques, although have become popular, are based on organic solvents. Possible toxicity in chronic dosing due to the presence of even traces of organic solvents in the dosage forms, the flammability, the environmental pollution associated with the use of large volume of organic solvents coupled with stringent governmental regulation that restricts their use have put into question its long term viability (Harris and Ghebre-Sellassie, 1989). Consequently, much research efforts have been concentrated on the development of microparticles using natural polymers as they are derived from natural sources, do not require organic solvent, easily available and qualified for a number of chemical modifications (Vyas and Khar, 2002). Sodium alginate, a hydrophilic biopolymer obtained from marine brown algae, appeared to be highly promising owing to its non toxic and biocompatible nature and has been investigated in details. Its unique property of forming water insoluble calcium alginate gel through ionotropic gelation with Ca^{2+} ions in a simple, mild and eco-friendly condition has made possible to encapsulate macromolecular bio-active agents like cell (Lamberti and Sefton, 1983), enzyme (Burns et al., 1985), protein (Polk et al., 1994) and vaccine (Bowersock et al., 1999). Recently much research efforts have been concentrated to develop calcium alginate (ALG) beads loaded with low molecular weight therapeutic agents. ALG beads loaded with various drugs like imipramine (Tomida et al., 1993) propranolol (Lim and Wan, 1997), Vitamin C (Cui et al., 2001), diclofenac sodium (Gonzalez – Rodriguez et al., 2002) have been developed and investigated. However, major disadvantages of ALG beads are low drug entrapment efficiency and rapid release of the loaded drugs. The loading efficiency of water soluble drugs, in particular, is much lower than that of water insoluble drugs (Aslani and Kennedy, 1996; Lee et al., 1999) and is due to leakage of drugs from ALG beads having large gel porosity (Liu et al., 1997). 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 within a few minutes (Gonzalez – Rodriguez et al., 2002) to a few hours (Tomida et al., 1993) and hence calcium alginate matrix alone do not seem suitable as an oral controlled release system (Østberg et al., 1994).

In an attempt to modify DEE and release rates of drug from ALG beads, several polymers like chitosan, pectin, methylcellulose have been used with sodium alginate (Pillay and Fassihi, 1999; El-kamel et al., 2003). Attempts have also been made to reduce and control the permeability and to increase the strength of gel network structure of islets of langerhans-loaded calcium alginate beads through interaction between alginate and poly-L-lysine (O'shea et al., 1984) or combination of poly-L-lysine and polyethyleneimine (Lim and Sun, 1980). Islets in the polycation-treated beads were reported to remain morphologically and functionally active for longer periods. Recently PEI has been used to prepare insulin-loaded dextran sulphate nanoparticles, which exhibited a prolonged hypoglycemic effect in diabetic rats (Tiyaboonchai et al., 2003). However, feasibility of using drug–resin complex (resinate), instead of free drug, in ALG beads and treating the resinate-loaded alginate (RALG) beads with PEI to modify DEE and release rates of drug has not been explored adequately.

The objective of this investigation was to develop and evaluate PEI treated or untreated ALG beads containing propranolol–resin complex in relation to DEE and release characteristics especially in SIF. The initial part of this work involved systematic study of the effect of formulation variables on physical characteristics of RALG beads. Subsequent study involved development of PEI treated RALG beads for prolonged release of the drug in SIF. Propranolol hydrochloride has been used in this study as a model drug.

2. Materials and methods

2.1. Materials

Propranolol–HCl (Sun Pharmaceutical Industries Ltd., Gujarat, India), sulphonic acid cation exchange resin in Na^+ form (Indion 254®, Ion Exchange (India) Pvt. Ltd., Mumbai, India) were obtained as gift

samples. Sodium alginate (S.D. Fine. Chem., India), polyethyleneimine (50%, w/v, Sigma–Aldrich Co., USA) and all other reagents were obtained commercially and used as received.

2.2. Methods

2.2.1. Preparation of drug-loaded ALG beads

Propranolol–HCl (20%, w/w of dry sodium alginate) was dispersed uniformly in 10 ml sodium alginate solution and homogenized for 10 min. Bubble-free dispersion was extruded through 22 bore glass syringe in a gently agitated $CaCl_2$ solution. Following gelation for predetermined times, the gelled beads were separated by filtration, washed with 3× 50 ml deionized water, air dried and finally vacuum dried for 24 h to constant weight. The following experimental parameters were varied:

(i) gelation time: 0.5, 1 and 2 h;
(ii) concentration of $CaCl_2$ solution: 1, 3 and 5% (w/v);
(iii) concentration of sodium alginate solution: 1.5, 2 and 2.5% (w/v).

