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Influence of enteric citric acid on the release profile of 4-aminopyridine from HPMC matrix tablets

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Abstract

A weakly basic experimental drug, 4-aminopyridine (4-AP), was taken as a model to study the influence of enteric citric acid (ECA) on the release profile from hydroxypropyl methylcellulose (HPMC) matrices, to set up a system bringing about gradual release of the drug. For this purpose, powder mixtures were wet granulated with water and compressed with a hydraulic press at 55 MPa. Dissolution studies were made using first 900 ml HCl 0.1 N, and then phosphate buffer pH 7.4. Dissolution curves were described by $M_t/M_{\inf} = kt^n$. As physically expected, increasing proportions (2–9%) of the in acid insoluble ECA decreased the release rate. In an acid medium, ECA acts as a physical barrier obstructing the diffusion path, dissolving after the pH change to 7.4. Both circumstances flattening the release profile. Apparent zero order release was observed at ECA concentrations of about 10%. The presence of ECA compensates the effect of decreased solubility of 4-AP at pH 7.4. Unexpectedly, higher ECA proportions (10–50%) act increasing the dissolution rate. This is attributed to a void space formation around the insoluble ECA, after HPMC hydration, which percolates after a critical ECA proportion of approximately 10%. Moreover, decreasing release constant values (k) show a logarithmic relationship with increasing values of the exponent (n). This indicates that an apparent zero-order release can be obtained at a given release constant.

Keywords: 4-Aminopyridine; Release mechanism; HPMC; Enteric citric acid; pH effect

1. Introduction

4-Aminopyridine (4-AP) is a drug used in the treatment of neurological diseases, in particular multiple sclerosis and Alzheimer disease (Masterson and Myers, 1996). 4-AP has been found to improve the conduction of nerve impulses, in consequence, alleviating the above-mentioned disease symptoms. 4-AP has been found to slow the potassium ion flow in nerve impulse transmission and, in that way, is effective in restoring conduction in blocked demyelinated nerves. 4-AP has been also used to overcome some conduction block by spinal cord injuries, producing significant improvements in electrophysiological and behavioral function in animals (Hanseabout and Blight, 1996). The oral daily dose of 4-AP applied to humans treatment is variable and between 10

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and 30 mg (Segal and Brunnemann, 1997). In the use of a drug for long-term therapy, as 4-AP, it is desirable that the drug be formulated so that it is suitable for once or twice-daily administration to aid patient compliance, such a formulation must result in a controlled release of drug to the systemic circulation and therapeutically effective blood levels throughout a given treatment period.

The use of hydrophilic polymers is actually the most used method in controlling the release of drugs in the formulation of oral pharmaceutical dosage forms. Hydroxypropyl methylcellulose (HPMC) is a polymer frequently used in the formulation of controlled release dosage forms. The mechanisms by which it retards drug release include its ability to form rapidly a gel layer at the matrix periphery exposed to aqueous fluids (Mandal, 1995). The drug is released from the matrix mainly by diffusion through water filled pores. Consequently, the release rate is associated to porosity and tortuosity of the pores and channels network. The porosity and tortuosity of a swellable matrix are primarily attributed to polymer swellability (Efentakis et al., 1997).

Variables such as the particle size, viscosity and proportion of HPMC modify the characteristics of porosity and tortuosity of the swollen matrix and therefore, modify the release rate of drugs. Increasing proportions of HPMC in the matrix decreases the release rate (Martini et al., 1995; Campos-Aldrete and Villafuerte-Robles, 1991). An increasing particle size of HPMC produces increasing release rates from the tablets (Campos-Aldrete and Villafuerte-Robles, 1997; Mitchell et al., 1993) and decreasing release rates occur often with an increasing viscosity grade (Campos-Aldrete and Villafuerte-Robles, 1997; Kim and Fassihi, 1997).

Changing several formulation factors, such as type of excipients and manufacture processes (Vázquez et al., 1992) can modify drug release from matrix tablets. Admixing another polymer may bring about different effects according to the type and strength of the interactions between the polymers forming the gel barrier (Traconis et al., 1997).

The effect of adding non-polymeric excipients to a polymer matrix has been claimed to bring about marked increases in the release rate of hydrosoluble 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., 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%.

The pH specificity of the drug or the formulation may often affect the controlled release profile. Weakly basic drugs with pH dependent solubility can experience problems on release from controlled release dosage forms in the small intestine. Penetration of intestinal juices with pH higher than that in the stomach may cause a conversion of the more ionizable drug to a less soluble base. This conversion, total or partial, brings down the solubility and therefore the diffusion rate of the drug through the matrix. This effect is dependent of the pK_a of the drug and related to the pH of the intestinal fluids. Because of this, formulation of this type of drug for oral administration can be expected to result in particularly decreasing release rates with increasing pH in the gastrointestinal tract (Van der Veen et al., 1991).

