Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 257 (2003) 253–264
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Effect of varying the restriction degree of 4-aminopyridine release from HPMC matrices on the mechanism controlling the process

Ilona Martínez-González, Leopoldo Villafuerte-Robles*

Departamento de Farmacia de la Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional de México, Carpio y Plan de Ayala s/n, Col. Santo Tomas, C. P. 11340 D.F. México, Mexico

Received 7 June 2002; received in revised form 14 February 2003; accepted 14 February 2003

Abstract

Among different technological variables that influence drug release from hydrophilic matrices, different proportions of the polymer and a water-soluble excipient have been used to control the drug release properties. These variables were used to modify the drug release rate and to examine its effect on the mechanism controlling the process. Tablets of the model drug 4-aminopyridine (4-AP) were prepared varying the matrix proportion of hydroxypropyl methylcellulose (HPMC) and citric acid (CA). The matrices release behavior (USP apparatus 2, paddle, at 50 rpm) was examined using 0.1N HCl and 0.2 M phosphate buffer as dissolution media. Dissolution curves were described by $M_t/M_{inf} = kt^n$, applied separately for each dissolution medium. The increase of the HPMC matrix content reduced the release rate of the drug. The release mechanism showed a linear trend toward higher n values with a continuous reduction of drug release. The addition of increasing proportions of CA produced the opposite. An increasing drug release rate produced logarithmic decreasing n values. The results demonstrate, as a general rule, that every restriction of the drug release rate is associated with increasing values of the mechanism-indicating exponent n. This relationship means a logarithmic movement away from a release mechanism controlled by diffusion toward a mechanism controlled by relaxation, erosion and dissolution of the polymeric matrix as the drug release rate is restricted. These results are attributed to an increasing hydration and dissolution of the polymeric matrix, as the drug release is subject to limitation.

Keywords: Sustained release; 4-Aminopyridine; Dissolution restriction; HPMC; Release mechanism

1. Introduction

In recent years, hydrophilic matrices are becoming very popular in controlling the release of soluble drugs from solid dosage forms. The properties of the gelling agent are the element in the formulation that is most responsible for the formation, by hydration, of a diffusion and erosion-resistant gel layer (Vazquez et al., 1992). The most widely used polymer for hydrophilic matrices is hydroxypropyl methylcellulose (HPMC). This polymer is considered among the water-soluble polymers (Rowe, 1984). A further point to consider is relative to the possible effects of interactions between the polymer forming the matrix and admixed excipients and drugs.

The effect of adding non-polymeric excipients to a polymer matrix brings about marked increases in the release rate of hydro-soluble active principles if the excipients are soluble like lactose and less important increases if the excipient is insoluble like tricalcium phosphate (Lapidus and Lordi, 1968; Holgado et al.,

* Corresponding author. Fax: +52-5396-3503.
E-mail address: lvillaro@encb.ipn.mx (L. Villafuerte-Robles).

0378-5173/03/$ – see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0378-5173(03)00150-9

1995; Espinoza and Villafuerte, 1999). However, the effect of adding non-polymeric excipients (soluble and insoluble) was not always demonstrated (Veiga et al., 1997). The release profile of theophylline from hydrophilic HPMC matrices stayed unchanged when lactose and tricalcium phosphate were added at concentrations of 11 and 22%.

In drug delivery systems of the matrix-type, it is visualized that the drug solids in the layer closer to the surface of the device are the first to elute, and when this layer become exhausted, the drug solids in the next layer then begin to be depleted. The thickness of the depletion zone becomes greater and greater as more drug solids elute out of the device. At a very early stage of the drug release process, only a small amount of drug has been released and the thickness of the depletion zone is so small that the drug system produces a constant drug-release profile. If the magnitude of the thickness of the depletion zone, after a finite time, becomes substantially large, a matrix diffusion-controlled process becomes the predominant step in the mechanism of drug release from a polymer matrix. The cumulative amount of drug released becomes directly proportional to the square root of time (Chien, 1982).

The drug release from swellable and erodible hydrophilic matrices involves several events. As the matrix comes in contact with the dissolution medium, the polymer undergoes a relaxation process and two fronts are established around the matrix. At the penetration front, the hydration, swelling and coalescence of polymer particles occurs, whereas at the dissolution front, polymer chain disentanglement and dissolution of the hydrated matrix occurs. The gel layer thickness, which determines the diffusional path length of the drug, corresponds to the distance between the penetration and dissolution fronts (Sung et al., 1996). Polymer dissolution occurs because at the gel matrix-diffusion layer interface chain entanglement becomes so weak that the matrix can no longer hold polymer chains together. Thus, polymer dissolution takes place at this interface (Ju et al., 1995).

Drug release from this type of matrices is attributed to polymer hydration and dissolution (relaxation/erosion mechanism) and to drug diffusion through the gel layer (diffusion mechanism) or a combination of both.

As the swelling process proceeds, the gel layer gradually becomes thicker resulting in progressively slower drug release rates that in certain proportion can be compensated with increased porosities of the gel layer. On the other hand, the continuous polymer hydration results in gradually increased polymer release rates, decreasing the depletion zone and increasing the dissolution rate. The contribution of both above mentioned processes determine the actual release mechanism.

Particularly, the HPMC release profiles are convex shaped. This indicates that the polymer dissolution rate increases with time (Sung et al., 1996). This means that the greater the time for polymer hydration, the greater the polymer dissolution rate. This allows the expectation that the relaxation and erosion of the matrix influence the release mechanism in a greater extent as the time to release the drug is prolonged. It takes more time to release a given drug quantity as the release rate decreases, giving opportunity for a greater matrix hydration, relaxation and erosion before this quantity of drug is released.

