Controlled Delivery of Diclofenac Sodium from Calcium Alginate Beads Loaded with a Drug–Resin Complex

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ABSTRACT: This study focused on a detailed investigation of the release of the nonsteroidal anti-inflammatory drug diclofenac sodium from strong anion resin particles, entrapped in ionotropically crosslinked alginate beads, in simulated gastric and intestinal fluids at 37°C. The percentage drug released from the beads in media of various pH values in 6 h was nearly 68.8 ± 2.6%, whereas, for the same duration, the drug–resin complex particles released 87.6 ± 3.2% drug. The amount of drug released from the beads depended on the composition of the beads, their degree of crosslinking, and the size of the crosslinker ions. Finally, the value of the release exponent was found to be 0.56, which thus indicated the diffusion-controlled mechanism of drug release from the alginate beads © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 112: 416–424, 2009

Key words: biocompatibility; drug delivery systems; ion exchangers; resins

INTRODUCTION

Ion-exchange resins are water-insoluble crosslinked polymers that contain acidic or basic functional groups and have the ability to exchange their counter ions with drug ions present in the aqueous solution surrounding them.[1] Drugs can be loaded onto the resins by an exchanging reaction, which thus results in the formation of a drug–resin complex (DRC) or drug resinate.[2] Drug release from a DRC in gastrointestinal fluid is driven by the exchange of ions toward an equilibrium, which is likely to occur with a substantial percentage of drug still bound to the resin, even under sink conditions.[3] The prolonged release of a drug can be obtained with semipermeable film-coated resinates[4,5] and by the selection of the degree of crosslinking and particle size of the resins without a coating process.[6] Moreover, the DRC may also be used as a drug reservoir in hydrophilic polymer tablets.[7]

The factors that control the release rate of a drug are the particle size of the resin, the degree of crosslinking, and the chemistry of the resin and complex.[8] The DRCs of phenyl propanolamine with amberlite IR NO120 (or XE 69) for sustained release required coating with an ethyl cellulose solution.[9] Cuna et al.[10] prepared a terbutaline–Dowex 50 W complex for controlled release suspensions. Betty et al.[11] patented a mixture of coated and noncoated sulfonic acid resins loaded with dextromethorphan for taste masking and sustained release. Similarly, the coating of pseudoephedrine–Dowex 50 WX8 complexes with carnauba wax for sustained release was reported by Patricia et al.[12] The coated DRC particles showed fracturing of the coat, which thus necessitated impregnation and so complicated the process feasibility. Although coated DRC particles have been frequently used for sustained release, their exact release kinetics have rarely been reported. Recently, Jeong et al.[13] prepared a drug dextromethorphan–resin complex and coated it with an aqueous colloidal dispersion of poly(vinyl acetate). They developed a comprehensive mathematical model with a mechanistic approach by considering diffusion, swelling, and ion-exchange processes solved by numerical techniques. Similarly, Vuorio et al.[14] developed a theoretical model to interpret the kinetic release data for different ion-exchange materials using a flow cell designed in house. Ion-exchange fibers (staple fibers and fiber cloth) were compared with commercially available ion-exchange materials (resins and gels). Thus, DRC particles have been exploited frequently to obtain sustained release formulations. However, the use of synthetic polymeric coatings on DRC particles limits their use *in vivo* because of toxic effects produced by the coatings materials. Therefore, the use of natural biopolymers such as

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chitosan sodium alginate as coating materials could be a better alternative for obtaining the sustained release of bioactive material from DRC particles. Here, in this article, we report a unique approach to the preparation of DRC particles entrapped in ionically crosslinked calcium alginate beads for the sustained release of the model drug diclofenac sodium under physiological conditions. The significance of this work lies in the fact that the rate of drug release from the drug resinate can be easily controlled by the variation of formulation parameters such as the degree of crosslinking, concentration of alginate, and size of crosslinking ions. Moreover, the use of the biopolymer sodium alginate for the entrapment of DRC particles is also a favorable factor for possible use of these formulations *in vivo*. Because ion-exchange resins are insoluble crosslinked polymer networks, the probability of their interacting with components of the human gastrointestinal tract are almost nil. It was reported[15] that the resins are totally nontoxic and harmless, and they are used in a number of pharmaceutical formulations for the delivery of bioactive agents and oral suspensions.

The alginate ion is a polysaccharide, which contains various amounts of 1,4′-linked β-D-mannuronic acid and α-L-guluronic acid residues. It has a fair reputation as an immunogenetic,[16] biocompatible,[17] bioadhesive,[18] and nontoxic[19] biopolymer, and it forms stable gels with divalent cations, such as Ca^{2+}, Zn^{2+}, and Ba^{2+}. These properties have enabled its widespread use in the preparation of controlled release products.

Diclofenac sodium is a nonsteroidal anti-inflammatory drug that is mainly absorbed in the small intestine. The major reasons behind the selection of this drug include its shorter biological half-life[20] and the presence in its molecular formula of a carboxylate group (i.e., $-COO^-$), which allows its ion-exchange process with the resin seralite, which contains exchangeable Cl^- ions.