Considering that the addition of soluble excipients increase the release rate of HPMC matrices and that the intestinal pH decreases the release rate of weakly basic drugs, both processes could be combined to compensate the decreased drug solubility with increased matrix porosity. Enteric coatings are those which are insoluble in the gastric juices, but dissolve readily on passage into the small intestine. Thus, water soluble excipients protected with an enteric coating can be used to increase the porosity and the release rate of a restricting gel layer, to compensate a decreased release rate of a weakly basic drug. Moreover, the presence in the matrix of in acid insoluble particles is expected to physically decrease the diffusion path of the matrix, decreasing the release rate in the acidic medium. It is presumed that these circumstances would flatten or smooth the drug

release profiles toward a desired zero order release.

The aim of this work is to study systematically and quantitatively the possibilities of modulating the 4-AP release through HPMC matrices added of different amounts of an enteric coated water soluble excipient, enteric citric acid (ECA).

2. Materials and methods

2.1. Materials

The pharmaceutical excipients Metolose 90SH-4000SR (Shin-Etsu Chemical Co., Ltd.), a brand of HPMC obtained from Nutrer-Mexico, anhydrous citric acid USP (Helm-Mexico), Eudragit L 12.5%, isopropanol/acetone solution (Helm-Mexico), talc (Helm-Mexico), polyvinylpyrrolidone (Plasdone K 29–32 USP—Helm-Mexico) and the experimental drug 4-AP (ICN Biochemicals, Inc.) were used as received.

2.2. Methods

2.2.1. Matrix preparation

HPMC was used to produce matrices containing 20 mg 4-AP loading in 300 mg of mixtures of different ratios of HPMC:ECA. 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 4 h at 40 °C. Tablets containing 20 mg 4-AP, HPMC in a range from 150 to 294 mg and 6–150 mg ECA were prepared by compression of the granules 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.

2.2.1.1. Enteric citric acid. Polyvinylpyrrolidone (7.12 g) is dissolved in a mixture of isopropanol (35.6 g) and water (35.6 g). This solution is applied to seal the citric acid crystals in a fluid bed (total coating of 3% w/w). Thereafter, citric acid is coated with a dispersion composed of 1280 g of a solution of Eudragit L (12.5%) in acetone–isopropanol added under stirring with 717 g of isopropanol and 48 g of talc (total coating of 5, 8 and 10% w/w). The effectiveness of the enteric coating was tested under the same conditions as dissolution test. An evident insolubility of a tablet made of coated crystals in HCl 0.1 N, for 3 h, and rapid dissolution in phosphate buffer pH 7.4, in no more than 5 min, are indicative of an effective enteric coating. The seal with polyvinylpyrrolidone was applied to avoid a delay in dissolution of the enteric coat due to the suppression of ionization of the enteric polymer by the acidic core (Crotts et al., 2001).

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 HCl 0.1 N and then, in a second vessel, for the following 5 h, the medium was phosphate buffer pH 7.4. The pH was maintained within a variation of ± 0.1 after dissolution of 150 mg citric acid. The release profiles of 4-AP show the accumulated drug dissolved from both vessels 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 HCl 0.1 N and analyzed spectrophotometrically at a wavelength of 261 nm (Beckman DU-650 spectrophotometer). Dilution with HCl 0.1 N was used to keep the absorption wavelength at 261 nm, independently of the employed dissolution medium. The withdrawn dissolution medium (3.0 ml) was considered to calculate the amount of drug dissolved. Dissolution studies were performed in triplicate for each batch of tablets and the results registered as an average.

The solubility of 4-AP in HCl 0.1 N 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-AP from HPMC matrices

Release data from swellable systems can be analyzed according to the power law expression shown in Eq. (1) (Korsmayer–Peppas equation). 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, 1995).

$$M_t/M_{\inf} = kt^n \quad \text{or} \quad \ln(M_t/M_{\inf}) = n\ln(t) + \ln(k) \tag{1}$$

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 kinetic constant; and n, the exponent indicative of 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 considered 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).

Dissolution data for release of 4-AP from matrices containing 150 mg HPMC per tablet produced straight-line plots as a result of application of Eq. (1). This application was made first on data corresponding to the drug released up to 3 h, in HCl 0.1 N. As can be seen in Fig. 1, the change to pH 7.4, after 3 h dissolution, slowed down the release rate. A better fit could be obtained by calculating the regression divided into two parts (Fig. 1). Matrices containing 150 mg HPMC per tablet are an example to show the drug dissolution behavior. Although with different dissolution rates, a similar behavior has been observed with matrices containing from 100 to 400 mg HPMC/tab.