The mechanism of drug dissolution could be moved in the direction of apparent zero-order kinetics through the restriction of the drug release (Vigoreaux and Ghaly, 1994). The restriction is understood as the act of subjecting to limitation the drug release. For a given swellable hydrophilic polymer matrix, a shift from a diffusion controlled drug release toward a relaxation/erosion controlled process could be obtained reducing the drug solubility or increasing the time for the drug to go through the matrix. The time to go through the matrix increases by increasing the diffusion path length or decreasing the drug diffusivity through the matrix. Soluble drugs, releasing from HPMC matrices, showed n values of about 0.67 while insoluble drugs showed n values about 0.86 (Ford et al., 1987). The restriction of drug release from HPMC matrices that dissolve in 0.1N HCl has been found to shift the release mechanism from diffusion ($n = 0.66$) toward relaxation/erosion ($n = 0.89$) (Martínez-González and Villafuerte-Robles, 2003). This occurs through addition of different proportions (2–9%) of an insoluble excipient, enteric citric acid (CA). Other release restriction alternatives include the obstruction of the matrix water acquisition (Vigoreaux and Ghaly, 1994).

The model drug used in this study is 4-aminopyridine (4-AP). This drug has been found to improve the

conduction of nerve impulses, in this manner, alleviating symptoms in multiple sclerosis patients. Moreover, this drug is used in spinal cord injured individuals to increase motor control and sensory ability and to reduce chronic pain and spasticity (Hansebout and Blight, 1996). 4-Aminopyridine has also been found to improve the mental functions in patients with Alzheimer's disease (Masterson and Myers, 1996). The oral daily dose of 4-AP for humans treatment is variable and between 10 and 30 mg (Segal and Brunnemann, 1997). Instead of 4-AP, its hydrochloride and its sulfate have been used before (Reynolds, 1982).

The purpose of this work is the verification of the relationship of a progressive restriction of drug release from a swellable hydrophilic matrix with the mechanism controlling the process, no matter which variables are moved. This circumstance is considered as a way to transform diffusion controlled processes into apparent zero-order release kinetics. The release restriction in this case obtained through increasing the matrix polymer proportion and the matrix size and decreasing the matrix content in a water-soluble excipient such as citric acid.

2. Materials and methods

2.1. Materials

The pharmaceutical excipients Metolose 90SH-4000SR (Shin-Etsu Chemical Co., Ltd.), a brand of hydroxypropyl methylcellulose (HPMC) obtained from Nutrer-Mexico, anhydrous citric acid USP (CA) obtained from Helm-Mexico and the experimental drug, 4-aminopyridine (4-AP) obtained from ICN Biochemicals Inc., were used as received.

2.2. Methods

2.2.1. Matrix preparation

To restrict progressively the 4-AP release through increasing the diffusion path length, different size and different composition matrices were produced with increasing polymer content. HPMC was used to produce matrices containing 20 mg 4-AP loading and six different HPMC quantities ranging from 50 to 400 mg.

To restrict progressively the 4-AP diffusivity through the matrix, HPMC matrices with a constant weight were produced containing decreasing proportions of CA from 50 to 5%. It is assumed that decreasing proportions of this water-soluble excipient produce lower matrix porosities restricting drug diffusivity. Mixtures with seven different HPMC/CA ratios were used to obtain matrices with two different constant weights, 200 and 300 mg. The powders (10 g) were mixed in a twin shell blender during 20 min at 22 rpm and then manually granulated with water (1–5 ml), kneading 15 min. The wet mass passed through a number 14 sieve. The granules were dried for 4 h at 40 °C. Tablets were prepared by compression of the granules for 20 s in a hydraulic press with 8-mm flat faced punch and die, at a compaction pressure of 55 MPa. No lubricant was used in the tablets.

2.2.2. Dissolution methodology

Dissolution studies were carried out at 37 °C and 50 rpm, with the USP dissolution apparatus II (paddle method) (Hansen Research) in 900 ml dissolution medium. For the first 3 h, the dissolution medium was 0.1N HCl and then, in a second vessel, for the following 5 h, the medium was phosphate buffer pH 7.4. The release profiles of 4-AP show the accumulated drug dissolved from each vessel at every time. A wide stainless spiral was used to avoid floating of the tablets but allowing tablet swelling.

Samples (3.0 ml) were withdrawn at predetermined time intervals, filtered, diluted with 10 ml of 0.1N HCl and analyzed spectrophotometrically at a wavelength of 261 nm (Beckman DU-650 spectrophotometer). The final dilution with 0.1N HCl was used to keep constant the absorption pattern of the drug molecule. The withdrawn dissolution medium (3.0 ml) was considered to calculate the amount of drug dissolved. Dissolution studies were performed with three individual tablets of each different batch. The results for each time point of the three different dissolution curves are registered as an average in the figures. The average of each time point was used to calculate the regression parameters of each dissolution curve representing a given formula or dissolution conditions.

The solubility of 4-AP in 0.1N HCl was determined as 95 mg/ml while in phosphate buffer was smaller, 78 mg/ml. The solubility in both media is high enough to consider the dissolution of tablets containing 20 mg in 900 ml under sink conditions.

