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Drug release from carbomer:carbomer sodium salt matrices with potential use as mucoadhesive drug delivery system

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Abstract

In vitro mucoadhesion, water uptake, and drug release of nystatin (N) from matrices of carbomer (C) and lyophilized carbomer sodium salt (CNa_L) mixtures were evaluated. Matrices with different ratios C:CNa_L were prepared by direct compression. Commercial C as well as lyophilized powder (C_L) were used. In vitro mucoadhesion increased as the proportion of C in the matrix was raised. The same effect was observed when C was replaced by C_L. Matrices in which C was replaced by C_L showed an increase of both water uptake and release rates. Besides, the release of N from matrices C_L:CNa_L exhibited a kinetics with Super Case II ($n > 1$) mechanism. However, for C:CNa_L matrices, drug release was slower and exhibited a biphasic profile with a first stage characterized by either an anomalous ($n < 1$, for C $\geq$ 50%) or a Case II ($n \sim 1.0$, C $<$ 50%) mechanisms. After that period, the mechanism changed to Super Case II transport ($n > 1$).

Keywords: Drug release; Carbomer; Mucoadhesive tablets; Nystatin; Water uptake; Super Case II transport

1. Introduction

The treatment of affections of the oral cavity using conventional pharmaceutical dosage forms (solutions, lozenges, mouthwash or gels) generally shows low efficacy due to the quick decrease of drug concentration below the therapeutic range. The two main problems associated with oral cavity dosage form include: (i) discontinuation of required drug concentration in the saliva and (ii) potential side effects derived from high amounts of swallowed drug.

The design of mucoadhesive forms to retain the device in the oral cavity during the period of delivery together with a sustained release of the drug to keep it concentration within the therapeutic range is a valid approach to overcome the shortcomings of conventional treatments (Weatherell et al., 1996; Machida and Nagai, 1999). Candidiasis is one of the most common pathologies manifested in the oral cavity (Carr et al., 1996). Treatment of candidiasis requires long-term administration of antifungicidal agents so a mucoadhesive sustained release formulation could be advantageous compared to commonly used conventional pharmaceutical dosage forms. Indeed, the design of different buccoadhesive pharmaceutical dosage forms containing N (Millns and Martin, 1996), miconazole (Bouckaert et al., 1992), and fungicidal agents (Codd and Deasy, 1998) have been reported.

In a previous work, Llabot et al. (2002) described the design of a double layered mucoadhesive tablet containing N, in which the polymeric layer was composed of C and hydroxypropylmetylcelulose (HPMC)

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in a 9:1 ratio. This matrix showed good mucoadhesion and was able to release the drug in a sustained fashion with an anomalous mechanism ($n = 0.82$) (Korsmeyer et al., 1983) Nevertheless, the high proportion of C in the mixtures gave strong acid characteristics to the matrix, which could produce some side effects in the mucosa.

In the present work, we have tried to evaluate the potential usefulness of carbomer:carbomer sodium salt (C:CNa_L) mixtures as polymeric matrices for mucoadhesive/sustained drug delivery systems. In order to evaluate the systems, "in vitro" mucoadhesion, water uptake, and drug release were measured and analyzed.

2. Materials and methods

2.1. Materials

Nystatin USP (Parafarm, Buenos Aires, Argentina) and Mucin Type III partially purified from porcine stomach (Sigma, St. Louis, MO, USA). Carbomer 934P (Acritamer 934) was a gift from RITA Corporation (Woodstock, IL, USA). All chermicals and solvents used were of analytical grade.

2.2. Methods

2.2.1. Materials (polymers) attainment

Both solids (CNa_L and C_L) were prepared by dispersing C in an aqueous solution of NaOH (2 M) and distilled water, respectively. Then, dispersions were processed with a mortar and pestle to achieve a homogeneous semisolid, which was frozen and lyophilized using the Freeze Dry System Freezone 6 Labconco (Labconco Corporation, Kansas City, MI, USA). Solid materials were subjected to particle size reduction (mesh 50) with mortar and pestle to prepare the particulate material for mixing and compression.

2.2.2. Tablet formulation

Tablets were prepared by direct compression as follows. A physical blend of the polymers was mixed with mortar and pestle for 15 min. Then the mixture was compressed in a single-punch (13-mm) eccentric press (Delfabro HPH 15, San Francisco, Córdoba) under 2500 kg/cm^2 for 5 s, resulting in a 2-mm-thick tablet.

