CHAPTER V

MICROENCAPSULATION OF DRUG-RESIN COMPLEX USING SODIUM ALGINATE AS NATURAL POLYMER
1. Introduction

The naturally occurring alginate polymer have a wide potential in drug formulation due to their extensive application as food additives and their recognized lack of toxicity. Alginates can be tailor-made to suit the demands of applicants in both the pharmaceutical and biomedical areas. This group of polymers possesses a number of characteristics that makes it useful as a formulation aid, both as a conventional excipients and more specifically as a tool in polymeric-controlled drug delivery. Alginate are natural polysaccharide polymers isolated from brown seaweed (Phaeophyceae). The seaweed is extracted with a dilute alkaline solution which solubilizes the alginic acid present. Free alginic acid is obtained on treatment of resulting thick and viscous mass with mineral acid. The alginic acid can then be converted to a salt of which sodium alginate is the major form currently used. Alginic acid is a linear polymer consist of D-mannuronic acid and L-guluronic acid residues that are arranged in the polymer chain in blocks. These homogeneous blocks (composed of either acid residue alone) are separated by blocks made of altering units of mannuronic and guluronic acids (Smidsrod and Draget, 1996). Alginate from different sources vary in their proportions of blocks. Hydration of alginic acid leads to the formation of a high viscosity ‘acid gel’ due to intermolecular binding. After gelation the water molecules are physically entrapped inside the alginate matrix, but are still free to migrate. This is of great importance in many application (e.g., alginate gels for cell immobilization/encapsulation). The water holding capacity of the gel is due to capillary forces. Heat-stable gels can develop at room temperature. The monovalent metal ions like Na\(^+\) form soluble salts with alginate whereas divalent and multi-valent cations (except Mg\(^{2+}\)) form gels or precipitates. The various cations show different affinity for alginate and selective ion binding is the basis for the ability of alginate to form ionotropic hydrogels. Alginate with a high content of guluronic acid blocks give gels of considerably higher strength compared to alginates rich in mannuronate as G residues exhibit a stronger affinity for divalent ion than M residues (Draget, et al., 1994). Transmittancy, swelling and visoelasticity of alginate gel membrane are highly affected by the M G ratio (Draget, et al., 1996). The ability of alginate to form two types of gel dependending on pH, i.e. an acid gel and ionotropic gel, gives the polymer unique properties compared to neutral macromolecules. The physiochemical properties of the
polymer system and the swelling process to activate the release of drugs will be dependent on the type of gel formed. The calcium alginate gels, formed by the binding of Ca\(^{+2}\) ions with carboxyl groups of GG-blocks of alginate via egg-box model (Sutherland 1991), are the most extensively studied. 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 and an almost immediate hydration of that alginate gel bead to create a hydrocolloidal layer of high viscosity which decrease the migration of small molecules (drugs) has made possible in the design of controlled delivery drug delivery system. Many workers have been investigated the controlled release phenomenon of water insoluble drugs using alginate.

Tomida et al (1993) prepared theophylline-loaded alginate gel capsules and studied the drug release characteristics. They reported that the efficiency of drug encapsulation decreased with an increase of the coating time, and increased with an increase of CaCl\(_2\) concentration and theophylline loading dose in the core dispersion. Similarly the coat thickness increased with coating time, and the CaCl\(_2\) concentration and as a result, the release rates were significantly reduced as the coat thickness increased.

Tateshita et al (1993) studied the dissolution and absorption of nifedipine from alginate gel beads and they reported that the release of nifedipine was affected by the composition of uronic acid in alginate and the nifedipine content in alginate beads.

Shiraishi et al (1993) prepared alginate gel beads containing indomethacin and studied the release of indomethacin at pH 1.2 and 6.8. They reported that though the indomethacin was not released from the beads at pH 1.2, it was released according to the swelling of alginate gel at pH 6.8 and the release decreased with the decreasing ratio of mannuronic acid (M) to guluronic acid (G) in alginate.

Torre et al (1998) prepared and characterized the calcium alginate beads containing ampicillin. They reported that the control of the drug release for different time intervals depended on the molecular weight of the polymer used, however, the pH-change test showed that this capacity was much lower in the case of acid-treated particles.

Sugawara et al (1994) reported that in a release study of alginate gel beads containing prednisolone, swelling and erosion of the beads were observed at pH 6.8,
whereas no swelling occurred at pH 1.2 and therefore, the amount of released prednisolone was greater at pH 6.8 than at pH 1.2.

Arica et al (2002) prepared 5-fluorouracil (5-FU) by gelation of alginate with calcium cations and reported that as the drug load increased, larger beads were obtained in which the resultant beads contained higher 5-FU content and the amount of 5-FU released from the alginate beads increased with decreasing alginate concentration.

Alginate gel beads have also been developed to encapsulate highly water soluble drugs.

Tomida et al (1993) prepared calcium alginate beads by simple soaking plain Ca-alginate gel beads in a imipramine solution. The release rates were also measured in HCl solution, NaCl solution and acetate buffers. They suggested that imipramine ions interacting with the acidic residues of alginate were replaced by cations in the release medium and therefore, Ca-alginate gel beads could be a useful vehicle for the controlled release of water soluble cationic drugs.

Lim and Wan (1997) prepared propranolol hydrochloride loaded calcium alginate beads and studied the characteristics of the drug-loaded beads. They reported that the efficiency of loading and extent of binding of a cationic drug such as propranolol in calcium alginate beads are influenced by the method of drug incorporation and the concentration of Ca\(^{2+}\), both bound and unbound, in the beads.

Segi et al (1989) investigated calcium-induced gel beads for propranolol, selected as a cationic model drug with particular attention to the effects of excess Ca\(^{2+}\) in the beads, pH and drug concentration in the bulk solution. They concluded that the loading capacity could be controlled by adjusting the pH of the medium, and the precipitated form of the drug possibly acts as a good reservoir for efficient drug release.

However, major disadvantages of ALG beads are low drug entrapment efficiency and rapid release of the loaded drugs, in particular, water soluble drugs. However, Ferreira Almeida and Almeida (2004) reported that calcium alginate beads are known to be unable to control the release of most insoluble drugs. The loading efficiency of water soluble drugs is much lower than that of water insoluble drugs.

Aslani and Kennedy (1996) entrapped paracetamol in alginate beads gelled with calcium or zinc and reported that due to rapid release in acidic condition and complete
release in simulated gastric fluid within 2h, the alginate beads loaded with a relatively water soluble drug will not provide satisfactory prolonged release orally.

Lee et al (1999) studied the trapping efficiency and release profile of alginate beads containing drugs with different solubility like ibuprofen, aspirin, cimetidine, melatonin and sodium salicylate in simulated gastric and intestinal fluids and suggested that a drug with high solubility than that of low solubility could be more readily released from the alginate beads during gelling process, resulting in low trapping efficiency and at same time highly water soluble drugs like sodium salicylate was released relatively rapidly than drugs with low solubility.

Ostberg et al (1994) studied the release properties of calcium alginate minimatrices containing three drugs having different aqueous solubility (paracetamol, theophylline and chloramphenicol) in simulated gastric and intestinal fluids. They reported that in simulated intestinal fluid the swelling and, in later case, erosion and dissolution of the matrices induced a rapid release of the encapsulated drugs which also depended on the solubility of the drugs. Therefore, they concluded that the minimatrices made of calcium alginate do not seem applicable as an oral controlled release system.

Gonzalez-Rodriguez et al (2002) prepared alginate/chitosan particles containing sodium diclofenac by ionic gelation (Ca$^{+2}$ and Al$^{+3}$) and examined to release the active substance as a function of pH of dissolution medium. They reported that the release of sodium diclofenac is prevented in acidic pH, while the release is complete in a few minutes when the pH is raised up to 6.4 and 7.2.

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.

Takka and Acarturk (1999) prepared controlled release nicardpine HCl gel microparticles using alginate and chitosan. They observed that the alginate-chitosan complex formation reduced the erosion of the matrix at pH 7-7.5 and consequently retarded the release.

El-Kamel et al (2003) prepared methylcellulose-Ca-alginate beads containing diltiazem hydrochloride and observed an extended release pattern in both the pH (1.2 and 6.8).
Tapia et al (2004) used mixture and/or polyelectrolyte complexes for both chitosan-alginate and chitosan-carrageenan as prolonged drug release system and concluded that chitosan-alginate system is better than the chitosan-carrageenan as prolonged drug release matrix.

