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Dynamic Release of Propranolol HCl from Cationic Ion–Exchanger–Loaded Calcium Alginate Beads

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The dynamic release of drug propranolol HCl from the propranolol HCl–resin complex (PRC) loaded calcium alginate beads has been studied in the buffer media of pH 1.2 at the physiological temperature 37°C. The PRC encapsulated beads demonstrated nearly 58.04% release while naked PRC particles released 98.00% drug in 24 h in the gastric fluid. The amount of drug released was found to increase with and decrease in the amount of sodium alginate in the beads. Similarly, with the increase in the amount of entrapped PRC particles within the beads, the quantity of drug released was also observed to increase. The degree of crosslinking of beads also affected the release kinetics. Interestingly, the release from naked PRC particles followed 'first-order' kinetics while PRC particles, entrapped in calcium–alginate beads, exhibited 'diffusion controlled' release behavior as indicated by liner nature of fractional release vs. $\sqrt{t}$ plot.

Keywords: cation exchanger resin; drug release; 'first-order' kinetics; sodium alginates

1 Introduction

The ion exchange resins are frequently used for the purpose of removing toxic metal ions from the domestic waters as well as industrial effluents. However, in the year 1956, Suunders and Shrivastava (1) studied the uptakes and release of alkaloids from IER and suggested that these resins might act as a suitable chemical carrier for the development of sustained release formulations (2). IER have since been extensively explored in the pharmaceutical field (3), leading to the some important patents. The extensive research over the past two decades have revealed that IER are equally suitable in a variety of pharmaceutical formulations like chewable or dispersible tablets, chewing gum for buccal absorption (4), sustained release preparations (5) such as capsules (6), liquid orals (7), bioadhesive, systems, transdermal and ionotropically assisted transdermal systems (8), opthalmic delivery systems (9), nasal, topical and taste masked systems (10).

The ion exchange particles, loaded with a suitable drug have been frequently used as oral suspension (11). However, the need of careful handling and a little inconvenience in oral administration has promoted the pharmaceutical scientists to replace oral suspension by other forms such as capsules, tablets (12), etc. In this connection, we hereby propose a novel approach which involves entrapment of drug-loaded resin particles in calcium alginate beads and their use as formulations. The beauty of this work lies in the fact that the release of drug from resin particles can be easily controlled by varying degree of crosslinking and the amount of calcium alginate present in beads. Moreover, the calcium alginate beads are easy to handle and more convenient as compared to oral suspensions.

Alginate is naturally derived linear polysaccharide composed of (1–4)-linked–D mannuronic acid (M–units) and α-L–guluronic acid (G units) which vary in proportion and sequential distribution along the polymer chains (13). Alginate is considered as biocompatible and forms spherical beads in the presence of divalent cations like Ca^{2+} and Ba^{2+} through ionic gelation (14). Calcium crosslinked beads have been used in many biomedical applications (15). The drug propranolol HCl is frequently used for the treatment to prevent some heart conditions, reduce the symptoms of angina pectoris (chest pain), lower blood pressure in people with hypertension, and improve survival after a heart attack. Propranolol is sometimes used to prevent migraine headaches, to reduce movement associated with essential tremor, and to reduce performance anxiety (16).

2 Experimental

2.1 Materials

Materials were obtained from commercial sources: Sodium alginate (SA, average molecular mass 60000, M/G ratio

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1.75 ± 0.12, medium viscosity 200 cP for 1% aqueous solution at 20°C, (Research Lab, Pune, India), Seralite SRC-120; strongly cationic resin (SISCO, Research Lab, Mumbai, India), Drug Propranolol hydrochloride tablets (Cipla Pvt. Ltd., Manipur, India).The crosslinker calcium chloride and barium chloride were obtained from S.D. Fine–Chem. Ltd. (Mumbai, India). The double distilled was used throughout the investigations.

2.2 Purification of Resin

Seralite SRC-120, a strongly cationic resin in H^+ form, was purified by rinsing ~10 g of wet resin with 25 ml deionized water, 50 ml of 50% methanol and finally, again 50 ml deionized water. Each stage of treatment lasted for 1 h under constant stirring.