EXPERIMENTAL

Materials

Sodium alginate (average molecular mass = 60,000, M/G ratio (ratio of poly mannuronic acid to poly guluronic acid) = 1.75 ± 0.12, medium viscosity = 200 cP for a 1% aqueous solution at 20°C) was obtained from Research Lab (Mumbai, India). A strong anion resin, Seralite SRA-400, was donated by SISCO Research Lab (Mumbai, India), and the anionic drug diclofenac sodium (molecular weight = 318.18, molecular formula = $C_{14}H_{10}Cl_2NO_2{\cdot}Na$) was obtained from Merck Pvt., Ltd. (Mumbai, India). Sodium hydroxide, sodium dihydrogen phosphate, sodium chloride, and sodium bicarbonate were purchased from Himedia (Mumbai, India). Double-distilled water was used throughout the investigation. The structures of the drug diclofenac sodium, the anion exchange resin Seralite SRA-400, and the alginate are shown in Figure 1.

Methods

Purification of the anion exchange resin

We purified the resin Seralite SRA-400 by rinsing about 20 g of wet resin with 50 mL of deionized water, 100 mL of 50% methanol, and finally again with 50 mL of deionized water. Each stage of treatment lasted 1 h under constant stirring.

Preparation of the DRC

The diclofenac sodium–resin complex was formed by a batch process, in which the previously purified Seralite resin (5 g of dry weight) was agitated with drug solutions of different concentration in the range 1660–6660 μg/100 mL for a period of 24 h.[21] The DRC particles were washed with deionized water to remove unreacted drug, dried to constant weight, and placed in desiccators. The concentration of the drug eluted in each wash was used to calculate the

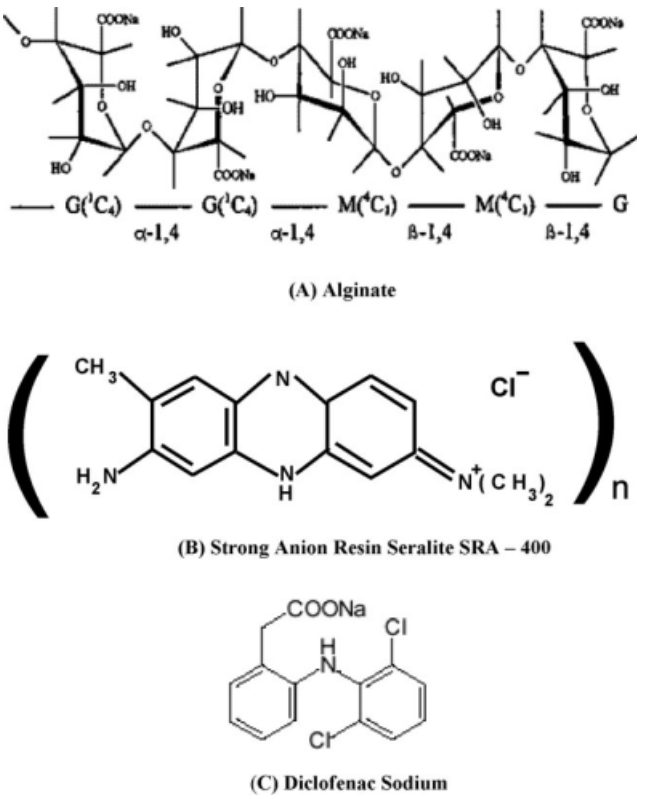


Figure 1 Chemical structures of (A) sodium alginate, (B) Seralite resin, and (C) diclofenac sodium.

percentage loading, which is given by the following equation:[22]

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

Preparation of the DRC-particle-loaded alginate beads

A 0.6-g quantity 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 a homogeneous suspension. A 5-mL pipette was used to drop the mixture into a 6% $CaCl_2$ solution under constant stirring.[23] The beads were cured for 30 min to ensure complete crosslinking. They were then removed, washed with distilled water, and allowed to dry in a dust-free chamber until they attained a constant weight. Figure 2 shows overviews of both plain beads, a cross-sectional view of the DRC-loaded bead, and its magnified view. It was clear that there was almost uniform distribution of DRC particles within the bead matrix.

Bead size measurement

To determine size of the beads, 15 dried beads from each formulation were selected, and their size was measured with the help of a micrometer screw gauge (Kayco, India) with an accuracy of ±0.01 mm.