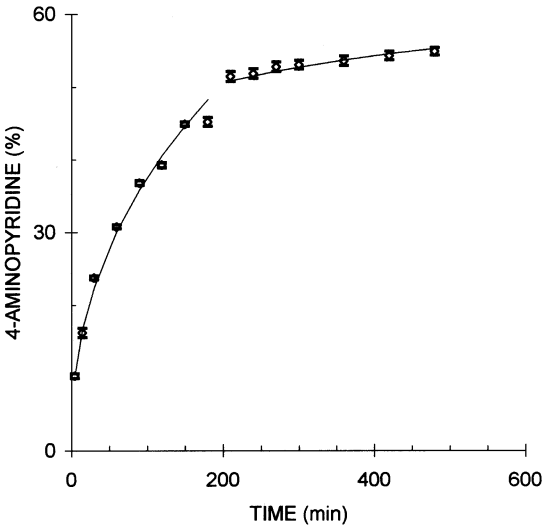

Fig. 1. Release profile of 4-AP (20 mg) from a 150 mg HPMC matrix tablet, dissolving first in HCl 0.1 N (0–3 h) and then in phosphate buffer pH 7.4 (3–8 h). Experimental points, standard deviation and regression in two parts.

It is clear a decrease in the 4-AP dissolution rate, greater than that expected for dissolution at a constant pH, when the pH of the medium was changed to 7.4. This is attributed to a change in solubility of 4-AP. This could be accounted for by the conversion, total or partial, of the 4-AP hydrochloride to the less soluble 4-AP free base. This concept comes from titration of 4-AP with hydrochloric acid. The pH change during the titration showed an inflexion point at about 7.0 which was attributed to a change of the amino group of 4-AP to produce the hydrochloride. The effect of a decreased solubility at pH 7.4 is a decreased diffusion of 4-AP through the gel barrier. In other cases, instead of 4-AP the hydrochloride and the sulfate have been used (Reynolds, 1982).

3.2. Significance of enteric citric acid loading on release kinetics

As expected, the addition of increasing proportions of ECA in a range from 2 to 9% decreases the release rate of 4-AP in HCl 0.1 N as well as the degree of curvature of the entire release profiles (Fig. 2). The reduction of the degree of curvature

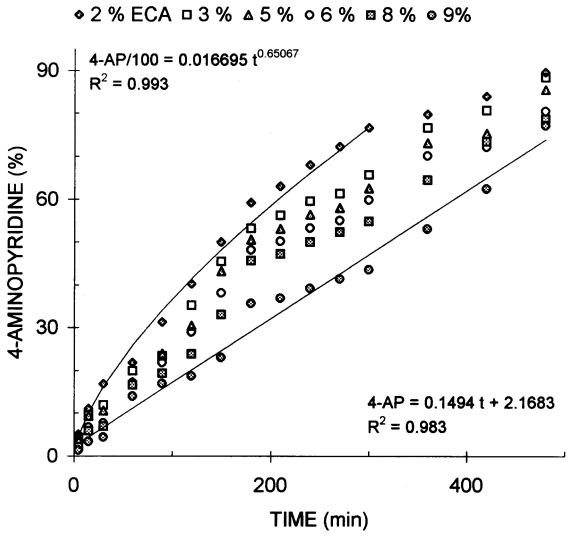

Fig. 2. Release profile of 4-AP (20 mg) from HPMC matrices (300 mg) containing different proportions (2–9%) of ECA (5% w/w Eudragit L-talc), dissolving in HCl 0.1 N (0–3 h) and in phosphate buffer pH 7.4 (3–8 h).

toward an apparent zero order release occurs by one or both circumstances: (a) reducing the release rate in the first hours or (b) increasing the release rate in the second part of the process. A reduction of release rate in the first hours is attributed to a physical obstruction of the diffusion path of the drug by the in acid medium insoluble ECA particles. The insoluble ECA particles dispersed in the HPMC matrix decrease the surface available for drug diffusion and the water transport, increasing at the same time the tortuosity of the diffusion path. This occurs in spite of formation of a void space around the insoluble ECA particles after swelling of HPMC. The ECA particles are considered enclosed rather than joined to HPMC particles, however isolated from each other.