2.3 Preparation of Propranolol HCl–Resin Complex (PRC)

The propranolol HCl–resin complex (PRC) was formed by a batch process, in which the previously purified seralite SRC-120 resin (5 g dry weight) was placed in 18.2×10^{-3} g per 100 ml drug solution of propranolol HCl and agitated for 24 h (17). The PRC particles were washed with deionized water to remove the unreacted drug, dried to a constant weight, and placed in desiccators. The concentration of drug eluted in each wash was used to calculate % loading, given as the following equation and was found to be 71.23%.

$$\%\text{Loading} = \frac{\text{Drug retained in resins}}{\text{Initial drug loaded}} \times 100 \qquad (1)$$

2.4 Entrapment of PRC Particles in Alginate Beads

A definite amount 0.6 g of drug loaded resin particles was mixed into 20.0 ml of sodium alginate solution (4% w/v) and stirred thoroughly for a period of 1 h to get uniform suspension. Now, with the help of a pipette (5 ml, Corning, India), the mixture was dropped into a 4% $CaCl_2$ solution with constant stirring (18). The beads were formed and cured for 30 min to ensure complete crosslinking, then taken out, washed with distilled water and allowed to dry in a dust-free chamber till they attained constant weight. Figure 1 shows an optical micrograph of both plain and

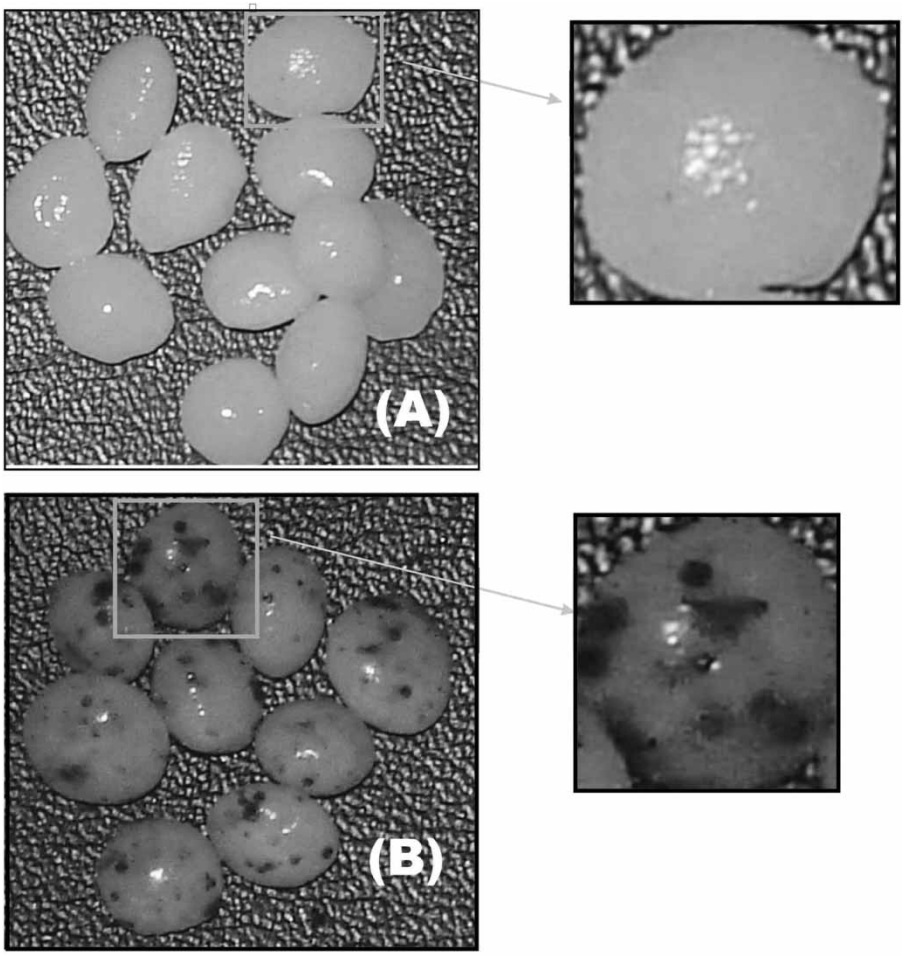


Fig. 1. Optical Micrograph of (A) Plain beads sample and (B) PRC loaded beads.

