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Influence of admixed carboxymethylcellulose on release of 4-aminopyridine from hydroxypropyl methylcellulose matrix tablets

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Abstract

Among different technological variables that influence drug release from hydrophilic matrices, the use of mixtures of polymers represents a potential way of achieving a variety of release properties. Tablets of the model drug 4-aminopyridine with hydroxypropyl methylcellulose were prepared with different proportions of polymer content as well as with different proportions of admixed carboxymethylcellulose (CMC) in the range up to 35% (based on the total polymer content). The matrices release behavior was examined by absorption of samples at 261 nm (USP 23 apparatus 2, paddle, at 50 rpm) using 0.1 N HCl and 0.2 M phosphate buffer as dissolution media. Increasing proportions of CMC in the polymer mixture lead to decreasing dissolution rates, in a range of $k = 0.094–0.036$ for HCl and $k = 0.044–0.009$ for phosphate buffer. The release mechanism in HCl is predominantly controlled by diffusion ($n = 0.46–0.62$), while in phosphate buffer it is controlled, as reported previously, by diffusion/relaxation ($n = 0.58–0.85$) and near zero order release at high CMC concentrations. Approximately doubling the total polymer content gives lower release rates for HCl in the range $k = 0.038–0.015$ and for phosphate buffer $k = 0.0099–0.0034$. Near zero order release is observed only at pH 7.4 ($n = 0.79–0.96$). Decreasing release constant values show a logarithmic relationship with increasing values of the exponent n. This indicates that zero-order release occurs with sufficiently reduced release rate.

Keywords: 4-Aminopyridine; Matrix tablets; Release mechanism; Polymer mixtures; Hydroxypropyl methylcellulose; Carboxymethylcellulose

1. Introduction

In recent years, hydrophilic matrices have become very popular for controlling the release of soluble drugs from solid dosage forms. These systems are attractive approaches from an economic as well as process development point of view. The gelling agent is 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). There are also possible effects of interactions between the

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polymer forming the matrix and other components of the formula, such as admixed excipients and drugs.

The use of mixtures of polymers represents a potential way of achieving required release properties. Mixtures of different nonionic cellulose ethers have been used to give different viscous efficiencies i.e., different viscosities at the same proportion water. Mixtures of nonionic and ionic varieties can be formulated with hydrosoluble active principles to give zero-order release profiles (Baveja and Ranga Rao, 1986; Baveja et al., 1987; Ranga Rao et al., 1988).

The most widely used polymer for hydrophilic matrices is hydroxypropyl methylcellulose (HPMC). This water-soluble polymer (Rowe, 1984) has been studied in its interactions with sodium carboxymethylcellulose (CMC), another water-soluble polymer. According to Walker and Wells (1982), the addition of CMC to HPMC (Methocel® E4M) gives an average viscosity increase of 111% over the calculated viscosity. This synergism is dependent on the chain-lengths. Methocels® (HPMC) of the type E5, E15 and E50 produced less synergism because of their short chain-lengths that drastically reduce the number of hydroxyl groups available for physical crosslinking with CMC, through hydrogen bonding.

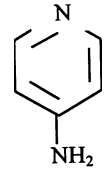
The strength of interpolymer interactions between nonionic and ionic polymers can some times be greater than intrapolymer interactions, due to greater and stronger hydrogen bonding (physical crosslinking). The polymer's degree of substitution, position of the hydroxyl groups and viscosity grade also contributes to the synergism observed. However, these factors can be ignored if the polymer is kept constant. Although physical crosslinking occurs in a certain magnitude in HCl 0.1 N as well as in buffer pH 7.4, physical crosslinking is expected to decrease release rates at low solubilities of CMC (acidic medium), while an increased solubility of CMC, as the pH increases (i.e. at 7.4), is expected to combine the physical crosslinking with a facilitated erosion of CMC. These coupled factors contribute to determine release rates in hydrophilic matrices made of these mixtures.

The purpose of an orally administered hydrophilic matrix is generally to prolong delivery with zero-order kinetics to maintain a constant in vivo plasma drug concentration, and with this to maintain a constant pharmacological effect. Mixtures of HPMC/CMC have been used to obtain zero-order release of drugs using water as the release medium (Ranga Rao et al., 1988) or using simulated gastric media (Baveja et al., 1987; Baveja et al., 1988) with no apparent effect of pH on dissolution. The chosen drugs have pH solubility dependence but show an apparent pH independent dissolution. An observed trend to zero-order release with these mixtures has been detected, coming together with a reduction in release rate as the polymer content increases. Increases in the matrix content of single polymers that reduce dissolution rates have also been observed to go together with a trend toward zero-order release kinetics.