To increase the drug release rate in phosphate buffer pH 7.4 contributes the ECA particles dissolution. The enteric coating (Eudragit L) begins to dissolve at pH 6.0, producing a matrix with higher porosity and decreased tortuosity. The void spaces left after dissolution of ECA particles allow a faster penetration of water, increasing the matrix hydration. The increased hydration allows a greater relaxation of the matrix structure. Dissolution of ECA particles at pH 7.4 is observed in Fig. 2 as a sudden increase in the 4-AP dissolved, compensating in a given magnitude the reduction in the drug solubility. The continuous polymer hydration during the matrix swelling process will decrease the matrix polymer concentration to a critical value called 'disentanglement concentration', which results in gradually increased polymer release rates or erosion of the gel layer (Sung et al., 1996). The sudden increase in dissolution rate after about 300 min could be attributed to the beginning of erosion (Fig. 2). All these circumstances contribute to increase the drug dissolution rate in phosphate buffer as the content of ECA particles in the matrix increases.

The matrix relaxation influences the release mechanism in a greater extent by reduced release rates than by matrices releasing faster. It takes more time to release a given quantity of drug as the release rate decreases, giving opportunity for a greater matrix hydration and matrix relaxation before this quantity of drug is released.

The sum of the above-mentioned effects on 4-AP dissolution is observed in Fig. 2. There is a trend to smaller degrees of curvature of the release profiles as the ECA matrix content increases. The exponent n increases from 0.65 to 0.89, changing the release profile from a predominant diffusion controlled process to an apparent zero-order release kinetics. Apparent zero-order release kinetics can be obtained adjusting the degree of obstruction of the diffusion path in HCl 0.1 N and the increase in dissolution rate in phosphate buffer.

The extrapolation from the results obtained with HPMC matrices containing up to 9% ECA (Tables 1 and 2) allows the prediction of higher values of the exponent n and smaller release constants (k) as the matrix ECA proportion increases. However, this is not the case (Fig. 3). ECA loading in the range from 10 to 50% of the matrix total weight (300 mg), while keeping constant the drug content (20 mg), significantly affected the release process but not according to the extrapolation. As the ECA matrix content increases, the ability of the matrix to sustain drug release decreases (Fig. 3). These results indicate that in spite of the ECA insolubility in HCl 0.1 N, the dissolution rate increases from the first and

Table 1
Regression parameters of 4-AP dissolution curves from HPMC/ECA matrices (300 mg), in their first part, using HCl 0.1 N as medium and covering the time up to 3 h

ECA (%)	Slope (n)	Intercept	r^2	k
10	1.0094	−5.5837	0.967	0.003759
20	0.8430	−4.5639	0.990	0.010422
30	0.7622	−4.0427	0.987	0.017551
40	0.6713	−3.5237	0.971	0.029491
50	0.5209	−2.9036	0.992	0.054828
2	0.6606	−4.0611	0.989	0.017230
3	0.6814	−4.3178	0.977	0.013329
5	0.7024	−4.4725	0.987	0.011418
6	0.7557	−4.8272	0.986	0.008009
8	0.8088	−5.1843	0.979	0.005604
9	0.8933	−5.8460	0.976	0.002892

Enteric coating = 5% w/w.

Table 2
Regression parameters of 4-AP dissolution curves from HPMC/ECA matrices (300 mg), dissolving first in HCl 0.1 N, 0–3 h, and then in phosphate buffer pH 7.4, 3–8 h

ECA (%)	Slope (n)	Intercept	r^2	k
10	0.8265	−4.9826	0.933	0.006856
20	0.6868	−4.0493	0.944	0.017434
30	0.6219	−3.5792	0.941	0.027898
40	0.5395	−3.0900	0.925	0.045500
50	0.4745	−2.7420	0.974	0.064443
2	0.6507	−4.0206	0.991	0.017943
3	0.6870	−4.3309	0.989	0.013155
5	0.7024	−4.4725	0.987	0.011418
6	0.7557	−4.8272	0.986	0.008009
8	0.8080	−5.1759	0.989	0.005651
9	0.8918	−5.8408	0.988	0.002907

Enteric coating = 5% w/w.

along the whole dissolution process. Although ECA dissolves in phosphate buffer pH 7.4, increasing the porosity of the matrix, no important effect was observed in terms of flattening the release profile.

The comparison of Fig. 2 and Fig. 3 show that the trend toward decreasing release constant values as the matrix ECA content increases show a turning point at about 10% ECA. After about 10% in the ECA matrix content the release constant values begin to increase instead of decrease. Around the turning point (10% ECA)