PRC-loaded beads, clearly indicating that the PRC particles are almost uniformly distributed within the beads matrix.

2.5 Beads Size Measurement

Each sample of the completely dried beads from each formulation was selected and their size was measured with the help of a micrometer screw gauge (Kayco, India) with an accuracy of ± 0.01 mm.

2.6 Fourier Transform Infrared Spectroscopy (FTIR)

Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for calcium alginate beads (a), drug propranolol HCl, (b) and DPRC particles loaded polymeric beads, (c), using FTIR spectrophotometer (Shimadzu; Model No 8400S). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400–4000 cm^{-1} and the resolution was 2 cm^{-1}.

2.7 Drug Release Studies

Completely dried and pre-weighed PRC loaded beads were put in 25 ml of simulating gastric fluid (SGF) of pH 1.2 at the physiological temperature 37°C. The amount of drug released at different time intervals was monitored UV spectrophotometrically (19). After each measurement, the beads were put in fresh release media. The amount of drug released was computed by comparing the absorbance with standard curve prepared for the pure drug in the appropriate concentration region. All release experiments were repeated five times and the average values have been reported in the data.

The release pattern was analyzed quantitatively using Eq. (2) (20):

$$F = kt^n \tag{2}$$

where F is the fractional release at time 't', n and k are the release exponent and gel characteristic constant, respectively. The release data was also applied to 'First order' kinetic model (21). The release of drug was studied under different parameters such as composition of beads, degree of crosslinking, amount of PRC in beads, etc.

3 Results and Discussion

3.1 FTIR Spectral Analysis

Figure 2 shows the FTIR spectra of (a) sodium alginate powder, (b) pure drug propranolol HCl, and, (c) PRC alginate beads. The spectrum of sodium alginate powder shows various distinct peaks of alginate: hydroxyl at 3263.33 cm^{-1}, carbonyl at 1710.81 cm^{-1}, and carboxyl and carboxylate at about 1000–1400 cm^{-1} (a).

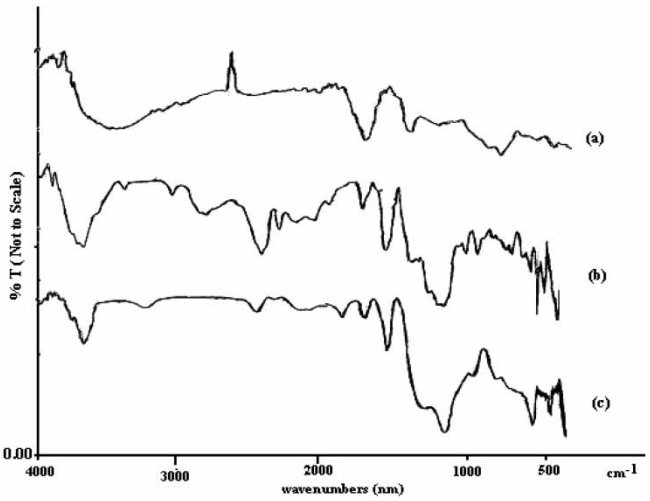


Fig. 2. FTIR spectra of (a) sodium alginate powder, (b) drug propranolol HCl and, (c) PRC calcium alginate beads.

The characteristics OH stretching at 3471 cm^{-1}, NH stretching of secondary amine at 3219.30 cm^{-1}, C-H stretching at 2891 cm^{-1} and C═O stretching at 1741 cm^{-1} of pure drug remains unchanged in the spectrum of encapsulated polymeric beads. The results suggest drug stability during the encapsulation process (b and c).