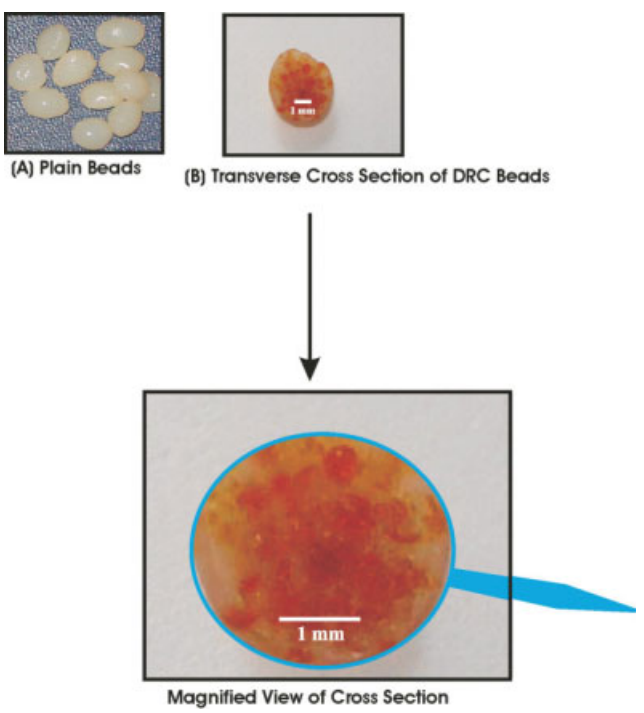


Figure 2 Optical micrographs of (A) plain beads, (B) a DRC-loaded bead, and (C) a cross section of the DRC-loaded bead (magnified view). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Preparation of the simulated gastric fluid (SGF; pH 1.2)

An aqueous solution of HCl with a pH of 1.2 (0.1*M*) was used as the SGF.

Preparation of the simulated small intestinal fluid (SIF; pH 6.4)

We prepared the SIF (pH 6.4) by mixing 130 mL of a 0.1*M* sodium hydroxide solution with 500 mL of a 0.1*M* sodium dihydrogen phosphate solution and making the volume up to 1000 mL by adding distilled water. Finally, precalculated quantities of the salts NaCl and $NaHCO_3$ were dissolved to give Cl^- and HCO_3^- ion concentrations of 105 and 45 m equiv/L, respectively.[24]

Lambert–Beer plot

We obtained the Lambert–Beer plot for the drug diclofenac sodium by measuring the absorbances of various aqueous solutions of the drug in the concentration range 10–250 μ g/dL at 276 nm[25] using a Shimadzu (Kyoto, Japan) 1700 ultraviolet–visible spectrophotometer. The linear plot obtained of the concentration versus absorbance was used to determine concentration of the drug released in the physiological fluids.

In vitro drug-release studies

To mimic the transition of the DRC-loaded calcium alginate beads from the mouth to small intestine, the beads were exposed to SGF (pH 1.2) for 2 h and were then transferred into SIF (pH 6.4) at a physiological temperature of 37°C. For this, preweighed dried beads were put in 50 mL of SGF in a dissolution test system (model 2100 B, Distek, North Brunswick, NJ) under constant stirring at a rate of 100 rpm. Aliquots of 5 mL were withdrawn at predetermined time intervals of 30 min, followed by the replacement after withdrawal with the same volume of fresh buffer.[26] The aliquots were analyzed spectrophotometrically to determine the amount of drug released. After 2 h, the beads were put in SIF (pH 6.4), and the amount of drug released was determined at regular time intervals in a similar manner as mentioned previously. The cumulative amount of drug released was computed by comparison of the absorbance with the standard Lambert–Beer plot. To get continuous release of a drug from the resinates, it is necessary to change almost all of the release medium to maintain the ion-exchange process, which is

the driving force for the observed drug release.[3] However, the total replacement of medium may introduce more complications in the release process or even introduce errors. To solve this problem, the sampling of the release medium to analyze the concentration of drug released and the replacement with fresh medium to the system should be done after the appropriate procedure.

All of the release experiments were repeated five times, and the average values are reported. The solubility of diclofenac sodium in distilled water was nearly 35×10^2 μ mol/L,[27] whereas the maximum amount of drug present in the formulations was nearly 2 μ mol/L; this indicated that the sink condition was well maintained during the release experiments.

The release data were analyzed quantitatively with the following double-logarithmic equation:[28]

$$\ln M_t/M_\infty = \ln k + n \ln t \quad (2)$$

where M_t and M_∞ are the amounts of drugs released at time t and at equilibrium, n and k are the release exponent and gel characteristic constant, respectively. The release of the drug was studied under different parameters, such as the composition of beads, degree of crosslinking, and amount of DRC particles in the beads.

Measurement of the porosity of the DRC-loaded beads and resin

We determined the volume of the pores within the DRC-loaded beads, resin, and bead and resin particles that were interconnected and assessable to the surface by measuring the total volume of porous beads and the amount of solvent required to fill the porous component. In brief, individual DRC-loaded beads and resin particles were placed in a graduated cylinder filled with a known volume of *n*-heptane (V_1). The total volume after immersion (V_2) was recorded. The beads were removed with the entrapped solvent in the pores, and the remaining volume of heptane in the graduated cylinder was denoted V_3. The total volume of the beads (V_T) was calculated according to eq. (3):[29]

$$V_T = V_2 - V_3 \quad (3)$$

The porosity was determined as follows:

$$\text{Porosity} = [(V_1 - V_3)/V_T] \times 100 \quad (4)$$

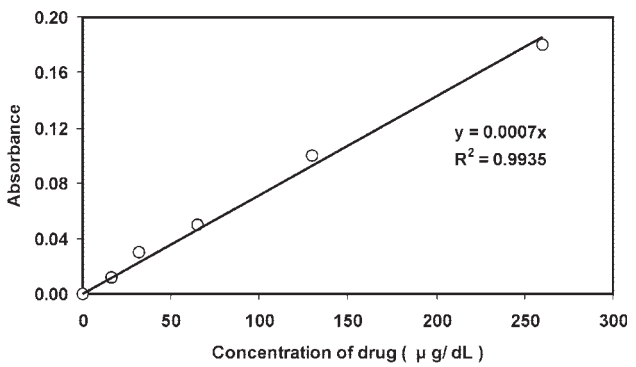


Figure 3 Lambert–Beer plot for aqueous solutions of the drug diclofenac sodium.