2.2.2. Preparation of drug–resin complex (resinate)

Resins (300–350 mesh) were washed with deionized water (200 ml) and methanol (2× 50 ml) to remove impurities. The resins were activated by recycling alternately thrice with 1(M) NaOH (60 ml) and 1(M) HCl (60 ml) and washing after each treatment with deionized water. The resins in hydrogen/acid form were washed with deionized water until the elute was neutral and were, then, vacuum dried at 50 °C to constant weight.

About 50 mg resins, accurately weighed, were stirred at 30 °C in 75 ml propranolol–HCl solution (0.5 mg/ml) for 6 h. The resulting resinates were separated by vacuum filtration and washed with deionized water till the filtrate showed no absorbance at 290 nm for propranolol. The resinate was vacuum dried at 50 °C to constant weight.

2.2.3. Preparation of RALG beads

Resinate (30%, w/w of dry sodium alginate)-loaded RALG beads were prepared following the method of preparation of ALG beads as described in Section 2.2.1.

2.2.4. Preparation of RALG–PEI beads

Resinate (30%, w/w) was uniformly dispersed in 10 ml 2.5% sodium alginate solution and homogenized for 10 min. Bubble-free dispersion was extruded through 22 bore glass syringe in a gently agitated 3% $CaCl_2$ solution. Following gelation for 5 min, the beads were washed with 3× 50 ml deionized water. Removing the surface water with tissue paper, the beads were exposed to PEI solution (1–4%, w/v) for different periods (5–30 min). The resulting RALG–PEI beads were removed, washed with deionized water, air-dried and finally vacuum dried for 24 h.

2.2.5. Drug entrapment efficiency (DEE)

About 20 mg, accurately weighed, ALG, RALG, RALG–PEI beads were shaken for 48 h in 250 ml USP phosphate buffer solution (pH 6.8) and then filtered. The filtrate, following suitable dilution, was assayed spectrophotometrically (Hitachi, 200-20, Japan) at 290 nm. DEE was determined from the following relation:

$$\text{DEE} = \frac{\text{experimental drug content}}{\text{theoretical drug content}} \times 100$$

2.2.6. Drug release study

In vitro release of propranolol from ALG, RALG and RALG–PEI beads were monitored in 900 ml SGF and SIF at 37 ± 1 °C using programmable dissolution tester (paddle type, Electrolab, model TDT-06P (USP), India) at, respectively, 100 and 50 rpm. Aliquots were removed at predetermined times and were replenished immediately with the same volume of fresh media. The aliquots, following suitable dilution, were assayed spectrophotometrically at 290 nm. In-vitro release study of propranolol from RALG beads in deionized water at 50 rpm was also done in the same way.

2.2.7. Scanning electron microscopy (SEM)

RALG, RALG–PEI beads and their cross-sections were mounted onto stubs using double sided adhesive tape and vacuum coated with gold film using sputter coater (Edward S 150, UK). The coated surface was observed under SEM (Jeol, JSM-5200, Japan).

2.2.8. Swelling behavior of study

Dried RALG and RALG–PEI beads were incubated in HCl solution (pH 1.2) and phosphate buffer solution

(pH 6.8) and diameter of each swelling particle, taken out of the solution at predetermined times, was measured from four different positions with a digital calliper (Mitutoyo, Model CD – 6″CS, Japan) and an average of 10 particles was calculated. Swelling ratio was determined from the relation:

$$\text{swelling ratio} = \frac{\text{diameter of the beads at time } t - \text{initial diameter}}{\text{initial diameter of beads}} \times 100$$

2.2.9. Statistical analysis

Each formulation was prepared in duplicate and each analysis was duplicated. Statistical analysis of the data were performed using analysis of variance (ANOVA: single factor) with the aid of Microsoft Excel 2002. Difference was considered significant when $p < 0.05$.

