Imipramine Release from Ca-Alginate Gel Beads

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Ca-alginate gel beads loaded with a model cationic drug imipramine were prepared, and their drug release characteristics were examined. By soaking plain Ca-alginate gel beads in an imipramine solution, the slightly translucent beads were transformed into white beads, seemingly due to the precipitation of a drug-alginate complex. The amount of drug uptake in the beads increased linearly as the initial drug concentration increased (1—10 mg/ml). However, no significant difference in uptake efficiency was observed between the beads prepared over various periods of curing time. The drug release rate from the beads was in the following order: JP XII disintegration test solution No. 1 (pH 1.2) > 0.9% (w/v) NaCl ≒ test solution No. 2 (pH 6.8) > distilled water. The release rates were also measured in HCl solutions, NaCl solutions, and acetate buffers with varying pHs. It was suggested that imipramine ions interacting with the acidic residues of alginates were replaced by cations in the release medium and diffused out of the beads. Therefore, Ca-alginate gel could be a useful vehicle for the controlled release of water-soluble cationic drugs.

Keywords alginate gel bead; imipramine hydrochloride; controlled release; uptake efficiency; cationic drug

Alginates, polysaccharides found in brown seaweeds, have been widely empolyed in the food and pharmaceutical industries as suspending agents, emulsion stabilizers, gelling agents, and so forth.[1]

Alginates form tough gels through reactions with various cations such as H^+, Ca^{2+} and other divalent metal ions.[2,3] Attempts have been made to utilize alginate gel beads as controlled drug release vehicles, especially calcium-induced alginate gel (Ca-alginate gel), because of its excellent physical qualities and its non-toxic properties.[4-8] Useful applications of alginate gel beads in the design of controlled release formulations of some agricultural chemicals such as herbicides 2,4-D and dichlobenil, which have poor water solubility and relatively high vapor pressure, have been described in several studies.[9-12]

On the other hand, the release rates of substrates with high water solubility and low molecular weight have not yet been sufficiently controlled by the use of gels. For example, substrates such as glucose (mol wt. 180) and L-tryptophan (204) could diffuse freely into and from 2% Ca-alginate gel beads,[13] and the diffusion coefficients of benzoic acid (122), indigo carmine (204), and bromocresol green (698) from 4% Ca-alginate gel beads were about 20—30% lower than those in water.[14] However, cations liberated by the dissociation of basic drugs can interact strongly with the acidic residues of alginates,[15,16] and their release rates from gels are expected to be greatly reduced.

In this article, we present some experimental results which concern the uptake of a cationic model drug imipramine (pK_a 9.5) by Ca-alginate gel beads, as well as the effects of ionic components in a dissolution medium on their drug release properties. We also assess the ability of the gel to serve as a vehicle for the controlled release of water-soluble cationic drugs.

Experimental

Materials Sodium alginate was obtained from Sigma Chemical Co., Ltd, U.S.A.; the viscosity of 2% solution at 25 °C was 250 cps. The mannuronate/guluronate molar ratio (M/G ratio) was 1.4, which was determined according to the CD method of Morris *et al.*[17] Imipramine hydrochloride was also obtained from Sigma. All other chemicals were of reagent grade.

Preparation of Ca-Alginate Gel Beads The gel beads were prepared by dropping of a 2% sodium alginate solution into 0.1 M $CaCl_2$ solution at a rate of 20 drops/min using a peristaltic pump. One hundred beads were formed in 100 ml $CaCl_2$ solution. After a curing period of up to 48 h in $CaCl_2$ solution, the beads were filtered and washed with 100 ml of distilled water. They were then suspended in 200 ml of distilled water and were gently agitated for the removal of excess Ca^{2+} ions. After 30 min of agitation, the beads were filtered; they were translucent spheres with an average diameter of 2.5 mm. All steps were carried out at 25 °C.

Preparation of Imipramine-Loaded Gel Beads One hundred Ca-alginate gel beads were placed in an L-type glass test tube to which 10 ml of imipramine hydrochloride solution (1—10 mg/ml, pH about 5.5) was added, and the mixture was agitated at 25 °C for a given period of time (10—120 min). After being filtered and rinsed with 100 ml of distilled water for 1 min, the beads were dried at 40 °C for 1 d and then at room temperatue for one more day under reduced pressure. Finally, irregular shaped white beads were obtained; their average size was 1.5 × 1.0 mm and the average weight was 0.8 mg.

