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International Journal of Pharmaceutics 323 (2006) 34–42
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Swelling studies and in vitro release of verapamil from calcium alginate and calcium alginate–chitosan beads

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Received 20 August 2005; received in revised form 12 April 2006; accepted 24 May 2006
Available online 2 June 2006

Abstract

The aim of the present work was to investigate the swelling behavior and the in vitro release of the antihypertensive drug verapamil hydrochloride from calcium alginate and chitosan treated calcium alginate beads. Calcium–alginate beads, chitosan-coated alginate beads and alginate–chitosan mixed beads were synthesized and their morphology was investigated by scanning electron microscopy. The swelling ability of the beads in different media was found to be dependent on the presence of the polyelectrolyte complex between alginate and chitosan, the pH of the aqueous media and the initial physical state of the beads. The results revealed that the encapsulation of verapamil in both calcium–alginate and calcium alginate–chitosan mixed beads exceeded 80%. Considering the in vitro stability of verapamil encapsulating beads, 70% of the drug released from wet and dry plain calcium alginate beads within 1 and 3 h, respectively. The presence of chitosan was found to retard significantly the release from wet beads. However, in the case of dry beads the presence of chitosan had no significant effect on the initial release stage and significantly increased the release on the later stage. The results were analyzed by using a semi-empirical equation and it was found that the drug release mechanisms were either "anomalous transport" or "case-II transport".

Keywords: Calcium alginate–chitosan beads; Hydrogels; Swelling; Verapamil hydrochloride

1. Introduction

Alginate is a natural biopolymer extracted from brown algae. It is composed of linear chains of the α-L-guluronic acid (G) and the β-D-mannuronic acid (M). Alginates form hydrogels in the presence of divalent cations like Ca^{2+} (Ouwerx et al., 1998; Bajpai and Sharma, 2004).

Nowadays, the use of alginate hydrogels in biotechnology and pharmaceutical industry is widespread due to the unique properties they possess such as high biocompatibility and biodegradability. The inert environment within the polymer network of alginates allows for the entrapment of a wide range of bioactive substances, cells and drug molecules, with minor interactions between them and the biopolymer (Griffith, 2000). Furthermore, the physical and chemical properties of alginates (e.g. porosity, degradability) can be easily modified in mild conditions (Gombotz and Wee, 1998).

Calcium alginate hydrogels are widely used as wound dressings (Kneafsey et al., 1996), cell immobilizing materials (Bandhyopadhyay et al., 2001) and scaffolds for tissue engineering (Leor et al., 2000; Kataoka et al., 2001). Calcium–alginate beads have been used in controlled drug delivery technology for the gastro-intestinal administration of proteins (Hari et al., 1996; Gombotz and Wee, 1998; Rasmussen et al., 2003), drug molecules (Bodmeier and Paeratakul, 1989; Sezer and Akbuga, 1999; Fernández-Hervás et al., 1998) or for ophthalmic drug delivery (Cohen et al., 1997).

Much attention has received the chitosan–alginate polyelectrolyte complex that has been studied thoroughly (Lee et al., 1996; Gåserød et al., 1998; Becherán-Marón et al., 2004). Chitosan is used either as a means of coating alginate beads in order to alter the diffusion rate of the encapsulated substances (Anal and Stevens, 2005) or as an additive for the bulk modification of the beads' structure (Lin et al., 2005; Gotoh et al., 2004). The behavior of calcium–alginate beads treated with chitosan in media that imitate the gastrointestinal fluids has been studied by several researchers (Hari et al., 1996; Sezer and Akbuga, 1999; González-Rodríguez et al., 2002).

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doi:10.1016/j.ijpharm.2006.05.054

Although many drugs have been extensively investigated using natural polymeric carriers, the studies on the release of antihypertensive drugs are limited. Sipahigil and Dortunc (2001) used beads prepared from the natural polymer carrageenan for the controlled release of verapamil HCl (VRP). In another study, Kurkuri et al. (2001) prepared polymeric sodium alginate interpenetrating network membranes containing VRP for transdermal application. Kilicarslan and Baykara (2003) prepared Eudragit microspheres containing VRP and examined the effect of drug/polymer ratios on the VRP loading. Soppimath et al. (1999, 2000, 2001) and Soppimath and Aminabhavi (2002) have reported the use of modified guar gum plant polysaccharide microspheres, cellulose based matrix for the release of a water-soluble (VRP) and a water insoluble (nifedipine) antihypertensive drug.

The improvement of the controlled drug delivery systems depends upon the properties of the materials used. Therefore, a better understanding of the biopolymers' properties is essential to improve the efficiency of the release systems. The aim of the current study was first the investigation of the swelling behavior of wet and dry calcium–alginate and calcium alginate–chitosan beads in different aqueous media. Then, in vitro release studies of the antihypertensive drug verapamil hydrochloride from calcium–alginate and calcium alginate–chitosan beads were performed in simulated gastric fluids and the release profiles were analysed by using a semi-empirical equation in order to characterize qualitatively the drug release mechanism.