3. Results and discussion

3.1. DEE of ALG bead

DEE of ALG beads containing unresinated propranolol–HCl varied from 48 to 57% depending on the preparative conditions like gelation time, $CaCl_2$ concentration and initial alginate concentration. Similar low DEE of ALG beads containing various unresinated water soluble drugs have been reported (Tomida et al., 1993; Lim and Wan, 1997) and is in agreement with the reports that drugs with higher solubility are more readily released from alginate beads during gelation process resulting in low DEE (Aslani and Kennedy, 1996; Lee et al., 1999).

3.2. DEE of RALG bead

Propranolol content of resinate was found to be $37.78 \pm 2.05\%$. The drug content of RALG beads prepared with a coat/core ratio of 7:3 is expected to be 10.97%. However, the actual drug content of RALG beads was less than the theoretical value and appeared to be related to the displacement of the drug by Ca^{2+} ions during the gelation process. The effect of preparative conditions on actual drug content of RALG beads have been presented in the form of DEE in Table 1.

Table 1
Effect of gelation time, $CaCl_2$ concentration, and initial alginate concentration on propranolol entrapment efficiency (DEE) of RALG beads

Gelation time (h)[a]	Diameter of the beads (μm) (%±S.D., $n = 10$)	DEE (%±S.D., $n = 4$)	$CaCl_2$ concentration[b] (%w/v)	Diameter of the beads (μm) (%±S.D., $n = 10$)	DEE (%±S.D., $n = 4$)	Initial alginate concentration[c] (%w/v)	Diameter of the beads (μm) (%±S.D., $n = 10$)	DEE (%±S.D., $n = 4$)
0.5	1015 (±44.2)	96.1 (±1.69)	1	1180 (±143.1)	97.6 (±0.98)	1.5	908 (±33.1)	92.6 (±1.59)
1	960 (±37.8)	80.6 (±2.01)	3	1015 (±57.8)	96.1 (±1.69)	2.0	992 (±51.5)	94.0 (±1.01)
2	816 (±27.3)	77.8 (±1.87)	5	945 (±88.0)	87.4 (±2.19)	2.5	1015 (±57.8)	96.1 (±1.69)

[a] Preparative condition: 2.5% alginate, 3% $CaCl_2$ solution.
[b] Preparative condition: 2.5%alginate, 0.5 h gelation time.
[c] Preparative condition: 3%$CaCl_2$ solution, 0.5 h gelation time.

Table 2
Propranolol content in the resinate following incubation in $CaCl_2$ solution for different period of time

Incubation time (h) in 3% $CaCl_2$ solution	Propranolol content (%) in resinate	0.5 h incubation in $CaCl_2$ solution (%w/v)	Propranolol content (%) in resinate
0.5	83.02 (±1.21)	1	87.31 (±1.28)
1	70.55 (±2.53)	3	83.02 (±1.21)
2	65.09 (±3.05)	5	77.29 (±3.01)

3.2.1. Effect of gelation time on DEE

Increase in gelation time during the preparation of RALG beads using 2.5% sodium alginate and 3% $CaCl_2$ solution decreased DEE considerably ($p < 0.05$). Increase in gelation time allows more Ca^{2+} ions to diffuse into the beads (Lim and Wan, 1997; Pillay and Fassihi, 1999). In addition to binding with GG-blocks of alginate via egg-box model during gelation (Sutherland, 1991), Ca^{2+} ions may also bind with sulphonic acid groups of the resin by displacing the bound drug. The free drug subsequently diffuses out of the beads into the aqueous medium resulting in a decrease in DEE.

3.2.2. Effect of $CaCl_2$ concentration on DEE

Keeping the alginate concentration and gelation time fixed at, respectively, 2.5% and 0.5 h, increase in $CaCl_2$ concentration also decreased the DEE significantly ($p < 0.05$). This can also been related to the displacement of bound drugs by Ca^{2+} ions. Alginate gel network scarcely affects the diffusion of small substance like Ca^{2+} ion. It is known that glucose (MW 180) can diffuse as freely into 2% Ca-alginate gel beads as in water (Tanaka et al., 1984). Thus higher the concentration of $CaCl_2$ solution, the larger the amount of Ca^{2+} ions diffused inwardly into the resinate-loaded alginate beads and consequently the larger the amount of the drug displaced from the resinate by the Ca^{2+} ions. The free drug subsequently diffused out of the beads resulting in a decrease in DEE.

