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Research paper

Comparative studies on polyelectrolyte complexes and mixtures of chitosan–alginate and chitosan–carrageenan as prolonged diltiazem clorhydrate release systems

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Abstract

The aim of this work was to evaluate the possibility of using mixtures and/or polyelectrolyte complexes from both chitosan-alginate and chitosan–carrageenan as prolonged drug release systems. Different dissolution profiles were obtained by changing the polymer matrix system (chitosan–alginate or chitosan–carrageenan) and the method used to include these polymers into the formulation (physical mixture or polyelectrolyte complex). Drug dissolution profiles from the matrices have been discussed by considering the swelling behavior of the polymers used. The swelling behavior of the chitosan–carrageenan and chitosan–alginate systems was analyzed by using the Hopfenberg model which permits to separate the diffusional contribution, k_f, from the relaxational contribution, k_r, involved in solvent penetration/sorption in glassy polymers. The chitosan–alginate system is better than the chitosan–carrageenan system as prolonged drug release matrix because the drug release is controlled at low percentage of the polymers in the formulation, the mean dissolution time is high, and different dissolution profiles could be obtained by changing the mode of inclusion of the polymers. Good agreement between t_d and k_f/k_r values for the system chitosan–alginate was found, which means that the swelling behavior of the polymers controlled the drug release from the matrix. In the case of the system chitosan–carrageenan, the high capacity of carrageenan promotes the entry of water into the tablet and therefore the main mechanism of drug release would be the disintegration instead of the swelling of the matrix.

Keywords: Chitosan; Alginate; Carrageenan; Polyelectrolyte complex; Prolonged drug release; Matrices

1. Introduction

Matrix systems based on physical mixtures of chitosan–alginate have been studied. These systems showed good properties as prolonged drug release matrices when 20% of the mixture was incorporated into the formulation and the weight ratio between both polymers was 1:1[1]. On the other hand, matrices containing carrageenan were found to be useful for controlling the theophylline and clorpheniramine maleate release[2]. Since chitosan and carrageenan also react forming a polyelectrolyte complex[3], we considered that it could be useful to study this system as a prolonged drug delivery system. Our interest in the polymers chitosan, alginate, and carrageenan is based on the fact that our country is an important producer of these polysaccharides. At the same time, since our national pharmaceutical industry uses basic technology for the manufacture of solid dosage forms, most of the procedures are based on wet and dry granulation techniques. We

Abbreviations: CS, chitosan; CB, chitosan; CSI, carrageenan type I; CAM, carrageenan; AS, alginate medium viscosity; MCS/CSI, mixture of chitosan/carrageenan type I; CCS/CSI, polyelectrolyte complex chitosan/carrageenan type I; MCB/CAM, mixture of chitosan/carrageenan; CCS/CAM, polyelectrolyte complex chitosan/carrageenan; MCS/AS, mixture of chitosan/alginate medium viscosity; MCB/AS, mixture of chitosan/alginate medium viscosity; CCS/AS, polyelectrolyte complex chitosan/alginate medium viscosity.

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consider that the study of the physical mixtures and polyelectrolyte complexes could allow development of prolonged drug release matrices, which could easily be adapted to the standard manufacture procedures used in our local industry.

The aim of this work was to evaluate the possibility to obtain different prolonged drug dissolution profiles by changing the polymer matrix system (chitosan–alginate or chitosan–carrageenan) and the method used to include the polymers into the formulation (physical mixture or polyelectrolyte complex). Also, we tried to explain the drug dissolution profiles from the matrices considering the swelling behavior of the polymers used.

2. Materials and methods

2.1. Materials

Chitosan from Bioquímica Austral, Chile (CB) has a degree of deacetylation of 81% determined by ^{1}H-NMR spectroscopy. The intrinsic viscosity [η] calculated was 630 ml/g in 0.3 M acetic acid–0.2 M sodium acetate solution. The viscometric molecular weight of CB, using the constant in this solvent, $K = 0.076$ ml/g, $a = 0.76$ [4], was 1.43×10^5 Da.

Chitosan from Sigma, USA (CS) has a degree of deacetylation of 85%. The intrinsic viscosity [η] calculated for chitosan from Sigma (CS) was 1395 ml/g in 0.3 M acetic acid–0.2 M sodium acetate solution. Thus, the viscometric molecular weight of CS was estimated as 4.08×10^5 Da.

Alginic acid sodium salt medium viscosity from Macrocystis pyrifera (AS) (Sigma, USA) viscosity of 2% solution at 25 °C = 3500 mPas.

Carrageenan type I (Sigma, USA) (CSI), blended from various seaweeds. Contains predominantly kappa and lower amount of lambda carrageenan.

Carrageenan (Algas Marinas, Chile) (CAM), blended from *Eucheuma Cottini, Eucheuma Espinosum, Chondrus Crispus,*and *Iridaea Laminaroide*. Contains predominantly kappa and lower amounts of lambda carrageenan.

Diltiazem hydrochloride (Dr Reddy's Laboratory, India).

Magnesium stearate (CG Chemikalien, Germany).

Lactose monohydrate (The Lactose Company of New Zealand Ltd., New Zealand).

All other chemicals were of analytical grade.

2.2. Determination of the optimum ratio between chitosan/carrageenan

Solutions of chitosan and carrageenan in 0.2% acetic acid/sodium acetate buffer at pH 4 and 5 were prepared. Both solutions were mixed in different proportions to make 20 ml. The mixtures were incubated at 37 °C for 48 h, then they were centrifuged at 15,000 rpm for 20 min. Finally, the viscosity of the supernatant solution was measured at 25 °C by using a Cannon-Fenske viscometer [5]. The optimal ratio between chitosan and carrageenan was obtained when the supernatant viscosity was close to the solvent viscosity.

2.3. Preparation and characterization of chitosan–carrageenan polyelectrolyte complex

Chitosan (CB) and carrageenan (CSI) solutions with a concentration of 0.2% by weight in acetic acid/sodium acetate buffer were mixed in a 20:80% v/v and 50:50% v/v ratio. The precipitated product was separated from the solution by centrifugation at 15,000 rpm, then it was washed with distilled water, dried at 105 °C for 2 h, and milled in a mortar. This product was analyzed by FT-IR (Bruker, IFS55) using the KBr disc method.

2.4. Preparation of polyelectrolyte complexes of chitosan–alginate and chitosan–carrageenan for swelling and dissolution studies

The chitosan–alginate polyelectrolyte complex (CCSAS 50:50) was prepared from chitosan (CS) solution at 4.0% w/v in 1% w/w acetic acid solution and alginate (AS) solution at 4.0% w/v in water. The chitosan–carrageenan polyelectrolyte complex (CCSCSI 50:50) was prepared from chitosan (CS) solution at 4.0% w/v in 1% w/w acetic acid solution and carrageenan (CSI) solution at 4.0% w/v in 5.7% NaCl solution.

Each solution was heated separately at 70–80 °C. Both solutions were mixed at 75 °C with agitation until the mixture reached room temperature. Then it was left to rest for 2 h. The polyelectrolyte complex (PEC) was thoroughly washed with distilled water and was then separated from water by centrifugation for 30 min at 10000 rpm. Thereafter, the PEC was again submerged in distilled water and left at 9 °C for 48 h. Then, the centrifugation step was repeated. Finally, the PEC was dried to constant weight in a vacuum oven at 70 °C, milled at −5 °C in a knife mill (JANKE and KUNKEL.IKA.LABORTECHNIK.Model A-10), and classified by sieving through 100- mesh sieves (ASTM E-11).

2.5. Evaluation of swelling behavior

Powder forms of chitosan, alginate, carrageenan, dry mixed polymers and PEC samples were classified by sieving through 100-mesh sieves (ASTM E-11). Then, they were tabletted using an infrared manual press to obtain tablets of 7.0 ± 0.1 mm diameter, 0.25 ± 0.1 mm thickness, and 110 ± 10 mg weight ($n = 10$). The polymers studied are shown in Table 1.

