# Study of the Release Mechanism of Diltiazem Hydrochloride from Matrices Based on Chitosan−Alginate and Chitosan−Carrageenan Mixtures†

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The aim of this work was to establish the diltiazem hydrochloride release mechanism from the chitosan−alginate matrix tablet (MCB/AS) and chitosan−carrageenan matrix tablet (MCS/CSI). The weight loss for MCS/CSI is mainly due to the weight loss of the matrix while for MCB/AS it is mainly due to the diltiazem hydrochloride released from the tablet. Using the Peppa's model the release order for MCS/CSI was $n = 1.07 \pm 0.13$ and for MCB/AS was $n = 0.76 \pm 0.02$. Thus, MCS/CSI has a transport mechanism, and for MCB/AS the drug release mechanism is a combined process of diffusion and relaxation. MCB/AS has an elastic modulus ($G' = 10^5$ Pa) one order of magnitude higher than MCS/CSI ($G' = 10^4$ Pa). MCB/AS is able to uptake solvent without disrupting the microstructure due to its high elastic modulus. Instead MCS/CSI showed a quick erosion process, which conducted to the tablet disintegration due to a fast solvent uptake process.

## 1. Introduction

pH-sensitive hydrogels have been most frequently used to develop controlled release formulations for oral administration. The pH in the stomach (<3) is quite different from the neutral pH in the intestine, and such a difference is large enough to elicit pH-dependent behavior of polyelectrolyte hydrogels.[1] Chitosan[2] is a copolymer of *N*-acetyl-D-glucosamine and D-glucosamine. It is a weak base with a p$K_a$ value of the D-glucosamine residue of about 6.2−7.0 and, therefore, is insoluble at neutral and alkaline pH values. Alginate[3,4] is a block copolymer composed of homopolymeric regions of $\beta$-D-mannuronate (M) and α-L-guluronate (G), termed M- and G-blocks respectively, interspersed with regions of alternating structure (MG-blocks). The dissociation constants (p$K_a$) for mannuronic and guluronic acid monomers are 3.38 and 3.65, respectively. The most abundant commercial alginate, the alginate from *Macrocystis pyrifera*, shows an unusual sequential arrangement of the monomers characterized by a high content of alternating structure together with some very long G-blocks. Thus, the *Macrocystis* alginates show a better correlation by plotting the modulus of rigidity against the average G-block length instead of a function of α-L-guluronate (G) content. The carrageenans[5] are linear, sulfated polysaccharides extracted from various species of the *Rhodophyta* (marine red algae). The carrageenan backbone is based on a repeating disaccharide sequence of $\beta$-D-galactopyranose residues linked glycosidically through positions 1 and 3 and α-D-galactopyranose residues linked glycosidically through positions 1 and 4. The carrageenan mixture has, namely, three types of carrageenan:[6] $\kappa$-carrageenan, $\iota$-carrageenan, and $\lambda$-carrageenan. $\kappa$-Carrageenan has one sulfate group per two galactose residues (produces a weak gel which suffer syneresis), $\iota$-carrageenan has two sulfate groups per two galactose residues (produces an elastic gel without syneresis), and $\lambda$-carrageenan has three sulfate groups per two galactose residues (no gelling). The order of charge density is[7] $\lambda$-carrageenan > $\iota$-carrageenan > $\kappa$-carrageenan.

It is known that chitosan produces controlled drug release matrices based on its gelling capacity and that the addition of sodium alginate to a tablet formulation containing chitosan allows the drug release period to be extended.[8] Previous studies[9,10] with chitosan−alginate mixtures showed that approximately 50% (w/w) of chitosan in the mixture produces the highest degree of interaction between polymers. The incorporation of the mixture chitosan−alginate (50:50) at 20% (w/w) in tablet formulation resulted in a prolonged diltiazem hydrochloride release matrix with a mean dissolution time of 4.3 h. The study of the swelling behavior of the chitosan−carrageenan mixtures in acid media[11] showed that the system CB (chitosan from Bioquímica Austral, Chile)/

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CAM (Carrageenan from Algas Marinas, Chile) has a higher degree of swelling than the system CS (Chitosan from Sigma, U.S.A.)/CSI (Carrageenan type I from Sigma, U.S.A.) and that the rate of swelling of the CB/CAM system is higher than that of CS/CSI system with the same proportions in the mixture. Thus, the MCS/CSI mixture is more adequate than the MCB/CAM mixture as a prolonged drug release matrix. The polymeric matrix based on mixtures of chitosan−carrageenan at 20% (w/w) in the tablet show a low retardant capacity of drug release due to the high capacity of carrageenan to promote the entry of water into the tablet. Moreover, CB swells faster than CS and a higher erosion rate was also observed for CB compared with CS.