2. Materials and methods

2.1. Materials

Calcium chloride dihydrate ($CaCl_2{\cdot}2H_2O$), low-viscosity (250 cps of 2% solution) alginic acid sodium salt and verapamil hydrochloride (minimum 99.0%) were purchased from Sigma–Aldrich (Athens, Greece). High viscosity chitosan was purchased from Sigma–Aldrich (Athens, Greece) and used as received. The degree of deacetylation (DD) of chitosan was calculated by the FTIR method (Domszy and Roberts, 1985; Khan et al., 2002) and was found to be 61%.

2.2. Preparation of calcium–alginate beads

Calcium solution of 100 mmol and alginate solution of 4% (w/v) were prepared by dissolving the appropriate amounts of calcium chloride dihydrate and sodium alginate, respectively, in ultrapure water (conductivity $< 0.1\ \mu S\ cm^{-1}$). The calcium–alginate beads were prepared by dropwise addition of 10 ml of alginate solution into 20 ml of calcium chloride solution through a fine 21 gauge stainless steel needle. The distance between the edge of the needle and the surface of the calcium solution was 6 cm. The beads were left in the gelling medium for 15 min, then separated from the solution through a stainless steel grid and left at room temperature for 15 min before used for further studies. The mean diameter of the calcium alginate beads was determined by measuring 20 beads under an optical microscope system (Carl Zeiss Axioskop 2, Germany) using the software Image Tool (Wilcox et al., 2002). In the case of drug loaded calcium–alginate beads the appropriate amount of VRP was added to the alginate solution. The mixture was dissolved under magnetic stirring and the formation of the beads was performed by ionic gelation as previously described.

2.3. Preparation of alginate–chitosan mixed beads

Alginate chitosan-mixed beads were used for the swelling experiments and for the release studies of VRP. Empty or loaded beads were prepared as previously described with the exception that the gelling medium was a chitosan solution of 0.1% (w/v) in diluted HCl (pH 1.2) containing 100 mmol calcium.

2.4. Preparation of alginate–chitosan coated beads

Chitosan-coated alginate beads were used for the swelling studies. Chitosan solution of 0.1% (w/v) was prepared by dissolving the appropriate quantity of chitosan into 20 ml of ultrapure water. The pH was adjusted to 1.2 by the addition of HCl. The calcium alginate beads were transferred into chitosan solution and remained for 15 min under gentle magnetic stirring. Then the beads were separated from the solution using a stainless steel grid and left before use for 15 min at room conditions.

2.5. Swelling studies

Swelling studies were conducted using both wet and dry beads. The term wet refers to the state of the beads immediately after the preparation and the term dry to beads that were left to dry for 24 h at 30 °C in air. Swelling studies of calcium–alginate, chitosan-coated alginate and alginate–chitosan mixed beads were carried out in three aqueous media: pure water, phosphate buffer saline (PBS, pH 7.4) and simulated gastric fluid (SGF, pH 1.2). SGF was prepared by dissolving 2 g of NaCl (Merck, pro analysis) and 7 ml of concentrated HCl in 1 l of ultrapure water. Accurately weighed amounts of beads (ranging from 2.5 to 3 g) were immersed in 25 ml of SGF solution and at fixed time intervals the beads were separated from the medium using a stainless steel grid. Immediately, they were wiped gently with paper and weighed. The dynamic weight change of the beads with respect to time was calculated according to the formula:

$$\%\ \text{weight change} = \frac{W_s - W_i}{W_i} \times 100\% \quad (1)$$

where W_s is the weight of the beads in the swollen state and W_i is the initial weight of the beads.

2.6. Release studies

The in vitro release studies were performed in SGF. Accurately weighed amounts of beads (ranging from 2.5 to 3.0 g) were placed in conical flasks containing 25 ml of the release medium. The samples were incubated at 37 ± 0.1 °C under shaking at 50 rpm. At predetermined time intervals, samples of 0.5 ml were collected from the release medium and were replaced with fresh SGF solution. The concentration of VRP in the solution

was assayed by UV spectroscopy (Hitachi U-2800) at 278 nm using a standard curve of known concentrations in the range of 10–60 ppm with correlation coefficient $R = 0.99$.

After preparing the beads, the amount of VRP entrapped into the beads was calculated by measuring the absorbance of the gelling medium at 278 nm. The VRP encapsulation efficiency was estimated according to the formula:

$$\text{Encapsulation efficiency}\,(\%) = \frac{M_i - M_d}{M_i} \times 100\% \qquad (2)$$

where M_i is the initial mass of drug dissolved in the alginate solution and M_d is the mass of drug measured in the gelling media right after the preparation of the drug-loaded beads. The drug to polymer ratio (%, w/w) was expressed as the weight of drug encapsulated in the beads divided by the weight of alginate used.