The tablets were immersed and maintained at 37 °C for 2 h in 0.1 N HCl dissolution bath pH 1.2 with mechanical agitation and then they were transferred to boric acid solution (pH 8.0) for two more hours. The swelling degree was determined by observation of the change of

Table 1
Polymers alone, physical mixtures and PEC used in the swelling studies

Polymers	Mode of preparation	Polymer ratio %
CS	None	100
CB	None	100
MCS/CSI	Physical mixture	20:80
MCS/CSI	Physical mixture	35:65
MCS/CSI	Physical mixture	50:50
CCS/CSI	Polyelectrolyte complex	50:50
MCB/CAM	Physical mixture	20:80
MCB/CAM	Physical mixture	35:65
MCB/CAM	Physical mixture	50:50
CCB/CAM[a]	Polyelectrolyte complex	50:50
MCS/AS	Physical mixture	50:50
MCB/AS	Physical mixture	50:50
CCS/AS	Polyelectrolyte complex	50:50
AS	None	100
CSI	None	100
CAM	None	100

Tablets of 7.0 ± 0.1 mm of diameter, 0.25 ± 0.1 mm of thickness, and 110 ± 10 mg of weight were made using an infrared manual press. CB, chitosan (Bioquímica Austral, Chile); CS, chitosan (Sigma, USA); MCS/CSI, mixture of chitosan (Sigma)/carrageenan type I (Sigma); CCS/CSI, polyelectrolyte complex chitosan (Sigma)/carrageenan type I (Sigma); MCB/CAM, mixture of chitosan (Bioquímica Austral, Chile)/carrageenan (Algas Marinas, Chile); CCS/CAM, polyelectrolyte complex chitosan (Sigma)/carrageenan (Algas Marinas, Chile); MCS/AS, mixture of chitosan (Sigma)/alginate medium viscosity (Sigma); MCB/AS, mixture of chitosan (Bioquímica Austral, Chile)/alginate medium viscosity (Sigma); CCS/AS, polyelectrolyte complex chitosan (Sigma)/alginate medium viscosity (Sigma); AS, alginate medium viscosity (Sigma); CSI, carrageenan type I (Sigma); CAM, carrageenan (Algas Marinas, Chile).
[a] This polyelectrolyte complex was disintegrated immediately.

the diameter of the tablet over a plastic coated sheet with a millimeter scale by using a magnification lens (Wild M3, Heerbrugg, Germany, magnification 6.4). Each assay was done with five replicates.

2.6. Formulation and preparation of the tablets

The formulations studied are shown in Table 2. The materials used was classified by sieving through a 100-mesh sieve (ASTM E-11). For each 10 g of formulation the polymers were manually dry mixed in a plastic bag for 10 min with diltiazem hydrochloride, lactose and magnesium stearate to make 500-mg tablets. The tablets were obtained by direct compression by using a Wilhelm Fette type EIIN.270 excentrical tabletting machine. The compression pressure was adjusted depending on the compactibility of the formulation studied.

2.7. Dissolution test

This was performed in a dissolution apparatus (Pharmatest, type PTW SIII) at 37 °C and 100 rpm. The basket method (USP type 1) [6] was used. The tablets were submerged into 900 ml of 0.1 N HCl solution (pH 1.2) for 2 h. These were then transferred to an alkaline solution (0.2 N boric acid, pH 8.0) and left in this media for another 5 h. Aliquots of 5 ml were taken at different times, which were replaced with an equal volume of medium, and the content of diltiazem hydrochloride was determined by UV spectroscopy (UV/Visible UNICAM UV3 spectrometer) at a wavelength of 236 nm. Each assay was done in triplicate.

2.8. Swelling analysis by using the modified Hopfenberg equation

The swelling behavior of the chitosan–carrageenan and chitosan–alginate systems was analyzed by using the Hopfenberg model[7], which permits separation of diffusional contribution from the relaxational contribution involved in solvent penetration/sorption in glassy polymers.

The Hopfenberg equation is:

$$M_t = M_\infty\left[1 - \frac{6}{\pi^2}\sum_{n=1}^{n=10}\frac{1}{n^2}e^{-n^2k_f t}\right] + M_\infty\left(1 - e^{-k_r t}\right) \quad (1)$$

This equation can be modified as follows in terms of tablet diameter:

$$V_t\rho_t = V_\infty\rho_\infty\left[1 - \frac{6}{\pi^2}\sum_{n=1}^{n=10}\frac{1}{n^2}e^{-n^2k_f t}\right] + V_\infty\rho_\infty\left(1 - e^{-k_r t}\right) \quad (2)$$

$$\frac{\pi}{4}D_t^2 h_t\rho_t = \frac{\pi}{4}D_\infty^2 h_\infty\rho_\infty\left[1 - \frac{6}{\pi^2}\sum_{n=1}^{n=10}\frac{1}{n^2}e^{-n^2k_f t}\right] + \frac{\pi}{4}D_\infty^2 h_\infty\rho_\infty\left(1 - e^{-k_r t}\right) \quad (3)$$

if the expression is divided by D_0

$$\left(\frac{D_t}{D_0}\right)^2(h_t\rho_t) = \left(\frac{D_\infty}{D_0}\right)^2(h_\infty\rho_\infty)\left[1 - \frac{6}{\pi^2}\sum_{n=1}^{n=10}\frac{1}{n^2}e^{-n^2k_f t}\right] + \left(\frac{D_\infty}{D_0}\right)^2(h_\infty\rho_\infty)\left(1 - e^{-k_r t}\right) \quad (4)$$

$$\left(\frac{D_t}{D_0}\right)^2 = \left(\frac{D_\infty}{D_0}\right)^2\frac{(h_\infty\rho_\infty)}{(h_t\rho_t)}\left[1 - \frac{6}{\pi^2}\sum_{n=1}^{n=10}\frac{1}{n^2}e^{-n^2k_f t}\right] + \left(\frac{D_\infty}{D_0}\right)^2\frac{(h_\infty\rho_\infty)}{(h_t\rho_t)}\left(1 - e^{-k_r t}\right) \quad (5)$$

Finally, the expression used for the analysis of swelling data is

$$\left(\frac{D_t}{D_0}\right)^2 = A\left[1 - \frac{6}{\pi^2}\sum_{n=1}^{n=10}\frac{1}{n^2}e^{-n^2k_f t}\right] + A\left(1 - e^{-k_r t}\right) \quad (6)$$

where D_t = tablet diameter at time t; D_0 = initial tablet diameter; k_f = Fickian diffusion constant; k_r = relaxation rate constant.

Table 2
Tablet formulations studied

Components	C1 (%)	C2 (%)	C3 (%)	C4 (%)	C5 (%)	C6 (%)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
Diltiazem. HCl	18	18	18	18	18	18	18	18	18	18	18	18
Lactose	81	61	61	61	61	61	61	61	61	61	61	61
CS	–	–	–	20	–	–	–	–	–	–	–	–
CB	–	–	20	–	–	–	–	–	–	–	–	–
CSI	–	–	–	–	20	–	–	–	–	–	–	–
CAM	–	–	–	–	–	20	–	–	–	–	–	–
AS	–	20	–	–	–	–	–	–	–	–	–	–
MCS/CSI 50:50	–	–	–	–	–	–	20	–	–	–	–	–
MCB/CAM 50:50	–	–	–	–	–	–	–	20	–	–	–	–
CCS/CSI 50:50	–	–	–	–	–	–	–	–	20	–	–	–
MCS/AS 50:50	–	–	–	–	–	–	–	–	–	20	–	–
MCB/AS 50:50	–	–	–	–	–	–	–	–	–	–	20	–
CCS/AS 50:50	–	–	–	–	–	–	–	–	–	–	–	20
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Diameter (mm) $n = 10$	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1
Hardness (K_p) $n = 10$	8.9 ± 0.6	7.8 ± 1.0	8.1 ± 0.6	7.8 ± 0.8	7.5 ± 1.2	5.5 ± 0.5	8.8 ± 0.5	8.2 ± 0.7	5.9 ± 0.8	7.2 ± 0.4	6.8 ± 0.5	5.8 ± 0.5

CB, chitosan (Bioquímica Austral, Chile); CS, chitosan (Sigma, USA); CSI, carrageenan type I (Sigma); CAM, carrageenan (Algas Marinas, Chile); AS, alginate medium viscosity (Sigma); MCS/CSI, mixture of chitosan (Sigma)/carrageenan type I (Sigma); MCB/CAM, mixture of chitosan (Bioquímica Austral, Chile)/carrageenan (Algas Marinas, Chile); CCS/CSI, polyelectrolyte complex chitosan (SIGMA)/carrageenan type I (Sigma); MCS/AS, mixture of chitosan (Sigma)/alginate medium viscosity (Sigma); MCB/AS, mixture of chitosan (Bioquímica Austral, Chile)/alginate medium viscosity (Sigma); CCS/AS, polyelectrolyte complex chitosan (Sigma)/alginate medium viscosity (Sigma).