The drug release kinetics of controlled-release matrix tablets can be determined by both the erosion behavior of the hydrogel and the diffusion processes of water and drug through the hydrogel. They depend on the synergistic macromolecular interactions and relaxation of the polymer chains. Such relaxation−diffusion dependence can be evaluated in terms of both kinetic parameters of water penetration into hydrophilic matrices and rheological peculiarities of their gel layers.[12]

The aim of this work was to establish the release mechanism of diltiazem hydrochloride from matrices based on physical mixtures of chitosan−alginate and chitosan−carrageenan. A simple tablet formulation was developed which contained 30% drug (equivalent to 90 mg of drug, which is normally the dose used in commercial diltiazem hydrochloride prolonged release tablets), 20% polymer mixture, and 49% lactose and 1% of magnesium stearate, which are commonly used in tablet preparation as the hydrophilic filler and lubricant, respectively.

## 2. Experimental Section

**2.1. Materials.** Chitosan was from Bioquímica Austral, Chile (CB), with a degree of deacetylation of 81% determined by $^1$H NMR spectroscopy. The intrinsic viscosity of CB, $[\eta] = 630$ mL/g, was determined in a 0.3 M acetic acid−0.2 M sodium acetate solution. The viscosity molecular weight of CB, $1.43 \times 10^5$ Da, was determined by using the Mark−Howink constants in this solvent, $K = 0.076$ mL/g and $a = 0.76$.[13]

Chitosan from Sigma, U.S.A. (CS), had a degree of deacetylation of 85%. The intrinsic viscosity $[\eta]$ determined for CS was 1395 mL/g in 0.3 M acetic acid−0.2 M sodium acetate solution. The viscosity molecular weight of CS was estimated as $4.08 \times 10^5$ Da.

Alginic acid sodium salt with medium viscosity was from *M. pyrifera* (AS; Sigma, U.S.A.) with a viscosity of the 2% solution at 25 °C of 3500 mPa·s.

Carrageenan type I (CSI), blended from various seaweeds, was obtained from Sigma, U.S.A., containing predominantly $\kappa$-carrageenan and in a lower extent $\lambda$-carrageenan.

Diltiazem hydrochloride was from Dr. Reddy's Laboratory, India.

Magnesium stearate was purchased from CG Chemikalien, Germany.

**Table 1.** Tablet Formulations Studied

| components (%, w/w) | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| diltiazem HCl | 30 | 30 | | |
| lactose | 49 | 49 | 79 | 79 |
| CS | 10 | | | 10 |
| CB | | 10 | 10 | |
| CSI | 10 | | | 10 |
| AS | | 10 | 10 | |
| magnesium stearate | 1 | 1 | 1 | 1 |

Lactose monohydrate was from the Lactose Company of New Zealand Limited, New Zealand.

All other chemicals were of analytical grade.

**2.2. Formulation and Preparation of the Tablets.** The formulations studied are shown in Table 1. The materials used were classified by sieving through 100 mesh sieves (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 300 mg tablets, with 12 mm of diameter and 2 mm of thickness. The tablets were prepared by direct compression using a Wilhelm Fette type EIIN.270 excentrical tabletting machine. The compression pressure was adjusted depending on the compactability of the formulation studied.

**2.3. Erosion, Swelling, and Dissolution Behavior Evaluation.** The evaluation of erosion, swelling, and dissolution behavior was performed in a dissolution apparatus (Pharmatest, type PTW SIII) at 37 °C and 50 rpm.[14] All assays were done in triplicate.

*2.3.1. Evaluation of Erosion Behavior.* The basket method (USP apparatus 1) was used. The tablets from formulations F1 (MCS/CSI 50:50) and F2 (MCB/AS 50:50) were submerged into 900 mL of 0.1 M HCl + 0.2 M KCl (pH 1.2; solution A) for 2 h. These tablets were then transferred to an alkaline solution (0.2 M $H_3BO_3$ + 0.2 M KCl, adjusted to pH 8.0 with 0.1 M NaOH solution; solution B) and left in this medium for another 5 h. At different times the tablets were removed and placed in an aluminum can. The tablets were dried in a vacuum oven at 70 °C and 100 mmHg until constant weight. The erosion was evaluated by weight loss of the tablets.