Drug release from matrix systems can be influenced by the aqueous solubility of the drug. Moreover, the aqueous solubility of drugs considered weak bases decrease with increasing pH of the solvent. Because of this, diffusion based formulations of such drugs for oral administration can be expected to result in decreasing release rates with increasing pH in the gastrointestinal tract (Van der Veen et al., 1991).

The addition of some organic acids to matrix tablets has been used to minimize the environmental pH effects on the release rate of drugs from non-swelling insoluble matrices (Gabr, 1992); however, for swelling matrices, a synchronization of release profiles of drug and the acids is necessary to allow the control of pH in the microenvironment (Espinoza et al., 2000).

4-Aminopyridine is a substance reported to reverse the effects of non-depolarising muscle relaxants and to have analeptic effects. Improvement of myasthenia gravis has also been reported (Martindale, 1982). This experimental drug was taken as a model drug for this study since its solubility is decreased by increasing pH, changing its dissolution.



The purpose of this work is the evaluation of a progressive restriction of drug dissolution, in a hydrophilic matrix, as a way to transform diffusion controlled processes into zero-order kinetics. The release restriction is obtained through changes in polymer proportion and composition as well as drug solubility. The results should contribute to a better understanding of release rates with hydrophilic matrices.

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, sodium CMC obtained from Drogería Cosmopolita-Mexico and Pharmatose DCL 11, a brand of spray-dried lactose monohydrate obtained from Helm-Mexico, were obtained of pharmaceutical quality and used without further treatment. 4-Aminopyridine was obtained from ICN Biochemicals Inc.

2.2. Methods

2.2.1. Granulation mixtures

Ten grams of each different formula were prepared by gently mixing in a mortar the corresponding proportions of 4-aminopyridine and HPMC for 20 min. Each mixture was moistened with 2 ml of distilled water, kneaded for 5 min and sifted using a sieve number 12. The resulting granulations were dried at 40°C for 3 h in beds with a thickness up to 5 mm.

All tablets contained 20 mg 4-aminopyridine. The effects of the following variations in tablet formulae on dissolution rates were examined.

Tablets were made containing granules with a fixed quantity of 4-aminopyridine (20 mg/tab.), HPMC (80 mg/tab.), and increasing quantities of 0, 10, 20, and 40 mg/tab. of CMC. This means that the total weight of the tablets increased according to the added CMC. In a second series of tablets, the 4-aminopyridine content was maintained at 20 mg/tab., while the fixed HPMC content was 180 mg/tab., with increasing quantities of CMC of 0, 40, 80 and 100 mg/tab. The total weight of the tablets increased according to the added CMC. The components were tumble mixed for 20 min. No lubricant was used in the tablets.

2.2.2. Tableting

Flat-faced tablets of 8-mm diameter were compressed for 10 s on a hydraulic press at a compaction pressure of 82 MPa.

2.2.3. Dissolution studies

The dissolution rates were determined with USP 23 apparatus 2 (paddle) (USP 23-NF 18) at 50 rpm. 900 ml of 0.1 N hydrochloric acid and/or 0.2 M phosphate buffer pH 7.4 was used as dissolution medium, maintained at 37°C. A wide stainless steel spiral was used to avoid floating of the tablets but allowing tablet swelling. Filtered samples (2 ml) of dissolution medium, taken at different times, were diluted with 8 ml HCl 0.1 N and assayed for their 4-aminopyridine content using ultraviolet absorption at 261 nm. Dilution with HCl 0.1 N was used to keep the absorption wavelength at 261 nm, independently of the employed dissolution medium. Dissolution studies were performed in triplicate for each batch of tablets and the results were registered as an average.

3. Results and discussion

3.1. Release profile of 4-aminopyridine/hydroxypropyl methylcellulose matrices

In a first approach and as reference, dissolution profiles were determined from tablets made of 4-aminopyridine/Pharmatose DCL 11. When using either HCl 0.1 N or phosphate buffer pH 7.4 as dissolution medium, practically complete dissolution was observed after 5 min (90%) and complete dissolution after 15 min. Dissolution in phosphate buffer produced a slightly lower concentration, which was attributed to experimental noise (Fig. 1). These results are similar because of

the high solubility of 4-aminopyridine in both media. Although the solubility in HCl 0.1 N is higher, 95 mg/ml, the solubility in phosphate buffer 0.2 M of pH 7.4, is also considered high, 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.