Sezer and Akbuga (1999) investigated the possible applicability of chitosan treated alginate beads containing timolol maleate and concluded that chitosan treated alginate beads may be used for a potential controlled release system of small molecule drugs with high solubility, instead of alginate beads.

Pillay and Fassihi (1999) investigated the crosslinking of sodium alginate, low methoxylated pectin and their binary mixture with calcium ions through ionotropic gelation and studied the controlled release pattern of diclofenac sodium in different pH medium.

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. This part of the work was intended to encapsulate drug-resin complex with alginate and to evaluate the resulting microbeads as prolonged release devices for highly water soluble drugs. It was also intended to further modify the resinate-loaded alginate beads by treating with PEI with a view to characterize the PEI-treated resinate-loaded alginate beads with respect to drug entrapment efficiency and release of drug in different pH media.
2. Materials

<table>
<thead>
<tr>
<th>Materials</th>
<th>Grade</th>
<th>Supplier</th>
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<tr>
<td>Sodium alginate</td>
<td>Laboratory Reagent</td>
<td>S.D. Fine. Chem., Mumbai, India</td>
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<tr>
<td>Polyethyleneimine (50% w/v)</td>
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<td>Sigma-Aldrich Co., USA</td>
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<td>Calcium Chloride (Dihydrate)</td>
<td>Laboratory Reagent</td>
<td>Qualigens® Fine Chemicals.; Mumbai, India</td>
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<td>Sodium hydroxide pellets</td>
<td>Laboratory Reagent</td>
<td>Quest Chemicals.; Kolkata, India</td>
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<td>Potassium dihydrogen-orthophosphate</td>
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<td>D.I. Laboratories.; Kolkata, India</td>
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<td>Hydrochloric acid</td>
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<td>E. Merck (india).; Mumbai, India</td>
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3. Methods:

3.1. Preparation of diltiazem – loaded ALG beads:

Diltiazem – HCl (20 % w/w of dry sodium alginate) was dispersed uniformly in 10ml sodium alginate solution and homogenized for 10 min. Bubble – free dispersion was extruded through 22 bore glass syringe in a gently agitated 3% CaCl₂ solution. Following gelation for 30 min, the gelled beads were separated by filtration, washed with 3x50ml deionized water, air dried and finally vacuum dried for 24h to constant weight.

3.2. Preparation of propranolol – loaded ALG beads:

Propranolol-loaded ALG beads prepared following the same method as described in 3.1.

3.3. Preparation of RALG beads:

Resinate (30 % w/w of dry sodium alginate)-loaded alginate (RALG) beads were prepared following the method of preparation of ALG beads as described in 3.1. and following experimental parameters were varied:

(i) Concentration of sodium alginate solution: 1.5, 2 and 2.5% w/v
(ii) Concentration of CaCl₂ solution: 1, 3 and 5% w/v
(iii) Incubation time: 0.5, 1, 2 and 4 h
(iv) Resin size: 100-200, 240-300 and 300-350 mesh
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<tr>
<th>Formula 1</th>
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<td>Alginate: 250mg</td>
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<tr>
<td>Deionized water: 10ml</td>
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<tr>
<td>CaCl&lt;sub&gt;2&lt;/sub&gt; solution in: 3% w/v (100ml)deionized water</td>
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<td>Deionized water: 10ml</td>
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<td>CaCl&lt;sub&gt;2&lt;/sub&gt; solution in: 3% w/v (100ml)deionized water</td>
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<td>CaCl&lt;sub&gt;2&lt;/sub&gt; solution in: 1% w/v (100ml)deionized water</td>
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Formula 9
Resinate (containing: 107mg 38.41% diltiazem)
Resinate Size: #240-300
Alginate: 250mg
Deionized water: 10ml
CaCl₂ solution in: 3% w/v
(100ml) deionized water
Incubation time: 0.5h

Formula 10
Resinate (containing: 107mg 38.41% diltiazem)
Resinate Size: #100-200
Alginate: 250mg
Deionized water: 10ml
CaCl₂ solution in: 3% w/v
(100ml) deionized water
Incubation time: 0.5h

Formula 11
Resinate (containing: 107mg 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl₂ solution in: 3% w/v
(100ml) deionized water
Incubation time: 0.5h

Formula 12
Resinate (containing: 107mg 39.78% propranolol)
Resinate Size: #300-350
Alginate: 200mg
Deionized water: 10ml
CaCl₂ solution in: 3% w/v
(100ml) deionized water
Incubation time: 0.5h

Formula 13
Resinate (containing: 107mg 39.78% propranolol)
Resinate Size: #150-300
Alginate: 250mg
Deionized water: 10ml
CaCl₂ solution in: 3% w/v
(100ml) deionized water
Incubation time: 0.5h

Formula 14
Resinate (containing: 107mg 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl₂ solution in: 3% w/v
(100ml) deionized water
Incubation time: 0.5h

Formula 15
Resinate (containing: 107mg 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl₂ solution in: 3% w/v
(100ml) deionized water
Incubation time: 2h

Formula 16
Resinate (containing: 107mg 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl₂ solution in: 1% w/v
(100ml) deionized water
Incubation time: 0.5h

Formula 17
Resinate (containing: 107mg 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl₂ solution in: 5% w/v
(100ml) deionized water
Incubation time: 0.5h
3.4. 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 % CaCl₂ solution. Following gelation for 5 min, the beads were washed with 3x50ml deionized water. Removing the surface water with tissue paper, the beads were exposed to PEI solution for different periods. The resulting RALG – PEI beads were removed, washed with deionized water, air dried and finally vacuum dried for 24 h. The following experimental parameters were varied:

(i) Concentration of PEI solution: 1, 2 and 4% w/v
(ii) Exposure time in PEI solution: 5, 15 and 30 min
(iii) Size of resinate: 100-200, 240-300 and 300-350 mesh
(iv) Resinate loading (%w/w): 10, 30, and 50
**Formula 22**

Resinate (containing: 107mg 38.41% diltiazem)  
Resinate Size: #300-350  
Alginate: 250mg  
Deionized water: 10ml  
CaCl₂ solution in: 3% w/v (100ml) deionized water  
Incubation time: 5min  
PEI solution (50ml): 1% w/v  
Exposure time in PEI: 30min

**Formula 23**

Resinate (containing: 107mg 38.41% diltiazem)  
Resinate Size: #300-350  
Alginate: 250mg  
Deionized water: 10ml  
CaCl₂ solution in: 3% w/v (100ml) deionized water  
Incubation time: 5min  
PEI solution (50ml): 2% w/v  
Exposure time in PEI: 5min

**Formula 24**

Resinate (containing: 107mg 38.41% diltiazem)  
Resinate Size: #300-350  
Alginate: 250mg  
Deionized water: 10ml  
CaCl₂ solution in: 3% w/v (100ml) deionized water  
Incubation time: 5min  
PEI solution (50ml): 1% w/v  
Exposure time in PEI: 5min

**Formula 25**

Resinate (containing: 107mg 38.41% diltiazem)  
Resinate Size: #240-300  
Alginate: 250mg  
Deionized water: 10ml  
CaCl₂ solution in: 3% w/v (100ml) deionized water  
Incubation time: 5min  
PEI solution (50ml): 1% w/v  
Exposure time in PEI: 5min

**Formula 26**

Resinate (containing: 107mg 38.41% diltiazem)  
Resinate Size: #100-200  
Alginate: 250mg  
Deionized water: 10ml  
CaCl₂ solution in: 3% w/v (100ml) deionized water  
Incubation time: 5min  
PEI solution (50ml): 1% w/v  
Exposure time in PEI: 5min

**Formula 27**

Resinate (containing: 107mg 38.41% diltiazem)  
Resinate Size: #300-350  
Alginate: 250mg  
Deionized water: 10ml  
CaCl₂ solution in: 3% w/v (100ml) deionized water  
Incubation time: 5min  
PEI solution (50ml): 1% w/v  
Exposure time in PEI: 5min

**Formula 28**

Resinate (containing: 250mg 38.41% diltiazem)  
Resinate Size: #300-350  
Alginate: 250mg  
Deionized water: 10ml  
CaCl₂ solution in: 3% w/v (100ml) deionized water  
Incubation time: 5min  
PEI solution (50ml): 1% w/v  
Exposure time in PEI: 5min

