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Study of Dissolution Behavior of Matrices Tablets Based on Alginate–Gelatin Mixtures as Prolonged Diltiazem Hydrochloride Release Systems

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ABSTRACT The aim of this work was to develop prolonged diltiazem hydrochloride release matrices based on alginate-gelatin mixtures and establish the drug release mechanism. The erosion, swelling, and dissolution behavior of the tablets in different medium were evaluated. The different polyelectrolyte behavior and gel strength between type A Gelatin and type B Gelatin would explain the different swelling, erosion and dissolution behavior in the media with sudden pH change. The similar dissolution behavior in the pH, which simulates the physiological pH through the gastrointestinal tract, should be explained because the same main species for gelatin A and Gelatin B would be present in this media.

KEYWORDS Alginate, Gelatin, Prolonged drug release, Matrices

INTRODUCTION

Alginate is a block copolymer composed of homopolymeric regions of β-D-mannuronate and α-L-guluronate (G), termed M- and G-blocks, respectively, interspersed with regions of alternating structure (MG-blocks). In general, alginates rich in guluronate residues form strong, brittle gels, while M-rich alginates form softer, more elastic gels (Moe et al., 1995; Dornish et al., 2001). Alginate has been widely used in the development of controlled drug release systems. Most of the dosage forms developed based on alginate have been beads and microparticles, and less work has been done with matrix tablets. Matrix tablets containing sodium alginate as the release-retarding agent have been prepared by using direct compression, granulation, compression coating, and spray coating (Liew et al., 2006). It is known that when hydrophilic matrix tablets are exposed to the dissolution medium, drug release is modulated by diffusion through matrix, swelling, and dissolution/erosion at the matrix periphery (Kim & Fassihi, 1997). Matrices formed by calcium alginate are usually very permeable and little drug release can actually be controlled in the case of soluble drugs (Lin et al., 1992; Østberg et al., 1994, Giunchedi et al.,

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2000). This difficulty has been overcome by mixing alginate with other polymers such as pectin (Liu et al., 1999), and chitosan (Tapia et al., 2002; Tapia et al., 2005). Also, it has been pointed out that a compressed alginate tablet will have a much closed structure compared to a gel bead, and the degree of sustained release effect will therefore be higher in tablet (Tonnesen & Karlsen, 2002).

Gelatin-alginate mixtures have been proposed as controlled drug release matrices. Radiographical studies in human volunteers have shown that the uncoated gelatin capsules disintegrated in the stomach within 15 min of ingestion. Instead, gelatin capsules coated with 20% w/v of alginate and cross-linked with calcium chloride, remained intact in the stomach and then migrated to the ileocecal region of the intestine and disintegrated (Narayani et al., 1995). The release rates of cefadroxil were much lower for interpenetrating polymer networks (IPNs) of gelatin-alginate compared with Na-Alg beads (Kulkarni et al., 2001). Recombinant adenoviruses encapsulated in coacervate microspheres comprised of gelatin and alginate followed by stabilization with calcium ions, showed a sustained release of adenovirus (Kalyanasundaram et al., 1999). The aim of this work was to develop prolonged diltiazem hydrochloride release matrices based on alginate-gelatin mixtures, evaluate the effect of two types of gelatin with different polyelectrolyte behavior and gel strength over drug dissolution, and establish the drug release mechanism.

MATERIALS AND METHODS

Materials

Alginic acid sodium salt medium viscosity was obtained from *Macrocystis pyrifera* (Sigma, St. Louis, MO, USA) viscosity of 2% solution at 25°C=3500 mPas.

Gelatin type A (G2500 Aldrich, St. Louis, MO, USA) was obtained from porcine skin by acid-cured tissue. Degree of gelification=300 Bloom. Isoelectric point=8.0, pK_1=5.2, pK_2=11.5 (Kroshwitz, 1985).

Gelatin type B (G9382 Aldrich, St. Louis, MO, USA) was obtained from bovine skin by limed-cured tissue. Degree of gelification=225 Bloom. Isoelectric point=5.0, pK_1=3.6, pK_2=7.8 (Kroshwitz, 1985).

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

Magnesium stearate was obtained from CG Chemikalien, Germany.

Lactose monohydrate was procured from The Lactose Company of New Zeland Limited, New Zeland.

All other chemicals were of analytical grade.