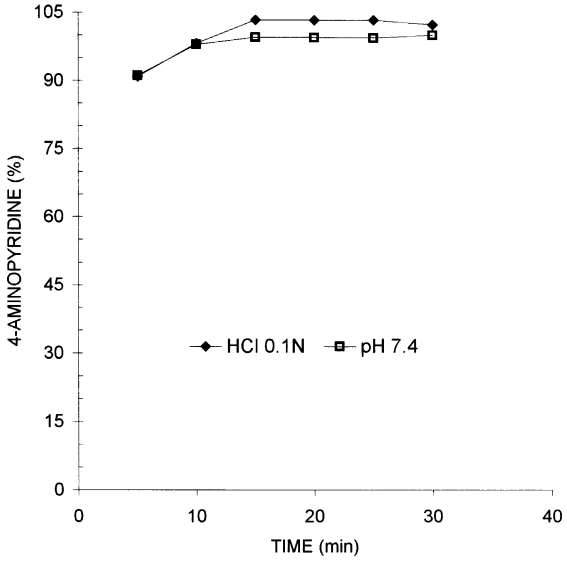


Fig. 1. Dissolution profile of 4-aminopyridine (20-mg)/Pharmatose DCL 11 (180-mg) tablets in two different media, HCl 0.1 N and phosphate buffer pH 7.4.

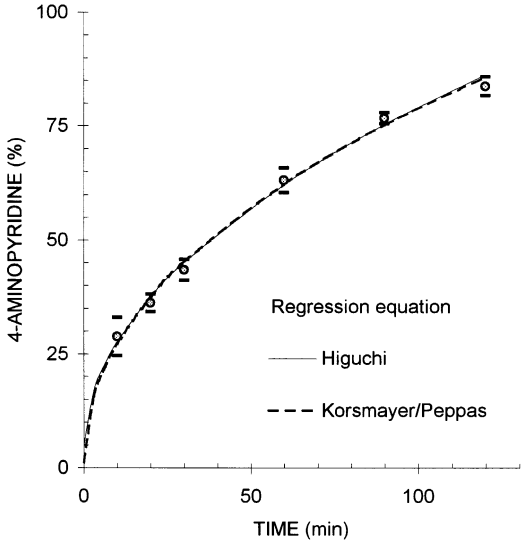


Fig. 2. Release profile of 4-aminopyridine/Metolose 90SH-4000SR (20:80) matrices using HCl 0.1 N as dissolution medium. Experimental points with calculated S.D., and regression using two different equations.

Release curves from matrix tablets have been described with the square root or Higuchi equation (Ford et al., 1985a, 1987; Kuu et al., 1992; Traconis et al., 1997). In general, the release data from swellable matrix drug delivery systems can also be analyzed according to the power law equation or Korsmeyer/Peppas equation. This equation has been used to treat dissolution data from tablets containing different drugs and physical characteristics (Baveja et al., 1987; Colombo et al., 1992; Vigoreaux and Ghaly, 1994; Mandal, 1995; Tros de Ilarduya et al., 1997; Espinoza and Villafuerte, 1999). These equations are based on different assumptions, producing different interpretations of results.

Dissolution data for the release of 4-aminopyridine from matrices containing 80 mg/tab. of HPMC and dissolving in each individual medium yield straight lines with the Higuchi or the Korsmeyer/Peppas equations (Fig. 2). As shown below, the Korsmeyer/Peppas equation can be used to analyze the dissolution data and to explain the results. When delay in release or lag time do not exist, this equation can be expressed as follows:

$$\mathrm{Mt/Minf} = kt^n \quad \text{or}$$

$$\ln(\mathrm{Mt/Minf}) = n\ln(t) + \ln(k).$$

The terms in this equation are as follows: Mt, the amount of drug released at time t; Minf, the total drug released over a long time period; k, the kinetic constant; and n, an exponent related to the mechanism of drug release.

In this equation, the values of n range from 0.5 ($t^{1/2}$ dependence, generally referred to as Fickian release) to 1.0 (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 (Ranga Rao et al., 1988; Brazel and Peppas, 2000). 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).