**Formula 29**

Resinate (containing: 250mg 39.78% propranolol)  
Resinate Size: #300-350  
Alginate: 250mg  
Deionized water: 10ml  
CaCl₂ solution in: 3% w/v (100ml) deionized water  
Incubation time: 5min  
PEI solution (50ml): 1% w/v  
Exposure time in PEI: 5min
**Formula 30**
Resinate (containing 107mg, 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl$_2$ solution in: 3%w/v
(100ml)deionized water
Incubation time: 5min
PEI solution (50ml): 2%w/v
Exposure time in PEI: 5min

**Formula 31**
Resinate (containing 107mg, 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl$_2$ solution in: 3%w/v
(100ml)deionized water
Incubation time: 5min
PEI solution (50ml): 4%w/v
Exposure time in PEI: 5min

**Formula 32**
Resinate (containing 107mg, 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl$_2$ solution in: 3%w/v
(100ml)deionized water
Incubation time: 5min
PEI solution (50ml): 1%w/v
Exposure time in PEI: 15min

**Formula 33**
Resinate (containing 107mg, 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl$_2$ solution in: 3%w/v
(100ml)deionized water
Incubation time: 5min
PEI solution (50ml): 1%w/v
Exposure time in PEI: 30min

**Formula 34**
Resinate (containing 107mg, 39.78% propranolol)
Resinate Size: #240-300
Alginate: 250mg
Deionized water: 10ml
CaCl$_2$ solution in: 3%w/v
(100ml)deionized water
Incubation time: 5min
PEI solution (50ml): 2%w/v
Exposure time in PEI: 5min

**Formula 35**
Resinate (containing 107mg, 39.78% propranolol)
Resinate Size: #100-200
Alginate: 250mg
Deionized water: 10ml
CaCl$_2$ solution in: 3%w/v
(100ml)deionized water
Incubation time: 5min
PEI solution (50ml): 2%w/v
Exposure time in PEI: 5min

**Formula 36**
Resinate (containing 27.78mg, 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl$_2$ solution in: 3%w/v
(100ml)deionized water
Incubation time: 5min
PEI solution (50ml): 1%w/v
Exposure time in PEI: 5min

**Formula 37**
Resinate (containing 250mg, 39.78% propranolol)
Resinate Size: #300-350
Alginate: 250mg
Deionized water: 10ml
CaCl$_2$ solution in: 3%w/v
(100ml)deionized water
Incubation time: 5min
PEI solution (50ml): 1%w/v
Exposure time in PEI: 5min
3.5. Diltiazem entrapment efficiency (DEE):

About 20mg, accurately weighed, ALG, RALG, RALG-PEI beads were shaken for 48 h in 250 ml USP phosphate buffer solution (pH 7.2) and then filtered. The filtrate, following suitable dilution, was assayed spectrophotometrically (Hitachi, 200-20, Japan) at 236nm for diltiazem hydrochloride. DEE was determined from the following relation:

\[
    \text{DEE} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100
\]

3.6. Propranolol entrapment efficiency (DEE):

Propranolol entrapment efficiency (DEE) was determined following the same method described in 3.5.

3.7. Water absorption profile of resin-loaded ALG beads:

20 dry ALG beads containing drug – free resin were immersed in 50 ml deionized water. The beads were removed at predetermined times, freed from surface water with tissue paper and weighed in an electronic balance (Precisa, XB 600M-C, Switzerland). The amount of water absorbed was determined from the relation:

\[
    \% \text{ water absorbed} = \frac{\text{Weight of the beads at time t} - \text{initial weight of beads}}{\text{Initial weight of beads}} \times 100
\]

3.8. Diltiazem release study:

In-vitro release of diltiazem from ALG, RALG and RALG-PEI 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 236 nm. In vitro release of diltiazem from ALG beads in deionized water was studied in the same way.

3.9. Propranolol release study:

In-vitro release of propranolol from ALG, RALG and RALG-PEI was monitored following the same method described in 3.8. The amount of propranolol released from ALG beads in deionized water was monitored in the same way.
3.10. 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).

3.11. Differential scanning calorimetry (DSC) study:

The thermal events of alginate and alginate – PEI films were observed under nitrogen atmosphere in a differential scanning calorimeter (Perkin – Elmer, DSC – 7) fitted with intra – cooler 1 and calibrated with indium. About 5 mg samples was sealed in aluminium pan by quick press and heated at a scan speed of 10°C/min from -30°C – 200°C.

3.12. Fourier – transform infra – red spectroscopy (FTIR) study:

FTIR spectra of alginate and alginate – PEI films were recorded in a FTIR spectrophotometer (FTIR 670, JASCO, Japan) at a scan speed of 2 mm/sec from 4000 cm⁻¹ to 400 cm⁻¹ using KBr pellets.

3.13. Swelling behavior study:

Dried RALG and RALG – PEI beads were incubated in HCl solution (pH1.2) 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 the average of 10 particles was calculated. Swelling ratio was determined from the relation:

\[
\text{Swelling ratio} = \frac{\text{Diameter of the beads at time } t - \text{ initial diameter}}{\text{Initial diameter of beads}} \times 100
\]

4. Results and discussion

4.1. DEE of diltiazem and propranolol hydrochloride loaded ALG bead:

DEE of ALG beads containing unresinated diltiazem and propranolol -HCl varied from 47.2 to 54.6% and 48 to 57% respectively depending on the preparative conditions like gelation time, CaCl₂ concentration and initial alginate concentration. Similar low DEE of ALG beads containing unresinated water soluble drugs have been reported (Tomida et al., 1993). Lim and Wan (1997) have reported that only 38.34% w/w
propranolol hydrochloride could be loaded in alginate beads prepared with 2 % w/v alginate and 2.5% w/v CaCl₂ solution for 2h. This 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 & Kennedy, 1996; Lee et al., 1999).

4.2. DEE of diltiazem and propranolol hydrochloride loaded RALG bead:

Diltiazem and Propranolol content of resinate were found to be respectively 38.41±1.05 % and 37.78±2.05 %. At a coat/core ratio of 7:3, diltiazem and propranolol content of RALG beads are expected to be respectively 10.97 % and 11.51 %. However, the actual drug content of RALG beads was less than the theoretical value and appeared to be related to the displacement of the drugs by Ca²⁺ 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 Tables 1 and 2.
Table 1
Effect of gelation time, CaCl$_2$ concentration, initial alginate concentration and size of resinate particles on diltiazem entrapment efficiency (DEE) and diameter of RALG beads.

<table>
<thead>
<tr>
<th>Gelation time (h)$^a$</th>
<th>Diameter of the beads (µm) (%±s.d., n=10)</th>
<th>DEE (%±s.d., n=4)</th>
<th>CaCl$_2$ concentration$^b$ (%w/v)</th>
<th>Diameter of the beads (µm) (%±s.d., n=10)</th>
<th>DEE (%±s.d., n=4)</th>
<th>Initial alginate concentration$^c$ (%w/v)</th>
<th>Diameter of the beads (µm) (%±s.d., n=10)</th>
<th>DEE (%±s.d., n=4)</th>
<th>Resin size (mesh)$^d$</th>
<th>Diameter of the beads (µm) (%±s.d., n=10)</th>
<th>DEE (%±s.d., n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1074 (±51.3)</td>
<td>95.49 (±1.91)</td>
<td>1</td>
<td>1210 (±44.5)</td>
<td>98.23 (±1.54)</td>
<td>1.5</td>
<td>934 (±21.9)</td>
<td>91.08 (±1.23)</td>
<td>100-200</td>
<td>1105 (±55.5)</td>
<td>92.53 (±1.19)</td>
</tr>
<tr>
<td>1</td>
<td>961 (±27.4)</td>
<td>82.69 (±2.17)</td>
<td>3</td>
<td>1074 (±51.3)</td>
<td>95.49 (±1.91)</td>
<td>2.0</td>
<td>985 (±41.3)</td>
<td>92.08 (±2.01)</td>
<td>240-300</td>
<td>1091 (±48.7)</td>
<td>93.81 (1.21)</td>
</tr>
<tr>
<td>2</td>
<td>915 (±31.1)</td>
<td>79.48 (±1.29)</td>
<td>5</td>
<td>933 (±39.6)</td>
<td>85.76 (±2.07)</td>
<td>2.5</td>
<td>1074 (±51.3)</td>
<td>95.49 (±1.91)</td>
<td>300-350</td>
<td>1074 (±51.3)</td>
<td>95.49 (±1.91)</td>
</tr>
<tr>
<td>4</td>
<td>885 (±22.8)</td>
<td>67.15 (±1.67)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Preparative condition: a- 2.5% alginate, 3% CaCl$_2$ solution, resin size 300-350 mesh; b- 2.5%alginate, 0.5h gelation time, resin size 300-350 mesh; c- 3%CaCl$_2$ solution, 0.5h gelation time, resin size 300-350 mesh; d- 2.5% alginate, 3% CaCl$_2$ solution, 0.5h gelation time.
Table 2

Effect of gelation time, CaCl$_2$ concentration, and initial alginate concentration on propranolol entrapment efficiency (DEE) and diameter of RALG beads.