Formulation and Preparation of the Tablets

The formulations studied are shown in Table 1. The materials used were classified by sieving through a 120 mesh sieves (ASTM E-11). For each 10 g of formulation the polymers were manually dry mixed in a plastic bag for 15 min with diltiazem hydrochloride, lactose and magnesium stearate to make 300 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.

Evaluation of Erosion Behavior

This was performed in a dissolution apparatus (Pharmatest, type PTW SIII) at 37°C and 50 rpm. The paddle method (USP type 2) (USP 24, 2000) was used. The tablets were placed over basket made of stainless steel mesh # 18 and submerged into 900 mL of 0.2 M HCl+0.2 M KCl (pH 1.2) (solution A) for 2 hr. 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 media for

TABLE 1 Tablet Formulations Studied

Components	F1(%)	F2(%)	F3(%)	F4(%)
Diltiazem HCl	30	30	30	30
Lactose	49	49	19	19
Alginate	10	10	25	25
Gelatin A	–	10	–	25
Gelatin B	10	–	25	–
Magnesium stearate	1	1	1	1
Diameter (mm), n=10	12 ± 0.1	12 ± 0.1	12 ± 0.1	12 ± 0.1
Thickness (mm), n=10	3.5 ± 0.1	3.5 ± 0.1	3.5 ± 0.1	3.5 ± 0.1
Hardness (Kp), n=10	5.0 ± 0.5	5.0 ± 0.3	4.0 ± 0.5	4.0 ± 0.4

Alginate: alginate medium viscosity (Sigma); Gelatin A: (G2500 Aldrich). Obtained from porcine skin by acid-cured tissue. Gelatin B: (G9382 Aldrich). obtained from bovine skin by lime-cured tissue.

another 6 hr. At different times the tablets were removed and placed in an aluminum can. The tablets were then dried in a vacuum oven at 70°C and 100 mmHg until constant weight. Each assay was done by triplicate.

Evaluation of Swelling Behavior

This was performed in the same dissolution apparatus and conditions. The tablets were placed over basket made of stainless steel mesh # 14 and submerged into 900 mL of solution A for 2 hr and then transferred to solution B for further 6 hr to complete a total of 8 hr. At each time of sampling the basket with the tablet was removed, the dissolution media was eliminated, and the basket was weighed. Each assay was done by triplicate.

The kinetics of liquid penetration into these hydrophilic matrices was analyzed according to the potential equation $Wp=Kpt^{np}$ described by Michailova (Michailova et al., 2000), where Wp is the weight gain of the swollen matrix (g of penetrant/g of dry polymer), Kp is the kinetic constant of water penetration, t is the penetration time and the exponent np represents the water penetration mechanism. Wp was estimated from the swelling data by weighing (mg of solvent uptake/mg of tablet). The kinetic constant of water penetration, Kp, was calculated by non lineal regression analysis (Table Curve ver 1.0, Jandel Scientific).

Dissolution Test

Dissolution Test Under Conditions with Sudden pH Change

This was performed in the same dissolution apparatus and conditions described above using the paddle method (USP type 2) (USP 24, 2000). The tablets were submerged into 900 mL of solution A for 2 hr and then transferred to solution B for further 6 hr to complete a total of 8 hr. Aliquots of 10 mL were taken at different times of sampling, which were replaced with an equal volume of medium, and the content of diltiazem hydrochloride was measured by UV spectroscopy by using a UNICAM UV3 UV-Visible spectrometer at the wavelength of 236 nm. Each assay was done by triplicate.

Dissolution Test Under Conditions which Simulate Physiological pH-time Profile

This was performed under the same conditions described in 2.5.1. The dissolution media was that described by Das and Gupta (1998). Tablets were added to 900 mL of the solution I (4.2 mL of HCl in 1 l, pH=1.4 ± 0.1). Every 30 min 5 mL aliquots of samples were taken off which were replaced with solution II (40 g of Na_2CO_3+50 g of $NaHC0_3$ in 1l, pH=9.3 ± 0.1) and repeated to complete 10 samples test. Then, the 5 mL aliquots were replaced by solution III (10 g of Na_2CO_3+20 g of $NaHC0_3$ in 1 L, pH=9.3 ± 0.1) until the experiment completed 8 hr. The content of diltiazem hydrochloride was measured by UV spectroscopy (UV-Visible UNICAM UV3 spectrometer) at 236 nm. Each assay was done by triplicate.

The dissolution data were analyzed according to Weibull's model (Caramella et al., 1993). The mean dissolution time was calculated by nonlinear regression analysis (Table Curve ver 1.0, Jandel Scientific).