3.2.3. Effect of alginate concentration on DEE

Decrease in initial alginate concentration decreased DEE significantly ($p < 0.05$) at a given gelation time (0.5 h) and $CaCl_2$ concentration (3%). Decrease in initial alginate concentration provides lesser number of binding sites of alginate for Ca^{2+} ions resulting in the formation of a less compact gel membrane, which, in turn, increases influx of Ca^{2+} ions leading to decrease in DEE.

3.3. Extent of drug displacement by cations

Incubation of propranolol–resin complex in $CaCl_2$ solutions for different periods simulating the condition of bead formation demonstrated that increase in both contact time and $CaCl_2$ concentration increased the loss of drug significantly ($p < 0.05$) from the resinate (Table 2). However, the drug loss from the resinate was not so high as could be apprehended. One of the possible causes relating to comparatively less drug loss from resinate may be the lesser affinity of Ca^{2+} ions for the sulphonic acid groups of the resin. Incubation of the resinates for 0.5 h in equimolar concentration of different cations under the condition of bead formation revealed that the displacement of the drug from the resinate decreased as the valency of the cations increased. The amount of propranolol displaced by the cations followed the order: H^+ (34.05%) > Na^+ (29.12%) > Ca^{2+} (16.50%) > Al^{3+} (13.85). This result is in agreement with the fact that exchange rate is quite rapid with smaller univalent cations and the rate of particle diffusion decreases markedly as the valency of the exchanging ions is increased. It may also be possible that total amount of the drug displaced by Ca^{2+} ions might not have diffused out of the beads. Instead, some of the displaced free drug remained in the alginate matrix. When dissolution study of RALG beads was conducted in deionized water, 17–33% drug was found to be released in 10 h (Fig. 1). It was further observed that the higher the gelation time, concentration of $CaCl_2$ and initial alginate concentration, the lesser was the amount of drug leaching out of the beads in deionized water. Moreover, increase in gelation time and the concentration of $CaCl_2$ significantly decreased ($p < 0.05$) the diameter of the beads (Table 1).

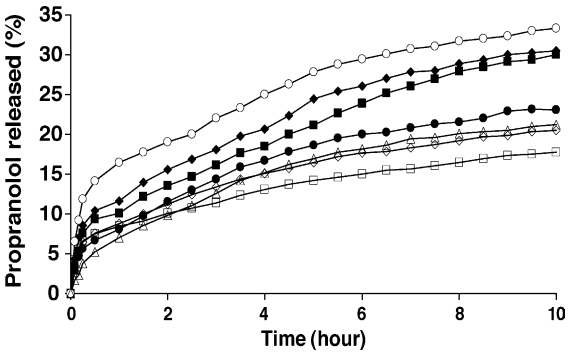

Fig. 1. Release profiles of propranolol in deionized water from RALG beads prepared under different gelation conditions: (◯) 1% $CaCl_2$, 2.5% alginate, 0.5 h gelation time, (♦) 3% $CaCl_2$, 1.5% alginate, 0.5 h gelation time, (■) 3% $CaCl_2$, 2% alginate, 0.5 h gelation time, (●) 3% $CaCl_2$, 2.5% alginate, 0.5 h gelation time, (△) 5% $CaCl_2$, 2.5% alginate, 0.5 h gelation time, (◊) 3% $CaCl_2$, 2.5% alginate, 1 h gelation time, (□) 3% $CaCl_2$, 2.5% alginate, 2 h gelation time.

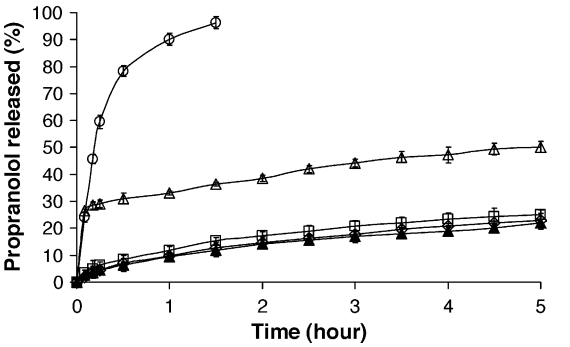

Fig. 2. Release profiles of propranolol from resinate (◯), ALG beads (△) and RALG beads prepared by gelling for 0.5 h (□), 1 h (◊) and 2 h (▲) in simulated gastric fluid.