3. Results and discussion

Fig. 1 shows how the supernatant viscosity changed when the chitosan–carrageenan weight ratio was varied. The optimum ratio between polymers is when the supernatant viscosity is close to 1. This means that both polymers have reacted completely to form an insoluble complex. This value was obtained when the percentage of chitosan in the mixture was between 30 and 40%. In the region of the curve where there is a high excess of carrageenan, the supernatant viscosity is determined mainly by the ionization degree of carrageenan, which did not react with chitosan. It can be observed from Fig. 1 that the supernatant obtained from mixture with CSI did not show any difference in the viscosity between pH 4 and 5. On the other hand, the supernatant obtained from the mixture with CAM showed a significant higher viscosity at pH 5 than at pH 4. This means that the number of ionized groups in CAM is higher than in CSI since the supernatant viscosity is controlled by the number of ionized groups present for a determined pH.

The precipitate obtained from the mixture CB/CSI at 20:80 and 50:50 weight ratio was analyzed by FT-IR and compared with the spectra of CB and CSI, according to the method described in Section 2.3. As it is seen from Fig. 2, the FT-IR spectrum of CSI showed a broad absorption band at 1446.4 cm^{-1} assigned to $-SO_4^{2-}$ groups. The FT-IR spectrum of chitosan showed an intense and broad absorption band at 1655.1 cm^{-1} assigned to the –NH group. The FT-IR spectra of the precipitate obtained from the mixture CB/CSI (50:50) showed a new absorption band at 1560.1 cm^{-1} assigned to $-NH_3^+$ groups. This absorption band is absent in the spectra of both CB and CSI. Moreover, the intensity of the absorption band assigned to $-SO_4^{2-}$

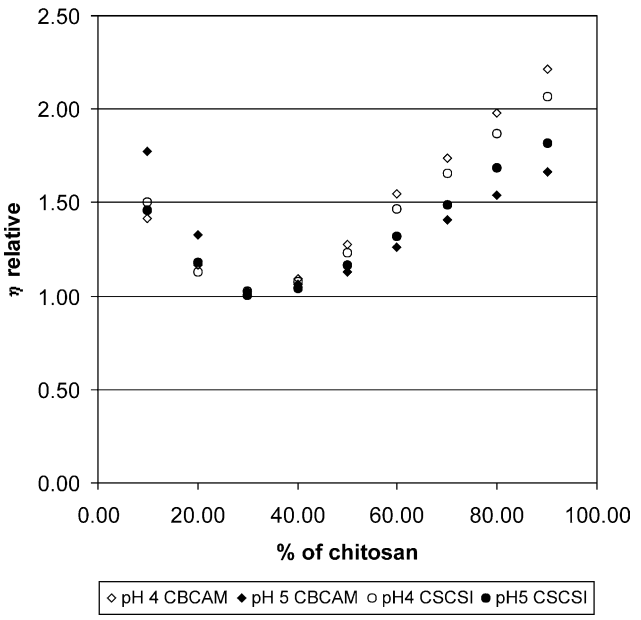


Fig. 1. Variation of relative viscosity values of supernatant from chitosan–carrageenan mixtures as a function of chitosan concentration. Each point represents the mean of three experiments.

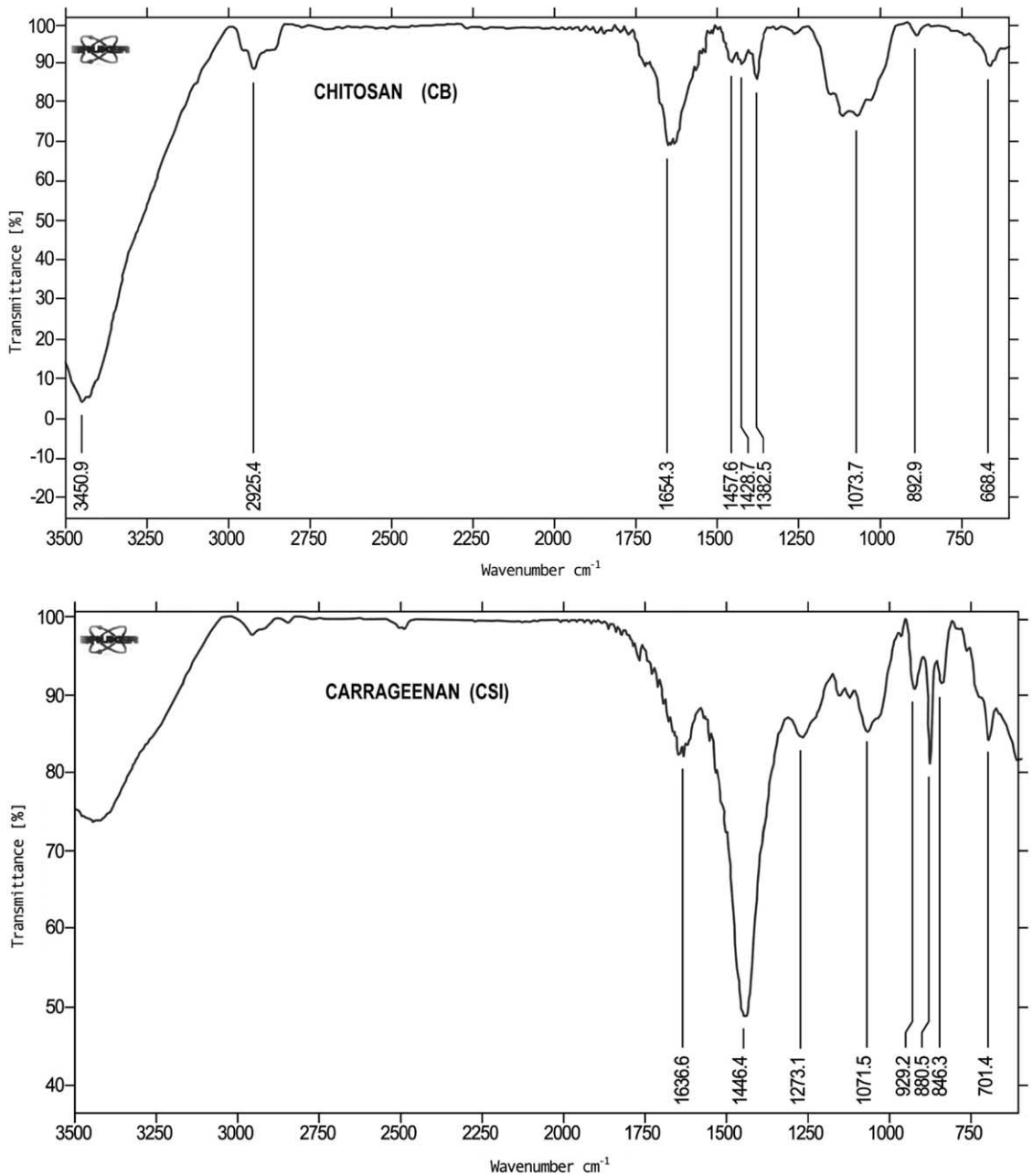


Fig. 2. FT-IR spectrum of chitosan and carrageenan.

groups, diminished and is displaced by 27 $cm^{-1,}$ from 1446.4 to 1419.4 cm^{-1} (see Fig. 3).

