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Calcium alginate microparticles for oral administration: III. The effect of crosslink agents and various additive polymers on drug release and drug entrapment efficiency

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The effect of various crosslinkers (Ca^{2+}, Ba^{2+}, Sr^{2+}) and additive polymers such as Carbopol® 941, hydroxypropylmethylcellulose and Eudragit® RS 30 on the release rate and entrapment efficiency of nicardipine HCL from alginate beads was investigated. The mean particle sizes and the swelling ratios of the beads were also determined. Ca alginate beads displayed prolonged release profiles when compared to the Ba and Sr alginate beads. The addition of various polymers increased the release rate of nicardipine HCl from the beads compared with the plain beads.

1. Introduction

Sodium alginate which is a water soluble salt of alginic acid has been widely used as a food additive and a pharmaceutical agent. Addition of di- and polyvalent cations to alginate solutions causes gel formation. Cations crosslink with gluronic acid in a three dimensional network and this procedure has been used to produce controlled release alginate gel beads [1–3]. Calcium chloride is commonly used as a crosslinking agent. The use of various crosslinkers [4, 5] as well as additive polymers [6–8] may affect the gel bead formation as well as drug release and drug entrapment efficiency properties of the gel beads.

The model substance of this investigation, nicardipine HCl (NC) is a calcium antagonist used for the treatment of hypertension [9].

In our previous studies, we investigated the effect of the sodium alginate type and of formulation factors on drug release and drug entrapment efficiency [10, 11]. The aim of the present study was to evaluate the effect of three different crosslinkers (Ca^{2+}, Ba^{2+} and Sr^{2+}) and some additive polymers such as Carbopol 941, hydroxypropylmethyl cellulose (HPMC) and Eudragit RS 30 on the NC release and NC entrapment efficiency of the beads.

2. Investigations, results and discussion

The beads were almost spherical. As can be seen from Fig. 1 the mean particle sizes of the formulations are close to each other except for formulations B3 and B4. The addition of Eudragit RS 30 to the calcium chloride solution increased the particle sizes of the beads.

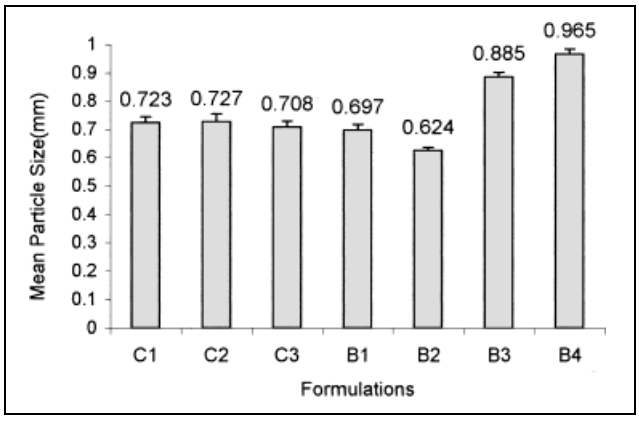

Fig. 1: Particle size of the alginate beads

Figs. 2 and 3 show the swelling ratio of the beads. When we examined the effect of the crosslinking agent on the swelling behaviour of the beads, the beads which were prepared with calcium chloride (C1) reached the highest swelling ratio at pH 4.5. They disintegrated in basic media. In the case of Ba^{2+} and Sr^{2+} the highest swelling ratio was obtained at pH 7 and 7.5. The more stronger beads were formed with Ba^{2+} and Sr^{2+} and they were not easily disintegrated in basic media. Fig. 3 depicts the swel-

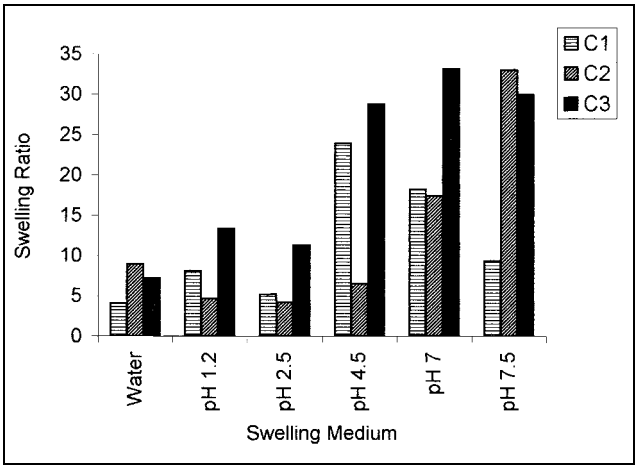

Fig. 2: Swelling ratio vs medium relationship of the Ca, Ba and Sr alginate beads