2.7. FT-IR spectroscopy

Individual beads were crushed with pestle in an agate mortar. The crushed material was mixed with potassium bromide (Merck IR spectroscopy grade) in 1:100 proportion and dried at 40 °C. The mixture was compressed to a 12 mm semitransparent disk by applying a pressure of 10 tons (Digilab press, Randolph, MA, USA) for 2 min. The FTIR spectra over the wavelength range 4000–400 cm^{-1} were recorded using a FTIR spectrometer (Digilab Excalibur, Randolph, MA, USA).

2.8. Scanning electron microscopy (SEM)

The microstructure and surface topography of the beads were evaluated by scanning electron microscopy. Randomly selected beads were dehydrated either by air at 40 °C or by transferring them in a series of increasing ethanol/water mixtures ranging from 30 to 100% ethanol. The beads were left for 10 min in each solution, separated and dried at 30 °C for 24 h. Then, the samples were attached to aluminum stubs with double side adhesive carbon tape and examined in a scanning electron microscope (Jeol 5200, SEM) equipped with an energy dispersive spectrometer (EDS) detector (Oxford). EDS spectra were acquired from the inner and outer surface of the chitosan coated beads for screening their elemental composition. The mean size expressed as the mean diameter of 20 beads calculated from the SEM photos using the software Image Tool (Wilcox et al., 2002).

2.9. Statistics

Data are represented as the mean value (standard deviation ± S.D.) of three experiments. The statistical analysis was done on release data with the unpaired Student's *t*-test, and $p < 0.05$ was used as a limit to indicate statistical significance.

3. Results and discussion

3.1. Morphology of the beads

Scanning electron micrographs of dry pure calcium–alginate and chitosan-coated alginate beads are illustrated in Figs. 1 and 2, respectively. In comparison with the size of the wet beads which was measured 3 ± 0.2 mm, dried beads were shrunk at about half and their diameter found to be 1.70 ± 0.08 mm. In the case of pure calcium alginate beads, air drying resulted an acceptable spherical shape as shown in Fig. 1a. Detailed examination of the surface structure (Fig. 1b)

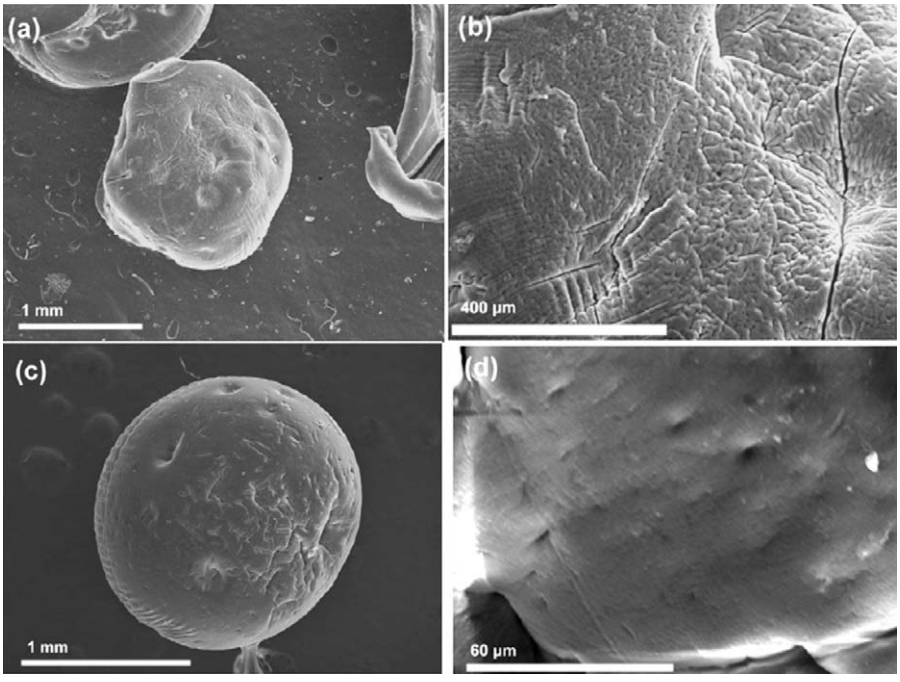

Fig. 1. SEM micrographs of pure calcium–alginate beads dried with two different methods; air (a and b) and ethanol (c and d); (a and c) show individual beads while (b and d) show the respective surface microstructures.