The FT-IR spectra of the precipitate obtained from the mixture CB/CSI (20:80) also showed a new absorption band at 1562.0 cm^{-1} together with a decrease in intensity and displacement of the $-SO_4^{2-}$ group absorption band to 1419.4 cm^{-1}. The appearance of a new absorption band at 1560–1562 cm^{-1} assigned to $-NH_3^+$ groups and the strong reduction in intensity and displacement of the absorption band of $-SO_4^{2-}$ groups from 1446.4 to 1419. 4 cm^{-1} evidenced the formation of strong polyelectrolyte complexes.

3.1. Swelling behavior studies

Tablets with diameter of 7 mm and thickness of 0.5 mm were prepared from the polymers described in Table 1 and then used for the swelling experiments. The swelling experiments were performed according to the procedure described in Section 2.5. It was considered that the swelling process was mainly radially oriented because of the large difference between diameter/thickness of the tablets. The swelling behavior of the chitosan–carrageenan and chitosan–alginate systems was analyzed by using the modified Hopfenberg model described in Section 2.8.

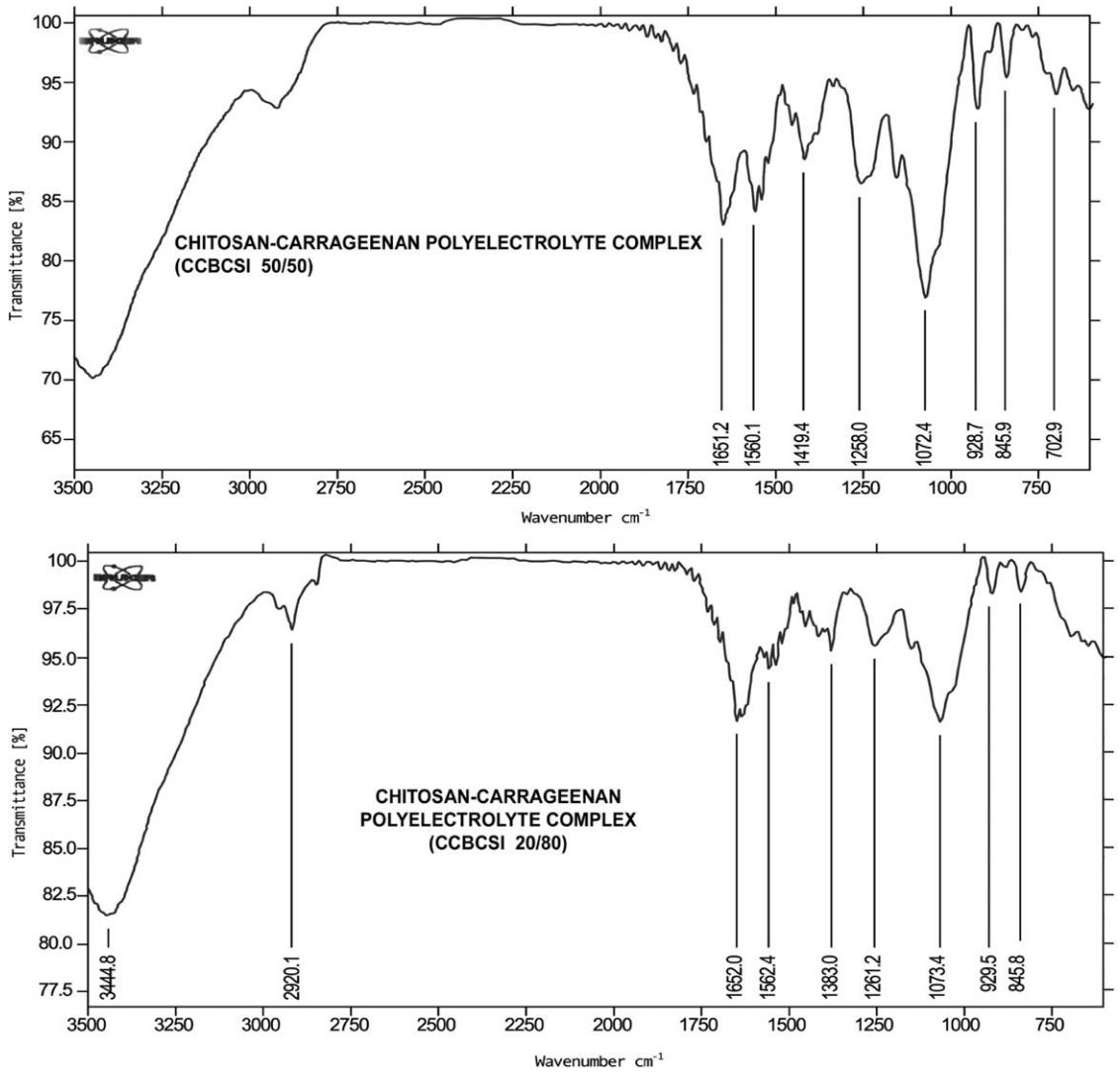
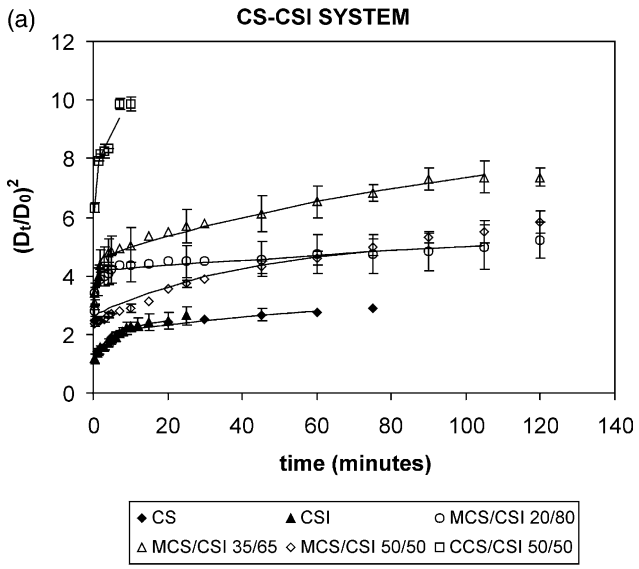


Fig. 3. FT-IR spectrum of chitosan–carrageenan complex.

Fig. 4 shows the swelling behavior of the chitosan–carrageenan system. It is clear that the system CB/CAM (Fig. 4b) has a higher degree of swelling than the system CS/CSI (Fig. 4a) and that the rate of swelling of the CB/CAM system is higher than the CS/CSI system with the same proportions in the mixture. In the case of the polyelectrolyte complex the degree of swelling is higher compared with the mixture at the same proportion of the polymers, see CCS/CSI (50:50) and MCS/CSI (50:50) in Fig. 4a. The swelling behavior of the polyelectrolyte complex CCB/CAM (50:50) is not shown because this swelled and disintegrated in less than 30 s.

The apparent charge density of chitosan chain segments at pH 1 is at a maximum. Indeed, the free amino groups of chitosan are completely protonated at this pH. Consequently, the electrostatic repulsions, the solvation of the ionic groups and the osmotic contribution are maximum, thus contributing to a maximum swelling[8]. It has also been described that in acid solution the sulfonate groups of carrageenan remain negatively charged[3]. Since both polymers are ionized at pH 1.2, the electrosmotic flux produced by the mixtures and complex of chitosan–carrageenan will be higher than chitosan alone, consequently, the degree of swelling and rate of swelling of the chitosan–carrageenan system will be higher than chitosan, as shown in Fig. 4. The large difference in swelling degree observed between CB/CAM and CS/CSI systems could be attributed to the properties of carrageenans used, since the carrageenan used in both mixtures was predominately κ-carrageenan. The carrageenan mixture has namely three types of carrageenan: κ-carrageenan, ι-carrageenan, and λ-carrageenan. κ-carrageenan has one sulfate group per two galactose residues (produces a weak gel which suffer sineresis), ι-carrageenan has two sulfate groups per two galactose residues (produces an elastic gel without sineresis), and λ-carrageenan has three sulfate groups per two galactose residues (no gelling) [9]. The order of charge density is λ-carrageenan > ι-carrageenan > κ-carrageenan