3.2 Effect of Concentration of PRC Beads Particles in Beads on Release

In order to investigate effect of concentration of PRC particles present in the beads on release rate, we synthesized samples $(CA)_{2.0}$ and $(CA)_{3.0}$ where subscripts 2 and 3 are the percent (w/v) of PRC particle suspended in 4% sodium alginate (w/v) solution and then crosslinked with 4% (w/v) $CaCl_2$ solution for the same time period. The amount of drug released was determined spectrophtometrically by measuring the absorbance at 289 nm (22).

The results as depicted in Figure 3 show that as the amount of PRC particles in the calcium alginate beads increases, the drug released at different time intervals also increases. This can be explained on the basis of the fact that with the increase in the amount of PRC particles more and more drug comes out due to ion exchange process between H^+ ions of gastric fluid and D^+ ions present in PRC particles in the beads. The initial release rates from the samples $(CA)_{2.0}$ and $(CA)_{3.0}$ were found to be 4.4×10^{-4} and 4.6×10^{-4} g^{-1} beads, respectively.

3.3 Effect of Crosslinker on Drug Release Study

The degree of crosslinking of alginate beads is also expected to govern the release of drug from PRC particles in the beads. To investigate this, we synthesized samples CA(4) and CA(6) where the number in parenthesis denoted the concentration of crosslinker $CaCl_2$ solution

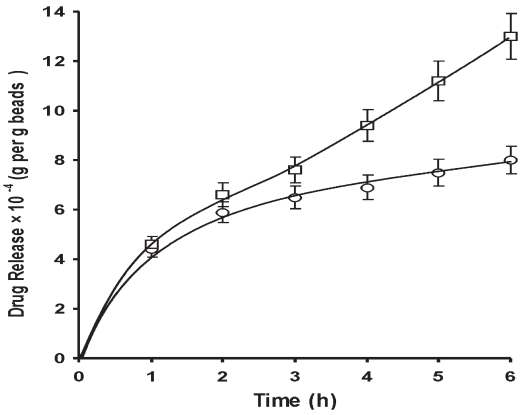


Fig. 3. Cumulative release of drug propranolol HCl from the PRC loaded beads samples $(CA)_{2.0}$ (O) and $(CA)_{3.0}$ (□) in the gastric media of pH 1.2 at the physiological temperature 37°C.

(w/v). The two beads samples contained the same amount of drug-loaded resin particles and were crosslinked for the same time.

The results, as depicted in the Fig. 4, clearly indicate that the sample CA(4) demonstrates faster release as compared to the sample CA(6). This may simply be explained on the basis of the fact that in sample CA(6), PRC particles are entrapped within highly more crosslinked calcium alginates chains and therefore ion–exchange process between D^+ and H^+ ions is rather slow. On the other hand drug comes out at a faster rate from the bead sample CA(4) due to relatively lower degree of crosslinking.

3.4 Effect of Size of Crosslinker Ion on Drug Release

The size of the crosslinking ions present in the 'egg-box' cavity in alginate beads (14) also influence the release of drug from the PRC particles entrapped in beads. To investigate this, we synthesized samples BA(4) and CA(4), prepared by crosslinking with 4% $BaCl_2$, and $CaCl_2$ solutions, respectively, keeping other parameters the same.

The results, as depicted in Fig. 5 clearly indicate that the drug is released at a faster rate from CA(4) beads. This may be explained on the basis of the size of the crosslinking ions (i.e. Ba^{2+} and Ca^{2+} ions). In the beads sample BA(4), the crosslinker Ba^{2+} ions are sufficiently large (i.e. 1.74 A°) to fit well within the egg– box cavities, thus producing a tight structure with smaller voids. This structural integrity of beads causes the slower ion – exchange process between D^+ and external H^+ ions, hence finally resulting is slower release. On the other hand, relatively smaller sized Ca^{2+} ions (1.14 A°) produce rather loose network within the beads and so results in faster D^+–H^+ ion exchange process. As a result, the drug is released at a faster rate from the bead sample CA(4).