<table>
<thead>
<tr>
<th>Gelation time (h)</th>
<th>Diameter of the beads (µm) (%±s.d., n=10)</th>
<th>DEE (%±s.d., n=4)</th>
<th>CaCl$_2$ concentration (%w/v)</th>
<th>Diameter of the beads (µm) (%±s.d., n=10)</th>
<th>DEE (%±s.d., n=4)</th>
<th>Initial alginate concentration (%w/v)</th>
<th>Diameter of the beads (µm) (%±s.d., n=10)</th>
<th>DEE (%±s.d., n=4)</th>
<th>Resin size (mesh)</th>
<th>Diameter of the beads (µm) (%±s.d., n=10)</th>
<th>DEE (%±s.d., n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1015 (±44.2)</td>
<td>96.11 (±1.69)</td>
<td>1</td>
<td>1180 (±143.1)</td>
<td>97.59 (±0.98)</td>
<td>1.5</td>
<td>908 (±33.1)</td>
<td>92.58 (±1.59)</td>
<td>100-200</td>
<td>1083 (±61.5)</td>
<td>93.05 (±0.87)</td>
</tr>
<tr>
<td>1</td>
<td>960 (±37.8)</td>
<td>80.61 (±2.01)</td>
<td>3</td>
<td>1015 (±57.8)</td>
<td>96.11 (±1.69)</td>
<td>2.0</td>
<td>992 (±51.5)</td>
<td>94.01 (±1.01)</td>
<td>240-300</td>
<td>1065 (±31.9)</td>
<td>94.86 (±1.17)</td>
</tr>
<tr>
<td>2</td>
<td>816 (±27.3)</td>
<td>77.79 (±1.87)</td>
<td>5</td>
<td>945 (±88.0)</td>
<td>87.41 (±2.19)</td>
<td>2.5</td>
<td>1015 (±57.8)</td>
<td>96.11 (±1.69)</td>
<td>300-350</td>
<td>1015 (±44.2)</td>
<td>96.11 (±1.69)</td>
</tr>
</tbody>
</table>

Preparative condition: as shown in Table 1
4.2.1. Effect of gelation time on DEE:

Increase in gelation time during the preparation of RALG beads using 2.5 % sodium alginate and 3 % CaCl₂ solution decreased DEE considerably. Increase in gelation time allows more Ca²⁺ ions to diffuse into the beads (Lim & Wan, 1997; Pillay & 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.

4.2.2. Effect of CaCl₂ concentration on DEE:

Keeping the alginate concentration and gelation time fixed at respectively 2.5% and 0.5 h, increase in CaCl₂ concentration also decreased the DEE although less drastically than gelation time. Lim and Wan (1997) have reported that with increase the concentration CaCl₂ from 0.25% to 7.5%w/v, the DEE of unresinated propranolol hydrochloride was reduced from 59.78% to 23.18%w/w. Studies on gelation kinetics of alginate beads revealed that at a given gelation time increase in CaCl₂ concentration increases the thickness of the outer gel membrane and thereby, decreases the influx of Ca⁺² ions into the beads (Blandino et al., 1999). Reduced influx of Ca⁺² ions was responsible for the lesser drug loss from RALG beads.

4.2.3. Effect of alginate concentration on DEE:

Decrease in initial alginate concentration decreased DEE at a given gelation time (0.5 h) and CaCl₂ 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.

4.2.4. Effect of resin size on DEE:

Since the beads were prepared keeping all other formulation variables like gelation time (0.5h), CaCl₂ concentration (3%w/v) and initial alginate concentration
(2.5% w/v) constant, the increase in DEE could be related to the higher equilibrium drug content in the resinates having smaller resin size. Decrease in resin size tended to increase DEE marginally (Tables 1 and 2). This could be related to higher equilibrium drug content in resinate having smaller size.

4.3. Water absorption by drug-free resin-loaded ALG bead:

If increase in gelation time, CaCl₂ concentration and initial alginate concentration result in higher degree of cross-links, then the dried beads will absorb less water as the degree of cross-linking increases. The dry resin-loaded alginate beads which were prepared using higher gelation time, CaCl₂ concentration and initial alginate concentration absorbed less water than those prepared using lower concentration of their counterparts (Figure 1). Decrease in water uptake reflects the formation of highly cross-

![Figure 1](image_url)

**Fig. 1.** Water absorption profiles of resin-loaded calcium alginate beads prepared under different gelation conditions: (O) 1% CaCl₂, 2.5% alginate, 0.5 h gelation time, (∆) 3% CaCl₂, 2.5% alginate, 0.5 h, (◊) 3% CaCl₂, 2.5% alginate, 2 h, (□) 3% CaCl₂, 1.5% alginate, 0.5 h.
linked gel matrix due to higher influx of Ca\(^{2+}\) ions into the beads or due to the formation of thicker outer gel membrane. Thus the factors which promote the entry of Ca\(^{2+}\) ions into the beads result in a decrease in DEE by displacing larger amount of drug.

4.4. Extent of drug displacement by cations

Incubation of diltiazem and 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 from the resinate (Table 3). However, the drug loss from the resinate was not so high as could be apprehended. A possible cause 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 resinate 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). Similarly, for diltiazem resin complex the order of drug displacement was: H\(^+\) (29.34%) >

Table 3

<table>
<thead>
<tr>
<th>Incubation time(h) in 3% CaCl(_2) solution</th>
<th>Diltiazem content (%) in resinate</th>
<th>Propranolol content (%) in resinate</th>
<th>0.5h incubation in CaCl(_2) solution (%w/v)</th>
<th>Diltiazem content (%) in resinate</th>
<th>Propranolol content (%) in resinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>90.51(±2.01)</td>
<td>83.02(±1.21)</td>
<td>1</td>
<td>93.123(±2.10)</td>
<td>87.31(±1.28)</td>
</tr>
<tr>
<td>1</td>
<td>76.55(±1.13)</td>
<td>70.55(±2.53)</td>
<td>3</td>
<td>90.51(±2.01)</td>
<td>83.02(±1.21)</td>
</tr>
<tr>
<td>2</td>
<td>72.81(±2.56)</td>
<td>65.09(±3.05)</td>
<td>5</td>
<td>79.29 (±2.61)</td>
<td>77.29(±3.01)</td>
</tr>
<tr>
<td>4</td>
<td>60.55(±2.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Na⁺ (25.88%) > Ca⁺² (14.23%) > Al⁺³ (11.45). 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, 17.7 to 47% drug was found to be released in 10h (Figures 2 and 3). It was further observed that the higher the gelation time, concentration of CaCl₂ 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 CaCl₂ significantly

![Graph showing release profile of diltiazem in deionized water from RALG beads prepared under different gelation conditions](image-url)

**Fig. 2.** Release profiles of diltiazem in deionized water from RALG beads prepared under different gelation conditions: (O) 1% CaCl₂, 2.5% alginate, 0.5 h gelation time, (◆) 3% CaCl₂, 1.5% alginate, 0.5 h gelation time, (■) 3% CaCl₂, 2% alginate, 0.5 h gelation time, (●) 3% CaCl₂, 2.5% alginate, 0.5 h gelation time, (△) 5% CaCl₂, 2.5% alginate, 0.5 h gelation time, (◇) 3% CaCl₂, 2.5% alginate, 1 h gelation time, (□) 3% CaCl₂, 2.5% alginate, 2 h gelation time.
Propranolol released (%) vs Time (hour)

Fig. 3. Release profiles of propranolol in deionized water from RALG beads prepared under different gelation conditions: (O) 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.