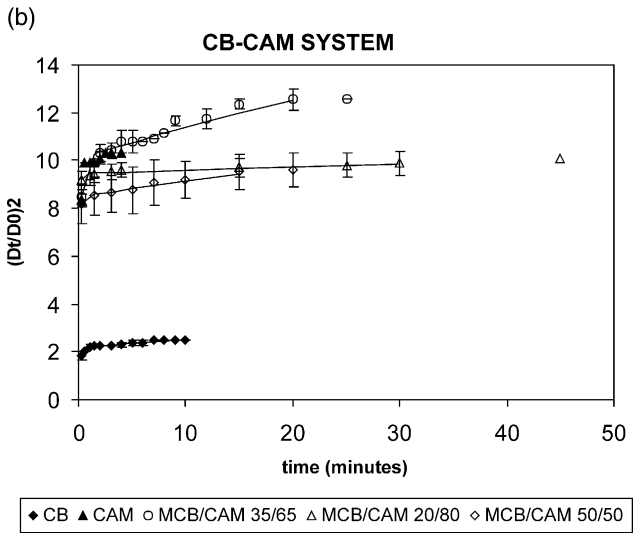


Fig. 4. Swelling behavior of chitosan–carrageenan system in acid media (pH 1.2). (a) CS–CSI system; (b) CB–CAM system. Each point represents the mean of five experiments. Each curve presents the data that are fitted to Hopfenberg's model by non-linear regression analysis.

[10]. Thus, the higher degree of swelling observed for the CB/CAM system compared with that of the CS/CSI system should be due to CAM having a higher charge density than CSI. This conclusion is supported by the higher degree of swelling of CAM compared with CSI, as shown in Fig. 4. The difference observed between swelling of the complex CS/CSI 50:50 and the mixture MCS/CSI 50:50 is due to the fact that the complex is polyelectrolyte in nature since both polymers are already in the ionized state, which can explain the higher degree of swelling attained in comparison to the mixture MCS/CSI 50:50.

The swelling behavior of the chitosan–alginate system is shown in Fig. 5. This system shows a lower degree of swelling than the chitosan–carrageenan system. It is observed for the CS–AS system that the polyelectrolyte complex (CCS/AS 50:50) has a higher degree of swelling in

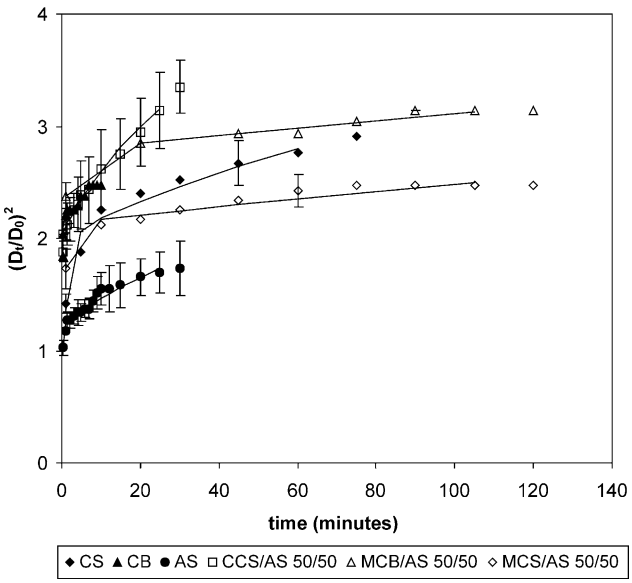


Fig. 5. Swelling behavior of chitosan–alginate system in acid media (pH 1.2). Each point represents the mean of five experiments. Each curve presents the data that are fitted to Hopfenberg's model by non-linear regression analysis.

comparison to a mixture with the same proportion (MCS/AS 50:50). The swelling degree of the mixture is lower than that of chitosan but is higher when compared with alginate. The CB–AS system showed similar behavior as the CS–AS system. The mixture MCB/AS 50:50 had a higher degree of swelling than the mixture MCS/AS 50:50.

Alginate at pH 1.2 is in its unionized form while chitosan, as mentioned before, is fully protonated at this pH. This fact explain the low degree of swelling of alginate. The swelling process is controlled by the Donnan potential [1], i.e. the process depends on the number of ionized groups in the mixture of polymers. Therefore, it is reasonable to expect that the mixtures show a similar or lower degree of swelling than chitosan. The difference observed between the mixtures is due to the difference between both chitosans. CB swells faster than CS. A higher erosion rate was also observed for CB compared with CS. This difference between the two chitosans is due to the fact that the molecular weight of CB is considerably much lower than the molecular weight of CS. This results in a much faster swelling and consequently the rate of erosion is much faster for the system containing CB.

The difference observed between swelling of the complex CS/AS 50:50 and the mixture MCS/AS 50:50 is due to the fact that the complex is polyelectrolyte in nature since both polymers are already in the ionized state, which can explain the higher degree of swelling attained in comparison to the mixture MCS/AS 50:50.

The swelling data obtained in acidic medium were fitted to the modified Hopfenberg's equation by considering the values of the diameter of swelled tablets until reaching the swelling equilibrium. The experimental and fitted values for chitosan–carrageenan and chitosan–alginate systems are

Table 3
Values of diffusional component (k_f) and relaxational component (k_r) involved in the swelling process estimated from Hopfenberg's equation

Polymers	$k_f \pm$ S.D. (min^{-1})	$k_r \pm$ S.D. (min^{-1})	d.f. Adj r^2 (# of data)	k_f/k_r	k_f + S.D./ k_r + S.D.	k_f-S.D./ k_r−S.D.
CS	$6.169 \times 10^{-1} \pm 1.614 \times 10^{-1}$	$7.938 \times 10^{-3} \pm 2.148 \times 10^{-3}$	0.9472 (8)	77.7	77.2	78.7
CB	5.185 ± 0.4049	$1.701 \times 10^{-2} \pm 2.075 \times 10^{-3}$	0.9628 (13)	305.0	293.0	320.2
CSI	6.205 ± 1.8247	$1.105 \times 10^{-1} \pm 1.963 \times 10^{-2}$	0.9724 (16)	56.2	61.7	48.2
CAM	5.054 ± 0.4972	$1.690 \times 10^{-2} \pm 7.950 \times 10^{-3}$	0.9460 (7)	299.1	223.4	509.1
MCS/CSI 20:80	2.479 ± 0.2474	$2.2873 \times 10^{-3} \pm 2.758 \times 10^{-4}$	0.9488 (18)	1084	1064	1109
MCS/CSI 35:65	1.687 ± 0.2418	$9.580 \times 10^{-3} \pm 1.160 \times 10^{-3}$	0.9725 (20)	176.0	179.5	171.5
MCS/CSI 50:50	6.287 ± 3.6180	$2.333 \times 10^{-2} \pm 6.82 \times 10^{-3}$	0.9305 (20)	269.5	328.5	161.7
CCS/CSI 50:50	5.4209 ± 1.2884	$4.512 \times 10^{-2} \pm 1.168 \times 10^{-2}$	0.9157 (7)	120.1	118.1	123.6
MCB/CAM 20:80	12.117 ± 1.1160	$1.533 \times 10^{-3} \pm 1.861 \times 10^{-4}$	0.9242 (9)	7899	7693	8162
MCB/CAM 35:65	5.347 ± 0.7027	$1.393 \times 10^{-2} \pm 1.698 \times 10^{-3}$	0.9376 (14)	383.9	387.2	379.8
MCB/CAM 50:50	11.030 ± 1.5370	$7.940 \times 10^{-3} \pm 9.613 \times 10^{-4}$	0.9441 (8)	1389	1412	1360
AS	4.938 ± 0.8556	$2.058 \times 10^{-2} \pm 2.381 \times 10^{-3}$	0.9423 (17)	240.0	252.3	224.3
MCS/AS 50:50	1.1597 ± 0.1541	$1.767 \times 10^{-3} \pm 3.371 \times 10^{-4}$	0.9334 (10)	656.3	624.4	703.3
MCB/AS 50:50	1.4571 ± 0.1218	$1.315 \times 10^{-3} \pm 2.061 \times 10^{-4}$	0.9735 (8)	1108	1038	1204
CCS/AS 50:50	7.6143 ± 0.8387	$3.088 \times 10^{-2} \pm 1.598 \times 10^{-3}$	0.9930 (14)	246.6	260.3	231.4