Estimation of Ionized Species of Gelatin at Different pH

Gelatin as a protein can be present as cationic, anionic and amphoteric species depending on the pH of dissolution media. Gelatin type A has an isoelectric point, pI=8.0, and its pKa values are, pK_{a1}=5.2 and pK_{a2}=11.5. Instead, gelatin type B has an isoelectric point, pI=4.9, and its pKa values are, pK_{a1}=3.6 and pK_{a2}=7.8 (Kroshwitz, 1985).

Thus, the different species of gelatin can be represented as follows:

$$\underset{anionic\ specie}{NH_2GelCO_2^-} \overset{K_{a2}}{\leftarrow} \underset{amphoteric\ specie}{NH_3^+GelCO_2^-} \overset{K_{a1}}{\leftarrow} \underset{cationic\ specie}{NH_3^+GelCO_2H} + OH^- \quad (1)$$

The equilibrium between the cationic and amphoteric species of gelatin can be expressed as:

$$NH_3{}^+GelCO_2H \overset{K_{a1}}{\Leftrightarrow} NH_3{}^+GelCO_2{}^- + H^+ \quad (2)$$

Thus K_{a1} can be expressed as:

$$K_{a_1} = \frac{(H^+)\,(NH_3{}^+GelCO_2{}^-)}{(NH_3{}^+GelCO_2H)} \quad (3)$$

The equilibrium between the amphoteric and anionic species of gelatin can be expressed as:

$$NH_3^+GelCO_2^- \overset{K_{a2}}{\Leftrightarrow} NH_2GelCO_2^- + H^+ \quad (4)$$

Thus K_{a2} can be expressed as:

$$K_{a_2} = \frac{(H^+)\,(NH_2GelCO_2^-)}{(NH_3^+GelCO_2^-)} \quad (5)$$

Also, this expressions can be related with the pH of dissolution media as follows

$$pH = pK_{a_1} + Log\frac{(NH_3^+GelCO_2^-)}{(NH_3^+GelCO_2H)} \quad (6)$$

$$pH = pK_{a_2} + Log\frac{(NH_2GelCO_2^-)}{(NH_3^+GelCO_2^-)} \quad (7)$$

Thus, the concentration of the different species of gelatin can be expressed in terms of its ionization constant and pH

$$\frac{(NH_3^+GelCO_2H)}{(NH_3^+GelCO_2^-)} = 10^{pK_{a_1}-pH} \quad (8)$$

$$\frac{(NH_2GelCO_2^-)}{(NH_3^+GelCO_2^-)} = 10^{pH-pK_{a_2}} \quad (9)$$

The total concentration of gelatin can be expressed as:

$$1 = (NH_3^+GelCO_2^-) + (NH_3^+GelCO_2H) + (NH_2GelCO_2^-) \quad (10)$$

Dividing Eq. (10) by $(NH_3^+GelCO_2^-)$:

$$\frac{1}{(NH_3^+GelCO_2^-)} = 1 + \frac{(NH_3^+GelCO_2H)}{(NH_3^+GelCO_2^-)} + \frac{(NH_2GelCO_2^-)}{(NH_3^+GelCO_2^-)} \quad (11)$$

Thus, the fraction of amphoteric species is:

$$(NH_3^+GelCO_2^-) = \frac{1}{1 + \frac{(NH_3^+GelCO_2H)}{(NH_3^+GelCO_2^-)} + \frac{(NH_2GelCO_2^-)}{(NH_3^+GelCO_2^-)}} \quad (12)$$

and expressed in terms of ionization constant and pH :

$$(NH_3^+GelCO_2^-) = \frac{1}{(1 + 10^{pK_{a1}-pH} + 10^{pH-pK_{a2}})} \quad (13)$$

The fraction of cationic species is:

$$(NH_3^+GelCO_2H) = \frac{10^{pK_{a1}-pH}}{(1 + 10^{pK_{a1}-pH} + 10^{pH-pK_{a2}})} \quad (14)$$

and by difference the fraction of anionic species is:

$$(NH_2GelCO_2^-) = 1 - (NH_3^+GelCO_2^-) - (NH_3^+GelCO_2H) \quad (15)$$

Estimation of Ionized Species of Alginate at Different pH

Alginates are linear copolymers of β-D–manuronic acid and α-L-guluronic acid. This monomers has one carboxylic group with a pK_a value of 3.38 and 3.20 respectively, being the pK_a of alginate close to these values (Martinsen et al., 1992).