3.5 Effect of Entrapment of PRC in Calcium Alginate Beads

As stated in the 'Introduction' section, the purpose of entrapment of PRC particles in calcium alginate beads was to make the release process slow and controllable. To justify, we compared release profiles obtained with naked PRC particles and PRC loaded calcium alginate beads in SGF at 37°C. The results, as depicted in the Fig. 6, clearly suggest that the release rate is suppressed appreciably due to entrapment of PRC particles in alginate beads. It was observed that nearly 49.8% drug was released from PRC–loaded alginate beads, while nearly 91.0% release occurred from naked PRC particles in the same duration. This implies that entrapment of propranolol HCl-resin complex particles in calcium alginate beads through ionotropic gelation appears to be an effective tool in controlling the release rate. Here it is worth mentioning that in the above experiment the amount of beads was so calculated that the beads contained almost the same quantity of drug as present in the naked beads.

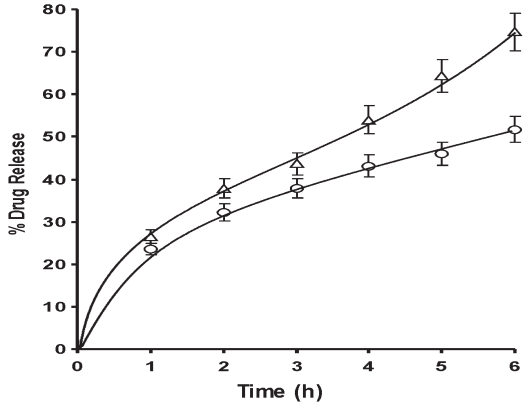


Fig. 4. Dynamic release of drug propranolol HCl from the varying crosslinked PRC loaded beads samples CA (4%) (△) and CA (6%) (□) in the gastric fluid pH 1.2 at the physiological temperature 37°C.

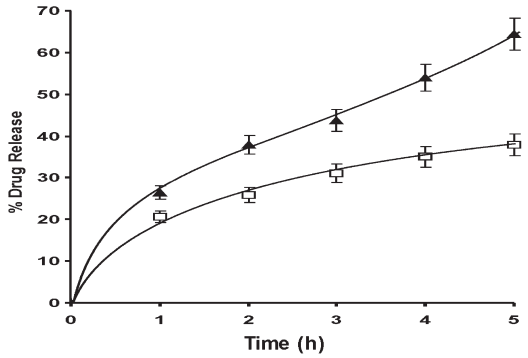


Fig. 5. Dynamic release of drug propranolol HCl from the varying size of crosslinked ion from the PRC beads samples CA (4%) (▲) and BA (4%) (□) in the gastric fluid pH 1.2 at the physiological temperature 37°C.

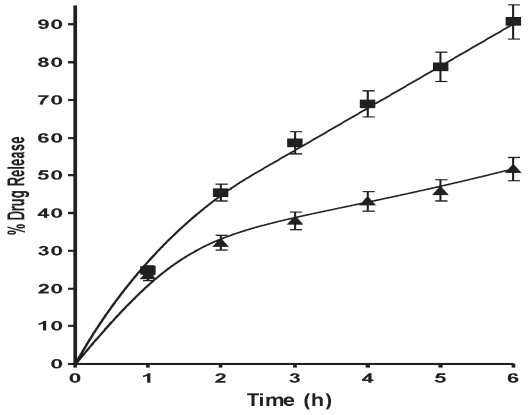


Fig. 6. Cumulative release of drug propranolol HCl from the PRC loaded beads samples $(CA)_{3.0}$ (▲) and naked PRC particles (■) in the gastric media of pH 1.2 at the physiological temperature 37°C.

Finally, the plots of fractional drug release M_t/M_∞ vs. $\sqrt{t}$ displayed almost linearity (Fig. 7) thus indicating that release took place in a diffusion–controlled manner from PRC–loaded alginate beads. The release exponent 'n' and gel characteristics constant 'k' were found to be 0.44 and 2.46×10^{-2}, respectively, thus indicating Fickian release.