*2.3.2. Evaluation of Swelling Behavior. 2.3.2.1. By Weighing.* The paddle method (USP apparatus 2) was used. The tablets from formulations F1 and F2 were placed into a basket made of stainless steel mesh No. 16 and submerged into 900 mL of solution A for 2 h and then transferred to solution B for a further 2 h to complete a total of 4 h. At each sampling time the basket containing the tablet was removed, the dissolution medium was eliminated, and the basket was weighed.

*2.3.2.2. By Diameter.* The same method and dissolution medium as above was used. The tablets from formulations F1 and F2 were placed into a basket made of stainless steel mesh No. 20 containing on the bottom a plastic coated sheet with a millimeter scale. At each sampling time, the basket with the tablet was removed and the tablet diameter was measured using a magnification lens (Wild M·, Heerbrugg, Germany, ×6.4).

*2.3.2.3. By Thickness.* The same method, dissolution medium, and basket type as those described in 2.3.2.2 was used here. At each sampling time the basket with the tablet was removed. The thickness of the tablets was directly measured from the millimeter scale.

The kinetics of liquid penetration into these hydrophilic matrices was analyzed according to the potential equation $W_p = K_p t^{np}$ described by Michailova,[12] where $W_p$ is the weight gain of the swollen matrix (g of penetrant/g of dry polymer); $K_p$ is the kinetic constant of water penetration; and $t$ is the penetration time, and the exponent np represents the water penetration mechanism. $W_p$ was estimated from the swelling data by weighing (mg of solvent uptake/mg of tablet). The kinetic constant of water penetration, $K_p$, was calculated by potential regression analysis (mean value ± SD, $n = 3$). The density change of the tablet due to the swelling process was estimated from the swelling data by weighing, diameter, and thickness measurements. The density was calculated by considering that the tablet maintains its cylindrical geometry during the swelling experiment.

*2.3.3. Evaluation of Dissolution Behavior.* The basket method (USP apparatus 1) was used. The tablets from formulations F1 and F2 were submerged into 900 mL of solution A for 2 h and then transferred to solution B for a further 5 h to complete a total of 7 h. Aliquots of 10 mL were taken at different sampling times and were replaced with an equal volume of medium. The content of diltiazem hydrochloride was measured by UV spectroscopy by using a UV−visible UNICAM UV3 spectrometer at 236 nm.

The dissolution data were analyzed according to Peppa's model.[15] The fraction of drug released was estimated considering $M_\infty$ as the dose present in the tablet (90 mg). The release order, $n$, was obtained from the dissolution data fitted to the Peppa's potential equation, $M/M_\infty = kt^n$, using Microsoft Excel 2000. From the $n$ value obtained for each tablet the mean value and standard deviation were calculated (mean value ± SD, $n = 3$).

**2.4. Evaluation of the Viscoelastic Behavior of the Matrix Tablet.** Formulation F3 consisting of a mixture of chitosan (CB) and alginate (AS) without diltiazem HCl was submerged for 2 h in 900 mL of solution A at 37 °C by using paddle agitation at 50 rpm. Formulation F4 consisting of a mixture of chitosan (CS) and carrageenan (CSI) without diltiazem HCl was placed in the same solution for 30 min. Then, the swollen tablets were placed in the rheometer (Haake, Rheostress RS100). The sensor system used was the plate−plate type. The radius of the plate was 10 mm, and the gap between the plates was 1.5 mm. The oscillation test was developed in the linear viscoelastic zone response for each formulation. The oscillation test for formulation F3 was developed at 100 Pa of shear stress and F4 at 70 Pa of shear stress. The frequency was varied from 0.0681 to 39 Hz, and the $G'$ and $G''$ were measured for both formulations.

**2.5. Characterization of the Matrix Microstructure.** The matrix microstructure characterization of tablets from formulations F3 and F4 was carried out in both the dry and the swollen states by using scanning electron microscopy (SEM). Prior to examination the dried tablets were gold-sputter-coated to render them electrically conductive. Formulation F3 was submerged in 900 mL of solution A at 37 °C and by using paddle agitation at 50 rpm for 2 h. Formulation F4 was placed in the same solution for 30 min. The SEM of swollen tablets was obtained by using the critical point drying method. In this method the tablet is desiccated with acetone, and then it was saturated with $CO_2$.