TABLE I
Data for the Lambert–Beer Plot

Concentration (μg/dL)	Absorbance (nm)
16	0.015
32	0.038
65	0.060
130	0.10
260	0.18

RESULTS AND DISCUSSION

Lambert–Beer plot

Figure 3 shows the linear plot obtained between the absorbance and concentration of the drug solutions. The regression value was nearly 0.977, which indicated a fair validity of the law over the concentration range studied. The data used to draw the Lambert–Beer plot are shown in Table I.

Loading of the drug in the DRC particles

The ion-exchange resins are well known for their tendency to entrap ionic drugs because of the ion-exchange process that usually takes place between the exchangeable or counter ions present within the resin matrix and external drug ions.[30] In this study, the overall ion exchange may be shown as follows:

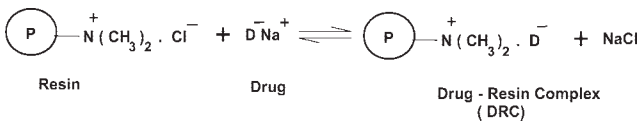


Figure 4 depicts the percentage loading of the drug in the resin particles when equilibrated in drug solutions of different initial concentrations ranging from 1660 to 6600 μg/dL. It is clear that, for all of the solutions, the drug loading was nearly 48–49%, which indicated that the percentage drug loading was almost independent of the initial drug concentration.

Preparation of the DRC-loaded beads

When the DRC particles were put in an alginate solution of definite concentration and the homogeneous mixture was dropped into crosslinker solutions

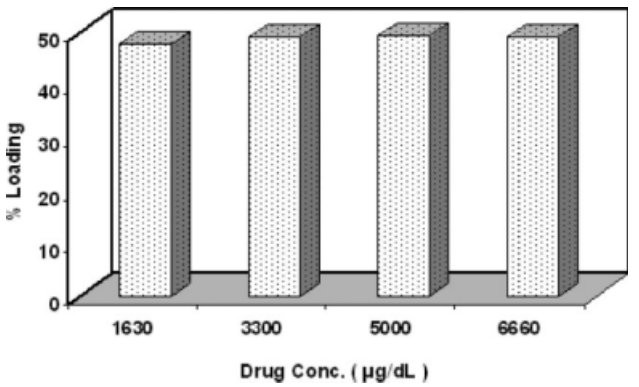


Figure 4 Bar diagram showing the loading percentage of the drug diclofenac sodium in resin particles

($CaCl_2$), the calcium alginate beads were formed because of the ionotropic gelation of the alginate chains by divalent calcium ions. The size of the beads was almost uniform and was found to be 3.0 ± 0.21 mm.

Drug release in media of various pH values

To study the release of diclofenac sodium from complex (DRC)-loaded beads in the media of various pH values, we prepared the sample $(CA)_2$, where the subscript indicates the weight percentage of DRC particles suspended in a 4% sodium alginate solution followed by crosslinking of the droplets with a 4% $CaCl_2$ solution.

The results of the release experiment, as depicted in Figure 5, clearly indicate that the release profile obtained for the $(CA)_2$ formulations in the media of continuous and various pH values, was biphasic in nature. The formulation released a small quantity of drug in first 2 h in the SGF (pH 1.2). However, when these beads were transferred into SIF (pH 6.4), the drug began to diffuse out at a faster rate, which was also indicated by a sudden vertical rise in the release profile. This interesting finding may be explained as follows: when the DRC-loaded beads were placed in the gastric fluid of pH 1.2, the beads remained almost intact because the alginate did not swell in acidic media.[31] Therefore, because of the compact structure of the beads, a relatively small amount of drug was diffused out of the DRC-loaded beads. However, when these beads were transferred into the medium of pH 6.4 (SIF), the alginate beads began to absorb water and swell because of the ion-exchange process between the Ca^{2+} ions present in the egg-box cavities within the crosslinked polyguluronate residues and external Na^+ ions present in the intestinal fluid. Because the radius of the Na^+ ions was small (0.95 Å) compared to that of the Ca^{2+} ions (1.14 Å), the presence of smaller sized sodium ions within the egg-box cavities made the overall bead structure loose or less compact. At the same time, the HCO_3^- and Cl^- ions present in the SIF began to undergo ion exchange with the drug anions present in the DRC within the bead matrix. Because the hydrated beads possessed a loose structure, the release took place at a faster rate. To further confirm the previously offered explanation regarding the mode of release in media of various pH values, we put the same quantities of beads in distilled water and observed the release.