2.2.3. Water uptake

The kinetics of water uptake of matrices were evaluated by using a modified version of the apparatus described in a previous work (Llabot et al., 2002) and distilled water.

2.2.4. "In vitro" mucoadhesion test

Mucoadhesion was measured as the force needed to pull out a tablet from a mucin gel layer (30%, w/w), simulating oral mucose, with an adapted Jolly Balance (Facultad de Astronomía, Matemáticas y Física, Córdoba, Argentina) (Llabot et al., 2002). The tablets were fixed to a support with cyanoacrylate adhesive, then suspended from a spring and lowered until they just contacted the surface of the mucin, with 50 μl of distilled water placed between the tablet and mucin gel. To produce adhesion, a 20-g force was applied to the tablets for 30 s. Then, the platform was raised at 0.74 cm/s until the tablet was separated from the mucin. This point represents the adhesive bond strength between these elements. This value was expressed in N/cm^2. For each mixture, the assay was performed for five different tablets and then averaged.

2.2.5. "In vitro" drug release

Release experiments of N in water from C:CNa_L and C_L:CNa_L matrices were carried out using a US Pharmacopoeia (USP) No II dissolution apparatus (Hanson SR II 6 Flask Dissolution Test Station Hanson Research Corporation, Chatsworth, CA, USA) at 37 °C and 75 rpm with distilled water (900 ml). The tablet was fixed with a cyanoacrylate adhesive to a metallic disk placed at the bottom of the vessel. Samples were withdrawn, filtered, and measured at 306 nm with a UV-Vis spectrophotometer (Shimadzu UV 160-A, Shimadzu Corporation, Kyoto, Japan).

Table 1
Compositions of C:CNa_L matrices (CNA_L, C, C_L)

Matrix	Composition (%)		
	CNa_L	C	C_L
D_1	60	40	
D_2	60		40
E_1	50	50	
E_2	50		50
F_1	40	60	
F_2	40		60

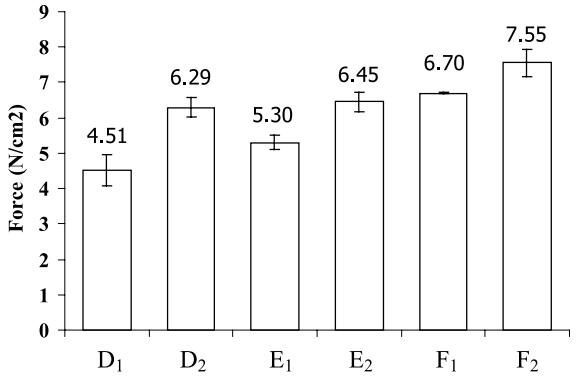

Fig. 1. "In vitro" mucoadhesion of C:CNa$_L$ matrices.

2.2.6. Data analysis

All data analysis was carried out according to Vergnaud (1993), Korsmeyer et al. (1983) and Peppas and Sahlin (1989) equations using Curve Expert program version 1.3. Linear or non-linear least squares fitting methods were used to determine the optimum values for the parameters present in each equation.

3. Results and discussion

3.1. "In vitro" mucoadhesion and water uptake

A set of C:CNa$_L$ and C$_L$:CNa$_L$ matrices, in which the composition was modified as is in Table 1, was subjected to "in vitro" mucoadhesion assays. Results shown in Fig. 1 reveal that although all matrices exhibited good "in vitro" mucoadhesion, the rise of the proportion of C or C$_L$ produces an increase in this property. Additionally, matrices containing C$_L$ instead of C exhibited higher adhesion. Thus, adhesion values

Table 2
Analysis of water uptake data from C:CNa$_L$ matrices using Eq. (1) ($W_t = kt^n$)

Matrix	k (min.$^{-n}$)	n	r^2
D$_1$	0.036	0.67	0.999
D$_1$ + N[a]	0.033	0.74	0.996
D$_2$	0.077	0.64	0.999
E$_1$	0.048	0.64	0.996
E$_1$ + N[a]	0.017	0.88	0.993
E$_2$	0.059	0.69	0.999
F$_1$	0.024	0.79	0.997
F$_1$ + N[a]	0.016	0.84	0.993
F$_2$	0.086	0.62	0.998

[a] Matrices containing N.