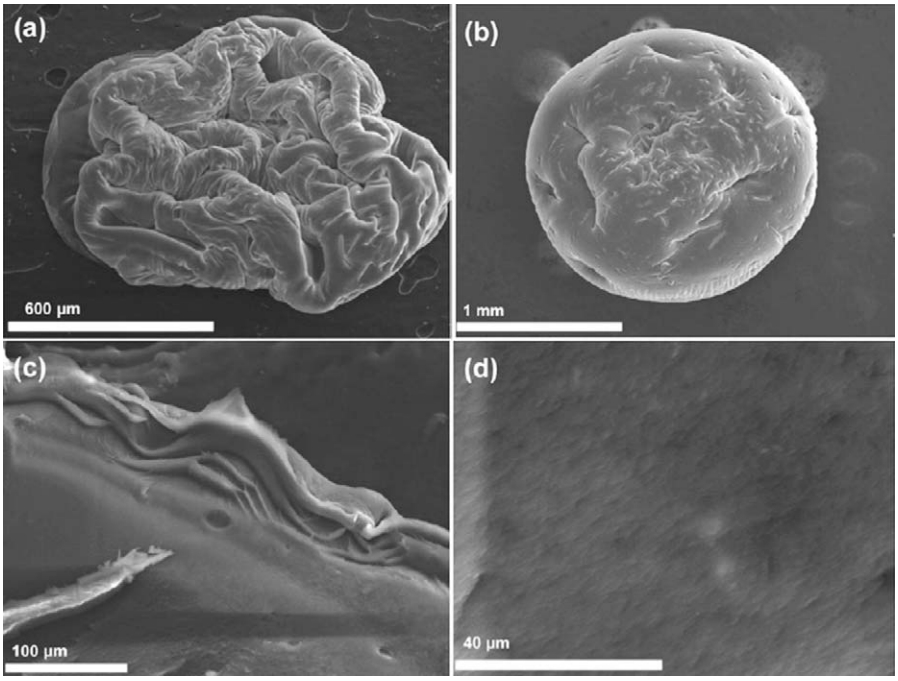

Fig. 2. SEM pictures of chitosan-coated alginate beads dried in air (a) and in ethanol (b–d); (c) shows a cross section of a chitosan-coated bead while (d) shows the outer surface microstructure.

reveals cracks caused by partial collapsing of the polymer network during dehydration. In addition, pores with diameter of a few micrometers and severe wrinkles are present. In contrast, ethanol drying caused significant improvement on the maintenance of the spherical shape and led to the decrement of the cracks on the surface (Fig. 1c and d).

Fig. 2a shows extended dehydration of the chitosan membrane surrounding the beads, leading to corrugations and loss of the spherical shape. On the other hand, ethanol treatment contributed substantially to the reduction of the roughness of the chitosan membrane and the elimination of the cracks observed on the surface (Fig. 2b). Furthermore, ethanol drying maintained the adhesion of the chitosan membrane with the alginate core (Fig. 2c) and resulted a smoother outer surface (Fig. 2d).

The presence of chitosan was confirmed by SEM/EDS microanalysis (Fig. 3). EDS spectra show changes in the element constituents of the sample at the inner and outer part. The presence of high intensity calcium peaks at the inner of the bead reveals that the presence of calcium is due to the crosslinks between calcium ions and carboxylate groups of alginate. In contrast, traces of calcium on the outer surface were identified proving the presence of chitosan, which does not interact with calcium ions. This small fraction of calcium ions on the chitosan membrane may be attributed to possible diffusion of the calcium ions to the outer surface of the beads during the synthesis process.

3.2. Swelling studies

3.2.1. Wet beads

Fig. 4 illustrates the swelling behavior of pure calcium–alginate beads, chitosan-coated beads and alginate–chitosan mixed beads in water, PBS and SGF. Pure calcium–alginate beads exhibit a swelling degree in water of about 115% (Fig. 4a). The swelling behavior can be well justified due to the

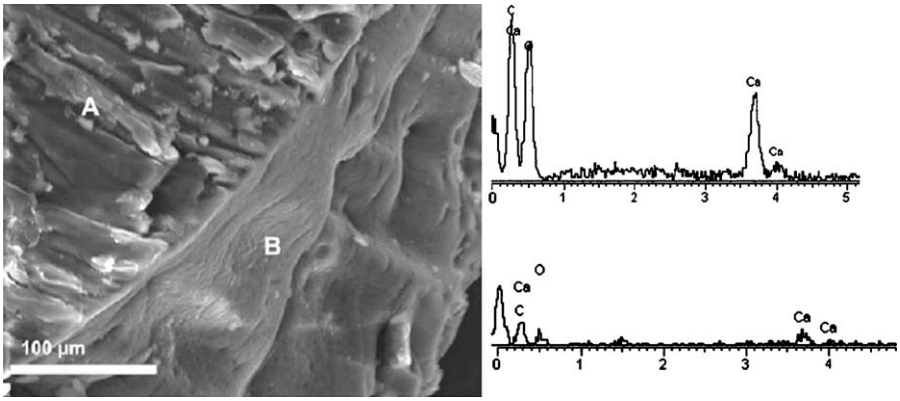

Fig. 3. SEM image of a cross section of a chitosan-coated alginate bead and the corresponding EDS analysis of the inner (A) and outer part (B).