decreased (p<0.05) the diameter of the beads (Tables 1 and 2). 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 (Tables 1 and 2), 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. However, the size of resin was found to have no significant effect on the diameter of RALG beads (p>0.05). 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.
4.5. Drug release in SGF

Release profiles of diltiazem and propranolol in SGF (pH 1.2) from resinate, ALG beads and RALG beads prepared using different formulation variables have been represented in Figures 4 and 5. While the release of drug from the resinate was rapid and

![Graph showing release profiles of diltiazem from resinate, ALG beads, and RALG beads prepared under different gelation conditions.](image)

Fig. 4. Release profiles of diltiazem from resinate (▲), ALG beads (●) and RALG beads prepared under different gelation conditions: (♦) 1% CaCl₂, 2.5% alginate, 0.5 h gelation time, (■) 5% CaCl₂, 2.5% alginate, 0.5 h gelation time, (O) 3% CaCl₂, 2.5% alginate, 0.5 h, (△) 3% CaCl₂, 2.5% alginate, 1 h, (□) 3% CaCl₂, 2.5% alginate, 2 h, (◊) 3% CaCl₂, 2.5% alginate, 4 h, (+) 3% CaCl₂, 2% alginate, 0.5 h and (×) 3% CaCl₂, 1.5% alginate, 0.5 h. in simulated gastric fluid.
Fig. 5. Release profiles of propranolol from resinate (▲), ALG beads (●) and RALG beads prepared under different gelation conditions: (♦) 1% CaCl₂, 2.5% alginate, 0.5 h gelation time, (■) 5% CaCl₂, 2.5% alginate, 0.5 h gelation time, (○) 3% CaCl₂, 2.5% alginate, 0.5 h, (△) 3% CaCl₂, 2.5% alginate, 1 h, (□) 3% CaCl₂, 2.5% alginate, 2 h, (◊) 3% CaCl₂, 2.5% alginate, 4 h, (+) 3% CaCl₂, 2% alginate, 0.5 h and (◊) 3% CaCl₂, 1.5% alginate, 0.5 h. in simulated gastric fluid.

Complete in 2.5 h, the release of drug from ALG beads was slow and incomplete (45% for diltiazem and 50% for propranolol were released in 4.5 h) following a burst release in the initial moment. Drug release from ALG beads depends on reswelling property of the beads (Yotsuanagi et al., 1987) Low swellability and insignificant relaxation of a cross-linked polymer contribute to slow and incomplete drug release (Pillay and Fassihi, 1999). Since ALG beads did not swell appreciably throughout the dissolution process at pH 1.2, the release of diltiazem was slow and incomplete. The release of drug from RALG beads was found to decrease further at pH 1.2. Moreover, the release profiles of RALG beads exhibited an initial time lag up to about 1 h in diltiazem release. A time lag in drug release from the alginate-pectinate beads has also been reported (Pillay and Fassihi, 1999). The time lag in initial release, however, disappeared when the beads were prepared with the lowest alginate concentration and was due to comparatively easy access of dissolution fluid through the less compact gel structure of the beads. Swelling study at pH 1.2 revealed that swelling of RALG beads was still lower than that of ALG beads (Figure 6).
Presence of resinate led to the formation of a more dense structure which further reduced the swelling of RALG beads. Reduced swellability coupled with complex drug release mechanism involving slow penetration of dissolution fluid into the almost unswelled beads followed by drug displacement from the resinate by the counter ions present in the dissolution fluid and subsequent diffusion of free drug out of the beads substantially reduced the release of diltiazem at pH 1.2. Figures 4 and 5 further demonstrated that increase in gelation time, concentration of CaCl₂ and initial alginate concentration used during the preparation of RALG beads, tended to decrease the release of drugs. The release of drug from RALG beads was also influenced by the size of the resin particles. Release of drug from RALG beads prepared using different sized resin particles have been shown in Figures 7 and 8. The smaller the size of resin particles the faster was the drug release. If the size of the resin particles is small, the diffusional path length through which the drug diffuses is also small. This results in faster drug release.
Fig. 7. Release profiles of diltiazem from RALG bead using different size of resinate particles in simulated gastric fluid (open symbol) and in simulated intestinal fluid (closed symbol) : (Ο) 300-350 mesh, (△) 240-300 mesh, (□) 100-200 mesh.

Fig. 8. Release profiles of propranolol from RALG bead using different size of resinate particles in simulated gastric fluid (open symbol) and in simulated intestinal fluid (closed symbol) : (Ο) 300-350 mesh, (△) 240-300 mesh, (□) 100-200 mesh.
4.6. Drug release in SIF

Release profiles of diltiazem and propranolol in SIF from resinate, ALG beads and RALG beads prepared using 2.5% sodium alginate, 3% CaCl$_2$ solution and different gelation time have been represented in Figures 9 and 10. The release profiles of the drug

Fig. 9. Release profiles of diltiazem from resinate (○), ALG beads (△) and RALG beads prepared by gelling for 0.5 h (●), 1 h (▲), 2 h (■) and 4 h (♦) in simulated intestinal fluid.
Fig. 10. Release profiles of propranolol from resinate (O), ALG beads (▲) and RALG beads prepared by gelling for 0.5 h (●), 1 h (▲) and 2 h (■) in simulated intestinal fluid.

from both the resinate and ALG beads was faster and complete in 2.5h. Similar rapid release of various 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 disadvantage of ALG beads 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 the release of diltiazem from RALG beads apparently appeared to be extended up to 5.5h, major portion (∼90%) of the drug was released only in 2.5h. Similar observation was noted in case of propranolol release where 90% of the drug was released from RALG beads in 3.5h although total drug release prolonged up to 6h. Following hydration, the beads swelled rapidly allowing the access of the dissolution medium into the beads. The counter ions of dissolution fluid displaced the drug from the resinate and subsequently the free drug diffused out the swollen beads. At the same time, the beads eroded due to break-down of the gel structure through interaction between the gel forming Ca$^{+2}$ ions and Na$^{+}$ ions present in dissolution fluid (Tomida et al. 1993) or due to
electrostatic repulsion developed between the ionized COOH groups of alginate as Ca\(^{2+}\) ions were exchanged (Kikuchi et al., 1997; Segi et al., 1989). Figures 9 and 10 further showed that increase in gelation time tended to decrease the drug release significantly (\(P<0.05\)) as evident by increase in time required for 50% drug release (\(t_{50\%}\)). Similarly increase in CaCl\(_2\) concentration and initial alginate concentration increased \(t_{50\%}\) significantly (Tables 4 and 5). With a view to investigate the effect of resin size on the release of drug in SIF, RALG beads were prepared under identical gelation conditions using 240-300 and 100-200 mesh resinate. The resulting RALG beads provided not only

### Table 4

**Effect of formulation factors on the time required for 50% release (\(t_{50\%}\)) of diltiazem from resinate (300-350 mesh)-loaded alginate beads.**

| Gelation time (h) \(\pm\) s.d., \(n=4\) | \(t_{50\%}\) (min) \(\pm\) s.d., \(n=4\) | CaCl\(_2\) concentration \(\%\) w/v | \(t_{50\%}\) (min) \(\pm\) s.d., \(n=4\) | Initial alginate concentration \(\%\) w/v | \(t_{50\%}\) (min) \(\pm\) s.d., \(n=4\)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>60((\pm)6.24)</td>
<td>1</td>
<td>42((\pm)5.29)</td>
<td>1.5</td>
<td>47((\pm)4.00)</td>
</tr>
<tr>
<td>1</td>
<td>65((\pm)5.57)</td>
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<td>60((\pm)6.24)</td>
<td>2.0</td>
<td>55((\pm)3.61)</td>
</tr>
<tr>
<td>2</td>
<td>76((\pm)4.00)</td>
<td>5</td>
<td>88((\pm)5.29)</td>
<td>2.5</td>
<td>60((\pm)6.24)</td>
</tr>
<tr>
<td>4</td>
<td>80.5((\pm)4.32)</td>
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</tr>
</tbody>
</table>

Preparative condition: as shown in Table 1

### Table 5

**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) \(\pm\) s.d., \(n=4\) | \(t_{50\%}\) (min) \(\pm\) s.d., \(n=4\) | CaCl\(_2\) concentration \(\%\) w/v | \(t_{50\%}\) (min) \(\pm\) s.d., \(n=4\) | Initial alginate concentration \(\%\) w/v | \(t_{50\%}\) (min) \(\pm\) s.d., \(n=4\)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.76((\pm)0.26)</td>
<td>1</td>
<td>1.50((\pm)0.26)</td>
<td>1.5</td>
<td>1.16((\pm)0.05)</td>
</tr>
<tr>
<td>1</td>
<td>2.08((\pm)0.14)</td>
<td>3</td>
<td>1.76((\pm)0.26)</td>
<td>2.0</td>
<td>1.50((\pm)0.25)</td>
</tr>
<tr>
<td>2</td>
<td>2.33((\pm)0.32)</td>
<td>5</td>
<td>2.25((\pm)0.18)</td>
<td>2.5</td>
<td>1.76((\pm)0.26)</td>
</tr>
</tbody>
</table>

Preparative condition: as shown in Table 1
reasonably high DEE (Tables 1 and 2) but also further prolongation of drug release in a controlled manner (Figures 7 and 8). Since under a fixed gelation conditions the thickness of the gel membrane is expected to remain constant, decrease in drug release with increase in resin size was attributed to the decreased desorption rate of the drug from the resinates having larger size. With a view to further sustain the drug release in a more controlled manner in SIF, RALG beads using 300-350 mesh resinate were prepared by gelation in 3% CaCl₂ solution for 5 min and then were treated with different concentration of PEI solution for different period of time.