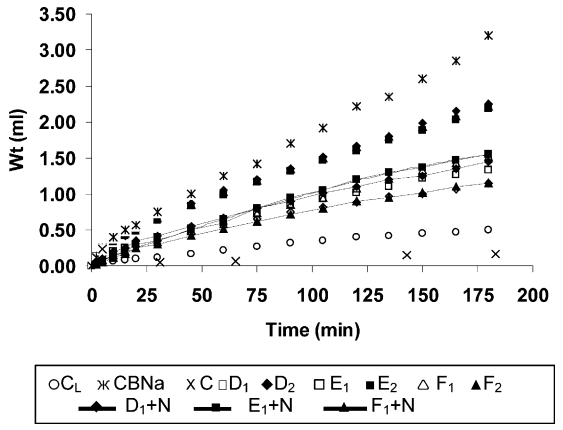

Fig. 2. Water uptake of C:CNa$_L$ matrices with N and without N.

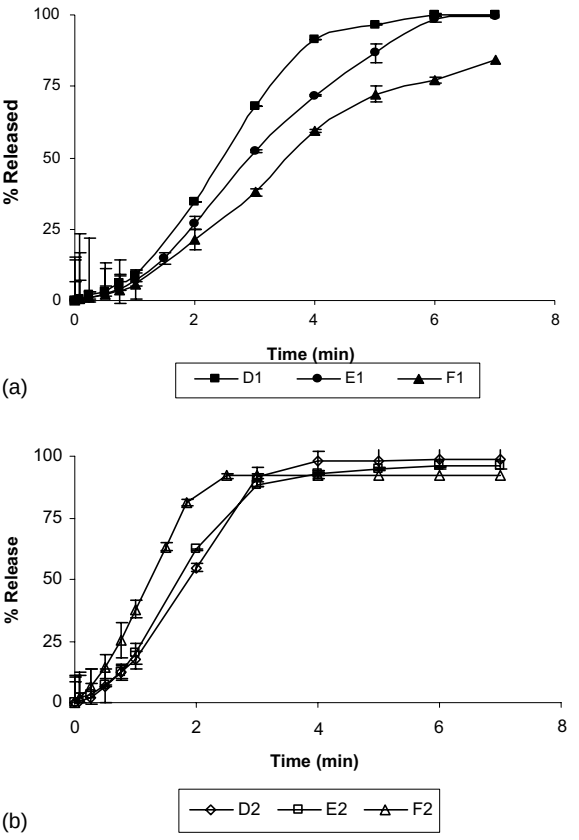

Fig. 3. N release from (a) C:CNa$_L$ and (b) C$_L$:CNa$_L$ matrices.

followed the order: F > E > D; and $F_2 > F_1$, $E_2 > E_1$, and $D_2 > D_1$. The physical state of the lyophilized material C_L could possibly facilitate and strengthen bioadhesive interactions. Results of water uptake depicted in Fig. 2 show that the binary mixture produces matrices with uptake rates highest for C:Na_L and lowest for C. Again, a key factor seems to be the physical state of C since matrices containing C_L (D_2, E_2, F_2) sorbed water at a higher rate and also exhibited greater uptake capacity than those containing commercial C. It is well-known that solid material obtained after the lyophilization present a very porous structure and a high specific surface. These characteristics facilitate the water uptake of the material (Jellinek, 1982; Fakes et al., 2000).

Variation of the proportion of C_L or C in each matrix series did not appear to produce a significant change in water uptake. On the other hand, the incorporation of N leads to a slight increase in water uptake of D_1 and E_1, while a decrease is observed for F_1.

Uptake data were also analyzed using the Vergnaud model (Vergnaud, 1993; Roy and Rohera, 2002), with the equation:

$$W_t = kt^n \qquad \text{Eq. (1)}$$

where W_t represents the amount of sorbed water (ml) at time t; k is the kinetic constant and n is proposed as an indicator of the water uptake mechanism. Table 2 shows that in all cases n lies in the range $0.62 < n < 0.88$, which is indicative of an anomalous mechanism of water uptake in which solvent diffusion, as well as polymer relaxation, are involved (Vergnaud, 1993). Incorporation of N in the matrices produced a decrease of k and an increase of n (see Table 2) indicating a lowering of polymer chain relaxation.

3.2. Drug release

Release rates of N in water from C:CNa_L and C_L:CNa_L matrices were measured and are depicted in Fig. 3. For D_1, E_1, and F_1, about 90% of N was released in 5–7 h. In line with water uptake results, C matrices (D_1, E_1, and F_1) released the drug slower than C_L ones (D_2, E_2, and F_2).