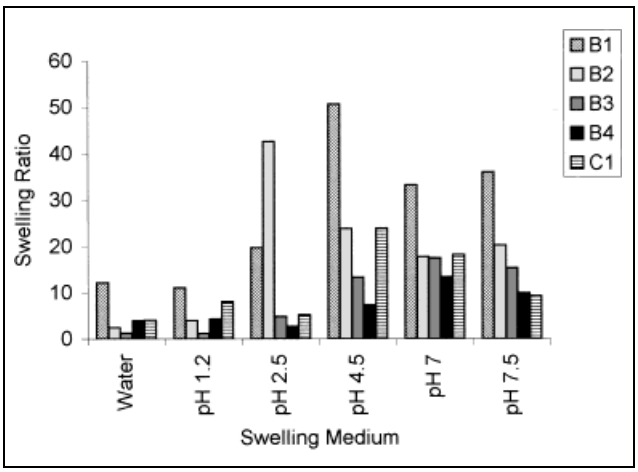

Fig. 3: Swelling ratio vs medium relationship of the beads which were prepared by the addition of various polymers

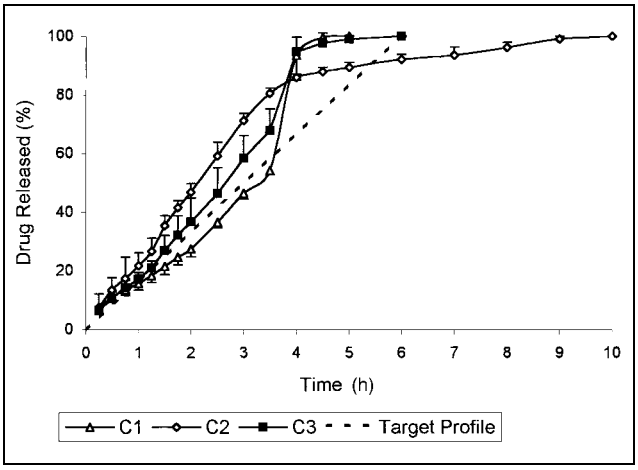

Fig. 4: Release of NC from the Ca, Ba and Sr alginate beads

Table 1: Formulation parameters, $t_{\%50}$ and drug entrapment efficiency values of the beads

Code	Crosslink agent	Additive polymer	Amount	$t_{\%50}$	Drug entrapment efficiency (%)
C1	$CaCl_2$	–	–	3.24	93.5 ± 6.2
C2	$BaCl_2$	–	–	2.25	62.7 ± 9.4
C3	$SrCl_2$	–	–	2.85	57.7 ± 9.4
B1	$CaCl_2$	Carbopol 941	0.5 g	2.75	100 ± 9.5
B2	$CaCl_2$	HPMC (% 2.5)	15 ml	2.80	84.7 ± 19.1
B3	$CaCl_2$	Eudragit RS 30	1.5 ml	2.55	61.7 ± 9.4
B4	$CaCl_2$	Eudragit RS 30	4 ml	2.70	32.9 ± 1.25

ling behaviour of the formulations B1–B4. Formulation B1 showed a swelling behaviour similar to C1. On the other hand the swelling behaviour of formulations B2–B4 was different. B2 reached the maximum swelling ratio at pH 2.5 whereas B3 and B4 reached the maximum swelling ratio at pH 7.

The drug content of the beads was between 32.9 and 100% (Table 1). The drug entrapment efficiency of the beads which were crosslinked with Ba^{2+} and Sr^{2+} was lower than those of Ca-alginate beads. The interaction between drug and Ca^{2+}-ions was more stronger than that with other crosslinkers.

If we compared formulations B1–B4, the highest drug entrapment efficiency was obtained with B1. The drug entrapment efficiency of the formulations B2–B4 was lower than that of C1 and B1. Addition of the polymer to the calcium chloride solution may effect the solubility of NC. Therefore the entrapment of the drug in the matrix form of the beads was reduced.