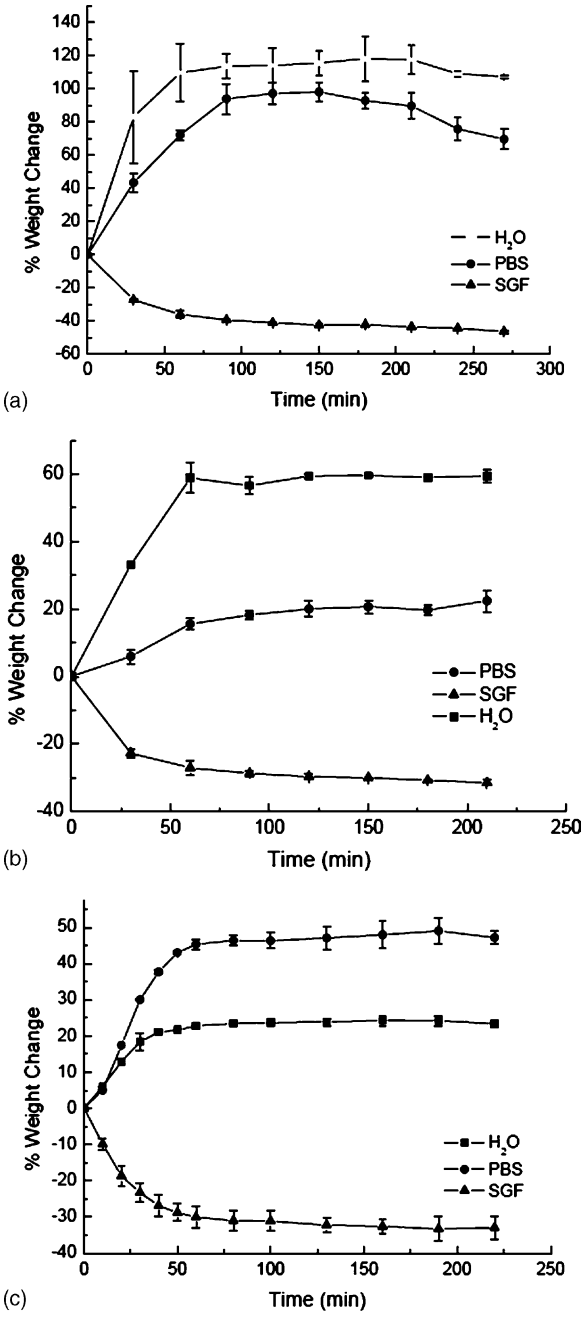

Fig. 4. Swelling profiles of wet beads in H_2O, PBS and SGF: (a) calcium alginate beads, (b) chitosan-coated alginate beads and (c) alginate–chitosan mixed beads. Values are mean ± standard deviation (S.D.) of three experiments.

fact that wet beads tend to absorb water (free or bulk water) in order to fill the void regions of the polymer network within the beads that remain dehydrated, until they reach the equilibrium state (Hoffman, 2002). The phenomenon is provoked by the relaxation of the polymer network at the presence of osmotic pressure. Swelling of the wet calcium–alginate beads in water lasts for about 60 min until the osmotic pressure equals the forces of the crosslinking bonds that maintain the structure of the polymer network stable. When these two forces are equal, no further water gaining from the beads is observed.

The same beads tend to shrink when exposed to the acidic environment of SGF. Ouwerx et al. (1998) have shown that at low pH values (<4) the carboxylate groups of alginate are protonized and hence the electrostatic repulsion among these groups lessens and shrinkage is favored. The swelling curve in the slightly basic environment of PBS begins to decline indicating dissolution or degradation. This has also been reported by Bajpai and Sharma (2004).

To gain information regarding the molecular structure of swollen calcium alginate beads, the FTIR spectra from pure calcium alginate beads were obtained after swelling in SGF, water and PBS. The spectra are shown in Fig. 5. In PBS and water, the peaks at 1614 and 1410 cm^{-1} are assigned to the asymmetric and symmetric carboxylate (COO^-) vibrations, respectively (Wang and He, 2002). In SGF the carboxylate band is protonated (COOH) and is present at 1737 cm^{-1}. The peak at 1614 cm^{-1} is decreased and shifted to 1633 cm^{-1}. In the case of the spectrum obtained from beads swollen in PBS two new peaks at 602 and 563 cm^{-1} are observed. The peaks can be assigned to the P–O asymmetric bending of the PO_4 group. The above indicate that the formation of calcium phosphate salts, and possibly hydroxyapatite occurred. Hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ is a calcium phosphate salt whose formation is favored at neutral and basic pH. In addition, the separation of the above peaks is an indicator of a crystalline phase (Termine and Posner, 1966). The main peak associated with the P–O around 1030 cm^{-1} is difficult to distinguish due to the overlapping with other bands of alginates at the same region.

Fig. 4b shows the swelling profiles of wet chitosan-coated alginate beads. It can be seen that they swell in water about three times less in comparison with the pure wet calcium–alginate beads. As already shown in the SEM microphotographs (Fig. 1b) coating of the calcium–alginate beads with chitosan caused significant reduction of micro/macroscopic pores and cracks observed on the surface which in turn lead to decreased permeability. This explains the lower swelling behavior in comparison with the uncoated beads. Chitosan-coated alginate beads also show lower degree of swelling when exposed in PBS which is