It can, thus, be stated that increase in gelation time and $CaCl_2$ concentration increased the degree of cross-linking which was also accompanied by dehydration of alginate molecule leading to decrease in mesh size of RALG beads. Although increase in initial alginate concentration increased the diameter of RALG beads, it led to the formation of denser fully cured gel structure, which reduced the diffusion of free drug out of RALG beads resulting in higher DEE. These results indicate that decrease in DEE was the cumulative effects of drug displacement by Ca^{2+} ions, degree of cross-linking of alginate gel matrix and extent of diffusion of free drug from RALG beads. However, DEE of RALG beads was considerably higher than that of ALG beads containing unresinated drug.

3.4. Drug release in SGF

Release of propranolol in SGF from resinate, ALG beads and RALG beads prepared using 2.5% sodium alginate, 3% $CaCl_2$ and different gelation time have been presented in Fig. 2. While the release of drug from the resinate was rapid and complete in 1.5 h, the drug release from ALG beads was slow and incomplete following a burst release in the initial moment and that from RALG beads was still slower. Similar release characteristics were observed with other RALG beads prepared using different concentration of $CaCl_2$ and sodium alginate. Swelling studies at pH 1.2 showed that ALG beads swelled less at pH 1.2 and the swelling of RALG beads was still slower (Fig. 3). Thus slow penetration of dissolution fluid into the almost unswelled RALG beads together with complex drug release mechanism involving displacement of the drug from the resinate by the counter ions present in the dissolution medium and subsequent diffusion of the free drug out of the beads were responsible for extremely slow release of the drug from RALG beads.

3.5. Drug release in SIF

Release profiles of propranolol in SIF from resinate, ALG beads and RALG beads prepared using 2.5% sodium alginate, 3% $CaCl_2$ and different gelation time have been presented in Fig. 4. The release profiles of the drug from both resinate and ALG beads were identical with complete release occurring rapidly in 1.5 h. Similar rapid release of various unresinated

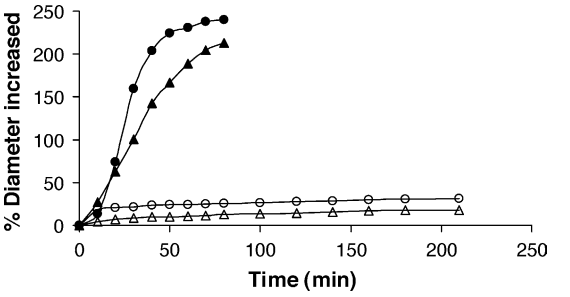

Fig. 3. Swelling behaviour of ALG beads (●) and RALG beads (▲) at pH 1.2 (open symbols) and pH 6.8 (closed symbols).

Table 3
Effect of formulation factors on the time required for 50% release ($t_{50\%}$) of propranolol from RALG beads in simulated intestinal fluid

Gelation time (h)	$t_{50\%}$(h) (mean ± S.D., $n = 4$)	$CaCl_2$ concentration (%w/v)	$t_{50\%}$(h) (mean ± S.D., $n = 4$)	Initial alginate concentration (%w/v)	$t_{50\%}$ (h) (mean ± S.D., $n = 4$)
0.5	1.76 (±0.26)	1	1.50 (±0.26)	1.5	1.16 (±0.05)
1	2.08 (±0.14)	3	1.76 (±0.26)	2.0	1.50 (±0.25)
2	2.33 (±0.32)	5	2.25 (±0.18)	2.5	1.76 (±0.26)

Preparative condition as shown in Table 1.

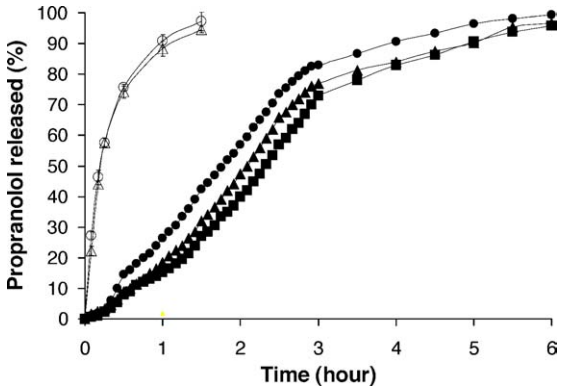

Fig. 4. Release profiles of propranolol from resinate (◯), ALG beads (△) and RALG beads prepared by gelling for 0.5 h (●), 1 h (▲) and 2 h (■) in simulated intestinal fluid.