The release profiles of NC from Ca, Ba and Sr alginate beads were shown in Fig. 4. It has been reported that the release of recombinant human tumor necrosis factor from Ba and Sr alginate beads was more extended than that of Ca alginate beads [5]. In contrast to this data we found that the release of NC from Ba and Sr alginate beads were faster than that from Ca alginate beads. The source of alginate, the type and molecular weight of the drug may affect the release behaviour. If we compare the $t_{50\%}$ values of formulations C1–C3 the highest value was obtained with C1 (Table 1). In fact, the affinity of alginate to Ba and Sr ions was higher than that of Ca ions and more stronger beads were obtained with Ba and Sr crosslinkers. These beads did not easily disintegrate in basic pH, but the release of drug was higher than that of Ca beads. The release profile of Ca-alginate beads showed the most

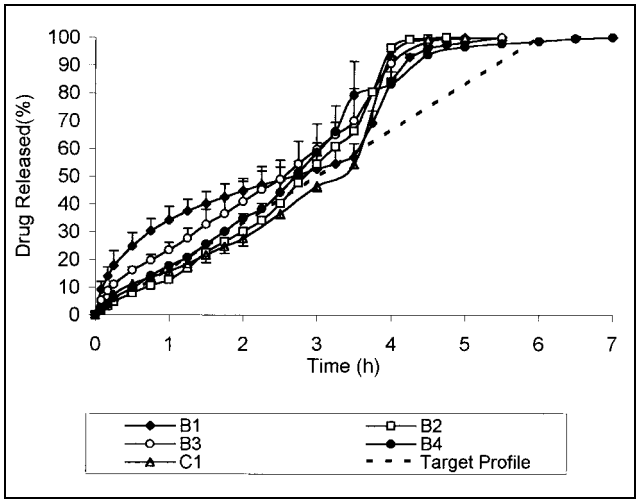

Fig. 5: Release of NC from the beads which were prepared by the addition of various polymers

Table 2: Kinetic constants (k), diffusional exponents (n) and determination coefficients (r^2) by linear regression of ln (M_t/M_∞) vs ln t

Code	n ± Cl	k ±Cl	r^2
C1	0.674 ± 0.113	0.012 ± 0.007	0.976
C2	0.922 ± 0.271	0.006 ± 0.009	0.987
C3	0.894 ± 0.064	0.005 ± 0.002	0.985
B1	0.477 ± 0.065	0.047 ± 0.019	0.989
B2	0.969 ± 0.084	0.003 ± 0.001	0.987
B3	0.662 ± 0.063	0.017 ± 0.003	0.990
B4	1.001 ± 0.202	0.003 ± 0.003	0.985

CI: Confidence interval

agreement with the target profile which was plotted from the pharmacokinetic parameters.

Fig. 5 depicts the release profiles of the other formulations. The Ca-alginate beads (C1) release the 50% of drug during the first 3 h. However the beads began to disintegrate about 3.5 h later and 100% of drug was released for 4 h at pH 7–7.5. Various polymers were used to extend to release after 4 h. However the most rapid release was obtained with the Carbopol alginate beads. Both alginate and Carbopol have anionic character, so the concentration of calcium chloride may not be high enough to form a strong alginate-gel complex. The loosed gel matrix showed rapid drug release.

HPMC is a nonionic polymer. Although it has no effect for the formation of the Ca-alginate complex, it can coat the beads. Not any prolonged effect of HPMC on NC release was found. In the case of Eudragit RS 30 more polymer caused a more prolonged release and the release profile of B4 beads was lower than those of B3 beads, but it was still higher than those of plain C1 beads. When we examined the $t_{50\%}$ values of formulations B1–B4, all of them were lower than that of C1. It can be said that the addition of a polymer did not affect the prolongation of the release rate of NC.

The release mechanism was investigated by the following equation given by Ritger and Peppas [12].

$$M_t/M_\infty = kt^n .$$

The initial portion of the release curve was used for the calculation. M_t/M_∞ = fraction of drug released up to time t, k = kinetic constant, n = release exponent which is related to the release mechanism.