CB, chitosan (Bioquímica Austral, Chile); CS, chitosan (Sigma, USA); CSI, carrageenan type I (Sigma); CAM, carrageenan (Algas Marinas, Chile); AS, alginate medium viscosity (Sigma); MCS/CSI, mixture of chitosan (Sigma)/carrageenan type I (Sigma); MCB/CAM, mixture of chitosan (Bioquímica Austral, Chile)/carrageenan (Algas Marinas, Chile); CCS/CSI, polyelectrolyte complex chitosan (Sigma)/carrageenan type I (Sigma); MCS/AS, mixture of chitosan (Sigma)/alginate medium viscosity (Sigma); MCB/AS, mixture of chitosan (BioquÍmica Austral, Chile)/alginate medium viscosity (Sigma); CCS/AS, polyelectrolyte complex chitosan (Sigma)/alginate medium viscosity (Sigma).

shown in Figs. 4 and 5, respectively. The diffusional component (k_f) and the relaxation component (k_r) involved in the swelling process was estimated from this equation. The values of these constants are shown in Table 3.

Table 3 shows clearly that for all the studied systems, the diffusional component predominates over the relaxation component. It is known that the diffusional processes are faster than the relaxation processes because the diffusion involves migration of the small molecules into pre-existing or dynamically formed spaces between polymer chains. Instead, relaxation of the polymer involves larger scale segmental motion resulting in an increased distance of separation between polymer molecules [7]. Thus the swelling process is mainly controlled by the diffusion of the solvent into the tablet.

The variation of k_f/k_r ratio as function of the percentage of alginate in the mixture and polyelectrolyte complex is shown in Fig. 6. In the CS–AS system the k_f/k_r ratio of AS is higher than CS and the mixture (MCS/AS 50:50) had a higher value compared with the complex (CCS/AS 50:50) and the individual polymers (CS, AS). In the CB–AS system the k_f/k_r ratio of CB is higher than AS and the mixture (MCB/AS 50:50) had a higher value compared with the individual polymers (CB, AS). These results support the different swelling behavior of both chitosans, which is reflected in the different swelling behavior of the mixtures. The mode of preparation (mixture or complex) modified the swelling behavior. The lower value of k_f/k_r ratio for the complex (CCS/AS 50:50) compared with the mixture (MCS/AS 50:50) pointed out that the relaxation process in the complex is more important than in the mixture, which means that the polyelectrolyte complex forms a more tight and ordered network type structure.

The variation of k_f/k_r ratio as a function of the percentage of carrageenan in mixtures and polyelectrolyte complex with chitosan is shown in Fig. 7. The different mixtures of chitosan–carrageenan for both systems (CS–CSI and CB–CAM) showed similar swelling behavior. The k_f/k_r values were higher for the CB–CAM system compared to the CS–CSI system due to the higher degree of swelling of the individual polymers. These high k_f/k_r values pointed out that the solvent diffuses quickly in the polymer mixture, which results in the disintegration process of the tablet. This

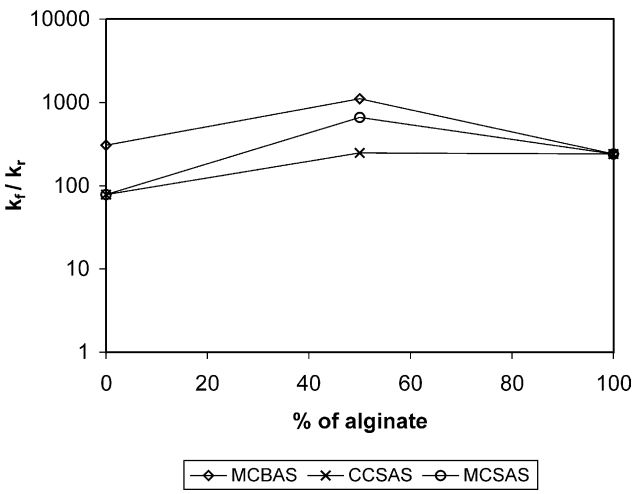


Fig. 6. k_f/k_r as a function of the percentage of alginate in the chitosan–alginate system. The k_f and k_r values are obtained from the swelling data fitted to Hopfenberg's model by non-linear regression.

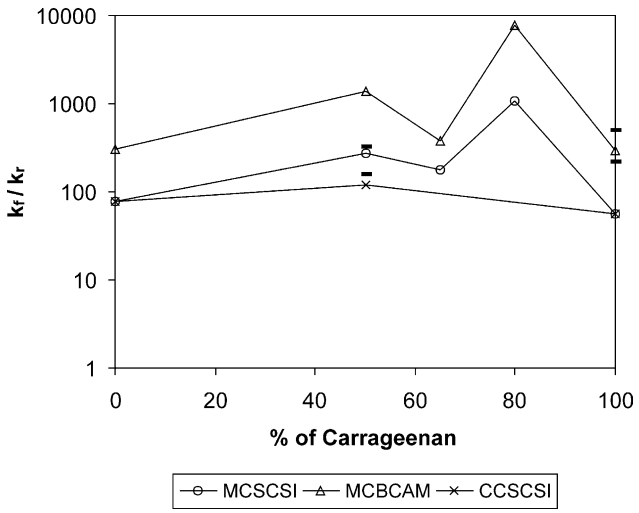


Fig. 7. k_f/k_r as a function of the percentage of carrageenan in the chitosan–carrageenan system. The k_f and k_r values are obtained from the swelling data fitted to Hopfenberg's model by non-linear regression.

effect could be due to the fact that both polymers are ionized at pH 1.2, which promotes the solvent penetration due to the increase of electrosmotic flux. Also, these high k_f/k_r values could be explained because the κ-carrageenan molecules, main component of the carrageenan mixtures, are in a rubbery state, which means that the polymer chains are very mobile and they can interact with water more easily [11]. The behavior observed at different proportions could be explained by the degree of interaction between the polymers. Thus, the viscometric results in Fig. 1 shows that the highest interaction between chitosan and carrageenan exists when the proportion of the polymers was 35:65. This result is in good agreement with the low k_f/k_r values obtained for both systems at this proportion. As it was observed in the CS–AS system, the k_f/k_r value for the complex (CCS/CSI 50:50) was lower than the mixture (MCS/CSI 50:50). This result could indicate a higher interaction between polymers in the complex compared with the mixture, which means that the polyelectrolyte complex forms a more tight and ordered network type structure.

The dissolution profiles of formulations based on the chitosan–carrageenan matrix system were studied. Fig. 8a shows the dissolution profiles of the formulations based on the CS–CSI system. F1 (contains the mixture MCS/CSI 50:50 as matrix) and F3 (contains the complex CS/CSI as matrix) did not show significant differences in their dissolution profiles, $f_2 > 50$ [12] (see Table 4). F1 and F3 showed significant differences in their dissolution profiles compared with single polymers, $f_2 < 50$ (see Table 4). The dissolution time, estimated according to the model of Weibull[13], of C4 (CS) ($t_d = 154.1 \pm 6.4$ min) is higher than F1 ($t_d = 86.5 \pm 2.7$ min) and F3 ($t_d = 105.0 \pm 2.0$ min). However, the dissolution time of C5 (CSI) ($t_d = 53.6 \pm 1.7$) is lower than F1 and F3. Fig. 8b shows