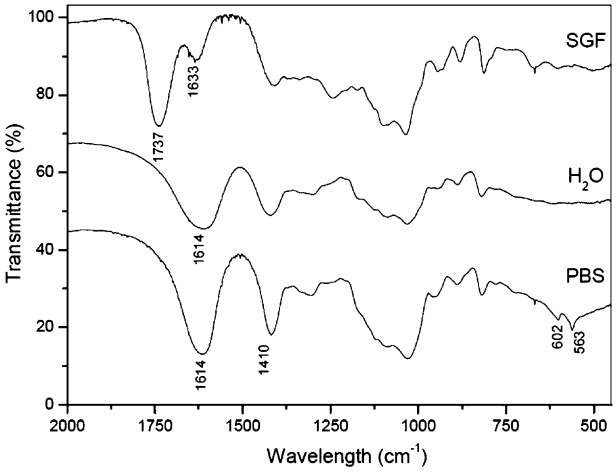

Fig. 5. FTIR spectra of calcium–alginate beads after swelling in SGF, H_2O and PBS. The spectra have been shifted vertically for clarity.

about four times lower than the pure calcium alginate beads. Although the degree of protonization of the free amino groups of chitosan at this slightly basic environment is low and can influence the complex with alginates, the chitosan membrane still inhibits the swelling of the calcium alginate core. The same shrinking behavior in SGF as in pure beads is also observed in the case chitosan-coated alginate beads. Chitosan is highly soluble and cationic charged in SGF due to conversion of amine units into soluble form NH_3^+. The interaction between amino groups and protonated carboxylic groups is weak leading to dissolution of membrane during swelling. Thus the total swelling behavior is dominated by the calcium alginate matrix.

Alginate–chitosan mixed beads swell even lesser in water than the chitosan-coated alginate beads (Fig. 4c) due to two factors: the formation of a more entangled system developed by the blending of alginate and chitosan (Lin et al., 2005) and the presence of the polyelectrolyte complex between the amino groups of chitosan and the carboxylate groups of alginate. These two parameters improve significantly the stability of the wet alginate–chitosan mixed beads. The polymer network is denser and exhibits increased resistance to osmotic pressure. Alginate–chitosan mixed beads exhibit higher weight change in PBS than in water. The poor solubility of chitosan at pH 7.4 and the low binding with alginate under these conditions leads to less stable beads. Furthermore the maximum swelling is about half in comparison to the non-chitosan treated beads showing that addition of small amounts of chitosan leads to the formation of more stable beads.

3.2.2. Dry beads

The results obtained in the case of dry beads vary substantially when compared to the wet beads in terms of maximum swelling rates which are higher of about one order of magnitude (Fig. 6). Swelling of the dry beads is mainly attributed to the hydration of the hydrophilic groups of alginate and chitosan (Hoffman, 2002). In this case free water penetrates inside the beads in order to fill the inert pores among the polymer chains, contributing to a greater swelling degree.

The ability of dry calcium–alginate beads to swell in water is lower when coated with chitosan (Fig. 6b). As already mentioned, the chitosan membrane reduces the permeability of the beads. In addition, a fraction of hydrophilic groups at the surface of dry calcium alginate beads form a polyelectrolyte complex with the amino groups of chitosan and hence it does not contribute to the entrapment of water molecules within the beads. The phenomenon is more obvious in the case of dry alginate–chitosan mixed beads that exhibit even lower degree of swelling (Fig. 6c). Alginate–chitosan mixed beads possess greater swelling resistance when exposed to aqueous media because of the greater physical entanglement of the polymer chains.

Fig. 6 also shows that all formulations tested exhibited significant swelling rates when exposed to the slightly alkaline environment of PBS. The swelling mechanism in this case is related with the Ca^{2+} and Na^+ exchange (Bajpai and Sharma, 2004) in the case of pure calcium alginate beads, and the low binding of chitosan with alginate due to the lower cationic nature