water soluble drugs from ALG beads at higher pH have been reported (Tomida et al., 1993; El-kamel et al., 2003) and has been considered as a major problem in sustaining drug release in SIF. Thus alginate beads alone do not seem suitable as an oral controlled release dosage form (Østberg et al., 1994). Although RALG beads appeared to extend drug release upto 6 h, major portion (about 90%) of the drug was released in 3.5 h and thus RALG beads provided marginal improvement in prolonging drug release in SIF. Comparatively slow release from RALG beads was related to slower swelling of the beads in comparison to that of ALG beads (Fig. 3). Fig. 4 further shows that increase in gelation time tended to decrease the drug release as evident from the significant ($p < 0.05$) increase in the time required for 50% drug release ($t_{50\%}$). Similarly, increase in $CaCl_2$ concentration and initial alginate concentration increased the $t_{50\%}$ significantly ($P < 0.05$) (Table 3). With a view to further sustain the drug release in a more controlled manner in SIF, RALG beads were prepared by gelation in 3% $CaCl_2$ solution for 5 min and then were treated with different concentration of PEI solution for different periods of time.

3.6. Effect of PEI treatment on DEE

Treatment of RALG beads with PEI solution adversely affected DEE, which decreased with increase in both PEI concentration and exposure time (Table 4). PEI solution diffuses into the beads with time as well as due to concentration gradient. PEI is a highly branched molecule having branched sites separated by secondary amine groups. The branching distribution provides many charged nitrogen atoms and makes the molecule cationic (Kim and Park, 2004). PEI may, therefore, bind with sulphonic acid groups of the resin by displacing the resin-bound drug, which diffuses out of the beads resulting in decrease in DEE. Incubation of resinates in different concentration of PEI solution for different periods confirmed the displacement of drug by PEI as propranolol content of the resinate decreased in a similar fashion as the drug was lost from RALG–PEI beads (Table 5).

Table 4
Effect of polyethyleneimine (PEI) concentration and exposure time on propranolol entrapment efficiency (DEE) of RALG–PEI beads

PEI concentration (%w/v)	DEE (%±S.D., $n = 4$)	Exposure time (min) in 1% PEI solution	DEE (%±S.D., $n = 4$)
1	96.1 (±1.19)	5	96.1 (±1.19)
2	75.3 (±2.03)	15	80.2 (±1.54)
4	61.6 (±2.09)	30	65.4 (±1.17)

Table 5
Effect of polyethyleneimine (PEI) concentration and exposure time on loss of propranolol from resinate

PEI concentration (%w/v)	Propranolol content (%) in resinate	Exposure time (min) in 1% PEI solution	Propranolol content (%) in resinate
1	87.32 (±2.56)	5	87.32 (±2.56)
2	69.37 (±2.05)	15	73.59 (±1.54)
4	48.01 (±3.13)	30	67.19 (±2.81)

3.7. SEM studies of RALG and RALG–PEI beads

The shape of RALG beads was spherical and the surface was almost smooth (Fig. 5a). The surface of RALG–PEI beads was, however, highly striated although the spherical shape was maintained (Fig. 5b). From the cross-sectional view, the internal structure of RALG beads appeared to be a resinate-loaded matrix with smooth outer periphery (Fig. 5c). On the other hand, the resinate-loaded matrix of RALG–PEI beads appeared to be enveloped with a membrane (Fig. 5d), which might be responsible for the formation of striated surface. Being cationic, PEI might have interacted with anionic alginate polymer to form polyelectrolyte complex membrane, the thickness of which tended to increase with increase in both concentration and exposure time in PEI solution.