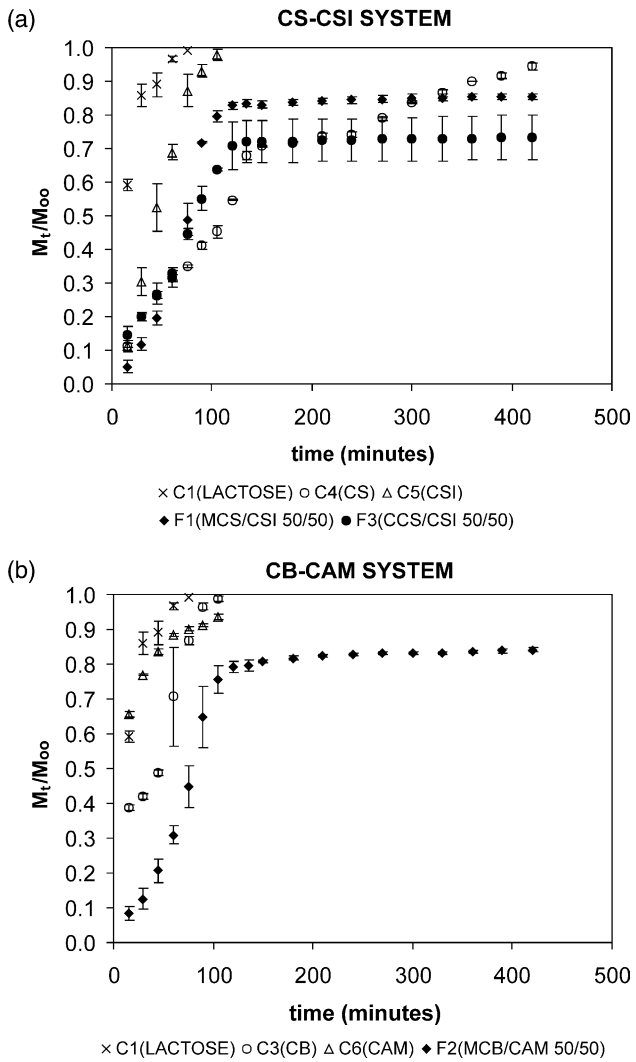


Fig. 8. Dissolution profiles of formulations based on chitosan–carrageenan matrix system. (a) CS–CSI system; (b) CB–CAM system. Each point represents the mean of three experiments.

the dissolution profiles of the formulations based on the CB–CAM system. F2 (contains the mixture MCB/CAM 50:50 as matrix) showed significant differences in its dissolution profile, $f_2 < 50$ (see Table 4) when compared with single polymers. The dissolution time of F2 ($t_d = 92.1 \pm 2.0$ min) is higher than C3 (CB) ($t_d = 50.7 \pm 3.3$ min) and C6 (CAM) ($t_d = 13.0 \pm 1.0$ min).

These results pointed out that the polymeric matrix based on mixtures or polyelectrolyte complex of chitosan–carrageenan at 20% w/w in the tablet have a low retardant capacity of drug release due to the high capacity of carrageenan to promote the entry of water into the tablet. It has been shown that a concentration of 70% v/v of κ-carrageenan decreases the swelling extent of theophylline matrix tablet and therefore the drug release was slowed down [11].

The dissolution profiles of formulations based on the chitosan–alginate matrix system were studied. Fig. 9a

Table 4
Values of the similarity factor, f_2, to compare dissolution profiles of the formulations

Formulations	f_2 value
Chitosan–carrageenan system	
C4 (CS)–C5 (CSI)	20.22
C4 (CS)–F1(MCS/CSI 50:50)	41.40
C5 (CSI)–F1(MCS/CSI 50:50)	29.22
C4 (CS)–F3 (CCS/CSI 50:50)	47.76
C5 (CSI)–F3 (CCS/CSI 50:50)	25.87
C3(CB)—C6(CAM)	33.80
C3(CB)–F2 (MCB/CAM 50:50)	25.07
C6(CAM)–F2 (MCB/CAM 50:50)	16.02
F1 (MCS/CSI 50:50)–F2 (MCB/CAM 50:50)	75.66
F1 (MCS/CSI 50:50)–F3 (CCS/CSI 50:50)	56.82
F2 (MCB/CAM 50:50)–F3 (CCS/CSI 50:50)	65.64
Chitosan—alginate system	
C4 (CS)–C2(AS)	51.98
C4 (CS)–F4 (MCS/AS 50:50)	28.42
C2(AS)–F4 (MCS/AS 50:50)	24.04
C4 (CS)–F6 (CCS/AS 50:50)	47.86
C2(AS)–F6 (CCS/AS 50:50)	57.57
C3(CB)–C2(AS)	26.73
C3(CB)–F5 (MCB/AS 50:50)	13.45
C2(AS)–F5 (MCB/AS 50:50)	26.90
F4 (MCS/AS 50:50)–F5 (MCB/AS 50:50)	63.16
F4 (MCS/AS 50:50)–F6 (CCS/AS 50:50)	27.00
F5 (MCB/AS 50:50)–F6 (CCS/AS 50:50)	29.86

CB, chitosan (Bioquímica Austral, Chile); CS, chitosan (Sigma, USA); CSI, carrageenan type I (Sigma); CAM, carrageenan (Algas Marinas, Chile); AS, alginate medium viscosity (Sigma); MCS/CSI, mixture of chitosan (Sigma)/carrageenan type I (Sigma); MCB/CAM, mixture of chitosan (Bioquímica Austral, Chile)/carrageenan (Algas Marinas, Chile); CCS/CSI, polyelectrolyte complex chitosan (Sigma)/carrageenan type I (Sigma); MCS/AS, mixture of chitosan (Sigma)/alginate medium viscosity (Sigma); MCB/AS, mixture of chitosan (Bioquímica Austral, Chile)/alginate medium viscosity (Sigma); CCS/AS, polyelectrolyte complex chitosan (Sigma)/alginate medium viscosity (Sigma).

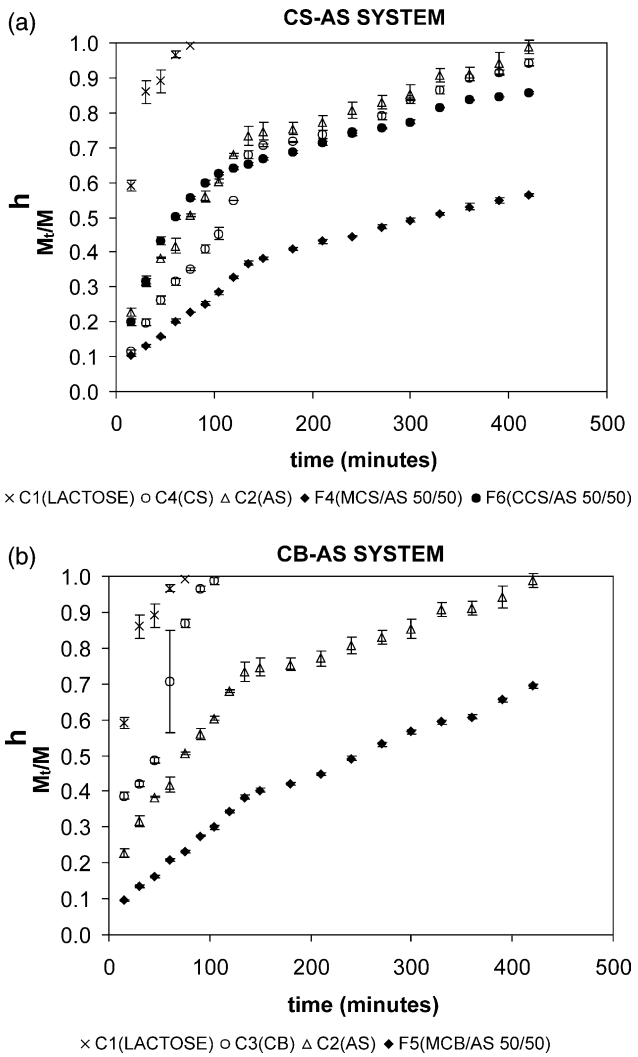


Fig. 9. Dissolution profiles for formulations based on chitosan–alginate matrix system. (a) CS–AS system; (b) CB–AS system. Each point represents the mean of three experiments.

shows the dissolution profiles of the formulations based on the CS–AS system. F4 (contains the mixture MCS/AS 50:50 as matrix) and F6 (contains the complex CCS/AS as matrix) showed significant differences in their dissolution profiles, $f_2 < 50$ (see Table 4). F4 showed significant differences in their dissolution profiles compared with single polymers, $f_2 < 50$ (see Table 4). F6 showed significant differences in its dissolution profiles compared with C4 (CS), $f_2 < 50$ (see Table 4), but did not show significant differences with C2(AS), $f_2 > 50$ (see Table 4). The dissolution time of F4 ($t_d = 551.2 \pm 16.2$ min) was higher than F6 ($t_d = 127.1 \pm 4.2$ min), C4(CS) ($t_d = 154.1 \pm 6.4$ min) and C2(AS) ($t_d = 115.4 \pm 6.6$ min). Fig. 8b shows the dissolution profiles of the formulations based on the CB–AS system. F5 (contains the mixture MCB/CAM 50:50 as matrix) showed significant differences in its dissolution profile, compared with single polymers, $f_2 < 50$ (see Table 4). The dissolution time of F5 ($t_d = 367.8 \pm 5.7$ min) was higher than C3 (CB) ($t_d = 50.7 \pm 3.3$ min) and C2 (AS) ($t_d = 115.4 \pm 6.6$ min).