The ionization of alginate can be expressed as:

$$Al - COOH \overset{K_a}{\Leftrightarrow} Al - COO^- + H^+ \quad (16)$$

Thus *K*a is:

$$K_a = \frac{(H^+)(Al - COO^-)}{(Al - COOH)} \quad (17)$$

The total concentration of alginate can be expressed as:

$$1 = (Al - COOH) + (Al - COO^-) \quad (18)$$

The unionized fraction of alginate is:

$$(Al - COOH) = \frac{1}{1 + 10^{pH-pK_a}} \quad (19)$$

and by difference the ionized fraction is:

$$(Al-COO^{-}) = 1-(Al-COOH) \qquad (20)$$

RESULTS AND DISCUSSION

Swelling Behavior

Fig. 1 shows that formulations F1 and F2 with 20% of polymer matrix (gelatin A or B/alginate 1:1) has lower degree of swelling and that the disruption of the tablets starts earlier compared to formulations F3 and F4 with 50% of polymer matrix (gelatin A or B/alginate 1:1). This result pointed out that tablets with 20% of polymer matrix were unable to produce a gellified structure, which regulates the access of dissolution media into the tablet. In the formulations with 50% of polymer matrix (F3 and F4) the change from pH 1.2 to 8.0 produces a sharp increase in the degree of swelling. F3 that contains gelatin B, reached a higher degree of swelling but began a fast erosion process, which means that the gellified structure of the tablet was broken. In the case of F4 that contains gelatin A, a slow erosion process began after reaching the maximum swelling degree.

The kinetics of liquid penetration into the tablet formulations F3 and F4 were analyzed according to the potential equation $Wp=Kpt^{np}$. Fig. 2 shows the sudden increase of the solvent uptake with the change of pH from 1.2 to 8.0 which means that this process is mainly dependent of the degree of ionization of the

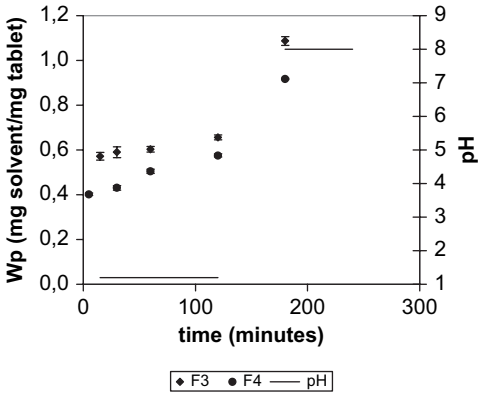

FIGURE 2 **Solvent Uptake Capacity of the F3 Formulation and F4 Formulation as a Function of Swelling Time. Each Point Represents the Mean of Three Experiments. Each Bar Represents the Confidence Interval at $p=0.05$.**

polymers which constitute the matrix of the tablets. In acid media, pH 1.2, the kinetic constant of water penetration, Kp of both formulations were calculated. F3; $Kp=0.468 \pm 0.014$ ($r=0.9645$, $n=8$); F4; $Kp=0.239 \pm 0.009$ ($r=0.9879$, $n=11$). Thus, the kinetics of water penetration for F3 formulation was significantly higher than F4. In a previous work (Tapia et al., 2005) with hydrophilic matrices tablets based on chitosan-alginate and chitosan-carrageenan mixtures we found that a high value of Kp correlates with a low value of G′. Thus, F3 would have a weaker gel structure compared with F4.

Erosion Behavior

Fig. 3 shows the degree of erosion of the formulations. Formulations F1 and F2, with 20% of polymer

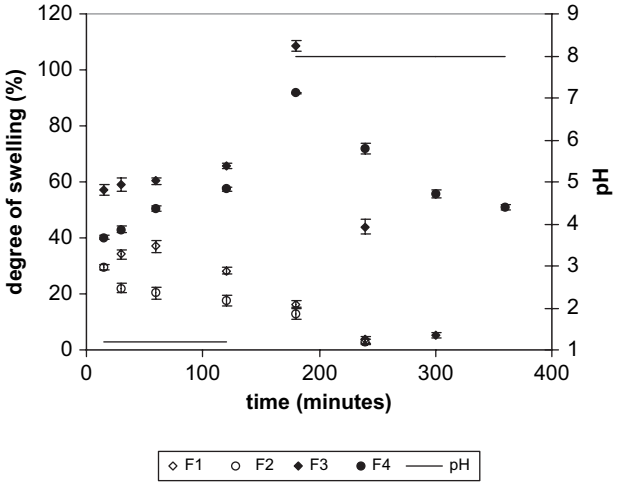

FIGURE 1 **Swelling Behavior of Formulations With Sudden pH Change (pH1 Media) Between 1.2 to 8.0. Each Point Represents the Mean of Three Experiments. Each bar Represents the Confidence Interval at $p=0.05$.**