A comparison of the two profiles revealed that the amount of drug released in the first 2 h in distilled water was greater than that obtained in SGF of pH 1.2. This supported our argument that the slow release in acidic pH was due to the compact structure of the alginate beads as discussed previously. However, after 2 h, the profile obtained in distilled water displayed a slower release compared to that obtained in SIF of pH 6.4. This was simply due to the fact that the ion-exchange mechanism, as discussed in previous paragraph, was no longer operative in distilled water; this resulted in slower release, compared to that in SIF, in which the presence of Na^+ ions induced an ion-exchange process with the crosslinker Ca^{2+} ions of the alginate beads and thus enhanced the release rate. Therefore, the overall comparison of the two profiles did support our argument that the formulations exhibited a slower release in gastric fluid, whereas a faster release was observed in SIF. To determine the factors responsible for the observed degradability of the beads, we put beads in media of various pH values (i.e., 2 h in SGF followed by immersion in SIF for 10 h) and compared their physical state with beads put in both SGF and SIF for the same

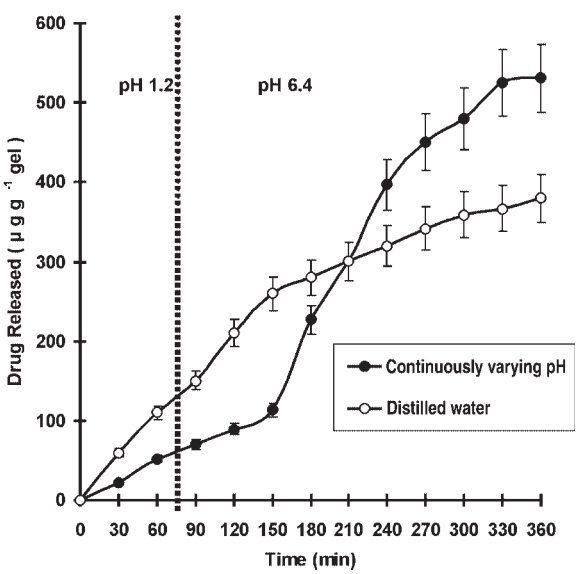


Figure 5 Cumulative release of the drug diclofenac sodium from DRC-loaded bead sample $(CA)_2$ (●) in media of varying pHs and (○) in distilled water at the physiological temperature of 37°C.