4.7. 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 (Tables 6 and 7). 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.

Table 6

Effect of polyethyleneimine (PEI) concentration and exposure time on diltiazem entrapment efficiency (DEE) of RALG-PEI beads.

<table>
<thead>
<tr>
<th>PEI concentration (%w/v)</th>
<th>DEE of (±s.d.,n=4)</th>
<th>Exposure time(m) in 1% PEI solution</th>
<th>DEE of (±s.d.,n=4)</th>
<th>Resin size(mesh)</th>
<th>DEE of (±s.d.,n=4)</th>
<th>Resinate loading (%w/w)</th>
<th>DEE of (±s.d.,n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95.58±1.69</td>
<td>5</td>
<td>95.58±1.69</td>
<td>100-200</td>
<td>88.85±0.98</td>
<td>10</td>
<td>97.84±1.09</td>
</tr>
<tr>
<td>2</td>
<td>71.63±1.81</td>
<td>15</td>
<td>82.89±1.45</td>
<td>240-300</td>
<td>94.38±1.78</td>
<td>30</td>
<td>95.58±1.69</td>
</tr>
<tr>
<td>4</td>
<td>51.37±2.25</td>
<td>30</td>
<td>74.71±2.29</td>
<td>300-350</td>
<td>95.58±1.69</td>
<td>50</td>
<td>87.01±1.89</td>
</tr>
</tbody>
</table>
Table 7

Effect of polyethyleneimine (PEI) concentration and exposure time on propranolol entrapment efficiency (DEE) of RALG-PEI beads.

<table>
<thead>
<tr>
<th>PEI concentration (%w/v)</th>
<th>DEE of (±s.d.,n=4)</th>
<th>Exposure time(m) in 1% PEI solution</th>
<th>DEE of (±s.d.,n=4)</th>
<th>Resin size(mesh)</th>
<th>DEE of (±s.d.,n=4)</th>
<th>Resinate loading (%w/w)</th>
<th>DEE of (±s.d.,n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Propranolol content(%)</td>
<td>Propranolol content(%)</td>
<td>Propranolol content(%)</td>
<td>Propranolol content(%)</td>
<td>Propranolol content(%)</td>
<td>Propranolol content(%)</td>
<td>Propranolol content(%)</td>
</tr>
<tr>
<td>1</td>
<td>96.13(±1.19)</td>
<td>5</td>
<td>96.13(±1.19)</td>
<td>100-200</td>
<td>90.29(±0.98)</td>
<td>10</td>
<td>98.19(±0.98)</td>
</tr>
<tr>
<td>2</td>
<td>75.34(±2.03)</td>
<td>15</td>
<td>80.19(±1.54)</td>
<td>240-300</td>
<td>94.39(±2.56)</td>
<td>30</td>
<td>96.13(±1.19)</td>
</tr>
<tr>
<td>4</td>
<td>61.59(±2.09)</td>
<td>30</td>
<td>65.44(±1.17)</td>
<td>300-350</td>
<td>96.13(±1.19)</td>
<td>50</td>
<td>84.45(±2.1)</td>
</tr>
</tbody>
</table>

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 and diltiazem content of the resinate decreased in a similar fashion as the drug was lost from RALG-PEI beads (Table 8). Decrease in resin size tended to

Table 8

Effect of polyethyleneimine (PEI) concentration and exposure time on loss of propranolol and diltiazem from resinate.

<table>
<thead>
<tr>
<th>PEI concentration (%w/v)</th>
<th>Propranolol content(%) in resinate</th>
<th>Diltiazem content(%) in resinate</th>
<th>Exposure time(m) in 1% PEI solution</th>
<th>Propranolol content(%) in resinate</th>
<th>Diltiazem content(%) in resinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87.32(±2.56)</td>
<td>89.09(±2.19)</td>
<td>5</td>
<td>87.32(±2.56)</td>
<td>89.09(±2.19)</td>
</tr>
<tr>
<td>2</td>
<td>69.37(±2.05)</td>
<td>67.32(±1.95)</td>
<td>15</td>
<td>73.59(±1.54)</td>
<td>75.32(±2.13)</td>
</tr>
<tr>
<td>4</td>
<td>48.01(±3.13)</td>
<td>45.44(±3.03)</td>
<td>30</td>
<td>67.19(±2.81)</td>
<td>69.41(±2.71)</td>
</tr>
</tbody>
</table>

increase DEE marginally (Tables 6 and 7). This could be due to higher equilibrium drug content in resinate having smaller size. In addition, increase in drug load by increasing the amount of resinate decreased the drug loading efficiency (Tables 6 and 7). The amount of resinate per unit bead increases with increase in the amount of resinate.
enhancing greater interaction with PEI. Thus the amount of drug displaced by PEI was increased resulting in a decrease in DEE.

4.8. SEM studies of RALG and RALG-PEI beads

The shape of the RALG beads was spherical with smooth surface. Increase in the intensity of the variables used to prepare calcium alginate beads did not change the shape and surface characteristics (Figures 9A, 9B, 9C, 9D, 9E and 9F). The surface of RALG-PEI beads was, however, highly striated although the spherical shape was maintained. Greater the time of exposure in PEI solution, greater was the surface striation and similarly, keeping the exposure time constant at 5 min, increase in PEI concentration from 1 to 4% increased the surface striation (Figures 10A, 10B, 10C and 10D). From the cross-sectional view, the internal structure of RALG beads appeared to be a resinate-loaded matrix with smooth outer periphery (Figure 9G). Initially it appeared that interaction between PEI and alginate might have collapsed the alginate matrix. When the cross-section of PEI treated beads was examined at higher magnification, a dense polyelectrolyte complex membrane was found to envelop the alginate matrix containing resinate and the thickness of which tended to increase with increase in both concentration and exposure time in PEI solution (Figures 11A, 11B, 11C and 11D). Being cationic, PEI might have interacted with anionic alginate polymer to form polyelectrolyte complex membrane. Striation developed at the surface of the beads was due to the formation of that polyelectrolyte membrane. To get a closure look at the formation of membrane, blank calcium alginate beads were treated with 1% PEI solution for different periods (1h and 4h). Similarly, keeping, the exposure time constant at 0.5h, the concentration of PEI solution was varied from 1% to 4%. Then the PEI treated alginate beads were processed as the resinate-loaded beads. Examination of cross-section of the beads under SEM clearly demonstrated the formation of a dense, non uniform continuous band surround the alginate matrix (Figures 12A, 12B, 12C and 12D). As the exposure time and the concentration of PEI solution were increased, PEI diffused inwardly and the thickness of the membrane increased considerably. The cross-section of PEI-RALG beads treated with 1% solution for 0.5h and 4h also demonstrated that a clears dense polyelectrolyte complex membrane surrounded the resinate loaded alginate matrix (Figures 12E and 12F).
Fig. 4A. Effect of curing time on the morphology of diltiazem-resin complex loaded (RDLG) beads prepared using 3% CaCl$_2$ solution and 2.5% alginate. Key: - (a) 0.5h (Formula 1), (b) 1h (Formula 4), (c) 2h (Formula 5) and (d) 4h (Formula 6).
Effect of curing time on the morphology of propranolol-resin complex bead (RALG) beads prepared using 3% CaCl₂ solution and 2.5% alginate. Key: (a) 1h (Formula 14) and (c) 2h (Formula 15).