3. Results and discussion

3.1. Release of 4-aminopyridine from HPMC/CA matrices

Release data from swellable systems can be analyzed according to the power law expression shown in Eq. (1). The kinetics and mechanism of drug release for each system was investigated by fitting the release data into this equation (Mandal, 1995; Vigoreaux and Ghaly, 1994):

$$\frac{M_t}{M_{inf}} = kt^n \quad \text{or} \quad \ln\left(\frac{M_t}{M_{inf}}\right) = n\ln(t) + \ln(k) \qquad (1)$$

The terms in this equation are as follows: M_t, the amount of drug released at time t; M_{inf}, the total drug released over a long time period; k, the kinetics constant; and n, the mechanism of drug release. The value of n ranges from 0.5 ($t^{1/2}$ dependence, generally referred to as Fickian release) to 1 (representing the case-II transport which is purely relaxation controlled). The values in between indicate an anomalous behavior corresponding to coupled diffusion/relaxation. When the value of n is greater than that of the case-II transport ($n > 1.0$), the release is said to be Super case-II transport (Brazel and Peppas, 2000; Ranga Rao et al., 1988). In the case of a matrix with cylinder form, n is said to be 0.45 instead of 0.5 and 0.89 instead of 1.0 (Kim and Fassihi, 1997).

Examples of release profiles of 4-AP from different size and different composition matrices containing different HPMC proportions as well as from matrices added of CA are depicted in Fig. 1. Fitting dissolution data into Eq. (1) produced straight lines for data corresponding to drug release up to 3 h and for data from 3 to 8 h (Fig. 1). Matrices with low HPMC content, that is, 50 mg per tablet, dissolved totally in 0.1N HCl while matrices with a higher HPMC content dissolved partially in both media. The change of pH after 3 h slowed down the release rate, changing the release profile. It is clearly a decrease in the 4-AP release rate when the pH of the medium was changed from 0.1N HCl to pH 7.4. This change in dissolution rate is greater than that expected for dissolution at a constant pH. This is attributed to the change in solubility of 4-AP. This could be accounted for by

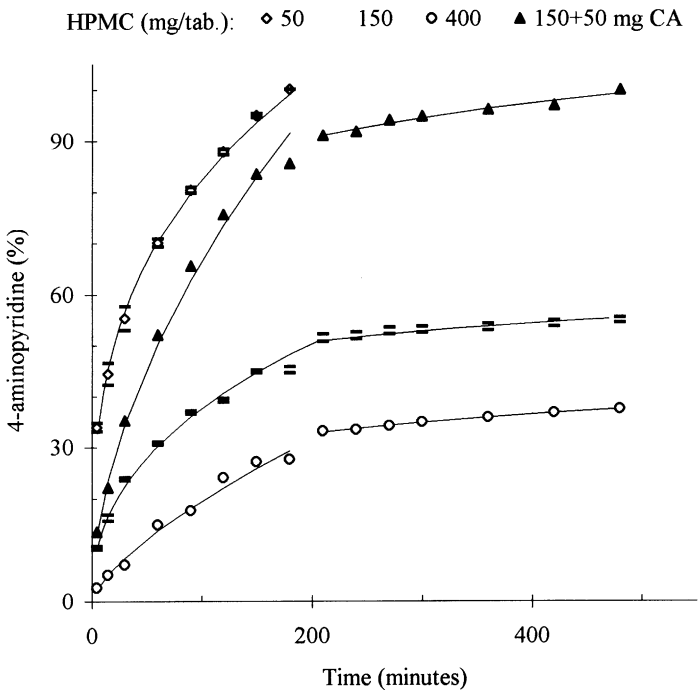

Fig. 1. Release profile of 4-AP (20 mg) from different size and different composition HPMC/CA matrices. Matrices that dissolve first in 0.1N HCl and thereafter in phosphate buffer pH 7.4. Experimental points, standard deviation and calculated regressions.

Table 1
Regression parameters of 4-AP dissolution curves from HPMC matrices, in their first part, using 0.1N HCl as dissolution medium and time up to 3 h

HPMC (mg per tablet)	Slope (n)	Intercept	r^2	k
50	0.30965	−1.61748	0.994	0.19840
100	0.41954	−2.97590	0.989	0.05100
150	0.42627	−2.94160	0.990	0.05278
200	0.38203	−2.64490	0.554	0.07101
300	0.69935	−4.84360	0.998	0.00788
400	0.70044	−4.86560	0.989	0.00771

$\ln(M_t/M_{inf}) = \ln(k) + n\ln(t)$, $k = 10.213 \times 1/\text{HPMC} - 0.0161$, $r^2 = 0.889$; $n = 0.0012 \times \text{HPMC} + 0.2535$, $r^2 = 0.837$.

the conversion of the 4-AP hydrochloride to the less soluble 4-AP free base, after the change in pH. The titration of 4-AP with HCl shows an inflexion point at a pH of 7.0, assuming that it corresponds with the most probably formed hydrochloride. The effect of this change in solubility is a decrease of the diffusion rate of 4-AP through the gel barrier. Loading of CA to a matrix containing the drug and HPMC increases importantly the release rate although maintaining unchanged the release pattern. This can be seen comparing the release profile of matrices containing 150 mg HPMC with and without 50 mg CA (Fig. 1).

3.2. Effect of release restriction on the release profile of 4-AP from HPMC matrices

The increase of HPMC, while keeping constant the matrix 4-AP content (20 mg per tablet), affected significantly the release process. Tables 1 and 2 show the regression parameters of release curves of matrices that dissolve in 0.1N HCl and in phosphate buffer pH 7.4, respectively. Eq. (1) was applied separately for each set of data from different dissolution media.

Fig. 2 shows the relationship between the exponents indicative of the release mechanism (n) and the matrix HPMC content. The exponent n values of the release profiles in 0.1N HCl (Table 1) and those obtained from phosphate buffer (Table 2) show a linear trend to increasing values as the HPMC matrix content increases. The increasing release restriction, given by increasing matrix HPMC proportions, changes the release mechanism from diffusion toward a relaxation/erosion-controlled process. The exponent n values of release profiles of matrices releasing the drug in phosphate buffer are higher. This can be attributed to hydration of the matrix for 3 h before the dissolution at pH 7.4 began and to the lower drug content in the matrix at this point.