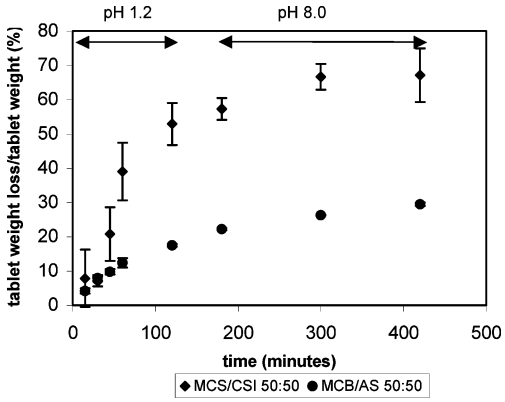


**Figure 1.** Erosion behavior of matrix tablets based on the chitosan−carrageenan mixture (F1, MCS/CSI, 50:50) and the chitosan−alginate mixture (F2, MCB/AS, 50:50). Each point represents the mean of three experiments. Each bar represents the standard deviation.

## 3. Results and Discussion

Figure 1 shows the erosion behavior of the tablets. Tablets from formulation F1 showed a fast erosion−dissolution process, 53% in acid medium and 67% in alkaline medium, at the end of the 7 h period. Nevertheless, the tablets from formulation F2 showed a slower erosion process, 18% in acid medium and 30% in alkaline medium, for the same period.

Figure 2 shows the total weight loss of F1 and F2 formulations due to erosion (Total). The weight loss of the tablet is due to diltiazem HCl dissolution, estimated from dissolution data (diltiazem HCl), and the difference between both which corresponds to the weight loss of the nondrug components of the tablet (matrix). It is clearly observed that the total tablet weight loss by erosion is significantly higher for F1 formulation compared with that of F2 formulation. The weight loss for F1 formulation is mainly due to the weight loss of the matrix while for F2 formulation the weight loss is mainly due to the diltiazem HCl released from the tablet.

Figure 3 shows a good fit of the swelling data to the potential equation $W_p = K_p t^{np}$ for both formulations (F1, $r = 0.9905$, $n = 4$; F2, $r = 0.9944$, $n = 4$). The kinetic constant of water penetration, $K_p$, values of 0.588 ± 0.094 (mg solvent uptake/mg of tablet) and 0.446 ± 0.016 (mg solvent uptake/mg of tablet) were obtained for F1 and F2 formulations, respectively. Thus, the kinetics of water penetration for F1 formulation was higher than that for F2 formulation, but not significantly (student's $t$ test, $p > 0.05$).

Figure 4 shows that for F1 formulation the density diminished quickly and that a value for density at equilibrium was not reached. Instead for F2 formulation less decrease of the density was observed, and a value for the density at equilibrium was attained. These results are in agreement with the higher $K_p$ value for F1 formulation compared with that

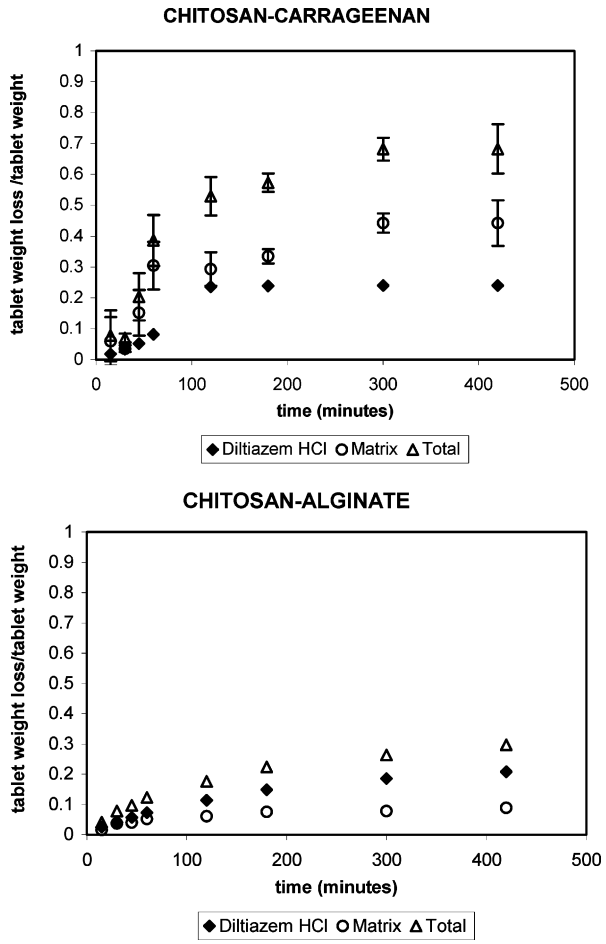


**Figure 2.** Tablet weight loss by total erosion. Drug dissolution and the loss of nondrug components for chitosan−carrageenan (F1) and chitosan−alginate (F2) formulations. Each data point represents the mean of three experiments. Each bar represents the standard deviation.