The mechanism of drug release from swellable matrices is determined by several physico-chemical phenomena. Among them, polymer water uptake, gel layer formation and polymeric chain relaxation are currently regarded as primarily involved in the modulation of drug release. Eq. (2) is currently used for the analysis of drug release process in order to categorize the predominant mechanism (Korsmeyer et al., 1983):

$$\frac{M_t}{M_\infty} = kt^n \qquad \text{Eq. (2)}$$

M_t/M_∞ is the proportion of drug released at time t, k is the kinetic constant, and the exponent n has been proposed as indicative of the release mechanism. In this context, $n = 0.5$ indicates Fickian release (diffusionaly controlled release) and $n = 1$ indicates a purely relaxation controlled delivery which is referred as Case II transport. Intermediate values indicate an anomalous behavior (non-Fickian kinetics corresponding to coupled diffusion/polymer relaxation) (Ritger and Peppas, 1987). Occasionally, values of $n > 1$ has been observed, which has been regarded as Super Case II kinetics (Ranga Rao et al., 1988; Ferrero et al., 2000; Munday and Cox, 2000).

The relative contribution of the diffusion and relaxation processes to the release mechanism can be analyzed according to the following equation (Peppas

Table 3
Analysis of release data from C:CNa_L matrices

Matrix	Eq. (2)			Eq. (3)		
	n	k (min.$^{-n}$)	r^2	k_d (min.$^{-0.46}$)	k_r (min.$^{-0.92}$)	r^2
D_1	1.30	0.055	0.9645			
D_2	1.40	0.059	0.9931	−0.038	0.010	0.9961
E_1	1.18	0.059	0.9759			
E_2	1.40	6.65E−4	0.9935	−1.49E−6	4.35E−7	0.9942
F_1	1.31	0.036	0.9704			
F_2	1.12	0.34	0.9936	−0.038	0.0149	0.9975

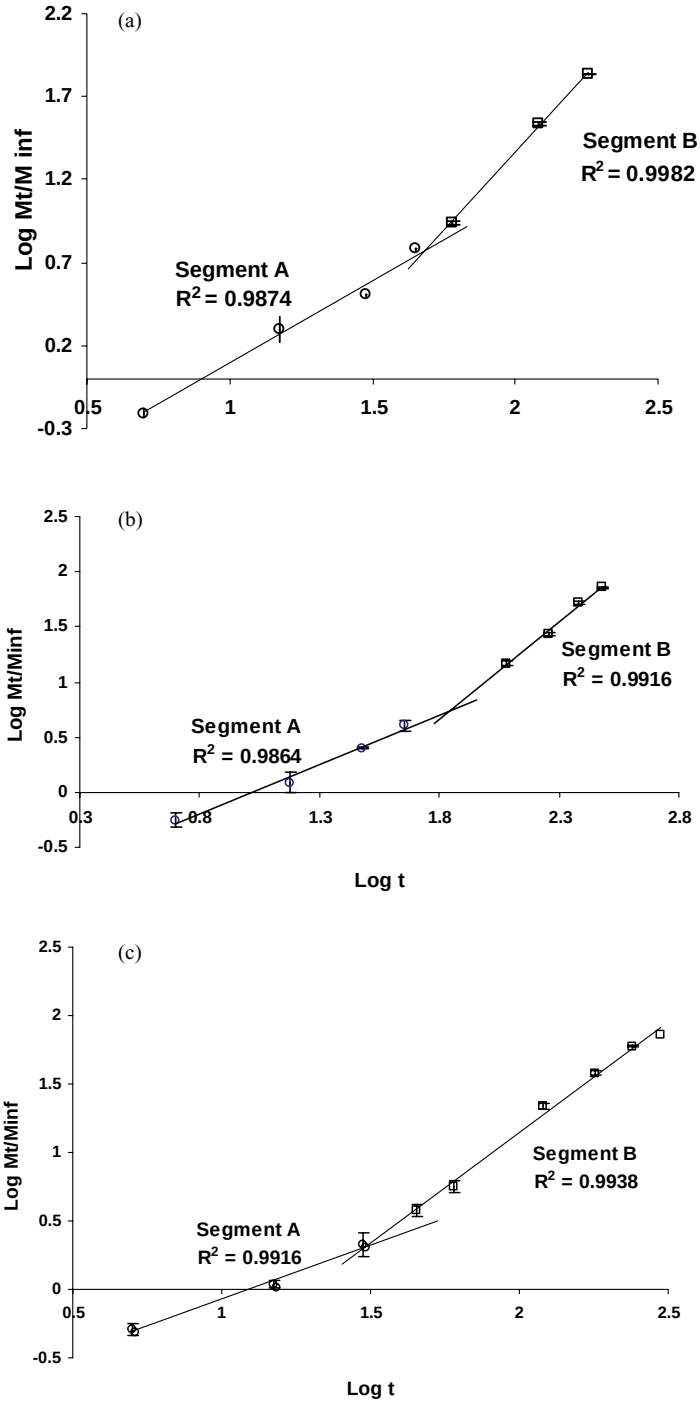

Fig. 4. Biphasic mechanism of N release from C:CNa$_L$ matrices: (a) D_1; (b) E_1; and (c) F_1 (using Eq. (2)).