Fig. 3 shows the magnitude of the 4-AP release restriction produced by increasing matrix HPMC proportions in both 0.1N HCl and phosphate buffer pH 7.4. The results are attributed to an increased tortuosity and a longer diffusional path length. The potential contribution to such an effect due to a measured increase in the diffusional path length (Baveja et al., 1987; Ford et al., 1985) and measured changes in surface areas of matrices because of the increased polymer content are not explicitly considered in the analysis; however, they are qualitatively used to restrict drug release rates.

Table 2
Regression parameters of 4-AP dissolution curves from HPMC matrices, in their second part, using phosphate buffer pH 7.4 as dissolution medium and covering the time from hour 3 to hour 8

HPMC (mg per tablet)	Slope (n)	Intercept	r^2	k
100	0.45978	−3.78620	0.952	0.022682
150	0.52439	−4.89320	0.974	0.007497
200	0.52757	−4.81410	0.956	0.008115
300	0.54164	−5.26830	0.851	0.005152
400	0.75783	−6.61930	0.989	0.001334

$\ln(M_t/M_{inf}) = \ln(k) + n\ln(t)$, $k = 2.5759 \times 1/\text{HPMC} - 0.0052$, $r^2 = 0.894$; $n = 0.0008482 \times \text{HPMC} + 0.3672$, $r^2 = 0.805$.

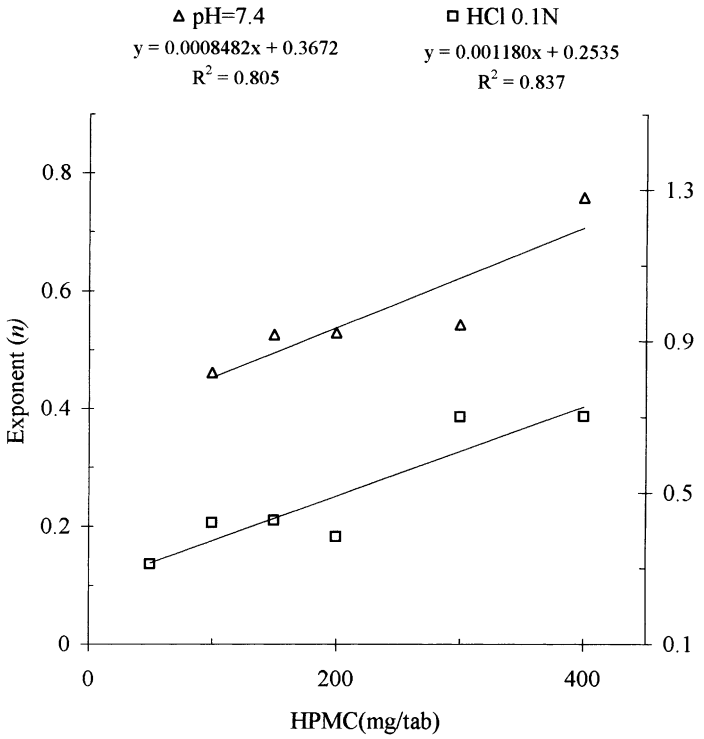

Fig. 2. Effect of the HPMC proportion on the exponent indicating the release mechanism (*n*) of release curves of 4-AP (20 mg) matrix tablets.

Fig. 4 shows the calculated response surface for the 4-AP release from HPMC matrices that dissolve in 0.1N HCl, as a function of the time and the matrix polymer content. As can be seen, the drug release rate and the degree of curvature of the release profile decrease as the polymer content of the matrix increases. Every restriction of 4-AP release is associated with an extended time of matrix exposition to the dissolution medium in order to release a given quantity of the drug. Consequently, every release restriction is associated to a higher degree of matrix hydration and a greater contribution of the matrix relaxation/erosion process to the predominant release mechanism. The hydration process of swellable hydrophilic matrices, as a function of time of exposure to an aqueous environment, involves progressively swelling, swelling/erosion and disentanglement/dissolution. Swelling or hydration of the polymer matrix occurs at a rate that is mainly a function of matrix composition and dissolution medium penetration into the matrix (Kim and Fassihi, 1997).

3.3. Effect of release restriction on the release profile of 4-AP from HPMC/CA matrices

Matrices loading with CA in the range of 5–50%, while keeping the drug and the matrix total weight constant (200 mg), affected the 4-AP release process (Tables 3 and 4), although in a lower extent than the increasing HPMC proportions. Decreasing proportions of CA in the matrix tablets restrict the 4-AP release rate (Fig. 5). The release constant values decrease linearly with a decreasing CA loading of the matrix tablets. This occurs when the matrices release 4-AP in 0.1N HCl as well as in phosphate buffer pH 7.4. Matrices with higher CA proportions (35 and 50%) dissolve fast completely the total drug content in 0.1N HCl. In these cases no drug was left to determine dissolution characteristics at pH 7.4. The effect of CA to speed drug dissolution is attributed to a loosening of the matrix structure through an increased porosity created after its dissolution and release. This process increases the porosity and reduces the tortuosity of