Table 1
Regression parameters for dissolution curves of 4-aminopyridine/Metolose/CMC (20:80:X-CMC) matrices using the Korsmayer/Peppas equation[a]

Components 4-Ap/Met/CMC	Intercept	Slope (n)	r^2	4-Ap_{2h} (%)	k
20:80:00	−2.3657	0.462	0.976	85.7	0.09388
20:80:10	−2.5524	0.4919	0.942	82.1	0.07789
20:80:20	−2.7774	0.5166	0.975	73.8	0.06220
20:80:40	−3.3334	0.6209	0.982	69.7	0.03567

[a] $\ln(Mt/Minf) = \ln(t) \times n + \ln k$. Dissolution medium HCl 0.1 N.

Table 2
Regression parameters for dissolution curves of 4-aminopyridine/Metolose/CMC (20:80:X-CMC) matrices using the Korsmayer/Peppas equation[a]

Components 4-Ap/Met/CMC	Intercept	Slope	r^2	4-Ap_{2h} (%)	k
20:80:00	−3.1286	0.5789	0.991	70.0	0.04378
20:80:10	−3.7375	0.7011	0.987	68.3	0.02381
20:80:20	−4.0844	0.7616	0.954	64.5	0.01683
20:80:40	−4.7288	0.8552	0.987	53.0	0.00884

[a] $\ln(Mt/Minf) = \ln(t) \times n + \ln k$. Dissolution medium phosphate buffer pH 7.4.

To assign these mechanisms, it has been considered that as the matrix swelling process and the drug elution proceeds the gel layer gradually becomes thicker and therefore the drug concentration gradient along the diffusional pathlength is decreased. The gradually decreased drug concentration gradient results in progressively slower drug release rates that in certain proportion can be compensated with increased porosities of the gel layer; these release profiles correspond with n values between 0.5 and 1.0. 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. When this erosion is sufficiently high, these release profiles correspond with n values greater than 1.0 (Sung et al., 1996).

The above-mentioned equation is especially convenient to assign a release mechanism to every drug-releasing matrix and to correlate this mechanism with a given release constant. This empirical equation has been used to describe drug release from matrices with different geometries (different length/thickness ratios) and to describe dissolution data up to 60%, however, it has been also used to describe dissolution up to 90% of the matrix drug content (Baveja et al., 1987; Ranga Rao et al., 1988; Dabbagh et al., 1999).

3.2. Release profile of 4-aminopyridine/hydroxypropyl methylcellulose matrices added of carboxymethylcellulose

Loading of CMC in the range of 10–40 mg/tab., while keeping the content of drug (20 mg/tab.) and HPMC (80 mg/tab.) constant, significantly affected the release process. Tables 1 and 2 show the regression parameters of release curves of these matrices.

The slopes of the release profiles in HCl 0.1 N (Table 1) and those obtained from phosphate buffer (Table 2) indicate a trend to increasing values of the exponent n as matrices increase their CMC content, as can be seen in Fig. 3. Greater proportions of CMC exhibit drug release profiles with a trend toward a relaxation/erosion controlled process. Release profiles of matrices releasing the drug in phosphate buffer are nearing zero-order when the CMC content is 40 mg/tab. ($n = 0.85$). These results show the same trend as

reported previously for formulations of hydrosoluble active principles (Baveja and Ranga Rao, 1986; Baveja et al., 1987; Ranga Rao et al., 1988). However, the release profiles obtained in HCl 0.1 N are all related by diffusional mechanism, at any CMC content in the matrix tablets, in spite of the trend toward higher exponent n values. These exponent n values in a range between 0.46 and 0.62 can be considered normal for diffusion-controlled processes (Baveja et al., 1987).

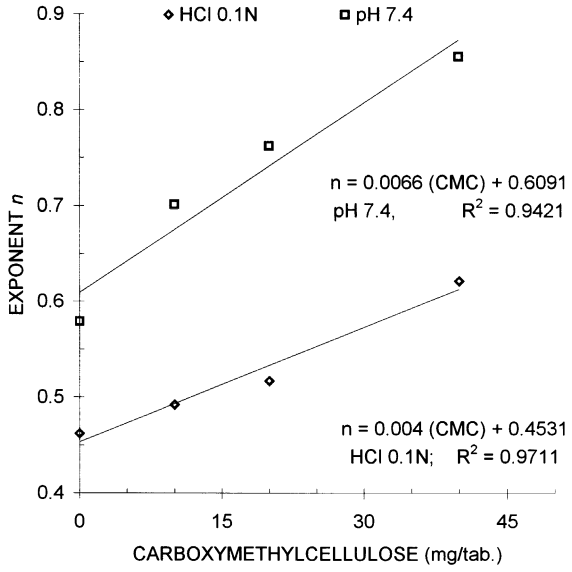


Fig. 3. Effect of addition of CMC on the exponent n of the release profile of 4-aminopyridine/Metolose (20:80:X-CMC) matrices. Dissolution medium HCl 0.1 N and phosphate buffer pH 7.4.