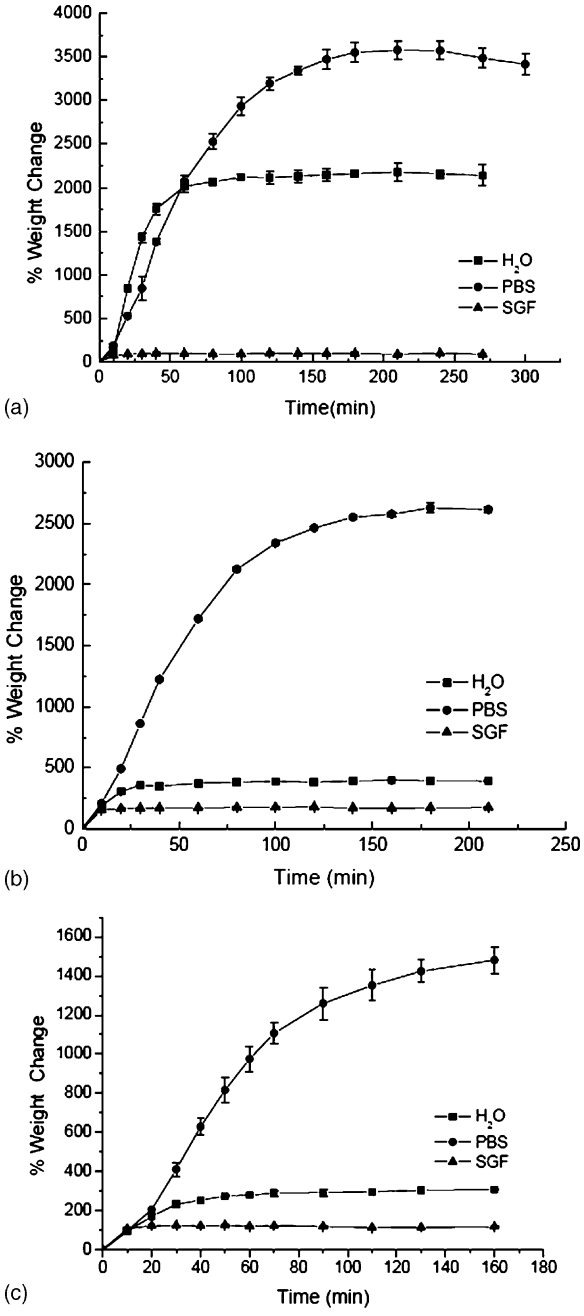

Fig. 6. Swelling profiles of dry beads in H_2O, PBS and SGF: (a) calcium–alginate beads, (b) chitosan-coated alginate beads and (c) alginate–chitosan mixed beads. Values are mean ± standard deviation (S.D.) of three experiments.

of chitosan at these conditions in the case of chitosan–alginate beads.

In contrast to the wet beads, which shrink in acidic conditions, dry beads exhibit a swelling degree ranging from 89 to 172% as shown in Fig. 6. Calcium–alginate dry beads gain weight due to the hydration of the hydrophilic groups. Chitosan treatment of the dry beads showed an unexpected swelling increment. Apart from the hydration of hydrophilic groups of chitosan treated beads, another important factor that influences their swelling behavior at low pH values is that protonization of the amino groups of chitosan creates a repulsive force, that causes the

swelling of the chitosan membrane. Thus, chitosan-coated alginate beads swell more than the pure beads. Protonization of the amino groups causes swelling increment in alginate–chitosan mixed beads too. However, the swelling is lower compared to the chitosan-coated alginate beads, because the chitosan polymer network is physically entangled with the polymer chains of alginate.

3.3. In vitro drug release of verapamil

3.3.1. Drug loading of the beads

Table 1 shows the encapsulation efficiency for two different drug to polymer ratios. In all cases the rate of encapsulation efficiency exceeded 80% regardless of the initial amount of drug used at the synthesis process or whether the beads were chitosan treated. Thus, the method followed for the entrapment of VRP in the beads proved to be effective in all cases.

3.3.2. In vitro release of verapamil from wet beads

Fig. 7a shows the % drug release of wet beads for 1 h. The release of VRP from calcium–alginate beads is much faster and statistically significant ($p < 0.05$) compared to the alginate–chitosan mixed beads. After 1 h, approximately 70 and 25% of VRP has been released from calcium–alginate and alginate–chitosan mixed beads, respectively, indicating that chitosan addition to the beads seems to have a significant effect on the release profile.

3.3.3. In vitro release of verapamil from dry beads

As shown in Fig. 7b during the first 30 min both formulations have the same behavior and then the difference becomes statistically significant ($p < 0.05$). Furthermore, both release profiles are characterized by a biphasic behavior. The first part, from zero to 30 min, includes two apparent mechanisms that govern the drug release out of the beads; swelling and diffusion. During the second phase from 30 to 160 min, the swelling of the beads is constant and hence, does not affect the drug release.

Comparing the drug release from wet and dry beads, one should expect that the chitosan treatment would lessen the release profile of the dry beads similarly to the wet beads. The results though, show that chitosan treatment of the dry beads does not affect the release profile at the early stage. In contrast, chitosan addition to the dry calcium–alginate beads increases significantly the release rate at the second stage.

Table 1
Drug to polymer ratio and encapsulation efficiency of pure calcium–alginate and alginate–chitosan mixed beads

Drug:polymer (%, w/w)	Encapsulation efficiency (%)	
	Calcium–alginate	Alginate–chitosan mixed
3.03	80.78	82.85
5.39	86.32	87.54