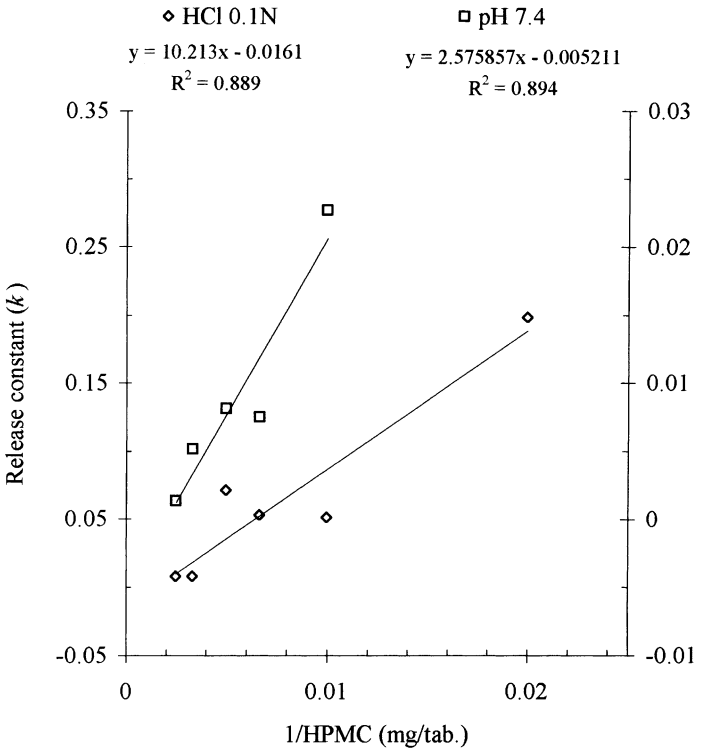

Fig. 3. Effect of the HPMC proportion on the release constant (k) of matrices of 4-AP (20 mg). Experimental points and regression lines.

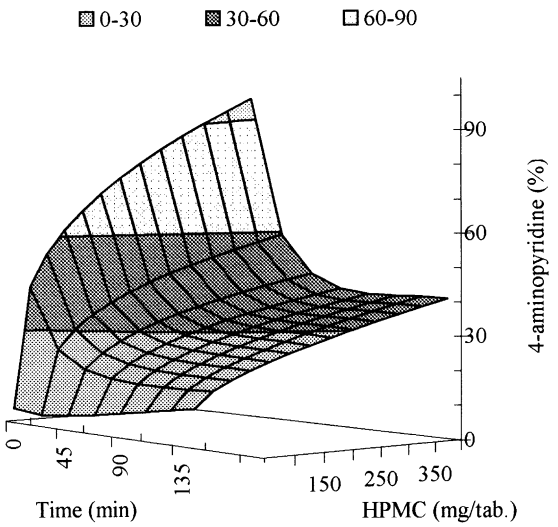

Fig. 4. Calculated response surface for the 4-AP (20 mg) release from different size HPMC matrices that dissolve in 0.1N HCl.

the diffusional path, withdrawing the original release restriction imposed by the HPMC gel layer.

The exponent n values increase logarithmically with the increasing release restriction imposed by decreasing proportions of CA in the matrix (Fig. 6). Table 3 summarizes release data corresponding to the 4-AP dissolution in 0.1N HCl that indicate an anomalous

Table 3
Regression parameters of 4-AP dissolution curves from HPMC/CA matrices (200 mg), in their first part, using 0.1N HCl as medium and time up to 3 h

CA (%)	Slope (n)	Intercept	r^2	k
5	0.57631	−3.42562	0.993	0.03253
10	0.57160	−3.29445	0.993	0.03709
15	0.55114	−3.21535	0.975	0.04014
20	0.54397	−3.09713	0.988	0.04518
25	0.54240	−2.90443	0.996	0.05502
35	0.54038	−2.83017	0.988	0.05900
50	0.53291	−2.61919	0.993	0.07286

$\ln(M_t/M_{inf}) = \ln(k) + n\ln(t)$, $k = 0.0009078 \times CA + 0.02808$, $r^2 = 0.981$; $n = -0.0203\ln(CA) + 0.6102$, $r^2 = 0.920$.

Table 4
Regression parameters of 4-AP dissolution curves from HPMC/CA matrices (200 mg), in their second part, using phosphate buffer pH 7.4 as dissolution medium and covering the time from hour 3 to hour 8

CA (%)	Slope (n)	Intercept	r^2	k
5	1.36167	−9.64833	0.936	0.0000645
10	1.08307	−7.49964	0.926	0.0005533
15	1.05978	−7.27098	0.925	0.0006954
20	1.10941	−6.95204	0.941	0.0009567
25	1.03317	−6.30401	0.893	0.0018290

$\ln(M_t/M_{inf}) = \ln(k) + n\ln(t)$, $k = 0.00007865 \times CA - 0.0003599$, $r^2 = 0.913$; $n = -0.1803\ln(CA) + 1.5923$, $r^2 = 0.744$.

transport for all cases. There is a logarithmic tendency to modify the release mechanism from diffusion toward relaxation/erosion as the release restriction increases. This increasing release restriction is imposed by a decreasing CA loading of the matrix. Matrices with a decreasing release restriction (increasing matrix proportions of CA) exhibit drug release profiles with a trend toward a diffusion-controlled process. This may be attributed to a faster penetration of the water front facilitated by CA dissolution. The consequence of this would be an earlier or faster hydration and establishment of a looser gel barrier as the CA content increases. Matrices with greater release restrictions, because of swelling restrictions like those with lower CA proportions, exhibit a shift towards drug release by a mechanism predominantly based on relaxation (Vigoreaux and Ghaly, 1994).

Table 5
Regression parameters of 4-AP dissolution curves from HPMC/CA matrices (300 mg), in their first part, using 0.1N HCl as medium and time up to 3 h

CA (%)	Slope (n)	Intercept	r^2	k
5	0.7695	−4.4521	0.996	0.01165
10	0.7365	−4.2273	0.981	0.01459
15	0.6894	−4.0968	0.983	0.01663
20	0.6084	−3.6414	0.996	0.02622
25	0.5802	−3.2073	0.998	0.04047
35	0.5765	−3.1134	0.972	0.04445
50	0.5745	−3.1076	0.982	0.04471

$\ln(M_t/M_{inf}) = \ln(k) + n\ln(t)$, $n = -0.1005\ln(CA) + 0.9394$, $r^2 = 0.89$; $k = 0.0008585CA + 0.008764$, $r^2 = 0.82$.