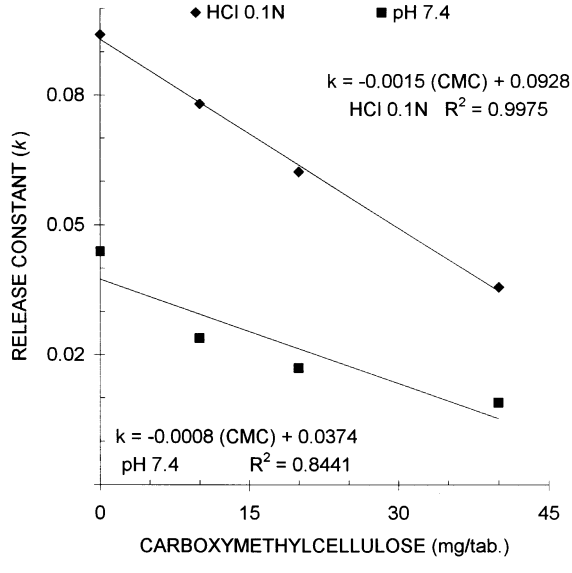


Fig. 4. Effect of addition of CMC on the release or kinetics constant (k) of 4-aminopyridine/Metolose (20:80:X-CMC) matrices. Dissolution medium HCl 0.1 N and phosphate buffer pH 7.4.

Fig. 4 shows that increasing concentrations of CMC in the matrix tablets reduce the release rate of 4-aminopyridine in both HCl 0.1 N and phosphate buffer pH 7.4 media. This reduction in release rate may be attributed to stronger hydrogen bonding between the carboxyl groups on CMC and the hydroxyl groups on the non-ionic HPMC leading to stronger crosslinking between the polymers (Walker and Wells, 1982; Ranga Rao et al., 1988). The potential contributions to such an effect due to an increase in the diffusional path length (Ford et al., 1985a; Baveja et al., 1987) and changes in surface areas of matrices because of the increased polymer content, are not explicitly considered in the analysis; however, they can be considered alternatives to modify release rates. No attempts were made to correct dissolution rates because of changes in surface area (Ford et al., 1985b) since the goal of this study is more qualitative.

The release rates in HCl were broadly triple the release rates in phosphate buffer. This increase in release rates was observed in spite of the fact that dissolution of 4-aminopyridine/Lactose tablets was similar and rapid in both media. These results anticipate an undesirably slower release of 4-aminopyridine after a pH change from HCl 0.1 N to phosphate buffer, which would lead to a fed-fast effect in vivo.

3.3. Release profile of matrices with carboxymethylcellulose and higher polymer content

The high dissolution rates discussed above are reduced by increasing the total polymer content. Matrices containing 20 mg 4-aminopyridine and 180 mg Metolose 90SH-4000SR show a significantly slower release rate ($k = 0.0376–0.0147$), compared to matrices containing 80 mg/tab.

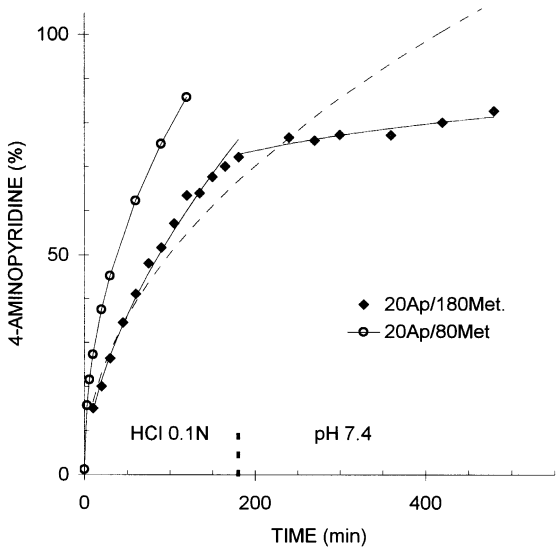


Fig. 5. Release profile of 4-aminopyridine/Metolose 90SH-4000SR matrices using HCl 0.1 N and phosphate buffer pH 7.4 as dissolution medium. Experimental points and regression in one and two parts.

Metolose ($k = 0.0939–0.0357$), when dissolving in HCl 0.1 N (Fig. 5). Complete results of regression parameters for dissolution of matrices containing different amounts of CMC are registered in Tables 3 and 4.