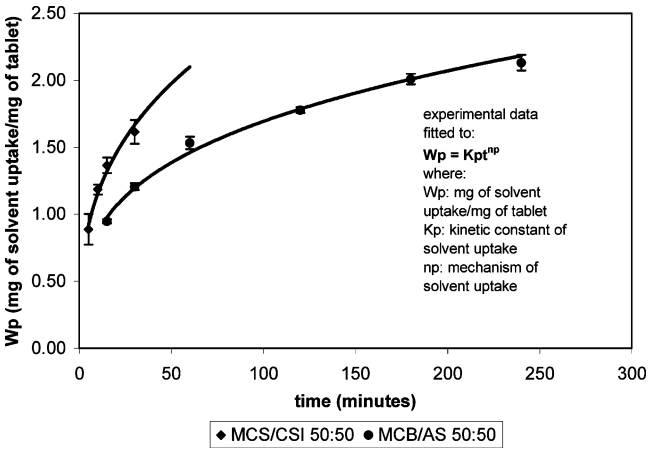


**Figure 3.** Solvent uptake capacity of the F1 formulation (MCS/CSI, 50:50) and F2 formulation (MCB/AS, 50:50) as a function of swelling time. Each point represents the mean of three experiments. Each bar represents the standard deviation, and the data were fitted by potential regression.

of F2 formulation. Moreover, the chitosan−alginate matrix incorporates less solvent in its structure, and, therefore, the tablet is able to maintain its integrity during the period studied. It has been described that the rate of penetrant uptake and compatibility of the polymer with a particular solvent leads to stresses occurring between the rubbery and the glassy

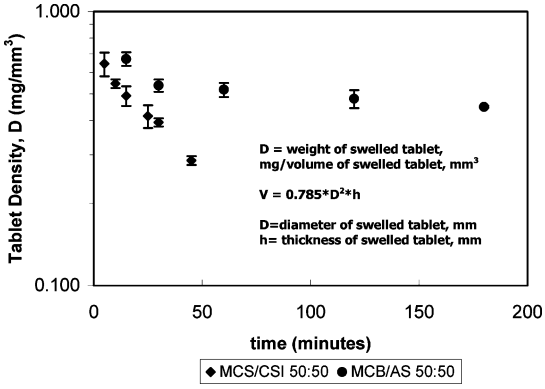


**Figure 4.** Tablet density for chitosan−carrageenan (F1, MCS/CSI, 50:50) formulation and chitosan−alginate (F2, MCB/AS, 50:50) formulation as a function of swelling time. Each data point represents the mean of three experiments. Each bar represents the standard deviation.

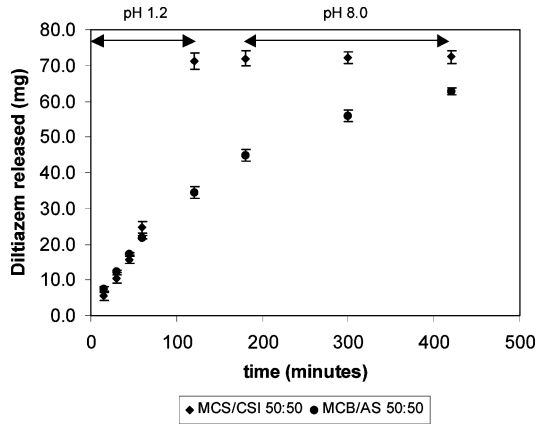


**Figure 5.** Dissolution profiles of tablet formulations based on chitosan−carrageenan (F1, MCS/CSI, 50:50) and chitosan−alginate (F2, MCB/AS, 50:50). Each point represents the mean of three experiments. Each bar represents the standard deviation.