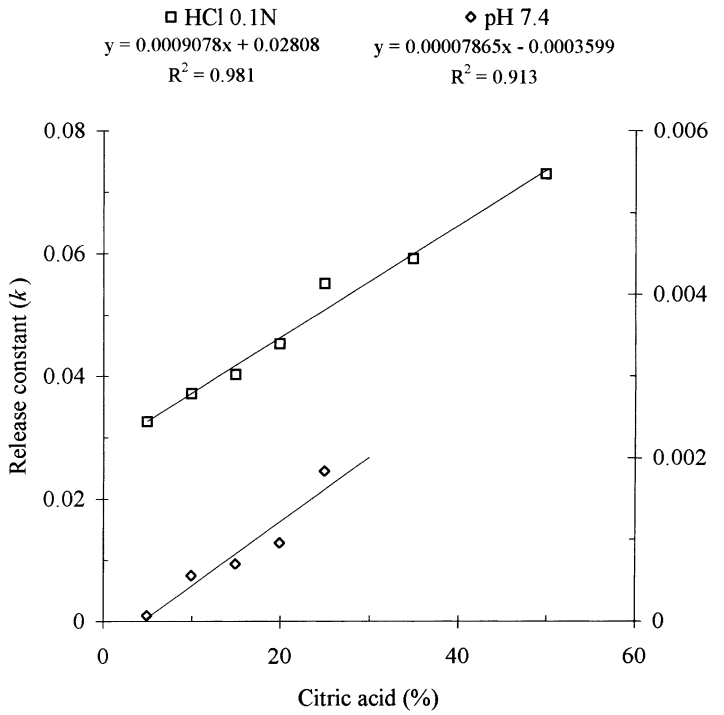

Fig. 5. Effect of CA proportion on the release constant (k) of 20 mg 4-AP from 200 mg-HPMC/CA matrices that dissolve first in 0.1N HCl and thereafter in phosphate buffer pH 7.4.

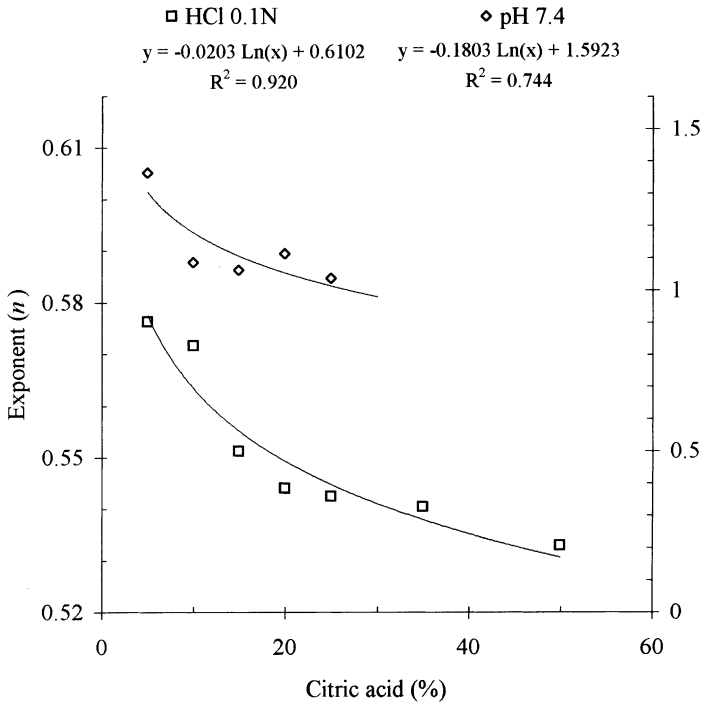

Fig. 6. Effect of CA on the exponent indicating the release mechanisms (n) of 20 mg 4-AP from 200 mg-HPMC/CA matrices that dissolve first in 0.1N HCl and thereafter in phosphate buffer pH 7.4.

Matrices that dissolve in phosphate buffer (Table 4) exhibit release profiles closer to apparent zero-order kinetics because of the higher matrix hydration. This higher matrix hydration was obtained by matrices maintained for 3 h in 0.1N HCl prior to drug release in phosphate buffer began.

Fig. 7 shows the calculated response surface for 4-AP dissolution as a function of time and the matrix CA content. This surface discloses the range of possibilities of modulating the sustained release of 4-AP from 200 mg matrices made of HPMC with different proportions of CA, when dissolved in 0.1N HCl.

Similar statements, as above-mentioned, can be applied to 4-AP release from 300 mg HPMC/CA matrices. As can be seen in Tables 5 and 6, the bigger matrix size (300 mg), for a given drug quantity (20 mg), produces a greater release restriction. This means higher exponent n values and corresponding smaller release constant values. Fig. 8 depicts the 4-AP release from HPMC/CA matrices, as a function of time and CA proportion. The higher drug release restriction obtained with 300 mg matrices allows a

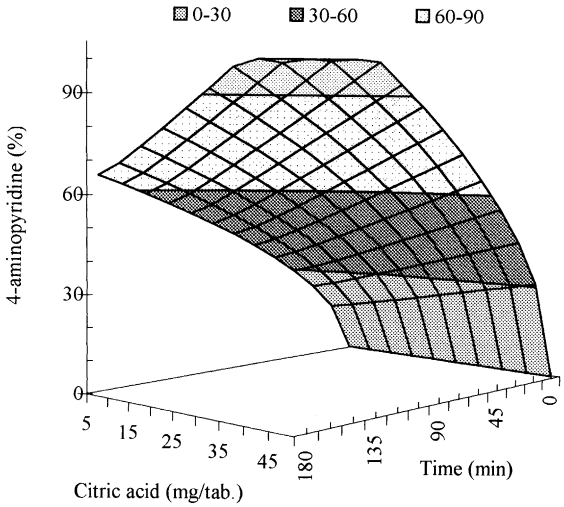

Fig. 7. Calculated response surface for the 4-AP (20 mg) release from 200 mg HPMC matrices containing different proportions of CA, matrices dissolving in 0.1N HCl.