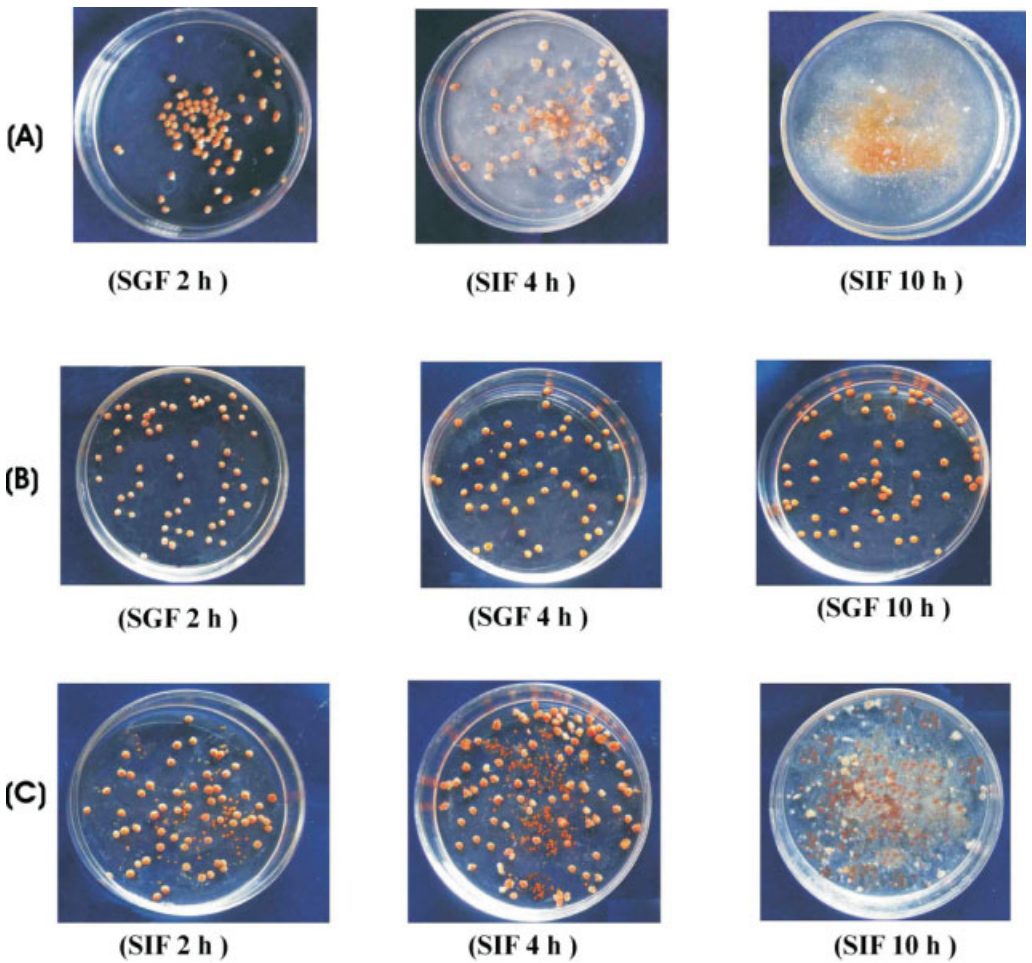


Figure 6 Photographs showing the physical states of beads at different time intervals in (A) media of varying pHs (2 h in SGF and the rest of the time in SIF), (B) SGF, and (C) SIF at 37°C. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

duration. The results, as depicted in Figure 6, reveal some interesting facts. Figure 6(A) reveals that the beads put in SGF of pH 1.2 for 2 h remained intact and began to disintegrate slightly when transferred into SIF of pH 6.4 and disintegrated completely in 10 h. However, the beads put in SGF only remained well intact throughout the duration of 10 h, as shown in Figure 6(B). Finally, the beads placed in SIF started to disintegrate even 2 h after their immersion in SIF of pH 6.4. The beads disintegrated almost completely after 10 h. The observed disintegration in SIF may simply be attributed to the presence of Na^+ ions in the buffer medium, which underwent ion exchange with the Ca^{2+} ions of the alginate beads and thus resulted in the loss of structural integrity of the beads. The beads transferred from SGF into SIF [middle photograph of Fig. 6(A)] exhibited faster degradation compared to the beads put into SIF for the same time period [middle photograph of Fig. 6(C)]. This indicated that the change from acidic to gastric fluid caused a faster degradation because of the acid-induced hydrolysis of the alginate.

Effect of the size of the crosslinker ions on drug release

The size of the crosslinking ions present in the egg-box cavity in the alginate beads was also responsible for the compact structure of beads. Therefore, it may have influenced the release of the drug from the DRC-particle-entrapped beads. To investigate this, we synthesized samples BA(4) and CA(4), prepared by crosslinking with 4% barium chloride and calcium chloride solutions, respectively, keeping other parameters the same.

The results, as depicted in Figure 7, clearly indicate that the bead sample crosslinked with calcium ions demonstrated a faster release than the barium-ion-crosslinked beads, and this difference in their release rates was much more pronounced when the beads were transferred into the SIF at pH 6.4. Initially, when the beads were put in SGF for 2 h, the almost compact and intact structure of beads did not permit the entrapped drug to come out at a faster rate. In other words, the drug was released from both the formulations, namely, CA(4) and BA(4), at a slower rate.

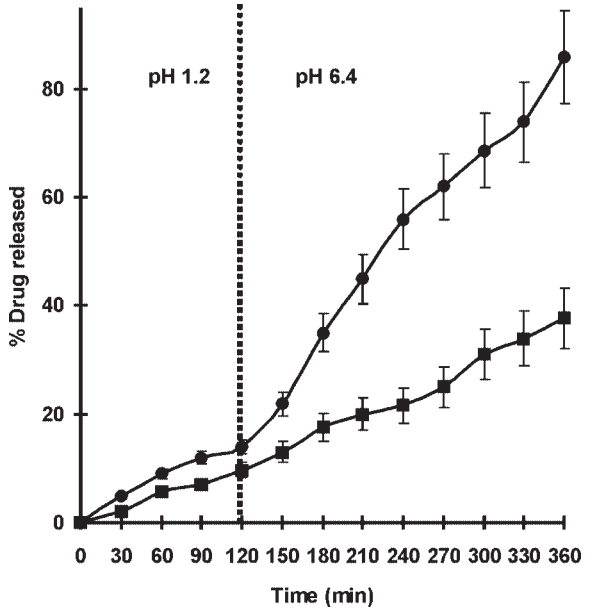
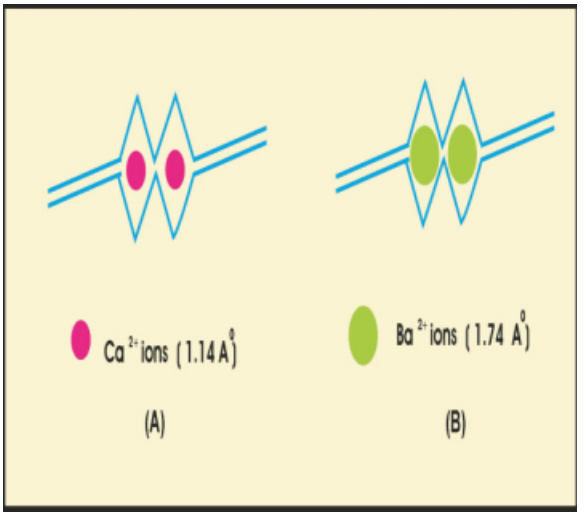


Figure 7 Dynamic release of the drug from DRC-loaded bead samples crosslinked with (■) $BaCl_2$ and (●) $CaCl_2$ solutions with a 4% concentration at 37°C.