As with matrices containing 80 mg/tab. HPMC, matrices containing 180 mg/tab. HPMC first exposed to HCl 0.1 N and thereafter in phosphate buffer show a trend toward higher values of the exponent n, as the CMC content increases (Fig. 6). Matrices releasing 4-aminopyridine in HCl 0.1 N maintain a predominant mechanism of diffusion, independent of the CMC content. The exponent n varies in a range of 0.58–0.70. These values of the exponent n are higher compared to those obtained for matrices with 80 mg HPMC (0.46–0.62). This can be attributed to a greater restriction of the 4-aminopyridine release with higher polymer content. It can be considered that the 4-aminopyridine-release restriction, through increased polymer content, produces a change in the release mechanism moving away from diffusion.

Values of the exponent n for dissolution in phosphate buffer of matrices first maintained 3 h in HCl 0.1 N (matrices swollen in a certain degree), show a release mechanism that could be attributed to erosion, i.e. n values higher than 1.0.

Table 3
Regression parameters for dissolution curves of 4-aminopyridine/Metolose/CMC (20:180:X-CMC) matrices using the Korsmayer/Peppas equation[a]

Components 4-Ap/Met/CMC	Intercept	Slope (n)	r^2	4-Ap$_{3h}$ (%)	k
20:180:00	−3.279	0.578	0.96	75.9	0.03765
20:180:40	−3.534	0.612	0.99	70.2	0.02918
20:180:80	−3.789	0.638	0.99	62.2	0.02263
20:180:100	−4.218	0.705	1.00	57.1	0.01472

[a] $\ln(Mt/Minf) = \ln(t) \times n + \ln k$. Dissolution medium HCl 0.1 N.

Table 4
Regression parameters for dissolution curves of 4-aminopyridine/Metolose/CMC (20:180:X-CMC) matrices using the Korsmayer/Peppas equation[a]

Components 4-Ap/Met/CMC	Intercept	Slope (n)	r^2	4-Ap$_{3h}$ (%)	k
20:180:00	−12.038	1.787	0.85	6.3	5.916E-06
20:180:40	−16.931	2.744	0.76	6.8	4.435E-08
20:180:80	−24.761	4.020	0.83	2.1	1.764E-11
20:180:100	−18.170	2.884	0.84	4.1	1.285E-08

[a] $\ln(Mt/Minf) = \ln(t) \times \text{Slope} + \ln k$. Dissolution medium phosphate buffer pH 7.4. Matrices first maintained 3 h in HCl 0.1 N.

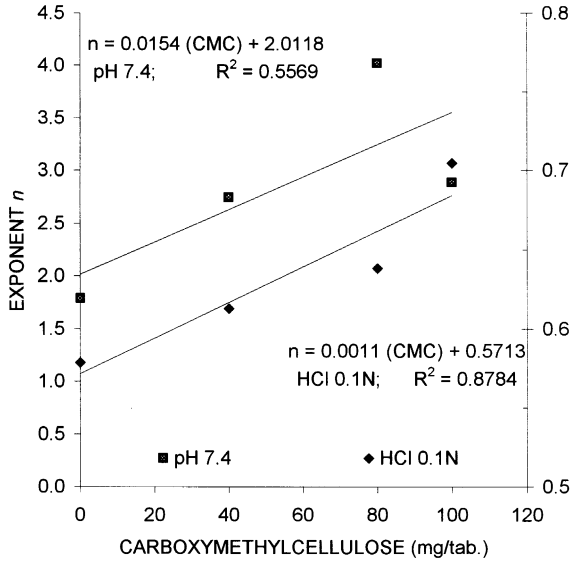


Fig. 6. Effect of addition of CMC on the exponent n of the release profile of 4-aminopyridine/Metolose (20:180:X-CMC) matrices. Dissolution medium HCl 0.1 N for 3 h and thereafter phosphate buffer pH 7.4.