These results pointed out that the polymeric matrix based on mixtures of chitosan-alginate at 20% w/w in the tablet, have a high retardant capacity of drug release due to the small degree of swelling of alginate.

In order to evaluate if the t_d value was controlled by the behavior of the matrix, the t_d values of each system studied was related to the k_f/k_r values of the corresponding matrix. Fig. 10 shows that there is a good agreement between t_d and k_f/k_r values for the system chitosan–alginate ($r = 0.9227$ for the CS–AS system, $r = 0.9660$ for the CB–AS system), which means that the swelling behavior of the polymers controlled the drug release from the matrix. In the case of the system chitosan–carrageenan a significant relationship between the swelling behavior of the polymers and the dissolution time of the matrices based on these polymers was not observed. The high capacity of carrageenan to

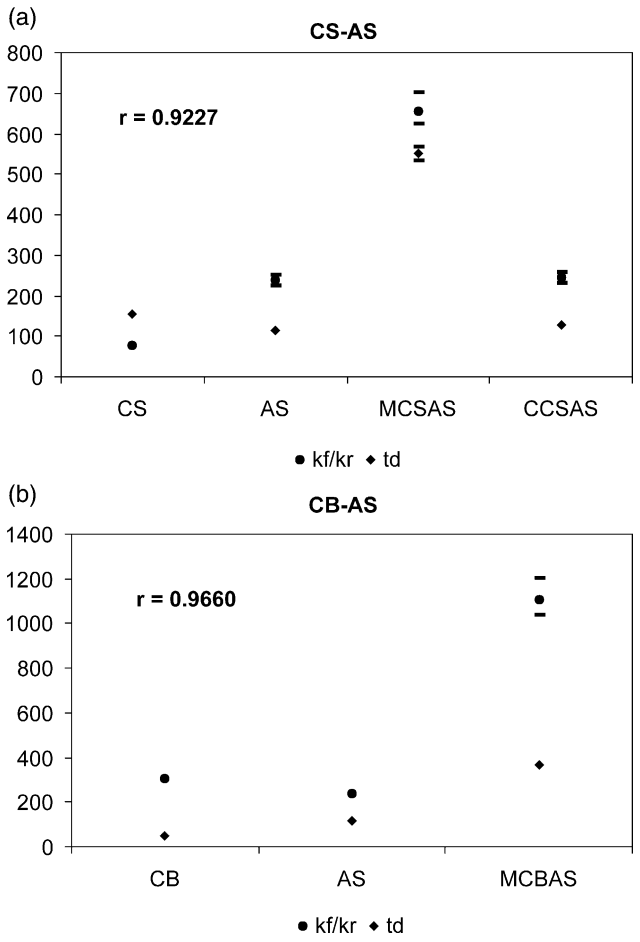


Fig. 10. Relationship between dissolution time of the formulations and k_f/k_r ratio for (a) CS–AS system and (b) CB–AS system. The t_d values are obtained from Weibull's model. The k_f and k_r values are obtained from Hopfenberg's model. Each bar represents the standard deviation.

promote the entry of water into the tablet could be responsible for the main mechanism of drug release, i.e. disintegration instead of the swelling of the matrix.

4. Conclusions

The chitosan–alginate system is better than the chitosan–carrageenan system as a prolonged drug release matrix system because the drug release is controlled at low percentage of the polymers in the formulation. The chitosan–alginate system showed a higher mean dissolution time than the chitosan–carrageenan system. Moreover, the chitosan–alginate system allows us to obtain different dissolution profiles by changing the mode of inclusion of the polymers. There is a good agreement between t_d and k_f/k_r values for the system chitosan–alginate, which means that the swelling behavior of the polymers controlled the drug release from the matrix. In the case of the system chitosan–carrageenan, the high capacity of carrageenan to promote the entry of water into the tablet could be responsible for the main mechanism of drug release, i.e. disintegration instead of the swelling of the matrix.

Acknowledgements

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References

[1] C. Tapia, E. Costa, M. Moris, J. Sapag-Hagar, F. Valenzuela, C. Basualto, Study of the influence of the pH media dissolution, degree of polymerization, and degree of swelling of the polymers on the mechanism of release of Diltiazem from matrices based on mixtures chitosan-alginate, Drug Dev. Ind. Pharm. 28 (2002) 217–224.

[2] V. Gupta, M. Hariharan, T. Wheatley, J. Price, Controlled-release tablets from carrageenans: effect of formulation, storage and dissolution factors, Eur. J. Pharm. Biopharm. 51 (2001) 241–248.

[3] T. Sakayama, C. Chu, T. Fujii, T. Yano, Preparation of a polyelectrolyte complex gel from chitosan and κ-carrageenan and its pH-sensitive swelling, J. Appl. Polym. Sci. 50 (1993) 2021–2025.

[4] M. Rinaudo, M. Milas, P. Le Dung, Characterization of chitosan. Influence of ionic strength and degree of acetylation on chain expansion, Int. J. Biol. Macromol. 15 (5) (1993) 281–285.

[5] K. Takayama, M. Hirata, Y. Machida, T. Masada, T. Sannan, T. Nagai, Effect of interpolymer complex formation on bioadhesive property and drug release phenomenon of compressed tablet consisting of chitosan and sodium hyaluronate, Chem. Pharm. Bull. (7) (1990) 1993–1997.

[6] The United States Pharmacopeia XXIV, 24th Rev., United States Pharmacopeial Convention, Rockville 2000

[7] A. Berens, H. Hopfenberg, Diffusion and relaxation in glassy polymer powders: 2. Separation of diffusion and relaxation parameters, Polymer 19 (1978) 489–496.

[8] L. Vachoud, N. Zydowicz, A. Domard, Physicochemical behavior of chitin gels, Carbohydr. Res. 326 (2000) 295–304.

[9] M. Roberts, H. Zhong, J. Prodolliet, D. Goodall, Separation of high-molecular-mass carrageenan polysaccharides by capillary electrophoresis with laser-induced fluorescence detection, J. Chromatogr. A 817 (1998) 353–366.

[10] N. Caram-Lelham, L. Sundelöf, The effect of hydrophobic character of drugs and helix-coil transition of κ-carrageenan on the polyelectrolyte–drug interaction, Pharm. Res. 13 (1996) 920–925.

[11] K. Picker, The use of carrageenan in mixture with microcrystalline cellulose and its functionality for making tablets, Eur. J. Pharm. Biopharm. 48 (1999) 27–36.

[12] V. Shah, Y. Tsong, P. Sathe, J. Liu, In vitro-dissolution profile comparison-statistics and analysis of the similarity factor, f_2, Pharm. Res. 15 (1998) 889–896.

[13] C. Caramella, F. Ferrari, M. Bonferoni, M. Sangalli, M. Bernardi, F. Feletti, M. Galmozzi, In vitro/in vivo correlation of prolonged release dosage form containing diltiazem HCl, Biopharm. Drugs Dispos. 14 (1993) 143–160.