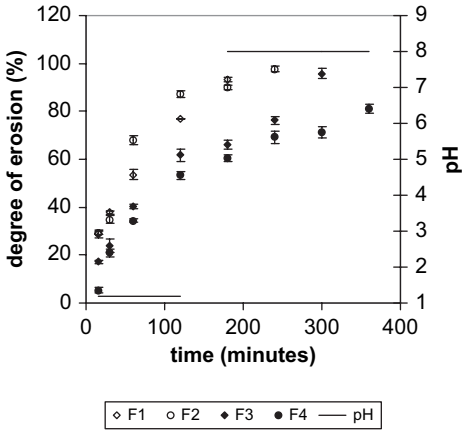

FIGURE 3 **Erosion Behavior of Formulations With Sudden pH Change (pH1 Media) Between 1.2 to 8.0. Each Point Represents the Mean of Three Experiments. Each Bar Represents the Confidence Interval at $p=0.05$.**

mixture in the matrix, show a higher degree of erosion compared with formulations F3 and F4 with 50% of polymer in the matrix. Also, the effect of the type of gelatin in the erosion of the tablets is observed. Formulation F3 that contains gelatin B shows a higher degree of erosion compared with F4 containing gelatin A.

Dissolution Behavior

Since a low degree of swelling and high degree of erosion for the formulations with 20% of polymer mixture was observed, it was decided to develop the dissolution studies only with the formulations containing 50% of polymer mixture as seen from Fig. 1.

The dissolution behavior of the formulations F3 and F4 in two different medium was studied, see Fig. 4. The first media used was that corresponding to a sudden pH change (pH SC) from pH 1.2 to 8.0, where the swelling and erosion studies were developed. The other media used was that proposed by Das and Gupta (1998), which simulates the physiological pH through the gastrointestinal tract (pH GI). In pH SC media, significant differences ($p < 0.05$) is only observed at pH 8.0 between the formulations F3 with gelatin B where 100% of drug was released at 300 min, instead F4 released the entire drug at 360 min. There were not significant differences between both formulations in pH GI media.

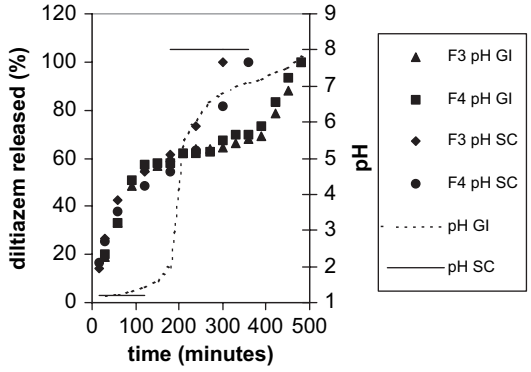

FIGURE 4 **Dissolution Behavior of Formulations F3 and F4 in a Media With Sudden pH Change (pH SC) and Media Which Simulate a pH in Gastrointestinal Transit (pH GI). Each Point Represents the Mean of Three Experiments. The Confidence Interval at $p=0.05$ is Smaller Than the Size of Point.**

The mean dissolution time of each formulation, in both media, was estimated according to the model of Weibull. The values obtained are shown in Table 2. In pH SC, F4 showed a more prolonged dissolution mean time that F3. In pH GI, there were not significant differences in the mean dissolution time between both formulations. The mean dissolution time of F3 was increased significantly when the dissolution media is changed from pH SC to pH GI, instead the mean dissolution time of F4 was not affected.