areas of the swollen polymer resulting in the tablets fracture, especially in the presence of good solvents.[16] The electrostatic attraction between the cationic amino groups of chitosan and the anionic groups of the other polyelectrolyte is the main type of interaction leading to the formation of the polyelectrolyte complex (PEC). To form a PEC, both polymers have to be ionized and bear opposite charges. This means that the reaction can only occur at pH values in the vicinity of the p$K_a$ interval of the two polymers.[17] Chitosan[2] is a weak base with a p$K_a$ value of the D-glucosamine residue of about 6.2−7.0. Thus, 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 contributions are maxima, thus, contributing to a maximum swelling.[18] Alginate[3,4] is a block copolymer composed of $\beta$-D-mannuronate and $\alpha$-L-guluronate. The dissociation constants (p$K_a$) for mannuronic and guluronic acid monomers are 3.38 and 3.65, respectively. The p$K_a$ value of the alginate polymer differs only slightly from those of the monomeric residues. Therefore, alginate at pH 1.2 is in its un-ionized form. It has been described that the sulfonate groups of carrageenan remain negatively charged in HCl solution; thus, the electrostatic bond between amino groups of chitosan and sulfonate groups of carrageenan will occur.[19] Previous studies[20] carried out on the swelling behavior of

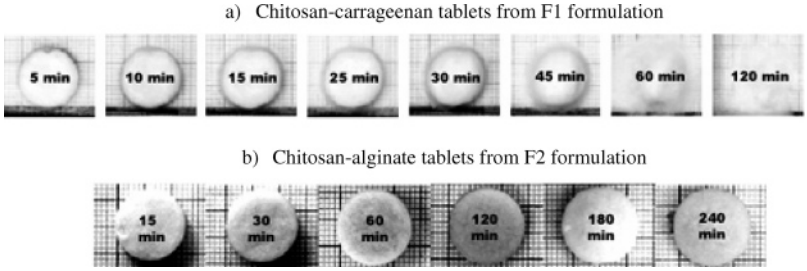


**Figure 6.** Change of tablet diameter as a function of swelling time. (a) Chitosan−carrageenan tablets from the F1 formulation. (b) Chitosan−alginate tablets from the F2 formulation. The tablet diameter was measured using a magnification lens with 6.4 of magnification.

MCS/CSI and MCB/AS mixtures in acid and alkaline solutions (pH 1.2 and 8.0, respectively) showed that the maximum degree of swelling was reached in acid medium and that the effect of pH changes from pH 1.2 to pH 8.0 on the degree of swelling was not significant (Duncan test, $p > 0.05$). The erosion, swelling, and dissolution studies carried out in this work were performed under the same conditions as those carried out for MCS/CSI and MCB/AS mixtures. Chitosan−alginate PEC was not formed in either acid or basic solutions. Instead, chitosan−carrageenan PEC was formed in acid solution. F1 formulation produced an electrosmotic flux higher than F2 formulation, due to the fact that both chitosan and carrageenan are ionized at pH 1.2. Consequently, the rate and degree of swelling of F1 formulation was higher than that of F2 formulation. The same results[11] were obtained for MCS/CSI and MCB/AS mixtures from the swelling studies carried out in acid medium (pH 1.2).

The dissolution studies with pH changes show that tablets from F2 formulation are able to control the diltiazem HCl release during 7 h. On the contrary, tablets from the F1 formulation release all the drug at 2 h; see Figure 5. These dissolution data are in agreement with the erosion data. A fast erosion process starts after 45 min for F1 formulation which conducted to the tablet disintegration between 60 and 120 min. Instead, F2 formulation maintains its integrity during 240 min; see Figure 6.

It was observed in our previous work[11] that the td value (mean dissolution time obtained from Weibull's model applied to dissolution data) of the drug released from the tablet showed a good agreement with the ratio kf/kr (ratio between kf, fickian diffusion constant, and kr, relaxation rate constant obtained from Hopfenberg's model applied to swelling data) of the matrix for chitosan−alginate system which means that the swelling behavior of the polymers controlled the drug release from the tablet. In the case of the system chitosan−carrageenan a significant relationship between the swelling behavior of the polymers and the dissolution time of the drug released from matrices based on these polymers was not observed. The high capacity of carrageenan to promote the entry of water into the tablet could be responsible for the main mechanism of drug release, that is, disintegration instead of the swelling of the matrix.