3.8. Effect of PEI treatment on drug release

The effect of PEI concentration on the release profiles of propranolol from RALG–PEI beads has been presented in Fig. 6. Following a burst release, no significant increase in drug release in SGF was observed. On the other hand, release of the drug in SIF was characterized by an initial slow release followed by gradual release in a more controlled manner over an extended period of time. Increase in PEI concentration decreased the release of drug. Similar release characteristics were observed from RALG–PEI beads, which

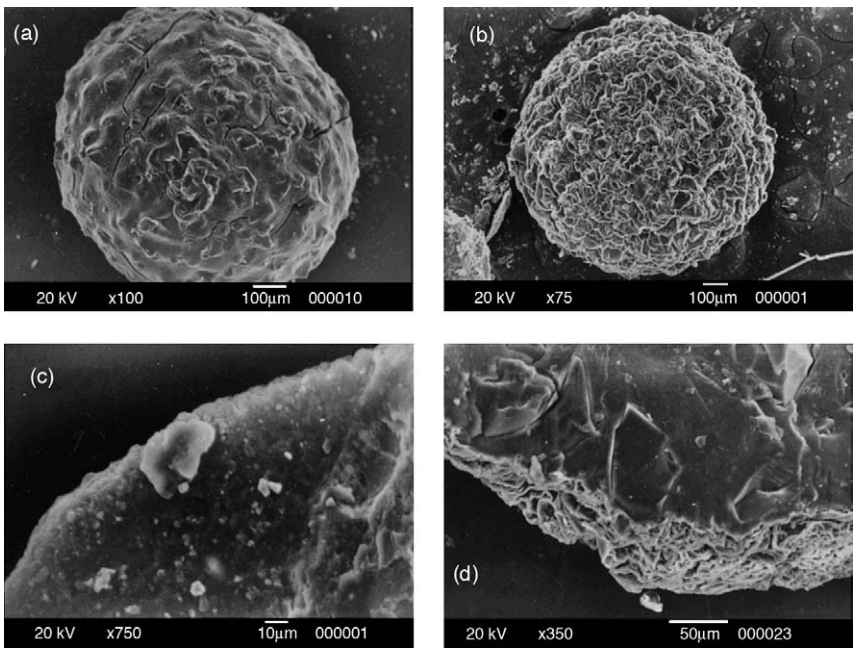

Fig. 5. Scanning electron micrographs of RALG bead (a), RALG–PEI bead (b), cross-section of RALG bead (c) and RALG–PEI bead (d).

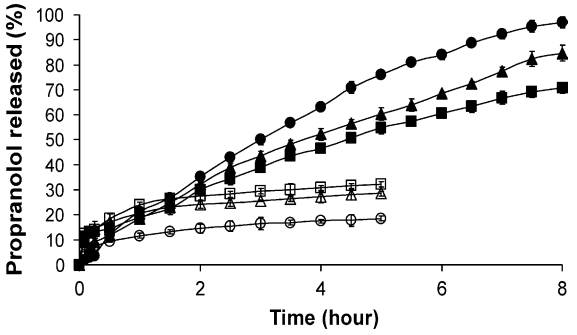

Fig. 6. Release profiles of propranolol from RALG–PEI bead in simulated gastric fluid (open symbol) and in simulated intestinal fluid (closed symbol): (◯) 1% PEI, 5 min, (△) 2% PEI, 5 min, (□) 4% PEI, 5 min.

were treated with 1%PEI solution for different periods (Fig. 7). Swelling of RALG–PEI beads at pH 1.2 and 6.8 have been represented in terms of increase in diameter in Fig. 8. Following an initial swelling, the beads did not swell appreciably at pH 1.2. The initial swelling was responsible for the burst release of propranolol in SGF. On the other hand, following an initial slow swelling, the beads swelled gradually at pH 6.8 and the degree of swelling and erosion decreased with increase in the concentration and exposure time in PEI solution. The drug release in SIF correlated well with the swelling behavior of RALG–PEI beads. Reduced swelling and erosion of RALG–PEI beads and consequent prolonged drug release in SIF was due to high molecular entanglement developed by the presence of highly branched PEI molecule and formation of polyelectrolyte complex membrane through interaction between alginate and PEI.

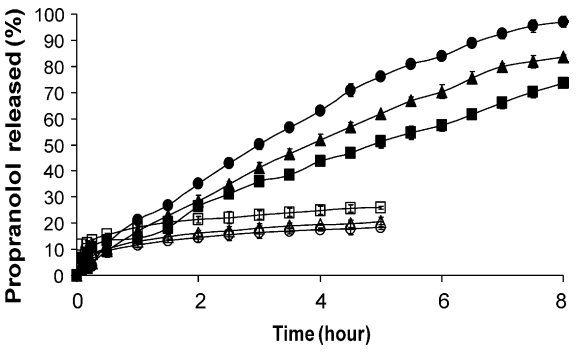

Fig. 7. Release profiles of propranolol from RALG–PEI bead in simulated gastric fluid (open symbol) and in simulated intestinal fluid (closed symbol): (◯) 1% PEI, 5 min, (△) 1% PEI, 15 min, (□) 1% PEI, 30 min.