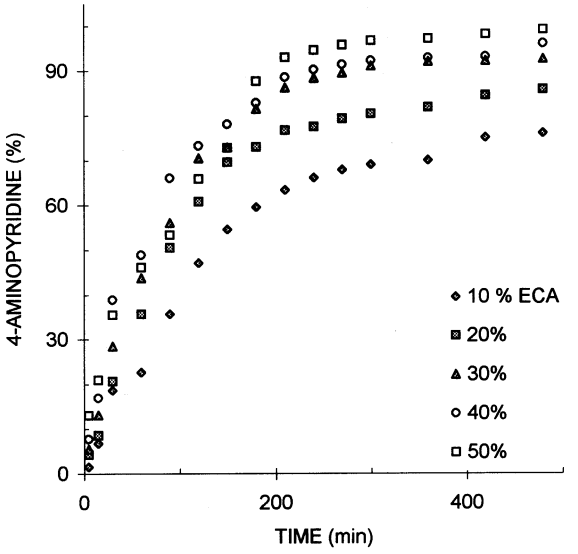

Fig. 3. Release profile of 4-AP (20 mg) from HPMC matrices containing different proportions of ECA (5% w/w Eudragit L-talc), dissolving in HCl 0.1 N (0–3 h) and in phosphate buffer pH 7.4 (3–8 h).

the release profile shows some variability due to experimental noise. However, the turning point is clearly seen by plotting the regression parameters of release curves (Tables 1 and 2) against the ECA matrix content.

The effect of ECA (10–50%) seems more the effect of a plain insoluble excipient. After swelling of the matrix, the non-swelling particles of ECA are surrounded by isolated void spaces that can form a continuous network in the matrix when these void spaces percolate. This has been called void space percolation (Bonny and Leunberger, 1993; Traconis et al., 1997). The percolation threshold is about 10% ECA. Increasing proportions of ECA in the matrix, greater than 10%, produce increasing dissolution rates (Tables 1 and 2).

Data registered in Tables 1 and 2 as well as in Figs. 2 and 3 correspond with an enteric coating of the citric acid of 5% w/w. Tables 3–6 register similar data corresponding with enteric coatings of 8 and 10% w/w. These thicker enteric coatings produce not the same but similar results as above-mentioned.

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

ECA (%)	Slope (n)	Intercept	r^2	k
10	1.1855	−6.5648	0.946	0.001409
20	0.8567	−4.8712	0.991	0.007664
30	0.8285	−4.6462	0.994	0.009598
40	0.7956	−4.4793	0.984	0.011342
50	0.7763	−4.3279	0.983	0.013196
2	0.7041	−4.3548	0.985	0.012846
3	0.7333	−4.6209	0.981	0.009844
5	0.7438	−4.7833	0.985	0.008369
6	0.7543	−4.8463	0.989	0.007857
8	0.7958	−5.1038	0.983	0.006073
9	1.0136	−6.1551	0.987	0.002123

Enteric coating = 8% w/w.

Table 4
Regression parameters of 4-AP dissolution curves from HPMC/ECA matrices (300 mg), dissolving first in HCl 0.1 N, 0–3 h and then in phosphate buffer pH 7.4, 3–8 h

ECA (%)	Slope (n)	Intercept	r^2	k
10	0.9920	−5.9239	0.928	0.002675
20	0.7592	−4.5430	0.973	0.010642
30	0.7302	−4.3166	0.974	0.013345
40	0.7096	−4.1880	0.970	0.015177
50	0.6880	−4.0298	0.968	0.017778
2	0.6913	−4.3033	0.988	0.013524
3	0.7110	−4.5379	0.985	0.010696
5	0.7438	−4.7833	0.985	0.008369
6	0.7543	−4.8463	0.989	0.007857
8	0.7871	−5.0686	0.990	0.006291
9	0.9291	−5.8765	0.984	0.002805

Enteric coating = 8% w/w.

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

ECA (%)	Slope (n)	Intercept	r^2	k
10	1.6218	−8.6255	0.901	0.000179
20	0.8992	−5.1491	0.984	0.005805
30	0.7857	−4.5655	0.974	0.010405
40	0.7563	−4.3641	0.962	0.012726
50	0.7283	−4.1919	0.972	0.015118
2	0.6800	−4.2965	0.969	0.013617
3	0.7449	−4.6858	0.960	0.009225
5	0.7647	−4.8785	0.977	0.007608
6	0.8035	−5.2021	0.987	0.005505
8	0.8581	−5.4000	0.986	0.004516
9	1.0085	−6.1723	0.981	0.002086

Enteric coating = 10% w/w.

Table 6
Regression parameters of 4-AP dissolution curves from HPMC/ECA matrices (300 mg), dissolving first part in HCl 0.1 N, 0–3 h, and then in phosphate buffer pH 7.4, 3–8 h

ECA (%)	Slope (n)	Intercept	r^2	k
10	1.2714	−7.4785	0.867	0.000565
20	0.7888	−4.7796	0.967	0.008399
30	0.7242	−4.3523	0.971	0.012877
40	0.6940	−4.1492	0.964	0.015778
50	0.6661	−3.9777	0.969	0.018730
2	0.6805	−4.2869	0.981	0.013748
3	0.7446	−4.6701	0.975	0.009371
5	0.7647	−4.8785	0.977	0.007608
6	0.8035	−5.2021	0.987	0.005505
8	0.8106	−5.2350	0.985	0.005327
9	0.9333	−5.9233	0.983	0.002676

Enteric coating = 10% w/w.