The dissolution data for F1 and F2 formulations, considering the dissolution times between 15 and 120 min and acid medium (pH 1.2), showed good fit to the Peppa's model (F1, MCS/CSI, $r = 0.9933$, $n = 4$; F2, MCB/AS, $r = 0.9989$, $n = 6$). For F1 formulation the release order was $n = 1.07 \pm 0.13$, and for F2 formulation the release order was $n = 0.76 \pm 0.02$. Thus, the MCS/CSI system has a transport mechanism where the solvent penetrated into the tablet is leached out of the drug from the matrix until the tablet is disintegrated. Instead, for the system MCB/AS the drug release mechanism is a combined diffusion and relaxation processes.

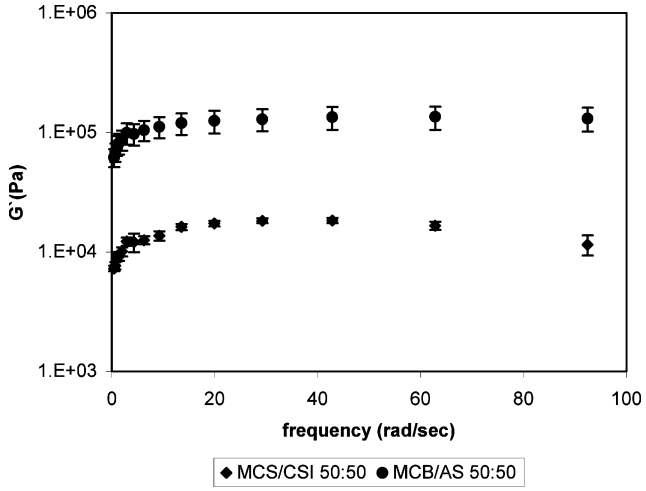


**Figure 7.** Mechanical spectrum of chitosan−carrageenan (F4, MCS/CSI, 50:50) and chitosan−alginate (F3, MCB/AS, 50:50) swollen tablets. Each point represents the mean of three experiments. Each bar represents the standard deviation.

The viscoelastic properties of F4 formulation of the tablets prepared from the chitosan−carrageenan mixture were measured. The tablets used for the experiments were those swollen for 30 min, the time where the tablet reaches the highest degree of swelling before the disintegration process starts. In the case of F3 formulation, the tablets were prepared from the chitosan−alginate mixture. These tablets reached the highest degree of swelling after 240 min; see Figure 6.

Tablets from both formulations were visually inspected to ensure the absence of nonswollen area before performing rheological measurements. As seen from Figure 7, the elastic modulus of F3 formulation (MCB/AS) has a value of $G' = 10^5$ Pa, one order of magnitude higher than that of F4 formulation (MCS/CSI; $G' = 10^4$ Pa). This means that the hydrogel formed from the chitosan−alginate mixture is a solid with high elasticity, which explains the low degree of erosion of the tablet. Swollen tablets from the chitosan−carrageenan mixture (F4 formulation) form a weaker network structure compared with that of swollen tablets prepared from the chitosan−alginate mixture (F3 formulation). This behavior is probably due to the relatively slow diffusion of the carrageenan chains leading to the formation of a more