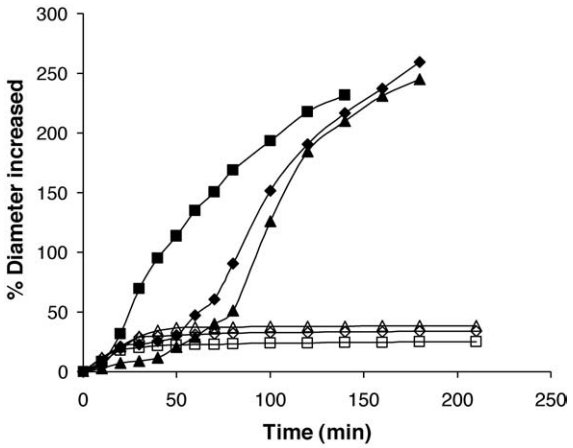

Fig. 8. Swelling behaviour of RALG–PEI beads prepared using different concentration of PEI for different time: 1%, 5 min (□), 1%, 30 min (◊), 4%, 5 min (△) at pH 1.2 (open symbols) and pH 6.8 (closed symbols).

3.9. Kinetics of drug release

Release of a drug from a simple swellable polymeric matrix follows power law expression $M_t/M_\alpha = Kt^n$ where the notations represent the usual meaning (Ritger and Peppas, 1987). If a drug release is accompanied with an initial time lag (t_1), modified power law expression $M_t/M_\alpha = K(t - t_1)^n$ can be used to describe drug release (Pillay and Fassihi, 1999). The release data (upto 75%) of propranolol from RALG beads were found to fit well in the modified power law expression. The values of n were greater than 0.5 but less than 1 indicating that the drug release followed anomalous transport. In addition, increase in gelation time, concentration of $CaCl_2$ and sodium alginate during the preparation of RALG beads tended to decrease the values of n (Table 6) due to decrease in swelling and erosion of the beads. The drug release from RALG–PEI beads also obeyed modified power law expression although the values of n were found to further decrease (Table 7) with increase in PEI concentration and exposure time and thus the release mechanism tended to shift from anomalous transport to Fickian transport as

Table 6
Effect of formulation factors on propranolol release kinetic data from RALG beads at pH 6.8

Gelation time (h)	k	n	r^2	Initial alginate concentration (%w/v)	k	n	r^2	$CaCl_2$ concentration (%w/v)	k	n	r^2
0.5	0.06	0.76	0.988	1.5	0.019	0.81	0.995	1	0.017	0.79	0.997
1	0.08	0.70	0.935	2.0	0.018	0.80	0.989	3	0.016	0.76	0.988
2	0.07	0.59	0.893	2.5	0.016	0.76	0.988	5	0.040	0.53	0.967

Preparative conditions as shown in Table 1.

Table 7
Effect of formulation factors on propranolol release kinetics data from RALG–PEI beads at pH 6.8

PEI concentration (%w/v)	k	n	r^2	Exposure time (min) in 1% PEI solution	k	n	r^2
1	0.022	0.60	0.985	5	0.022	0.60	0.985
2	0.026	0.56	0.997	15	0.021	0.60	0.987
4	0.030	0.52	0.988	30	0.035	0.49	0.997

the treatment with PEI further reduced the swelling and erosion of the beads.

4. Conclusion

This study reveals that alginate beads having reasonably high propranolol content can be prepared even from an aqueous preparative condition by incorporating the drug in the form of resinate into alginate beads. Rapid release of the drug at higher pH can also be prevented by treating RALG beads with PEI. PEI appears to interact with alginate to form a polyelectrolyte complex membrane having reduced swellability and possibly gel porosity and to provide a physical barrier to drug release. This novel and simple method seems to be suitable for prolonged delivery of propranolol, a highly water-soluble drug, in SIF in which alginate beads are highly sensitive.

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