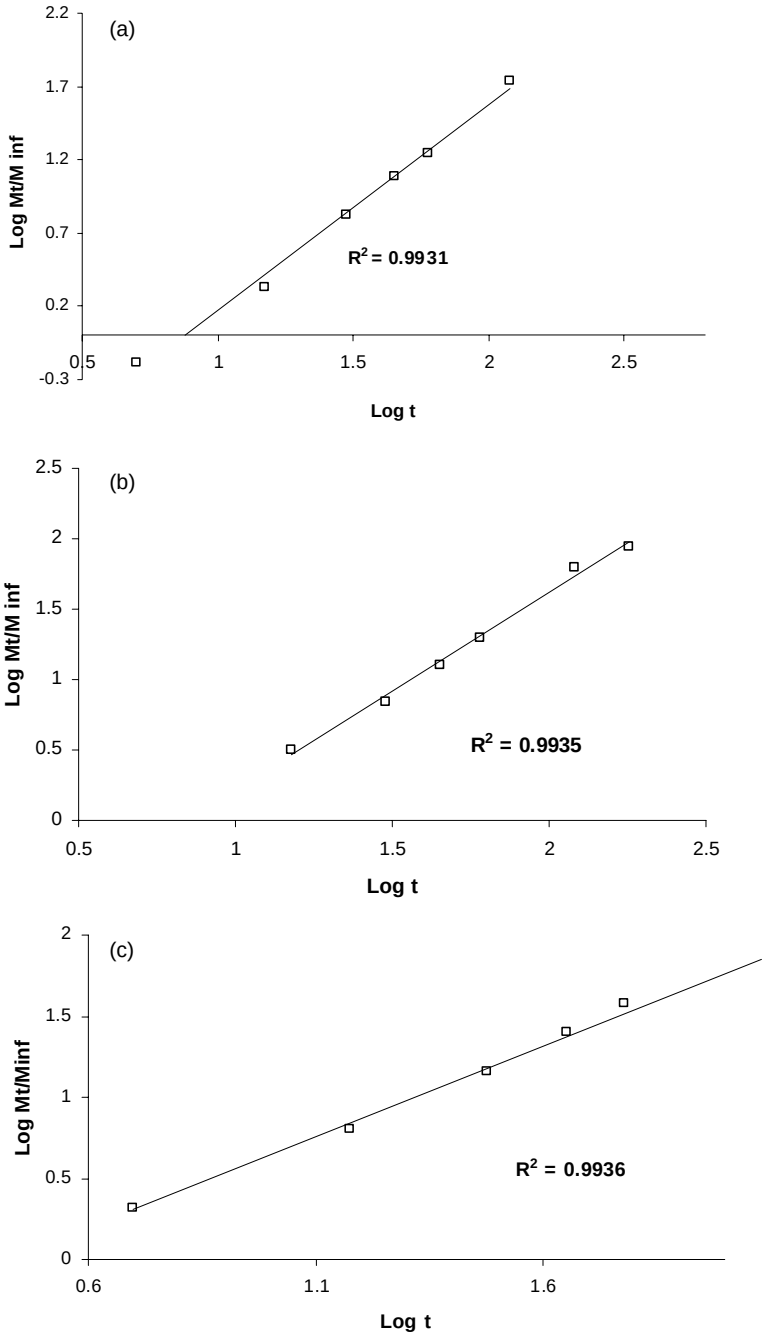

Fig. 5. N release form C_L:CNa_L matrices: (a) D_2; (b) E_2; and (c) F_2 (using Eq. (2)).