Scheme 1 (A) Calcium ions occupying egg-box cavities are easily exchanged with external sodium ions. (B) Barium ions, being bigger in size, are well fitted within the egg-box cavities; this produces a tight arrangement and hence discourages their exchange with external Na^+ ions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

However, after their transfer into SIF at pH 6.4, the formulation CA(4) began to swell and absorb water because of the appreciable extent of the ion-exchange process between the Ca^{2+} ions and external Na^+ ions, which made the beads structure rather loose or less compact, which thus finally resulted in the faster release of drug anions from the DRC-loaded beads. However, this was not the case with sample BA(4). Here, the beads did not exhibit appreciable swelling because the barium ions, being bigger in size (1.74 Å), were well fitted within the egg-box cavities (see Scheme 1) and thus provided almost compactness to the bead structure. Therefore, the beads remained almost intact, and hence, only a small quantity of drug anions was able to diffuse out. In this way, the bead sample BA(4) exhibited a much slower release. For the given crosslinker ion, the release rate could also be controlled by the variation of the amount of crosslinker in the gelation medium. We prepared the DRC-loaded beads in 4 and 6% (w/v) calcium chloride solutions and studied the release profiles in media of continuous various pH. The release demonstrated by the formulations crosslinked with 4 and 6% $CaCl_2$ solutions in 6 h was nearly 86 ± 32 and 68.7 ± 2.5%, respectively. Thus, the variation of the amount of crosslinker could be a convenient tool for regulating the release rates.

Role of sodium alginate

As stated in the Introduction, the purpose of the entrapment of the DRC particles in the calcium alginate beads was to make the overall release from the DRC particles slow and controllable. To verify, we compared the release profile of naked DRC particles with that of the DRC-loaded calcium alginate beads prepared with 4 and 6% $CaCl_2$ as ionic crosslinker. The results, as depicted in Figure 8, clearly suggest that release rate was suppressed appreciably because of the entrapment of DRC particles in the alginate beads. Nearly 46.8 ± 1.9 and 68.8 ± 2.6% drug was

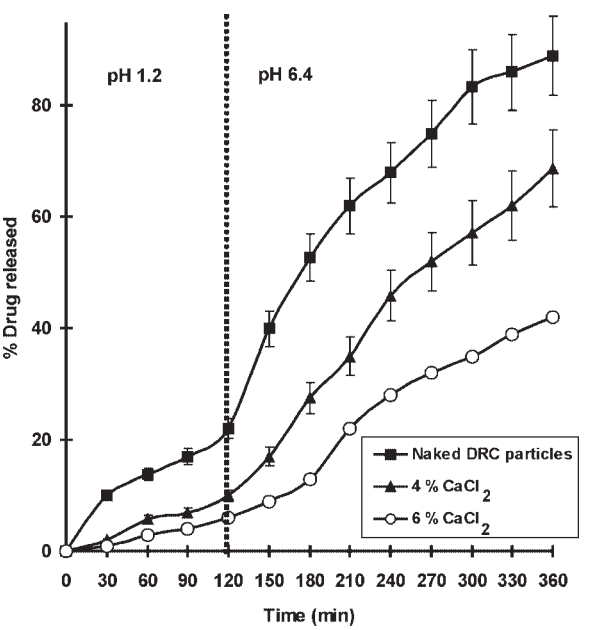


Figure 8 Cumulative release of diclofenac sodium (■) from naked DRC particles and (▲,○) from DRC-entrapped calcium alginate beads crosslinked with 4 or 6% $CaCl_2$ solutions, respectively.

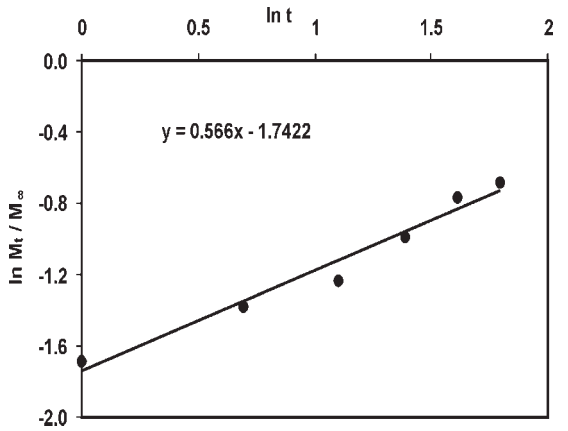


Figure 9 Plot of ln M_t/M_∞ versus ln t for the dynamic release of the drug from DRC-loaded beads in media of varying pHs at 37°C.

released from the DRC-loaded alginate beads crosslinked with 4 and 6% $CaCl_2$ solutions, respectively, whereas nearly 87.6 ± 3.2% release occurred from the naked DRC particles in the same duration of 6 h. This implied that the entrapment of the diclofenac sodium–resin complex particles in the calcium alginate beads through ionotropic gelation appeared to be a effective tool for controlling the release rate. In the previous experiment, the DRC-loaded beads were taken in such a quantity that they contained the same amount of drug present in the naked DRC particles. Moreover, to control the release rate, we also prepared beads with 3, 4, and 5% aqueous solutions of sodium alginate [i.e., samples CA(3), CA(4), and CA(5), respectively] and observed their release profiles. The total releases observed in 6 h from these sample were found to be 84.3 ± 2.3, 68.7 ± 2.5, and 50.9 ± 2.3%s, respectively. This could simply be attributed to the formation of a denser network with increasing alginate content.