Calculated slopes or n values for dissolution profiles of matrices like that shown in Figs. 2 and 3 were between 0.47 and 0.89 (Table 2). These data correspond to an enteric coating of 5% w/w, when calculated with only one regression. The calculated data cover a dissolution process, including dissolution in HCl 0.1 N and some points from dissolution in phosphate buffer pH 7.4. Values of the exponent n calculated for 4-AP dissolution in HCl 0.1 N were between 0.52 and 1.01 (Table 1). These data indicate that the drug release may be attributed to different mechanisms ranging from a predominant diffusion, an anomalous transport and to apparent zero-order release or a relaxation-controlled process, as would be expected for swellable matrices.

Considering data from matrices dissolving in HCl 0.1 N (Tables 1, 3 and 5), there is a cubic trend to increasing values of the exponent n as the matrices ECA content increases from 2 to 9%. This can be seen in Fig. 4. Matrices possessing greater proportions of ECA, i.e. 9%, exhibit a drug release closer to a relaxation-controlled process, n values around 1. Mechanistically, matrices with low ECA content (2%) show a drug release less dependent

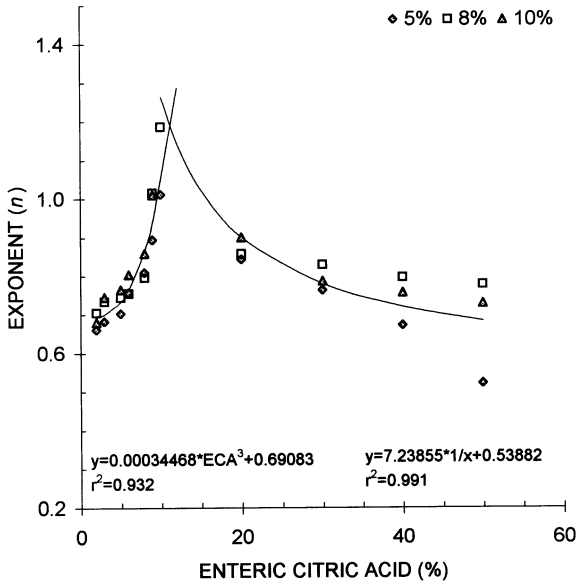

Fig. 4. Relationship between the exponent indicative of the release mechanism (n) of 4-AP and the ECA content of HPMC matrices (300 mg), dissolving in HCl 0.1 N. Enteric coating of 5, 8 and 10% w/w.

on polymer relaxation. This is considered due to faster penetration of the water front and hence to faster hydration and establishment of a gel barrier from the first, releasing greater quantities of the drug in a given time.

Matrices with higher ECA content (10–50%) result in an increased porosity and a decreased gel tortuosity. After a void space percolation threshold the void spaces surrounding the in acid insoluble ECA particles begin to form channels. These channels produce a faster penetration of water front and a faster hydration from the very beginning. Thus, the diffusion path would become less convoluted, increasing the diffusion rate. For matrices dissolving in HCl 0.1 N, containing 10–50% ECA, the values of n show a decreasing trend with increasing ECA proportions (Fig. 4). These results are practically a mirror image of the trend observed by ECA concentrations from 2 to 9%.

The n values of matrices containing citric acid coated with 5% (w/w) polymer mixture are smaller than those from matrices containing citric acid with thicker coatings (8 and 10%). This suggests a faster dissolution of ECA as the film becomes thinner. The average dissolution of tablets made of pure ECA coated with a film thickness corresponding to 5, 8 and 10% (w/w) dissolved in phosphate buffer pH 7.4 after 107, 158 and 185 s respectively.