Release Experiments The release of imipramine from the dried gel beads was studied using a JP XII dissolution test apparatus empolying a paddle method (100 rpm). The release media included distilled water, sodium chloride solutions, JP XII disintegration test solutions No. 1 (TS No. 1) and No. 2 (TS No. 2), and buffer solutions with various pH values (from 3.76 to 7.99). One hundred gel beads containing imipramine and 900 ml of release medium were placed in a test vessel, the temperature of which was maintained at 37 ± 0.5 °C in a thermostat. At appropriate intervals, 5 ml samples were withdrawn and assayed by absorption measurement at 250 nm. After each sampling, a volume of fresh medium equal to the volume withdrawn was added. In separate experiments, the intial imipramine content of the dried beads (10 beads) was determined spectrophotometrically after being dissolved in 100 ml of 0.05 M phosphate buffer (pH 7.0), and the drug content which was equivalent to that initially contained in 100 beads was used to calculate the cumulative percentage of released drug.

Results and Discussion

Imipramine Loading into the Ca-Alginate Gel Beads When the translucent Ca-alginate gel beads were placed in an imipramine solution, their color immediately turned to white. This suggests that imipramine cations form highly water-insoluble complexes with the acidic residues of alginate molecules in the gel matrix, as was previously demonstrated on several cationic drugs.[15,16] As can be seen in Table I, the amount of imipramine uptake in the gel beads reached a plateau at 1.5 h and was almost independent of the curing time for the gel bead preparation. Here, the amount of imipramine uptake was estimated based on the

TABLE I. Effect of Curing Time of 2% Alginate Gel Beads in 0.1 M $CaCl_2$ on the Imipramine Uptake

Curing time (h)	Amount of imipramine uptake (mg/100 beads)[a] at				
	10 min	30 min	60 min	90 min	120 min
1	29.7	38.9	43.1	44.9	44.8
3	29.6	36.9	41.6	42.7	42.5
8	29.3	36.4	40.6	41.3	41.9
24	28.3	34.9	40.3	41.7	42.1
48	26.2	35.9	41.1	42.0	42.4

a) Amount as imipramine HCl. The initial amount of imipramine HCl in solution (10 ml) was 100 mg throughout.

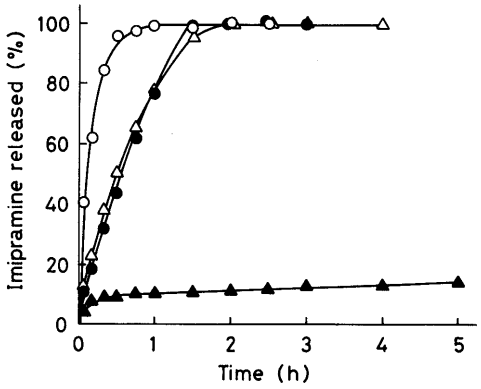

Fig. 1. Release Profiles of Imipramine from Ca-Alginate Gel Beads in Different Media

○, disintegration test solution No. 1; ●, disintegration test solution No. 2; △, 0.9% (w/v) NaCl; ▲, distilled water.

concentration decrease of the imipramine hydrochloride solution. With a curing time of 2 d and an uptake time of 1.5 h, the uptake amount increased linearly from the initial imipramine hydrochloride concentration over the concentration range studied, 1—10 mg/ml (data not shown). The uptake efficiency of gel beads, defined as the ratio of the amount of imipramine uptake in 100 beads to the initial imipramine amount in 10 ml of solution, was found to be about 42%. When drug molecules are physically included in the gel matrix of the beads, without having any interaction with alginate gels, the apparent uptake efficiency is estimated to be 7.6%.[18] Thus, the uptake efficiency of the alginate gel beads for imipramine cations was 5—6 times greater than that for non-interacting drug molecules, and about 80% ((42—7.6)/42 × 100) of the imipramine in the gel beads appeared to be strongly associated with the alginate molecules. The gel beads used for the following release study were prepared under the following conditions: a curing time of 2 d, an intial imipramine hydrochloride concentration of 10 mg/ml and an uptake time of 1.5 h.

Release Profiles of Imipramine from the Gel Beads Figure 1 showed the release profiles of imipramine from the gel beads in distilled water, TS No. 1, TS No. 2, and 0.9% (w/v) NaCl solution. The release rate was in the order of TS No. 1 > 0.9% (w/v) NaCl ≒ TS No. 2 > distilled water. The rates appeared to depend significantly on the ionic components of the release media. In distilled water, the free imipramine molecules in the beads seemed to result in a burst effect phenomenon. The most rapid release occurred in the most strongly acidic solution (TS No. 1, pH 1.2), and

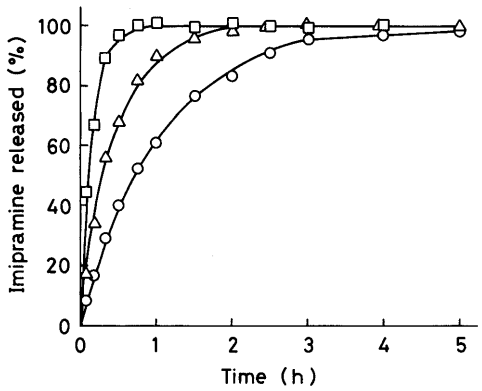

Fig. 2. Effect of HCl Concentration in Release Medium on the Imipramine Release from Ca-Alginate Gel Beads

HCl concentration (M): ○, 0.001; △, 0.01; □, 0.1.