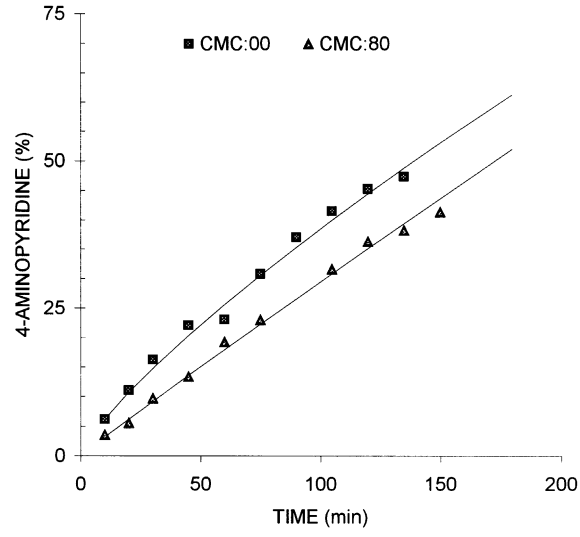


Fig. 7. Effect of addition of CMC on the release profile of matrices 4-aminopyridine/Metolose 90SH 4000SR (20:180:X-CMC) matrices. Dissolution medium phosphate buffer pH 7.4.

It is generally recognized that the operative principle controlling drug release in matrix tablets is that on exposure to aqueous fluids, the tablet surface becomes wet and the polymer starts to hydrate to form a gel layer. There follows an expansion or relaxation of the gel layer, increasing its thickness as soluble drugs diffuse through the gel barrier. Concomitantly the outer layers become fully hydrated and may dissolve, a process referred to as erosion.

Generally, a soluble drug may be released by diffusion from the gel layer, influenced by a continuous relaxation and possibly by tablet erosion whereas a less soluble drug may be released more importantly by tablet erosion (Ford et al., 1985a). A reduction in drug solubility can be considered as a restriction to its release. The higher the drug release restriction the greater the contribution of relaxation/erosion to release process.

Matrices containing 180 mg/tab. Metolose, dissolving directly in phosphate buffer, show a tendency toward zero-order release kinetics as the quantities of CMC in the matrix tablets increase. The exponent n increases from 0.79 to 0.96 (Table 5). Matrices containing 80 and 100 mg/tab. CMC ($n = 0.96$) show practically linear release profiles in the dissolution range shown in Fig. 7. This assumption is based on the proximity of the n values from that of zero-order release. On the

Table 5
Regression parameters for dissolution curves of 4-aminopyridine/Metolose/CMC (20:180:X-CMC) matrices using the Korsmayer/Peppas equation[a]

Components 4-Ap/Met/CMC	Intercept	Slope (n)	r^2	4-Ap$_{3h}$ (%)	k
20:180:00	−4.612	0.7936	0.93	61.2	0.0099
20:180:40	−5.012	0.8848	0.99	65.9	0.0067
20:180:80	−5.676	0.9668	0.97	51.9	0.0034
20:180:100	−5.491	0.9621	0.98	61	0.0041

[a] $\ln(\mathrm{Mt/minf}) = \ln(t) \times n + \ln k$. Dissolution medium phosphate buffer pH 7.4.

other hand, these matrices releasing directly in phosphate buffer show release constant values quite low ($k = 0.0099–0.0034$) compared to those observed when dissolving in HCl 0.1 N ($k = 0.0376–0.0147$). This is depicted in Fig. 8. These results also show the trend towards increased differences in release rates between the dissolution media, as release is restricted. While tablets containing 4-aminopyridine and Pharmatose DCL 11 show practically no differences in dissolution behavior as a function of pH, tablets containing 80 mg Metolose per tablet dissolving in HCl 0.1 N show release constants three times greater than matrices dissolving in phosphate buffer. With matrices containing 180 mg Metolose per tablet the release constants are broadly four times greater when dissolving in HCl 0.1 N, compared to matrices dissolving directly in phosphate buffer.

The reduced release rates of these matrices in phosphate buffer are attributable to a lower solubility of 4-aminopyridine and to increased polymer content. Moreover, it can also be attributed to a higher degree of crosslinking between HPMC and CMC as the CMC proportion in the matrix increases.

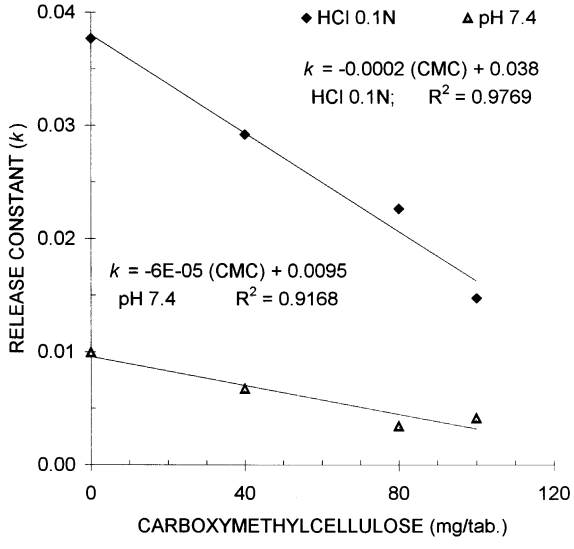


Fig. 8. Effect of addition of CMC on the release or kinetics constant (k) of 4-aminopyridine/Metolose (20:180:X-CMC) matrices. Dissolution medium HCl 0.1 N or phosphate buffer pH 7.4.