3.6 Effect of Sodium Alginate Concentration on Drug Release

The release rate of a PRC-encapsulated device can also be regulated by varying concentration of sodium alginate because the variation in sodium alginate concentration is accompanied by a change in network density of macromolecule chains of calcium alginate. To investigate this, we synthesized three beads samples which contained a different amount of sodium alginate i.e., 3, 4 and 5%, but were cross-linked with 6% $CaCl_2$ solution and contained the same amount of PRC particles.

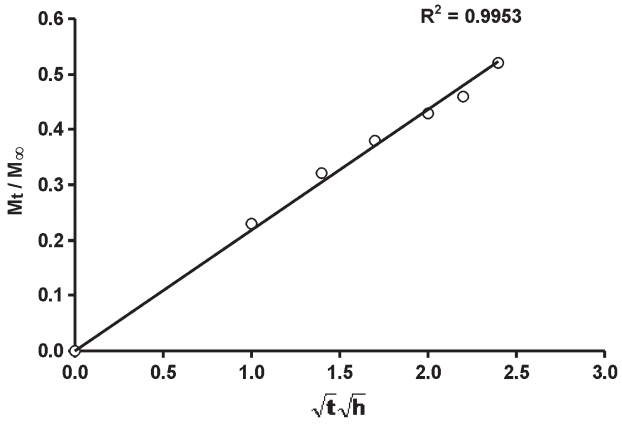


Fig. 7. Plots of fractional drug release M_t/M_∞ vs. square of the time (h) $\sqrt{t}$ for the PRC loaded beads samples $(CA)_{3.0}$ in the medium of pH 1.2 at 37°C.

It is clear from Fig. 8 that the dynamic release of drug propranolol HCl decreases with an increase in the concentration of sodium alginate. It was found that the percent of drug released from the beads prepared with 3, 4, and 5% sodium alginate was nearly 87.93, 58.04, and 40.80, respectively. This can be attributed to the fact that with increased sodium alginate concentrations within polymer matrix, a more dense polymer network is formed and ion exchange process between drug ions (D^+) and gastric ions (H^+) becomes slow, thus resulting is slower release.

3.7 First Order Kinetics in PRC Particles

The release of a bioactive material from a drug–loaded device can be represented as:

$$\text{Drug loaded device} + \text{solvent (excess)} \longrightarrow \text{Drug released in medium}$$

If Q_o is the initial amount of drug present in the device and Q_t is the amount of drug released in time 't' then for the first order kinetic model, we can write:

$$\frac{dQ_t}{dT} = k\,[Q_o - Q_t] \tag{3}$$

On integration, we have,

$$-\ln(Q_o - Q_t) = kt + A \tag{4}$$

where A is integration constant which can be evaluated using boundary conditions, and its value is $-\ln Q_o$

$$-\ln\frac{Q_o}{Q_o - Q_t} = kt \tag{5}$$

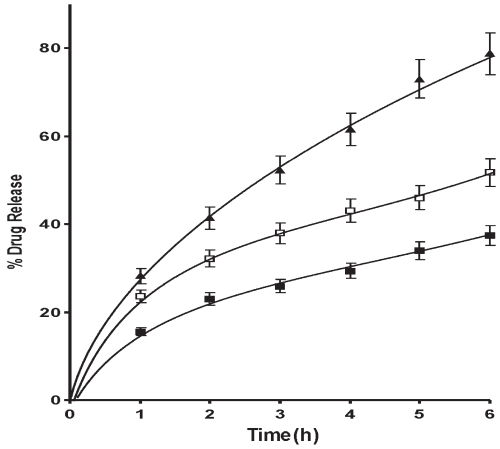


Fig. 8. Dynamic release of drug propranolol HCl from the varying concentration of sodium alginate 3% (▲), 4% (□) and 5% (■) based PRC beads samples in the gastric fluid pH 1.2 at the physiological temperature 37°C.