Finally, it was also interesting to determine whether the drug could directly be loaded into the alginate beads. To further explore this possibility, we mixed a known amount of the drug into alginate solution and prepared beads through ionic crosslinking in a 4% $CaCl_2$ solution. However, the amount of drug loaded in the beads was found to be extremely small (i.e., nearly 14 ± 2% entrapment). This may have simply been due to the fact that the solubility of the anionic drug diclofenac sodium was fair (i.e., 1300 mg/L), so when the drug containing alginate solution was dropped into calcium chloride solution and the beads so produced were cured for 20 min in gelation medium, an appreciable quantity of drug must have diffused out because of the ion exchange of drug ions with external Cl^- ions present in the $CaCl_2$ solution. In addition, a higher solubility also contributed to this leaching-out process. As a result, a very small quantity of drug remained within the beads. Such a low degree of entrapment raises the question of the utility of the drug-loaded alginate beads. Hence, the use of resin particles to load this drug appeared to be justified.

Finally, to get some idea about the quantitative interpretation of the release mechanism, ln(M_t/M_∞) values were plotted against ln t (see Fig. 9), and the slope was used to determine the release exponent n, as described in eq. (2). The value of n was found to be 0.56, which thus indicated that the release process was almost diffusion controlled.

Effect of the presence of blank resin particles in the DRC beads on the release rate

In an interesting study, calcium alginate beads, containing a homogeneous mixture of alginate beads that contained DRC particles and plain resin particles, were prepared, and their release behavior was compared with that of the beads that contained DRC particles only. The results, as depicted in Figure 10, show that the beads that contained a mixture of both DRC and plain resin particles demonstrated a faster release. This may be explained on the basis of the comparison of the porosity of the two type of formulations. Because the beads containing both DRC and plain resin particles had a greater number of resin particles within the matrix, they possessed a higher porosity (i.e. 50%), which caused a faster drug release. On the other hand, the beads containing DRC particles only possessed a lower porosity (i.e. 30%) because of the presence of a smaller number of resin particles, so these beads demonstrated a slower release. Both type of beads contained the same

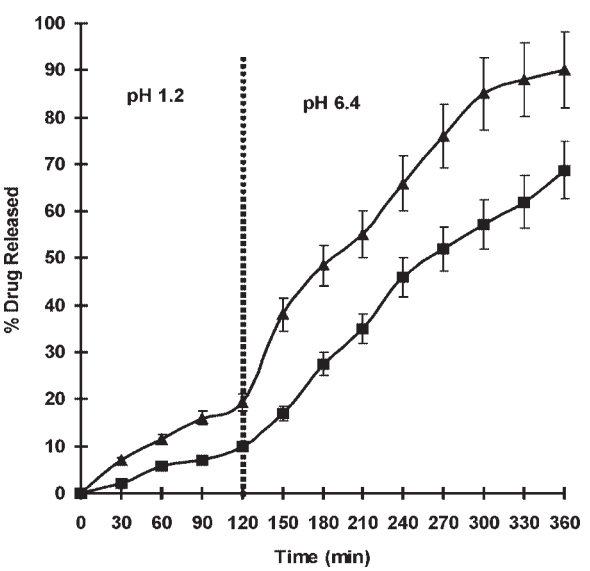


Figure 10 Cumulative drug release as a function of time from (■) DRC-loaded beads and (▲) plain resin particles containing DRC-loaded beads in media of varying pHs at 37°C.

concentration of DRC particles, whereas in one sample, plain resin particles were also present. Therefore, the release rate could also be varied by the introduction of plain resin particles into the beads. Moreover, we also prepared sample beads [$(CA)_2$ and $(CA)_3$] loaded with 2 and 3 wt % DRC particles, respectively, and observed that they released nearly 53.1 $\pm$ 1.2 and 64.8 $\pm$ 2.5% drug in 6 h. This was simply due to the fact that the increase in DRC content resulted in an increase in the overall drug content and the porosity of the beads, which thus enhanced the release rate.

CONCLUSIONS

From this study, we concluded that the entrapment of DRC particles into calcium alginate beads resulted in the formation of a new type of drug carrier that offered good control over the release rate. The release of the drug could be easily controlled by the variation of the physical parameters of beads, such as the degree of crosslinking, the nature of the crosslinking ions, and the amount of DRC particles entrapped within the beads, so the proposed system is a strong candidate for use as a small intestine drug-delivery system.

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