Table 4
Analysis of release data according to Fig. 4

Matrix	Segment A				Segment B			
	n[a]	K_d ($min^{-0.46}$)	k_r ($min^{-0.92}$)	r^{2}[b]	n[a]	k_d ($min^{-0.46}$)	k_r ($min^{-0.92}$)	r^{2}[b]
D_1	0.9917	−1.97E−3	1.93E−3	0.99	1.89	−5.03E−2	9.61E−3	0.99
E_1	0.8916	−9.49E−4	1.36E−3	0.99	1.77	−4.51E−2	8.35E−3	0.99
F_1	0.7857	4.56E−4	7.29E−4	0.99	1.62	−2.70E−2	7.29E−3	0.99

[a] Diffusion coefficient obtained from Eq. (2).
[b] Correlation coefficient for Eqs. (2) and (3).

et al., 1989)

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \qquad \text{Eq. (3)}$$

In which, the first term on the right is the diffusion contribution (Fickian), with a kinetic constant k_d and the second term is the relaxation contribution (Case II) with kinetic constant k_r. The coefficient m is a diffusional coefficient for a system with any shape which exhibits controlled release. In this paper, all matrices present an aspect ratio of 6, which corresponds to $m = 0.46$ Peppas and Sahlin (1989). N release data from C:CNa_L matrices were processed according to Eq. (2), while those of C_L:CNa_L were analyzed using both Eqs. (2) and (3). The results are summarized in Table 3.

Release rates from C_L matrices (D_2, E_2, and F_2) showed a good fit with both equations, with n value higher than 1 that reveals a Super Case II transport. This mechanism could result from an increased plasticization at the relaxing boundary (gel layer) (Ritger and Peppas, 1987). This type of transport has also been reported by other authors (Ranga Rao et al., 1988; Ferrero et al., 2000; Munday and Cox, 2000).

On the other hand, release rates from C matrices (D_1, E_1, and F_1) exhibited poor adhesion to Eq. (2). Inspection of the plots of Fig. 4 ($\log M_t/M_\infty$ versus $\log t$) reveals a break point in which the slope clearly changes to a higher value in all cases.

Release data corresponding to the first segment (A) and to the second (B) for D_1, E_1, and F_1 were separately analyzed using Eqs. (2) and (3). The results that are shown in Table 4 suggest that the release mechanism clearly changes during the course of delivery. In the first stage, a diffusion/relaxing combination (anomalous transport) for systems E_1 and F_1, and pure relaxation (Case II) for D_1 would modulate the release. After the break point, in the three matrices, the release mechanism changes to Super Case II as it is quantitatively reflected by their n values higher than 1. Conversely, negative values for k_d should be interpreted in terms of a non-significant diffusion process compared to the relaxation mechanism (Ferrero et al., 2000). In this way, the N release seems to be regulated through polymer relaxation ($k_r \gg k_d$).

The values for $n > 1$ (Super Case II transport) would be the consequence of a plasticization process in the gel layer (Ritger and Peppas, 1987) arising from a reduction of the attractive forces among polymeric chains that increases the mobility of macromolecules. If the drug has to diffuse through the matrix, the polymeric chains must first arrange (relax) to allow the diffusion process. In this way, the chain mobility is decisive for drug transfer kinetic, so diffusion rate increases with increase in relaxation rate of polymeric chains (Siepmann et al., 1999).

The change in delivery mechanism observed with matrices D_1, E_1, and F_1 would be associated with a concentration dependent plasticization effect of N. So, the concentration of the drug in the hydrogel layer should increase with time to reach a critical value that produces the break point.

With D_2, E_2, and F_2 this phenomenon was not observed because these systems behave as plasticized polymeric matrices from the beginning of the delivery process, owed principally to the high initial rate of water uptake and relaxation (see Fig. 5).

4. Conclusions

The C:CNa_L matrices showed “in vitro” mucoadhesive properties, high water uptake and were able to modulate the release of N. These properties may be modulated by changing the polymer ratio in the matrix. The physical state of the C has a direct influence over water uptake and mechanism of drug release.

Matrices containing C_L showed higher water uptake rate, greater uptake capacity, and faster release of N in a sustained fashion (90% in 3 h), with a Super Case II transport mechanism ($n > 1$). The increase in proportion of C in the matrix yielded a decrease in the drug release rate. These systems also showed a biphasic release mechanism. During the first stage of the release, an anomalous mechanism for E_1 and F_1 ($n < 1$); and Case II for D_1 ($n \sim 1.0$) were observed. After this period, the release changes to a Super Case II mechanism ($n > 1.0$), where a process of plasticization occurs due to N dissolution. In this way, the C:CNa_L matrices could be useful for the design of antimycotic mucoadhesive tablets, being the most promising the matrices containing higher proportions of C (F_1), which showed good mucoadhesion and sustained release of N.

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