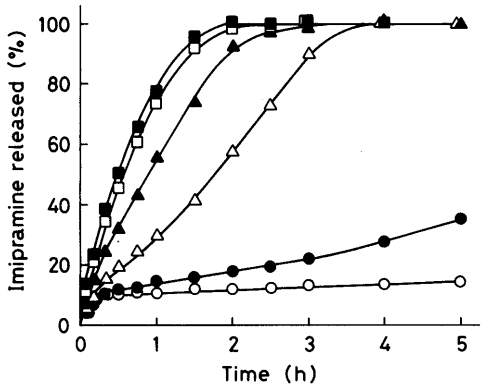

Fig. 3. Effect of NaCl Concentration in Release Medium on the Imipramine Release from Ca-Alginate Gel Beads

NaCl concentration (% (w/v)): ○, 0; ●, 0.001; △, 0.01; ▲, 0.1; □, 0.5; ■, 0.9.

the release rates into the media containing Na^+ ions were considerably higher than in distilled water, even though these media were at neutral pH region.

The release profiles and the change in appearance of the gel beads accompanied by the drug release, suggest that the release mechanisms are not all same in the varying media. Therefore, the imipramine release from the gel beads was studied further by employing HCl and NaCl solutions as release media.

The release profiles in the HCl solutions are shown in Fig. 2. A more rapid release was observed in a more acidic solution. The shape of the gel beads did not change in appearance. This suggested that the gel structure was maintained throughout the release process. Imipramine cations interacting with acidic residues of alginate were probably replaced by H^+ ions in the release medium and quickly diffused out of the beads.

The profiles in NaCl solutions are shown in Fig. 3. Though slower than in HCl solutions, the release rate increased with an increase in NaCl concentration. In contrast with the release in HCl solution, however, simultaneous dissolution of the gel beads was observed, and they disappeared at the same time that the drug release was completed. The gel structure was destroyed, probably by an ion exchange between the gel forming Ca^{2+} ions and the concentrated Na^+ ions. The release profiles in buffer solutions of the same Na^+ concentration were independent of their pH

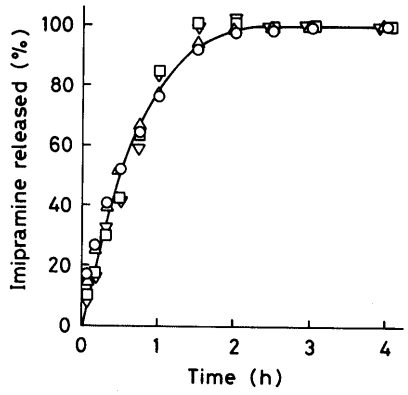

Fig. 4. Effect of the pH of the Release Medium on the Imipramine Release from Ca-Alginate Gel Beads

pH and buffer components: ○, 3.76 (CH_3COOH/CH_3COONa); △, 4.99 (CH_3COOH/CH_3COONa); □, 6.77 (NaH_2PO_4/Na_2HPO_4); ▽, 7.99 (NaH_2PO_4/Na_2HPO_4). These buffer solutions contained 0.154 M sodium ions.

values in the range from 3.8 to 8.0 (Fig. 4), and the beads also disappeared with drug release.

In conclusion, Ca-alginate gel is a very promising material for use as a vehicle for the controlled release of water-soluble cationic drugs because of its great binding capacity for drug ions. However, some ionic components in the release media affect the ionic interactions in the gel phase, and this may lead to considerable disadvantages, such as a breakdown of the drug ion-gel component interactions or of the gel structure itself.

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18) The value can be estimated as follows: the volume of 100 Ca-alginate gel beads with a diameter of 2.5 mm is $4/3 \times \pi \times 0.125^3 \times 100 = 0.82$ ml. After adding these beads to 10 ml of a drug solution containing A mg of the drug, the drug concentration in the solution, which is equal to that in the beads, becomes $A/10.82$ mg/ml. The uptake efficiency (%) is then estimated to be $(A/10.82 \times 0.82)/A \times 100 = 7.6$.