Effect of CaCl₂ concentration on the morphology of diltiazem-resin complex and (RALG) beads prepared using 0.5h curing time and 2.5% alginate. Key: (a) 3% (Formula 7) and (b) 5% (Formula 8).

Effect of CaCl₂ concentration on the morphology of propranolol-resin microparticles (RALG) beads prepared using 0.5h curing time and 2.5% alginate. Key: (a) 1% (Formula 16) and (b) 5% (Formula 17).
Fig. 13. Effect of alginate concentration on the morphology of diltiazem-resin complexes loaded (RALG) beads prepared using 3% CaCl₂ solution and 2.5% alginate. Key: (a) 2% (Formula 2) and (b) 1.5% (Formula 3).

Fig. 14. Effect of alginate concentration on the morphology of propranolol-resin complexes loaded (RALG) beads prepared using 3% CaCl₂ solution and 2.5% alginate. Key: (a) 2% (Formula 12) and (b) 1.5% (Formula 13).

Fig. 15. Cross-section of RALG beads prepared with 3% CaCl₂ solution, 0.5h curing time and 2.5% alginate.
Fig. 14. Effect of PEI concentration on the morphology of RALG-PEI beads containing diltiazem. Key: (a) 1% PEI (Formula 20), (b) 2% PEI (Formula 23) and (c) 3% PEI (Formula 24).
Fig. 10B. Effect of PEI concentration on the morphology of RALG-PEI beads containing propranolol. Key: - (a) 1% PEI (Formula 29), (b) 2% PEI (Formula 30) and (c) 4% PEI (Formula 31).

Fig. 10C. Effect of exposure time in 1% PEI solution on the morphology of RALG-PEI beads containing diltiazem. Key: - (a) 15 min (Formula 21) and (b) 30 min (Formula 22).

Fig. 10D. Effect of exposure time in 1% PEI solution on the morphology of RALG-PEI beads containing propranolol. Key: - (a) 15 min (Formula 32) and (b) 30 min (Formula 33).
Fig. 11A. Effect of PEI concentration on the cross-sectional view of RALG-PEI beads containing diltiazem. Key: - (a) 1% PEI (Formula 20), (b) 2% PEI (Formula 22) and (c) 4% PEI (Formula 24).
(c) Effect of PEI concentration on the cross-sectional view of RALG-PEI beads containing propranolol. Key: - (a) 1% PEI (Formula 29), (b) 2% PEI (Formula 30) and (c) 4% PEI (Formula 31).

(a) 15 min (Formula 21) and (b) 30 min (Formula 22).

Fig. 10. Effect of exposure time on the cross-sectional view of RALG-PEI beads containing propranolol. Key: - (a) 15 min (Formula 32) and (b) 30 min (Formula 33).
Fig. 12A. Cross-section of blank alginate beads treated with 1% PEI solution for 1h.

Fig. 12B. Cross-section of blank alginate beads treated with 1% PEI solution for 4h.

Fig. 12C. Cross-section of blank alginate beads treated with 1% PEI solution for 8h.
Fig. 12D. Cross-section of blank alginate beads treated with 4% PEI solution for 4h.

Fig. 12E. Cross-section of RALG-PEI beads treated with 1% PEI solution for 0.5h.

Fig. 12F. Cross-section of RALG-PEI beads treated with 1% PEI solution for 4h.
4.9. DSC study of alginate and alginate-PEI films

Neither alginate nor alginate-PEI film exhibited any endothermic peak up to 200°C. The films tended to become brown and then black above 200°C. However, the glass transition temperature (Tg) of alginate-PEI film was higher than that of alginate film (Table 9). Moreover, the on-set of transition was delayed and more heat was required to induce transition of alginate-PEI film. Generally, polymer chain movement or rotation does not occur in glassy state. Following absorption of energy, the chain movement begins from the glass transition state. Since, the on-set of transition was delayed and more energy was required for transition of alginate-PEI film, it may be assumed that the chain movement of alginate-PEI complex polymer was restricted either due to charge interaction or hydrogen bond formation. It indicates that PEI has reacted with alginate to form alginate-PEI polyelectrolyte complex.

Table 9
DSC data of alginate and alginate-PEI films.

<table>
<thead>
<tr>
<th>Film</th>
<th>Transition period in °C</th>
<th>Glass of transition temperature (Tg) in °C</th>
<th>Heat absorbed (J/gm/°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alginate</td>
<td>23.81-65.50</td>
<td>48.82</td>
<td>4.05</td>
</tr>
<tr>
<td>Alginate-PEI film</td>
<td>23.69-88.36</td>
<td>57.41</td>
<td>5.69</td>
</tr>
</tbody>
</table>

4.10. FTIR study of alginate and alginate-PEI films

The FTIR spectrum of alginate film (Figure 15) shows two peaks at 3472 cm⁻¹ and 1613 cm⁻¹ which are the characteristic peaks of respectively O-H vibration and COO⁻ anion stretching of alginate molecule. The presence of a peak at 3426 cm⁻¹ in the spectrum of alginate – PEI film indicates N-H stretching vibration of PEI. The drifting of the peak to lower frequency is probably due to hydrogen bonding between O-H of alginate and NH₂ group of PEI. The appearance of a peak at 1612 cm⁻¹ indicates that some unreacted COO⁻ anion of alginate was present in alginate-PEI film. In addition, two new peaks were observed in the spectrum of alginate–PEI film. The peaks at 1296 cm⁻¹ and 1099 cm⁻¹ were characteristic peaks of C-N stretching and C-N vibration which were absent in the spectrum of alginate. Moreover, both alginate and PEI were soluble in water. However, the alginate-PEI film was insoluble in water, phosphate buffer of pH 6.8 and organic solvents having dielectric constants ranging from 1.90 to 80.20. Although inconclusive without further experimentation, these studies indicate
Fig. 15. FTIR spectra of alginate (a) and alginate-PEI (b) films. that a polyelectrolyte complex membrane was formed through interaction between alginate and PEI.

4.11. Effect of PEI treatment on drug release

The effect of PEI concentration on the release profiles of diltiazem and propranolol from RALG-PEI beads have been presented in Figures 16 and 17. Following a burst release, no significant increase in drug release in SGF was observed. On the other hand, release of the drug in SGF was characterized by an initial slow release followed by gradual release in a more controlled manner over an extended
Fig. 16. Release profiles of diltiazem 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.

Fig. 17. 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.
period of time. Increase in PEI concentration decreased the release of drug. Similar 
release characteristics were observed from RALG-PEI beads which were treated with 
1%PEI solution for different periods (Figures 18 and 19). Swelling of RALG-PEI beads

![Figure 18](image1.png)

**Fig. 18.** Release profiles of diltiazem 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.

![Figure 19](image2.png)

**Fig. 19.** 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.
in SIF and SGF have been represented in terms of increase in diameter in Figure 20.

![Graph showing swelling behavior of RALG-PEI beads](image)

**Fig. 20.** Swelling behaviour of RALG-PEI beads prepared using different concentration of PEI for different time: 1% ,5 min (□), 1%, 30 min (◊), 4%, 5 min (△) in SIF (open symbols) and SGF (closed symbols). Following an initial swelling, the beads did not swell appreciably in SIF. 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 in SIF 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. The effect of resin size on drug release from PEI-treated alginate beads have been represented in Figures 21 and 22. The drug release followed a similar pattern as with other PEI-treated beads. However, decrease in resin size tended to increase the drug release. Faster release from the beads containing smaller resinate particles could be accounted for the smaller diffusional path length in smaller resinate particles. Increase in drug load by increasing
Fig. 21. Release profiles of diltiazem from RALG-PEI bead (1% PEI, 5 min.) using different size of resinate in simulated gastric fluid (open symbol) and in simulated intestinal fluid (closed symbol) Key: (□) 100-200 mesh, (Δ) 240-300 mesh, (○) 300-350 mesh.

Fig. 22. Release profiles of propranolol from RALG-PEI bead (2% PEI, 5 min.) using different size of resinate in simulated gastric fluid (open symbol) and in simulated intestinal fluid (closed symbol) Key: (□) 100-200 mesh, (Δ) 240-300 mesh, (○) 300-350 mesh.
the amount of resinate increased the drug release in SIF and SGF (Figures 23 and 24).