As can be seen from Table 2, n values of formulations C1, C3, B1 and B3 lying between 0.43–0.85 indicated non-fickian transport controlled both by diffusion and relaxation of the polymer. On the other hand, the n values of C2, B2 and B4 were greater than 0.85, the mechanism of drug release was determined as Case II transport indicating zero order release kinetics. The n value of formulation B4 was 1.00. The release was controlled by relaxation of the polymer. It was difficult to establish any relation between the release mechanism and the type of the formulations.

In conclusion, Ca^{2+} was the most effective agent to obtain extended release from the NC alginate beads and various polymers did not show any influence to prolong the NC release.

3. Experimental

3.1. Materials

Nicardipine HCl was kindly supplied by Novartis Co, Turkey. Sodium alginate (Manugel A7B618) was donated from Kelco Co, England. Carbopol 941 was from Sumitomo Seika, Japan. Hydroxypropylmethylcellulose was from Sigma, USA and Eudragit RS 30 was from Rhöm Pharma; Germany. All other chemicals and solvents were of analytical grade.

3.2. Preparation of the alginate gel beads

Gel beads were prepared using the method described previously [13]. The codes and content of the formulations were shown in Table 1. The concentration of sodium alginate solution was 2.5%. A concentration of 0.1 M crosslinking agent ($CaCl_2$, $BaCl_2$ or $SrCl_2$) was used. Carbopol 941 was added to the alginate-nicardipine dispersion (B1) whereas HPMC or Eudragit RS solutions were added to the $CaCl_2$ solutions (B2–B4).

3.3 Particle size determination

The particle size of 50 beads were measured with a micrometer and the mean particle size was determined.

3.4. Swelling studies

Alginate beads were placed in various buffer solutions and water at 37 °C. Beads were removed at selected time intervals and were weighted. Changes in their weight were measured during the swelling, then the swelling ratio was calculated.

3.5. Drug content determination

After disintegration of the beads in pH 7.5 phosphate buffer, NC was extracted with dichloromethane. The organic phase was evaporated and the drug was assayed spectrophotometrically at 240 nm.

3.6. Target profile

The target profile was plotted as described elsewhere [11].

3.7. Drug release studies

The release of NC from alginate gel microparticles was investigated by a flow-through cell apparatus (Sotax, USA). The flow rate was 4 ml/min. The gel microparticles equivalent to 10 mg NC were subject to pH 1.2, 2.5, 4.5, 7 and 7.5 dissolution media for 1, 1, 1.5, 1.5 and 3 h, respectively. The collected samples were assayed spectrophotometrically at 240 nm.

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Formulation and *in vitro/in vivo* investigation of carbamazepine controlled-release matrix tablets

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Carbamazepine controlled-release tablet formulations containing hydroxypropyl methylcellulose (HPMC) as matrix material at different concentrations were developed and evaluated *in vitro* and *in vivo*. The formulation containing 10% HPMC (HPMC-10) showed a controlled-release profile comparable to that of a commercially available, controlled-release carbamazepine preparation (Tegretol® CR 200). The kinetics of controlled-release carbamazepine tablets was examined in eight healthy volunteers. The peak plasma concentration of $1.99 \pm 0.56\ \mu g \cdot ml^{-1}$ was obtained for HPMC-10 at 15.0 ± 9.0 h, and $1.33 \pm 0.35\ \mu g \cdot ml^{-1}$ for Tegretol® CR 200 at 15.2 ± 8.9 h, and $AUC_{0-\infty}$ values of $85.2 \pm 30.8\ \mu g \cdot h \cdot ml^{-1}$ and $76.9 \pm 20.7\ \mu g \cdot h \cdot ml^{-1}$, respectively. Developed formulation (HPMC-10) was found to be bioequivalent to Tegretol® CR 200 and, controlled release was obtained with smoother concentration-time curve resulting in less fluctuations.

1. Introduction

Carbamazepine is a widely prescribed drug for the treatment of epilepsy [1]. It is characterized by a slow and irregular gastro-intestinal absorption due to its low water solubility [2]. During repeated administration, elimination half-life is strongly decreased due to auto-induction of the microsomal enzyme system. Its initial half-life is about 24 h, while on chronic dosing it is lowered to 12 h under monotherapy and 8 h in those patients who take other