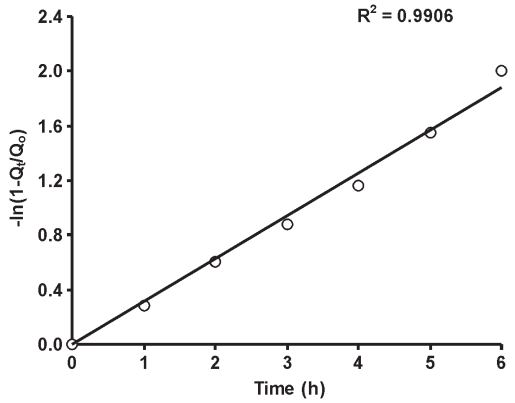


Fig. 9. Experimental plots of $-\ln(1 - Q_t/Q_o)$ and t for the PRC particles in the medium of pH 1.2 at 37°C.

or,

$$-\ln\left(\frac{Q_o}{Q_o - Q_t}\right) = kt \qquad (6)$$

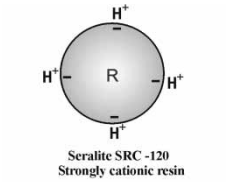
Therefore, if a linear plot, passing through origin, is obtained between $-\ln(1 - Q_t/Q_o)$ and t, this confirms first order release of drug from the device.

Figure 9 displays the experimental plots obtained between $-\ln(1 - Q_t/Q_o)$ and t. It can be seen clearly that the experimental curve yields almost a linear plot passing through origin, thus confirming this confirms first order release of drug from the naked PRC particles (without beads).

3.8 Drug Release Mechanism

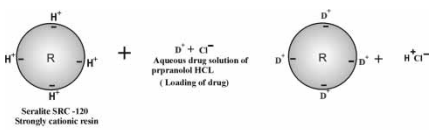
The overall process of loading of drug propranolol HCl into resin particles, entrapment of them into calcium alginate beads and then subsequent release in gastric fluid can be described as follows:

(a) Let us consider a resin particle 'R' with negatively charged integral ions and positively charged H^+ counter ions



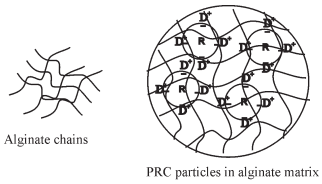
Cationic resin with exchangeable H^+ ions

(b) When the resin particle is placed in an aqueous drug solution, the D^+ ions enter into the resin matrix and replaces some of the counter H^+ ions as shown below:



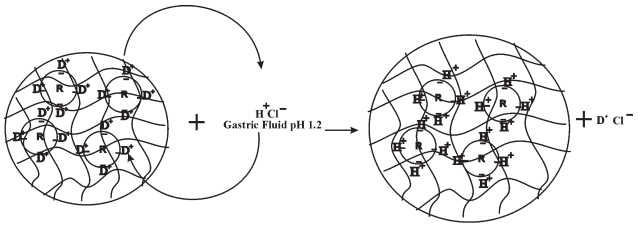
Loading of cationic drug ions (i.e. D^+ ions) into resin matrix via H^+-D^+ ion exchange

(c) Now these drug loaded resin particles are mixed with 4% sodium alginate solution and agitated for 24 h and a uniform mixture is dropped into a 4% $CaCl_2$ solution. The resulting beads may be illustrated as below:



Entrapment of DRC in alginate beads

(d) When the PRC loaded beads are placed in the gastric medium of pH 1.2, the H^+ ions, present in the gastric fluid, enter into the polymeric beads matrix, and replace the D^+ ions present within the resin inside the alginate beads.



Release of D^+ ions from DRC loadedd alginate beads

4 Conclusions

The above study reveals that the release of drug propranolol HCl from cation exchange resin can be controlled by encapsulating drug–loaded resin particles in calcium alginate beads. The release rate depends upon the amount of PRC particles, degree of crosslinking of beads, concentration of alginate in beads. The release of drug from the beads follows a diffusion–controlled mechanism, while release data for naked PRC particles is best interpreted in terms of first order kinetics model. Finally, these drug–resin complex loaded beads offer their strong candidacy for oral delivery of cationic drug propranolol HCl in a controlled manner.

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