Table 6
Regression parameters of 4-AP dissolution curves from HPMC/CA matrices (300 mg), in their second part, using phosphate buffer pH 7.4 as dissolution medium and covering the time from hour 3 to hour 8

CA (%)	Slope (n)	Intercept	r^2	k
5	2.6704	−17.8216	0.902	1.820E − 08
10	2.5273	−16.8002	0.901	5.056E − 08
15	2.4497	−16.1089	0.900	1.009E − 07
20	1.4809	−10.3862	0.932	3.086E − 05
25	1.4127	−9.0670	0.977	1.154E − 04

$\ln(M_t/M_{inf}) = \ln(k) + n\ln(t)$, $n = -0.8191\ln(CA) + 4.211$, $r^2 = 0.730$; $k = 0.000005232CA + 0.00004919$, $r^2 = 0.685$.

better analysis of the CA loading effect on the 4-AP release rate and the mechanism controlling the release process. Fig. 8 shows a lower release rate associated to a smaller degree of curvature of the 4-AP release profiles with a decreasing CA loading.

3.4. Effect of the drug release restriction on the mechanism controlling the release process

Every restriction of drug release obtained through a change in the matrix CA content, through an increase in the total polymer content or through a change in drug solubility by changing the release medium produces the effect of increasing the exponent n values. The release mechanism moves in the direction of a relaxation/erosion controlled process as the release restriction increases (release rate decreases).

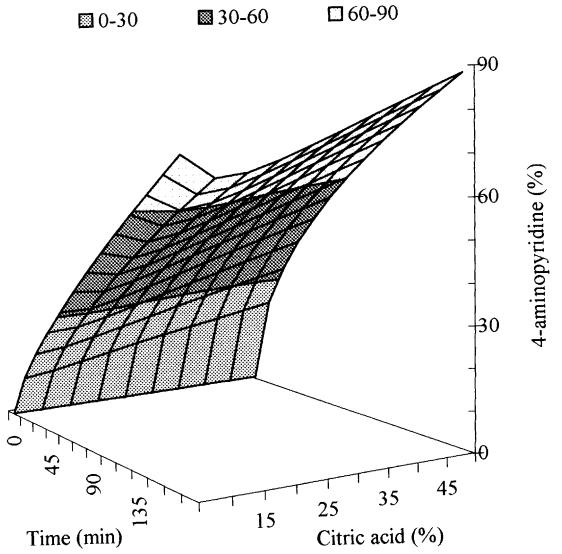

Fig. 8. Calculated response surface for the 4-AP (20 mg) release from 300 mg-HPMC matrices containing different proportions of CA, matrices dissolving in 0.1N HCl.

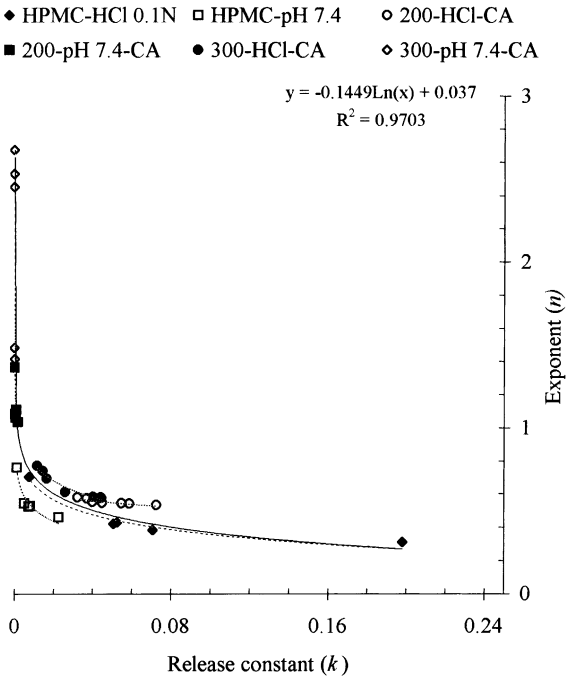

Fig. 9. Relationship between the release constant (k) and the exponent indicative of the release mechanism (n) of 4-AP from matrices containing HPMC and CA.

Fig. 9 shows the relationship between the release constant k and the mechanism-indicating exponent n. It can be observed that as the release constant decreases the release mechanism move away from diffusion, in the direction of a release mechanism controlled by relaxation/erosion. This logarithmic relationship is observed in each individual system or dissolution medium as well as relating all experimental points together, as a general relationship.