Explanation of Swelling, Erosion and Dissolution Behavior of Tablets Based on Polyelectrolyte Behavior of Gelatin and Alginate

The different behavior observed for formulations F3 and F4 could be attributed to the polyelectrolyte behavior of both types of gelatin. The percentage of different ionized species of both types of gelatin at pH 1.2 and 8.0 (pH SC) can be estimated by using the procedure described in 2.6 and 2.7. Table 3 shows that at pH 1.2, the main species for both types of gelatin is the cationic form and that the alginate is in its unionized form. Instead at pH 8.0 for gelatin A (F4), the main specie is the amphoteric form (99.8%) and for gelatin B (F3) both anionic (61.3%) and amphoteric (38.7%) species are present. For both formulations at pH 8.0 the alginate is in its anionic form. Fig. 1 shows that the change from pH 1.2 to 8.0 produces a sharp increase in the degree of swelling of formulations F3 and F4. Fig. 2 shows that the solvent uptake of formulation F3 was higher compared with F4. Fig. 3 shows that F3 has a higher degree of erosion compared with F4. Table 2 shows that F4 has a more prolonged dissolution mean time that F3. It is known that a high concentration of ions exists inside the ionized gels due to

TABLE 2 **Estimation of Mean Dissolution Time From Weibull's Model for Both Dissolution Media**

Formulation data	Sudden pH change			Simulate gastrointestinal pH change		
	td ± IC (min)	df adj R^2	# of data	td ± IC (min)	df adj R^2	# of data
F3	171 ± 10 ;	0.9752 ;	18	254 ± 16 ;	0.9104 ;	39
F4	249 ± 16 ;	0.9840 ;	18	237 ± 14 ;	0.9216 ;	39

TABLE 3 **Estimation of the Different Species of Gelatin and Alginate in Media With Sudden pH Change, pH 1.2 to 8.0, Using the Procedure Describe in 2.6 and 2.7**

Time		Species of gelatin B in F3, %			Species of gelatin A in F4, %			Species of alginate in F3 and F4,%	
Minutes	pH	Amphoteric	Cationic	Anionic	Amphoteric	Cationic	Anionic	Unionized	Anionic
15	1.2	0.4	99.6	0.0	0.0	100.0	0.0	99.2	0.8
30	1.2	0.4	99.6	0.0	0.0	100.0	0.0	99.2	0.8
60	1.2	0.4	99.6	0.0	0.0	100.0	0.0	99.2	0.8
120	1.2	0.4	99.6	0.0	0.0	100.0	0.0	99.2	0.8
180	8.0	38.7	0.0	61.3	99.8	0.2	0.0	0.0	100.0
240	8.0	38.7	0.0	61.3	99.8	0.2	0.0	0.0	100.0
300	8.0	38.7	0.0	61.3	99.8	0.2	0.0	0.0	100.0
360	8.0	38.7	0.0	61.3	99.8	0.2	0.0	0.0	100.0

dissociation of ionized groups in the gel and diffusion of counterions into the gel from the surrounding medium. Thus, the high ion concentration will increase water flow into the gel due to osmosis, resulting in an increase of swelling described by the Donnan equilibrium. Also, another factor contributing to increases in swelling is the interaction and repulsion of charges along the polymer chain (Brondsted & Kopecek, 1992). In this study, the electrostatic repulsion between anionic species of gelatin and anionic species of alginate in the mixture gelatin/alginate in F3 would be higher than in F4. Consequently, the degree of swelling of F3 was higher than F4, and the kinetics of water penetration, Kp, for F3 formulation was significantly higher than F4. The erosion studies reveals that F3 which contains gelatin B shows a higher degree of erosion compared with F4 which contains gelatin A, due probably to the fact that F3 forms weaker gel structure than F4. Gelatin B, F3, has low gel strength (225 Bloom) compared with F4 (300 Bloom). Also, as it has been mentioned above, a high Kp value correlates with a low G′ value. Finally, the electrostatic repulsion between anionic species of gelatin and anionic species of alginate in the mixture gelatin/alginate in F3 would promote the entry of water into the tablet, and consequently explain, the faster drug release from F3 tablet formulation compared with F4.

In the media that simulate the physiological pH through the gastrointestinal tract (pH GI), table 4 shows that there were no significant differences between formulations F3 and F4. These results can be explained because between pH 1 and 2 (30–180 min)

TABLE 4 **Estimation of the Different Species of Gelatin and Alginate in Media Which Simulate a pH in Gastrointestinal Transit, Using the Procedure Describe in 2.6 and 2.7**