The effect of the ECA loading on the drug release constant of matrices dissolving in HCl 0.1 N is shown in Fig. 5. In this figure, the changes in tortuosity and in water transport through the matrix are expressed as changes in the drug release constant. There is a linear relationship between the ECA matrix content and the release constant k, divided into two parts. The first part corresponds to ECA concentrations between 2 and 9%. In this case, a rising number of isolated ECA particles produce lesser release rates. The second part of the linear relationship includes ECA loadings in range from 10 to 50%. By these ECA proportions, the rising number of isolated ECA particles allows the interconnection or percolation of void spaces around each ECA particle to form channels. The increasing matrix channeling produces increasing release constant values. A greater degree of percolation means lower tortuosities, higher water transport and thus, higher release constants. ECA

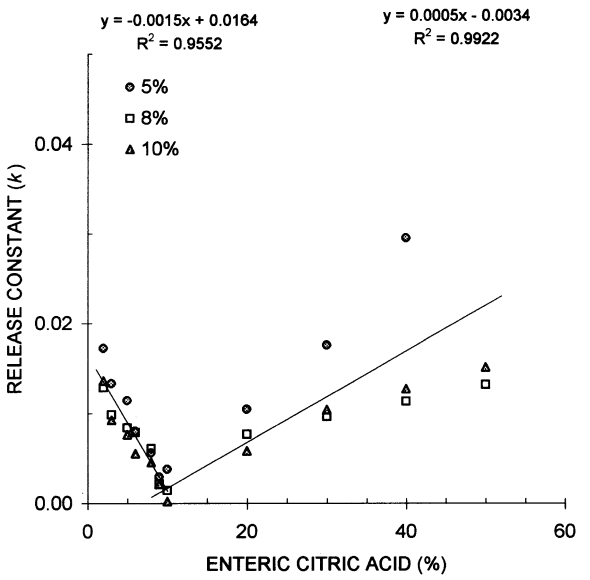

Fig. 5. Relationship between the release constant (k) of 4-AP and the ECA content of HPMC matrices (300 mg), dissolving in HCl 0.1 N. Enteric coating of 5, 8 and 10% w/w.

particles with a thinner enteric coating (5% w/w) dissolves faster than those with thicker enteric coatings (8 and 10%). Consequently, the faster appearing matrix porosity produces the higher drug release constants. This can be seen in Fig. 5 with a special emphasis by ECA proportions of 20% and higher.

The above-mentioned results obtained from regression parameters of release profiles of matrices dissolving in HCl 0.1 N are similar to those calculated for matrices dissolving first 3 h in HCl 0.1 N and thereafter in phosphate buffer pH 7.4 (Figs. 6 and 7).

3.3. Effect of release restriction on the exponent indicative of the release mechanism

The restriction or limitation of drug release from a hydrophilic swellable matrix has been observed to result in a shift to higher exponent n values. This means a shift from a diffusion controlled release toward a relaxation/erosion controlled process. Variables that restrict or reduce drug release from swellable porous matrices include the reduction of drug solubility and the obstruction or reduction of the diffusion path.

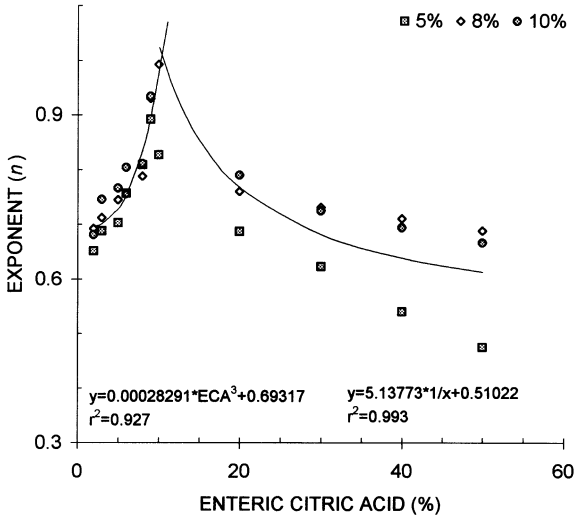

Fig. 6. Relationship between the exponent indicative of the release mechanism (n) of 4-AP and the ECA content of HPMC matrices, dissolving first in HCl 0.1 N and then in phosphate buffer pH 7.4. Enteric coating of 5, 8 and 10%.

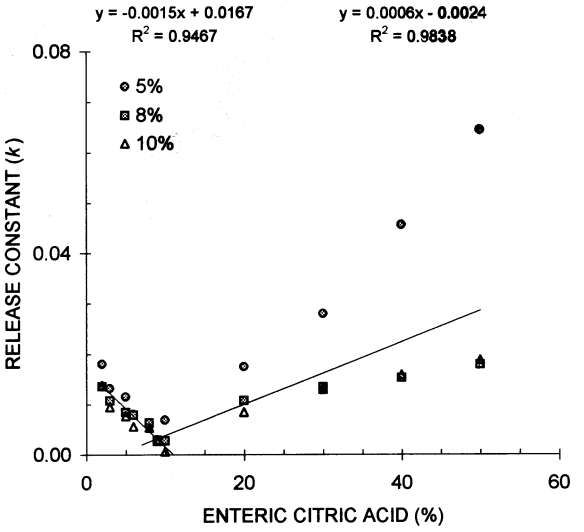

Fig. 7. Relationship between the release constant (k) of 4-AP and the ECA content of HPMC matrices (300 mg), dissolving first in HCl 0.1 N and then in phosphate buffer pH 7.4. Enteric coating of 5, 8 and 10% w/w.