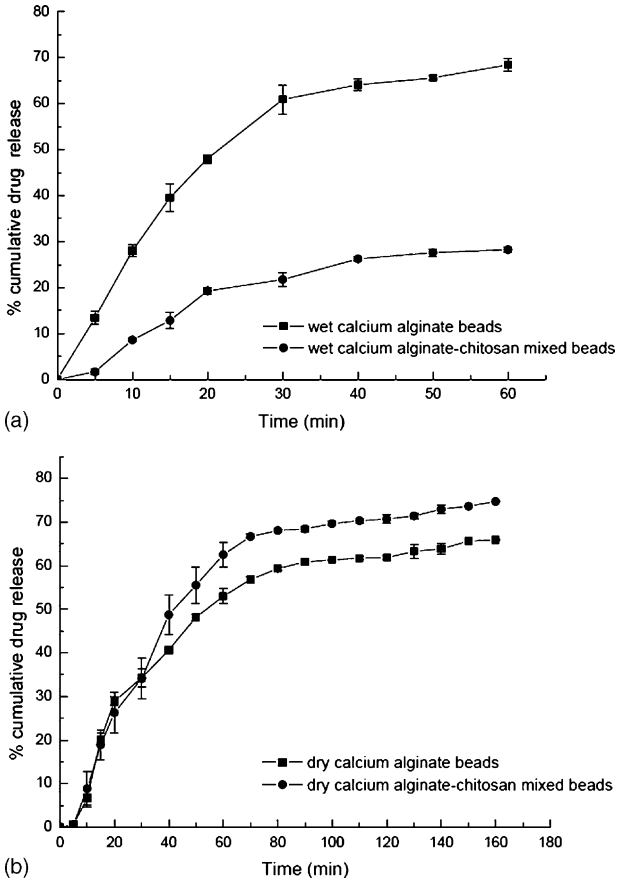

Fig. 7. Cumulative release of VRP from (a) wet calcium–alginate and alginate–chitosan mixed beads and (b) dry calcium–alginate and alginate–chitosan mixed beads. Values are mean ± standard deviation (S.D.) of three experiments.

3.3.4. Release kinetics

In order to understand the drug release mechanisms, the results were analyzed using a semi-empirical equation:

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

where M_t/M_∞, is the fractional release of the drug at time t, k the constant related to the structural and geometric characteristic of the device, and n is the swelling exponent, indicative of the drug release mechanism. The calculation of k and n was measured up to the initial 40% release of the drug. The diffusional exponent, n, specifies the mechanism of release. For spheres, values of n between 0.43 and 0.85 are an indication of both diffusion controlled drug release and swelling controlled drug release (anomalous transport). Values above 0.85 indicate case-II transport which relate to polymer relaxation during gel swelling (Siepmann and Peppas, 2001; Ritger and Peppas, 1987).

In addition, the diffusion coefficient was calculated according to the following equation, where r is the radius of the beads (Peppas, 1985):

$$D = \left(\frac{k}{4(\pi r^2)^n}\right)^{1/n} \tag{4}$$

Table 2
Estimated parameters and drug release mechanism for different formulations: system characteristic constant k, diffusional exponent n, correlation coefficient r, estimated diffusion coefficient D, and drug transport mechanism

Formulation	$k \times 10^2$	n	r	$D \times 10^5$ (cm^2/s)	Transport mechanism
Wet alginate–chitosan mixed beads	0.178	0.64	0.96	1.76	Anomalous transport
Dry alginate–chitosan mixed beads	0.052	0.86	0.95	96.47	Case-II transport
Dry calcium alginate beads	0.206	0.69	0.96	54.64	Anomalous transport
Wet calcium alginate beads	0.110	0.85	0.98	22.89	Case-II transport

The results shown in Table 2 indicate that the drug release mechanism is anomalous transport for dry calcium–alginate beads and wet alginate–chitosan mixed beads, and case-II transport mechanism for dry alginate–chitosan mixed beads beads and wet calcium–alginate beads, respectively. Categorization of the drug release mechanism of the beads, according to Peppas model, can be considered only under a phenomenological perspective and this is because the model describes swelling controlled devices (Peppas, 1985). Nevertheless, in our case wet beads do not swell but shrink in acidic conditions, and this must be the major mechanism of drug release.

Thus, the actual drug release mechanism of wet beads includes two apparent phenomena: shrinkage of the beads that expels amounts of water – and hence drug molecules – out of the beads, and the diffusion of drug molecules out of the beads as the acidic aqueous medium hydrates the beads.

The diffusion coefficient in the case of wet beads decreases significantly in the presence of chitosan inside the beads, because alginate–chitosan mixed beads are denser due to the increased polymer concentration involved in the formation of the hydrogel network.

The drug release mechanism of the dry beads is mainly controlled by the swelling of the polymer network at the early stage. It is also observed that chitosan treatment of the dry beads has almost doubled the diffusion coefficient. This could be explained by considering the fact that chitosan addition to the beads has increased the swelling degree about 30% and hence the solvent penetration inside the beads is faster, leading to greater drug release compared to the pure dry beads.

4. Conclusions

In conclusion, this study shows that swelling of calcium alginate or calcium alginate–chitosan beads is dependent on the presence of the polyelectrolyte complex between alginate and chitosan, the pH of the aqueous media and the initial physical state of the beads. Verapamil hydrochloride can be encapsulated in calcium–alginate beads. In vitro release of verapamil hydrochloride in SGF showed a controlled release profile and modification of the beads either by chitosan treatment or by changing their physical state by drying can influence the release behavior. Analysis of the release profiles using a semi-empirical equation showed that the drug release mechanisms were either “anomalous transport” or “case-II transport”.

Acknowledgements

The SEM work was performed at the microscopy facilities of The Institute of Chemical Engineering and High Temperature Chemical Processes (ICEHT/FORTH), Patras, Greece.

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