Fig. 23. Release profiles of diltiazem from RALG-PEI bead (1% PEI, 5 min.) using different resinate loading in simulated gastric fluid (open symbol) and in simulated intestinal fluid (closed symbol) Key: (□) 10%, (△) 30% and (○) 50%.

Fig. 24. Release profiles of propranolol from RALG-PEI bead (1% PEI, 5 min.) using different resinate loading in simulated gastric fluid (open symbol) and in simulated intestinal fluid (closed symbol) Key: (□) 10%, (△) 30% and (○) 50%.

Increase in drug loading by increasing the amount of resinate in the beads weakens the gel microstructure and results in a decrease in polymer concentration to a threshold
disentanglement value (Lee & Pappus 1987). This leads to a more rapid matrix disentanglement and drug dissolution leading to faster release of the drug.

4.12. Kinetics of drug release

The release of both the drugs from the resinate followed particle diffusion process as discussed earlier. However, drug release from RALG and RALG-PEI beads was found to deviate from the particle diffusion mechanism. A modified form of the equation $\frac{M_t}{M_a} = a^n$ (Harland et al., 1988; Ford et al., 1991; Kim and Fassihi 1997; El-Arini and Leuenberger 1998; Pillay and Fassihi 1999) for a simple swellable polymeric matrix was developed to accommodate the lag time (l) in the beginning of the drug release from the pharmaceutical dosage form: $\frac{M_{t-l}}{M_a} = a(t-l)^n$ where a is a constant incorporating structural and geometric characteristics of the dosage form, n is the release exponent, indicative of the drug release mechanism, and the function of t is $\frac{M_t}{M_a}$ (fractional release of drug). n=0.5 for Fickian diffusion whereas 0.5<n<1 indicates anomalous transport. Similarly, n=1.0 supports Case-II transport and the value of n higher than 1.0 denotes super Case-II transport. This mathematical model is also known as the Power Law expression. Many workers (Lin and Yang 1989; Sangalli et al.; 1994; Kim and Fassihi 1997) reported the drug release mechanism by this

<table>
<thead>
<tr>
<th>Gelation time (h)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
<th>Initial alginate concentration (% w/v)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
<th>CaCl₂ concentration (% w/v)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.011</td>
<td>1.02</td>
<td>0.990</td>
<td>1.5</td>
<td>0.006</td>
<td>1.13</td>
<td>0.999</td>
<td>1.0</td>
<td>0.006</td>
<td>1.18</td>
<td>0.993</td>
</tr>
<tr>
<td>1</td>
<td>0.015</td>
<td>0.91</td>
<td>0.978</td>
<td>2.0</td>
<td>0.006</td>
<td>1.13</td>
<td>0.980</td>
<td>3.0</td>
<td>0.011</td>
<td>1.02</td>
<td>0.990</td>
</tr>
<tr>
<td>2</td>
<td>0.013</td>
<td>0.90</td>
<td>0.967</td>
<td>2.5</td>
<td>0.011</td>
<td>1.02</td>
<td>0.990</td>
<td>5.0</td>
<td>0.016</td>
<td>0.81</td>
<td>0.957</td>
</tr>
<tr>
<td>4</td>
<td>0.026</td>
<td>0.80</td>
<td>0.988</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resin size (mesh)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-200</td>
<td>0.017</td>
<td>0.73</td>
<td>0.981</td>
</tr>
<tr>
<td>240-300</td>
<td>0.016</td>
<td>1.01</td>
<td>0.989</td>
</tr>
<tr>
<td>300-350</td>
<td>0.011</td>
<td>1.02</td>
<td>0.990</td>
</tr>
</tbody>
</table>

Preparative condition: as shown in Table 1
expression. The release data of diltiazem (upto 78%) and propranolol (upto 75%) from RALG beads were found to fit reasonably well in the above expression. The values of n determined from various RALG beads are presented in Tables 10 and 11. The values of Table 11

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

<table>
<thead>
<tr>
<th>Gelation time (h)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
<th>Initial alginate concentration (%w/v)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
<th>CaCl₂ concentration (%w/v)</th>
<th>a</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.06</td>
<td>0.76</td>
<td>0.988</td>
<td>1.5</td>
<td>0.019</td>
<td>0.81</td>
<td>0.995</td>
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<td>0.017</td>
<td>0.79</td>
</tr>
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<td>0.935</td>
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<td>0.80</td>
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</tr>
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<td>0.59</td>
<td>0.893</td>
<td>2.5</td>
<td>0.016</td>
<td>0.76</td>
<td>0.988</td>
<td>5</td>
<td>0.040</td>
<td>0.53</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resin size (mesh)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-200</td>
<td>0.020</td>
<td>0.66</td>
<td>0.999</td>
</tr>
<tr>
<td>240-300</td>
<td>0.018</td>
<td>0.64</td>
<td>0.999</td>
</tr>
<tr>
<td>300-350</td>
<td>0.06</td>
<td>0.76</td>
<td>0.988</td>
</tr>
</tbody>
</table>

Preparative condition: as shown in Table 1

n for diltiazem indicates that release mechanism shifted from case II transport (n>1) to anomalous transport (0.5<n<1) whereas the values of n for propranolol were greater than 0.5 but less than 1 indicating that the drug release followed anomalous transport. As the gelation time, CaCl₂ concentration, initial alginate concentration and size of resinate were increased, the value of n tended to decrease due to decrease in swelling and erosion of RALG beads with increase in the intensity of the factors related to gelation. Similarly, the values of n obtained from RALG-PEI beads decreased with increase in PEI concentration, exposure time, size of resinate and resinate loading and the release mechanism tended to shift from anomalous transport to Fickian transport (Tables 12 and 13) as the intensity of variables reduced the swelling and erosion of RALG-PEI beads.
Table 12

Effect of formulation factors on diltiazem release kinetics data from RALG-PEI beads at pH 7.2.

<table>
<thead>
<tr>
<th>5 min exposure in PEI solution (%w/v)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
<th>Exposure time(min) in 1% PEI solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.007</td>
<td>0.97</td>
<td>0.992</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>0.036</td>
<td>0.55</td>
<td>0.985</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>0.037</td>
<td>0.52</td>
<td>0.985</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resinate loading (%w/w)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
<th>Resin size(mesh)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.004</td>
<td>1.03</td>
<td>0.997</td>
<td>100-200</td>
</tr>
<tr>
<td>30</td>
<td>0.007</td>
<td>0.97</td>
<td>0.992</td>
<td>240-300</td>
</tr>
<tr>
<td>50</td>
<td>0.011</td>
<td>0.91</td>
<td>0.997</td>
<td>300-350</td>
</tr>
</tbody>
</table>

Table 13

Effect of formulation factors on propranolol release kinetics data from RALG-PEI beads at pH 6.8.

<table>
<thead>
<tr>
<th>PEI concentration (%w/v)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
<th>Exposure time(min) in 1% PEI solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.022</td>
<td>0.60</td>
<td>0.985</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>0.026</td>
<td>0.56</td>
<td>0.997</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>0.030</td>
<td>0.52</td>
<td>0.988</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resinate loading (%w/w)</th>
<th>a</th>
<th>n</th>
<th>r²</th>
<th>Resin size(mesh)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.013</td>
<td>0.68</td>
<td>0.991</td>
<td>100-200</td>
</tr>
<tr>
<td>30</td>
<td>0.022</td>
<td>0.60</td>
<td>0.985</td>
<td>240-300</td>
</tr>
<tr>
<td>50</td>
<td>0.039</td>
<td>0.55</td>
<td>0.997</td>
<td>300-350</td>
</tr>
</tbody>
</table>

5. Conclusion:

This investigation revealed that the release of both the drugs from RALG beads were prolonged than that of resonates and ALG beads, although the major portion of drug was released quite rapidly. For further prolongation of drug release, the RALG beads were treated with PEI which adversely affected the DEE of RALG-PEI beads. However, PEI treatment prolonged the release of both the drugs in identical manner. The prolonged release of both the drugs was the result of the formation of polyelectrolyte complex.
membrane as evident from SEM, FTIR and DSC analysis. The overall release mechanism of RALG-PEI beads was shifted from anomalous transport to Fickian transport. This study revealed that natural polymer like sodium alginate could be used for sustained release of water soluble drugs if the drugs are incorporated in resinate form instead of in free form.