Soluble drugs, releasing from HPMC matrices, showed n values of about 0.67, while insoluble drugs showed n values of about 0.86. This indicates a near zero-order release for those insoluble drugs (Ford et al., 1987). The solubility restriction to obtain an apparent zero-order release was extended to other release restrictions like that obtained from increased polymer content or mixtures of different polymers in the matrix (Juárez et al., 2001). It has been observed that decreasing release constants are logarithmically associated with increasing values of the exponent indicative of the release mechanism (n). This pointing out that an apparent zero-order release could be obtained adjusting the release rate to a given magnitude.

Values of the release constants obtained through manipulation of the ECA matrix content show also a logarithmic relationship with the exponent indicative of the release mechanism (n). This occurs calculating the regression parameters of release profiles obtained from HCl 0.1 N (Fig. 8) as well as calculating the regression parameters of accumulated release profiles obtained from HCl 0.1 N and phosphate buffer (Fig. 9).

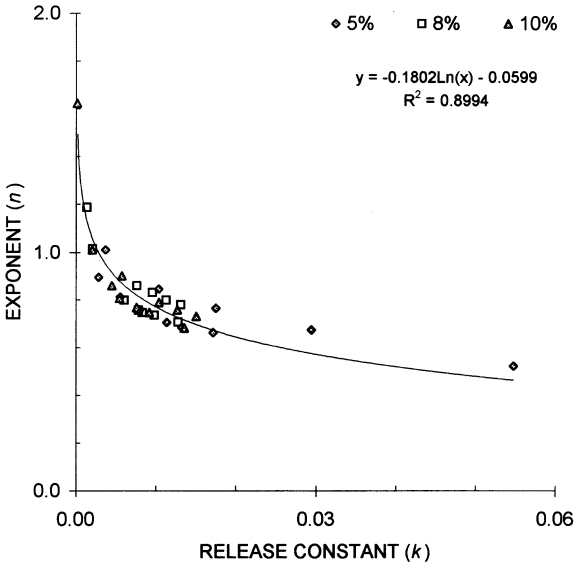

Fig. 8. Relationship between the release constant (k) and the exponent indicative of the release mechanism (n), from 4-AP/HPMC/ECA matrices dissolving in HCl 0.1 N.

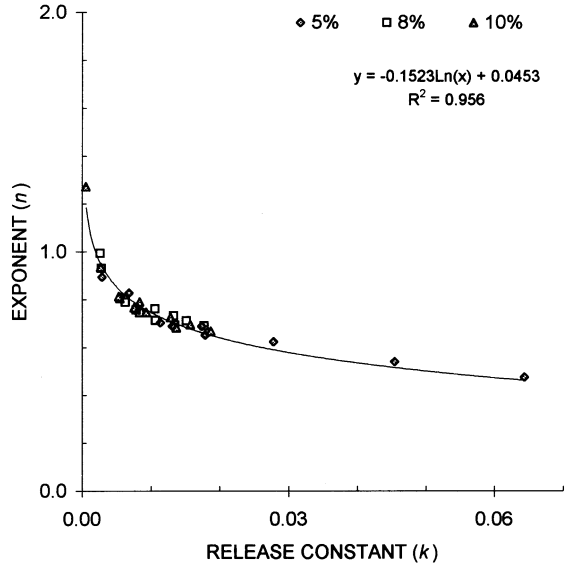

Fig. 9. Relationship between the release constant (k) and the exponent indicative of the release mechanism (n), from 4-AP/HPMC/ECA matrices dissolving first in HCl 0.1 N and then in phosphate buffer pH 7.4.

The restriction of drug release from HPMC matrices, obtained through increasing additions of ECA ($<9\%$) produces the effect of increasing the exponent n values. The release mechanism moves in the direction of a zero-order release as the restriction increases (release rate decreases). The restricted release rate of the drug from the matrix permits more time to form a hydrated gel layer before a given quantity of the drug is released. This extra time allows a higher hydration and accentuates the effect of relaxation on the gel layer. The release mechanism moves from diffusion in the direction of relaxation/erosion, and in this way have a tendency toward zero-order release kinetics. Figs. 8 and 9 show that adjusting the release constant k at a given value the release mechanism can be matched with an apparent zero-order release. Similar considerations can be made for matrices containing higher proportions of ECA (10–50%). In this case the factor reducing the release rate is the drop of the matrix channeling due to decreasing proportions of ECA.

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