With respect to the properties of CMC as a function of pH, it is recognized that the solubility of CMC is greater at higher values of pH (7.4). This increased solubility produces a higher degree of erosion resulting in an increased release rate. This has been used to compensate for the usually reduced release rate produced by an increased diffusional path length (Baveja et al., 1987). However, in the current study, though the CMC proportions in the mixtures with HPMC contribute to a certain degree of erosion that could increase the release rate, this effect appears to be sufficiently low compared to the effect of reducing the release rate by a higher degree of crosslinking between HPMC and CMC. HPMC is considered to behave independently of pH and in this sense does not contribute directly to the change in release rate.

Although explained in terms of soluble and insoluble drugs and not in terms of release restrictions, the effect of a decreased or restricted release rate on the mechanism-indicating exponent n has been observed previously (Ford et al., 1987). Soluble drugs, releasing from HPMC matrices, show n values of about 0.67, while insoluble drugs show n values about 0.86. This indicates a near zero-order release for insoluble drugs.

As can be seen in Table 4, matrices containing 180 mg/tab. Metolose, dissolving first in HCl 0.1 N (3 h) and thereafter in phosphate buffer pH 7.4, show the same trend toward a reduction in release rate as the quantity of CMC in the tablets increases. Further, it is noticeable that these release rates in phosphate buffer are very low compared to release rates in HCl 0.1 N.

The restriction of drug release, obtained through addition of CMC to matrix tablets, through an increase in the total polymer content or through a change in dissolution medium, 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). As the release rate of the drug is restricted, it seems that matrices get more time to form a hydrated gel layer before a given quantity of the drug is released. This extra time accentuates the effect of relaxation and erosion on the gel layer, displacing the release

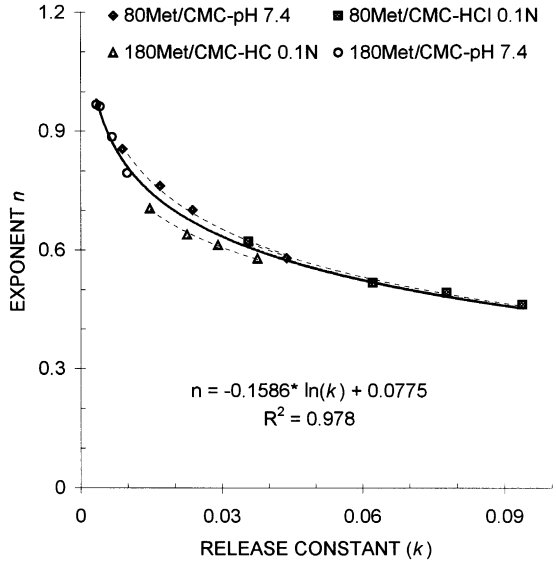


Fig. 9. Relationship between the kinetics or release constant (k) and the exponent n, as a value indicating the mechanism controlling drug release from 4-aminopyridine/Metolose/CMC matrices.

mechanism from diffusion to relaxation/erosion, and in this way tends toward zero-order release kinetics.

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 solvent as well as relating all experimental points together, as a general relationship.

4. Conclusions

Slight to zero differences in dissolution rates of 4-aminopyridine/Pharmatose DCL 11 tablets, when dissolving in HCl 0.1 N or phosphate buffer pH 7.4, increase considerably in matrix tablets made of the drug and Metolose, showing still greater differences in dissolution behavior as CMC is included in the matrix tablets. It seems that small or not observable differences in dissolution rates observed in lactose tablets by the change of pH from HCl 0.1 N to pH 7.4 become greater as dissolution is restricted. Although dissolution of high solubility drugs is not affected by pH when formulated for immediate release, extended release formulations are expected to show this undesirable effect, as dissolution is restricted.

The addition of CMC to HPMC matrices to get zero-order release kinetics could only be obtained by restricting the dissolution process. Every decrease in the release constant k obtained from 4-aminopyridine matrix tablets 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 relaxation/erosion control mechanism, as the release rate decreases. Zero-order release kinetics is obtained when the release is sufficiently restricted.

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