Time		Species of gelatin B in F3, %			Species of gelatin A in F4, %			Species of alginate in F3 and F4,%	
Minutes	pH	Amphoteric	Cationic	Anionic	Amphoteric	Cationic	Anionic	Unionized	Anionic
30	1.2	0.4	99.6	0.0	0.0	100.0	0.0	99.2	0.8
60	1.3	0.4	99.6	0.0	0.0	100.0	0.0	99.1	0.9
90	1.3	0.5	99.5	0.0	0.0	100.0	0.0	99.0	1.0
120	1.5	0.7	99.3	0.0	0.0	100.0	0.0	98.6	1.4
150	1.6	1.0	99.0	0.0	0.0	100.0	0.0	98.0	2.0
180	2.0	2.5	97.5	0.0	0.1	99.9	0.0	95.2	4.8
210	5.5	98.3	1.2	0.5	66.6	33.4	0.0	0.6	99.4
240	6.1	97.9	0.3	1.7	87.6	12.4	0.0	0.2	99.8
270	6.6	94.6	0.1	5.3	95.7	4.3	0.0	0.1	99.9
300	6.8	90.9	0.1	9.1	97.5	2.5	0.0	0.0	100.0
330	7.0	86.3	0.0	13.7	98.4	1.6	0.0	0.0	100.0
360	7.1	83.3	0.0	16.6	98.8	1.2	0.0	0.0	100.0
390	7.2	79.9	0.0	20.1	99.0	1.0	0.0	0.0	100.0

the main species for gelatin and alginate for both formulations were the same (cationic for gelatin and unionized for alginate). Between pH 5.5 to 7.2 (210–390 min), alginate exists in its anionic form and the main specie for both type of gelatin is the amphoteric.

Correlation of Dissolution Data and Swelling/Erosion Properties

As it was described earlier, the erosion and swelling studies were developed in a media with a sudden pH change (pH SC), thus, the dissolution data in this media were correlated with the erosion and swelling data.

Fig. 5 shows the significant linear correlation between the dissolution data and erosion data. Instead, there is no correlation between the dissolution data and swelling data. Then, the mechanism, which controls the diltiazem release from the tablets, is the erosion of the matrix.

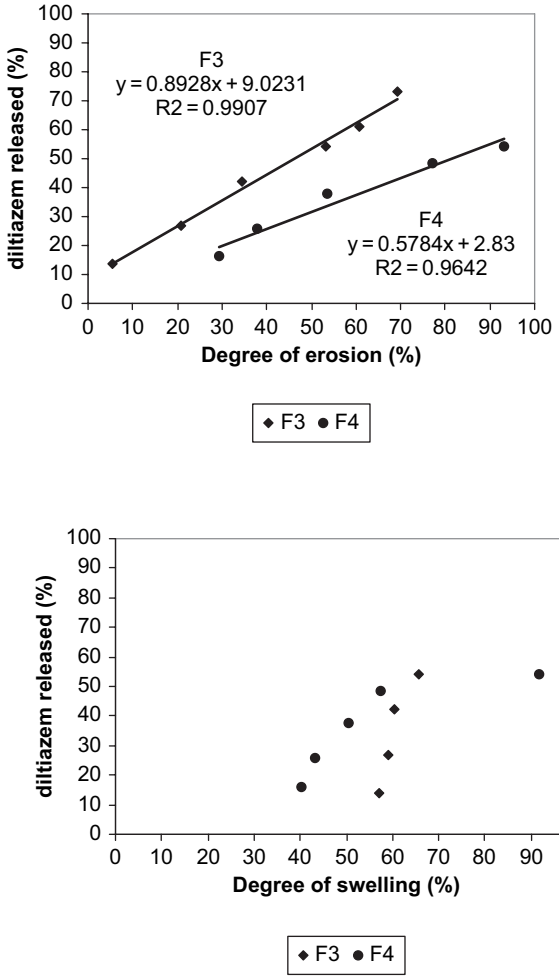

FIGURE 5 **Relationship Between (a) Diltiazem Released and Degree of Erosion and (b) Diltiazem Released and Degree of Swelling for Formulations F3 and F4 in a Media with Sudden pH Change (pH SC).**

CONCLUSION

The different behavior observed for formulations F3 and F4 could be attributed to the polyelectrolyte behavior and gel strength of both types of gelatin. In the media with sudden pH change, the higher electrostatic repulsion between anionic species of gelatin and anionic species of alginate in F3 compared with F4, could be explained by considering that the kinetics of water penetration for F3 formulation was significantly higher than F4, and also the faster drug release from F3 compared with F4. The higher degree of erosion of F3 compared with F4 could be explained by taking into account the different polyelectrolyte behavior of gelatin B, F3, and gelatin A, F4, and by the lower gel strength of gelatin B (225 Bloom) compared with gelatin A (300 Bloom) which would produce a weaker gel structure of F3 compared with F4. No differences was observed in the dissolution behavior between F3 and F4 in the pH GI because the main species for gelatin and alginate for both formulations were the same.