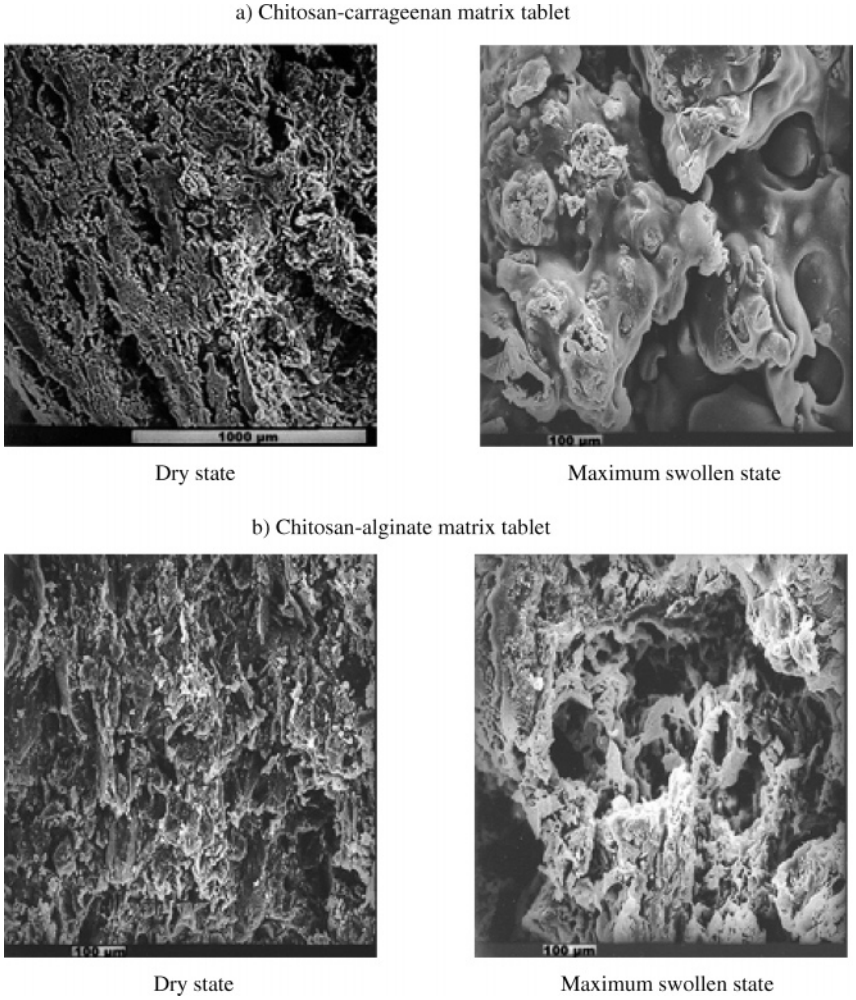


**Figure 8.** Microstructure of (a) chitosan−carrageenan tablets from the F4 formulation and (b) chitosan−alginate tablets from the F3 formulation. The microstructure of tablets in dry and at maximum swollen state was obtained by using SEM.

**Table 2.** Kinetic Water Penetration ($K_p$) for F1 and F2 Formulations and $G'$ Values for Chitosan−Alginate (F3 Formulation) and Chitosan−Carrageenan (F4 Formulation)

| system | $K_p$ ($min^{-n}$), mean ± SD | $G'$ (Pa) at 42.8 $s^{-1}$, mean ± SD |
|---|---|---|
| CS/CSI, 50:50 | $5.9 \times 10^{-1} \pm 9.4 \times 10^{-2}$ ($n = 3$), F1 | $1.8 \times 10^{4} \pm 9.5 \times 10^{2}$ ($n = 3$), F4 |
| CB/AS, 50:50 | $4.5 \times 10^{-1} \pm 1.6 \times 10^{-2}$ ($n = 3$), F2 | $1.3 \times 10^{5} \pm 2.9 \times 10^{4}$ ($n = 3$), F3 |

stable and more compact structure. This exerts and increases the swelling pressure on the imbibed liquid, which then exudes from the gel. This slow expulsion of imbibed liquid is called syneresis.[21] The carrageenan used in F4 formulation (MCS/CSI, 50:50) is a mixture containing mainly $\kappa$-carrageenan which is known to exhibit syneresis.[22]

The values of kinetic water penetration ($K_p$) for each system are compared with the values of $G'$, at a specific frequency where $G'$ is constant (Table 2). It can be observed that a high value of $K_p$ correlates with a low value of $G'$. In the hydrophilic matrices[12] with unlimited swelling, not only the relaxation behavior of the hydrated macromolecules but also the structure of the gel layer influences considerably the degree and the velocity of water penetration. The elastic nature of the system is considered to resist significantly against the penetrant uptake.

Figure 8 shows the microstructure of chitosan−carrageenan and chitosan−alginate tablets in the dry and swollen states. In the dry state, the chitosan−carrageenan matrix showed a great number of large channels with some pores of irregular form and size. On the contrary, large size structures without defined form were observed in the swollen chitosan−carrageenan tablet which pointed out that the initial matrix microstructure was lost by the swelling process. This could be explained by considering that the large amount of solvent penetrated into the matrix would produce a high mechanical pressure over the internal microstructure of the matrix resulting in its fracture. In the dry state, the chitosan−alginate matrix showed an irregular porous structure with a diameter between 10 and 60 $\mu$m. This structure is maintained in the swollen tablet with a significant increase of the pore diameter. The range of the pore diameter was between 20 and 120 $\mu$m.

## 4. Conclusions

The diltiazem hydrochloride drug release from tablets prepared from the chitosan−alginate mixture is controlled by a combined mechanism of diffusion and relaxation. The hydrogel formed is able to uptake solvent without disrupting the microstructure due to the high elastic modulus of the swollen tablet. On the contrary, tablets prepared from the

chitosan−carrageenan mixture showed a fast erosion process, which conducted to a tablet disintegration due to a fast solvent uptake process which produced the fracture of the microstructure.

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