4. Conclusion

It has been established before that an extended drug release in a dosage form can be obtained by restricting or subjecting to limitation the drug release rate. A swellable hydrophilic matrix restricts drug release

through formulation variables that include enlargement of the diffusion path length and reducing the drug diffusivity through the matrix. For a given polymer matrix its drug permeability increases as a function of time due to increasing polymer hydration. It has been established before that the polymer hydration occurs in the following steps: (a) swelling, (b) swelling/erosion, and (c) disentanglement/dissolution. In this way, every increase in the exposure to an aqueous environment increases hydration and dissolution of the polymer forming the matrix. Moreover, the HPMC dissolution rate increases with the time of exposure to the aqueous environment. All above-mentioned circumstances permit the inference that every drug release restriction, no matter what method is used, results in a higher matrix hydration. This increasing matrix hydration is the consequence of an increasing time to release the loaded drug and with this, a longer time of matrix exposure to the aqueous environment. This extended time to release the drug loaded in the matrix shifts the release mechanism from a diffusion controlled process to a process controlled by relaxation, erosion and dissolution of the polymeric matrix. In this way, it would be possible to select the drug release mechanism adjusting the matrix release restriction to a given magnitude.

The above-mentioned assumption was demonstrated by restricting the 4-AP release from HPMC matrices through increasing HPMC proportions and through matrix addition of decreasing CA proportions. Every restriction of the 4-AP release rate, expressed as a decrease in the release constant value (k), is associated with increasing values of the mechanism-indicating exponent n. This relationship, described by a logarithmic equation, means a movement away from a release mechanism controlled by diffusion toward a mechanism predominantly controlled by relaxation, erosion and dissolution of the polymeric matrix. A desired zero-order release kinetics could be obtained by adjusting the magnitude of the drug release restriction of a given polymeric matrix. This can be done by an initial selection of the appropriate polymer characteristics and the known formulation variables.

References

Baveja, S.K., Ranga Rao, K.V., Padmalatha Devi, K., 1987. Zero order release hydrophilic matrix tablets of β-adrenergic blockers. Int. J. Pharm. 39, 39–45.

Brazel, C.S., Peppas, N.A., 2000. Modeling of drug release from swellable polymers. Eur. J. Pharm. Biopharm. 49, 47–58.

Chien, Y.W., 1982. Novel Drug Delivery Systems. Marcel Dekker, New York, USA, pp. 465–574.

Espinoza, R., Villafuerte, L., 1999. Influence of admixed lactose on pelanserin hydrochloride release from hydroxypropyl methylcellulose matrix tablets. Pharm. Acta Helv. 74, 65–71.

Ford, J.L., Rubinstein, M.H., Hogan, J.E., 1985. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices. Int. J. Pharm. 24, 327–338.

Ford, J.L., Rubinstein, M.H., Mac Caul, F., Hogan, J.E., Edgar, P.J., 1987. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Int. J. Pharm. 40, 223–234.

Hansebout, R.R., Blight, A.R. United States Patent—5,545,648 (August 13, 1996).

Holgado, M.A., Caraballo, I., Álvarez-Fuentes, J., Fernández-Hervás, M.J., Fernández-Arévalo, M., Rabasco, A.M., 1995. Influence of diluents and manufacturing method on the in vitro dissolution of carteolol hydrochloride matrix tablets. Int. J. Pharm. 118, 151–160.

Ju, R.T.C., Nixon, P.R., Patel, M.V., 1995. Drug release from hydrophilic matrices. 1. New scaling laws for predicting polymer and drug release based on the polymer disentanglement concentration and the diffusion layer. J. Pharm. Sci. 84, 1455–1463.

Kim, H., Fassihi, R., 1997. Application of binary polymer system in drug release rate modulation. 2. Influence of formulation variables and hydrodynamic conditions on release kinetics. J. Pharm. Sci. 86, 323–328.

Lapidus, H., Lordi, N.J., 1968. Drug release from compressed hydrophilic matrices. J. Pharm. Sci. 57, 1292–1301.

Mandal, T.K., 1995. The influence of binding solvents on drug release from hydroxypropyl methylcellulose tablets. Drug Dev. Ind. Pharm. 21, 1389–1397.

Martínez-González, I., Villafuerte-Robles, L., 2003. Influence of enteric citric acid on the release profile of 4-aminopyridine from HPMC matrix tablets. Int. J. Pharm. 251, 189–193.

Masterson, J.G., Myers, M. United States Patent—5,580,580 (December 3, 1996).

Ranga Rao, K.V., Padmalatha Devi, K., Buri, P., 1988. Cellulose matrices for zero-order release of soluble drugs. Drug Dev. Ind. Pharm. 14, 2299–2320.

Reynolds, J.E.F., 1982. Martindale, The Extra Pharmacopeia, 28th ed. The Pharmaceutical Press, London, p. 1678.

Rowe, R.C., 1984. Materials used in the film coating of oral dosage forms. In: Florence, A.T. (Ed.), Materials Used in Pharmaceutical Formulation. Blackwell Scientific Publications, Oxford, UK, pp. 6–7.

Segal, J.L., Brunnemann, S.R., 1997. 4-Aminpyridine improves pulmonary function in quadriplegic humans with longstanding spinal cord injury. Pharmacotherapy 17, 415–423.

Sung, K.C., Nixon, P.R., Skoug, J.W., Ju, T.R., Gao, P., Topp, E.M., Patel, M.V., 1996. Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets. Int. J. Pharm. 142, 53–60.

Vazquez, M.J., Pérez-Marcos, B., Gómez-Amoza, J.L., Martínez-Pacheco, R., Souto, C., Concheiro, A., 1992. Influence of technological variables on release of drugs from hydrophilic matrices. Drug Dev. Ind. Pharm. 18, 1355–1375.

Veiga, F., Salsa, T., Pina, M.E., 1997. Influence of technological variables on the release of theophylline from hydrophilic matrix tablets. Drug Dev. Ind. Pharm. 23, 547–551.

Vigoreaux, V., Ghaly, E.S., 1994. Fickian and relaxational contribution quantification of drug release in a swellable hydrophilic polymer matrix. Drug Dev. Ind. Pharm. 20, 2519–2526.