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REFERENCES

Brondsted, H., & Kopecek, J. (1992). pH-sensitive hydrogels. In *Polyelectrolyte Gels*; Harland, R. S., Prud'homme, R. K., Eds.; ACS Symposium Series.: Washington, pp. 285–304.

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

Das, S., & Gupta, B. (1998). Simulation of physiological ph-time profile in vitro dissolution study : relationship between dissolution rate and bioavailability of controlled release dosage form. *Drug Dev. Ind. Pharm.*, *14*, 537–544.

Dornish, M., Kaplan, D., & Skaugrud, O. (2001). Standards and guidelines for biopolymers in tissue-engineered medical products. *Ann. N.Y. Acad. Sci.*, *944*, 388–397.

Giunchedi, P., Gavini, E., Moretti, M. D., & Pirisino, G. (2000). Evaluation of alginate compressed matrices as prolonged drug delivery systems. *AAPS PharmSciTech.*, *1*, E19.

Kalyanasundaram, S., Feinstein, S., Nicholson, J. P., Leong, K. W., & Garver, R. I. (1999). Coacervate microspheres as carriers of recombinant adenoviruses. *Cancer Gene Ther.*, *6*, 107–112.

Kim, H., & Fassihi, R. (1997). Application of a binary polymer system in drug release rate modulation.1. Characterization of release mechanism, *J. Pharm. Sci., 86*, 316–322.

Kulkarni, A. R., Soppimath, K. S., Aminabhavi, T. M., Rudzinski, W. E. (2001). In-vitro release kinetics of cefadroxil-loaded sodium alginate interpenetrating network beads. *Eur J Pharm Biopharm.*, *51*, 127–133.

Liew, C., Chan, L. W., Ching, A. L., & Heng, P. W. S. (2006). Evaluation of sodium alginate as drug release modifier in matrix tablets. *Int. J. Pharm*., *309*, 25–37.

Lin, S. Y., & Ayres, J. W. (1992). Calcium alginate beads as core carriers of 5-aminosalcylic acid. *Pharm. Res*., *9*, 1128–1131.

Liu, P., & Krishnan, T. R. (1999). Alginate–pectin-poly-L-lysine particulate as a potential controlled release formulation. *J. Pharm. Pharmacol*., *511*, 41–149.

Martinsen, A., Storro, I., & Skjak-Break, G. (1992). Alginate as immobilization Material: III. Difussional properties. *Biotechnol. Bioeng*., *39*, 186–194.

Moe, S., Draget, K., Skjak-Braek, G., & Smidsrod, O. (1995). Alginates. In *Food Polysaccharides and their applications*, Stephen, A., Ed., Marcel Dekker, Inc.: New York, pp. 245–286.

Michailova, V., Titeva, St., Kotsilkova, R., Krusteva, E., & Minkov, E. (2000). Water uptake and relaxation processes in mixed unlimited swelling hydrogels. *Int. J. Pharm.*, *209*, 45–56.

Narayani, R., & Rao, K. P. (1995). Polymer-coated gelatin capsules as oral delivery devices and their gastrointestinal tract behaviour in humans. *J. Biomater. Sci. Polym. Ed*., *7*, 39–48.

Østberg, T., Lund, E. M., & Graffner, C. (1994). Calcium alginate matrices for oral multiple unit administration: IV. Release characteristics formulation in different media. *Int. J. Pharm*., *112*, 241–248.

Rose, I. P. (1990). In Kroschwitz, J. I. (Ed.) *Concise Encyclopedia of Polymer Science and Engineering* (pp. 428–430). New York: John Wiley & Sons.

Tapia, C., Corbalán, V., Costa, E., Gai, M. N., & Yazdani-Pedram, M. (2005). Study of the release mechanism of diltiazem hydrochloride from matrices based on chitosan-alginate and chitosan-carrageenan mixtures. *Biomacromolecules*, *6*, 2389–2395.

Tapia, C., Costa, E., Moris, M., Sapag-Hagar, J., Valenzuela, F., & Basualto, C. (2002). 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*, 217–224.

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

Tonnesen, H. H., & Karlsen, J. (2002). Alginate in drug delivery systems. *Drug Dev. Ind. Pharm*., *28*, 621–630.