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Fronts movement as a useful tool for hydrophilic matrix release mechanism elucidation

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Abstract

The purpose of this study was to modify the fronts movement method proposed by Colombo et al. in order to apply it to uncoloured drugs and hydrophilic non-swellable matrices. Matrix tablets were prepared using theophylline as a model drug and sodium carboxymethylcellulose (NaCMC) or a new graft copolymer, hydroxypropylcellulose methylmethacrylate dried by lyophilization (HCMMAL), as polymer carriers. Drug release experiments were performed from the whole tablets. Radial drug release and fronts movement were also evaluated using special devices consisting of two Plexiglass® discs joined by means of four stainless steel screws. Release kinetics were determined by means of Higuchi, Korsmeyer and Peppas equations and were related to the fronts movement data. The analysis of drug release and fronts movement kinetics revealed a different release mechanism for both matrices. Drug release from NaCMC matrices was mostly controlled by relaxation, whereas drug diffusion through the porous network regulated drug release from HCMMAL matrices. A reduction in the surface exposed to the dissolution medium led to a decrease in the drug release rate, but the release mechanism was not essentially modified. Fronts movement was shown as a useful tool for matrix release mechanism elucidation. A new denomination for the different fronts observed in HCMMAL matrices was proposed.

Keywords: Hydroxypropylcellulose methylmethacrylate; Sodium carboxymethylcellulose; Moving front kinetics; Image analysis; Drug release mechanism; Matrix tablet

1. Introduction

In recent years, many attempts have been made to elucidate the mechanism of drug release from hydrophilic matrices. In this regard, moving front kinetics have become a useful tool to further understand the processes involved in drug release.

Most of the studies have been carried out with swellable matrices and the relative movement of the gel layer has been evaluated. This gel layer is physically delimited by the erosion (swollen matrix–solvent boundary) and swelling (glassy–rubbery polymer boundary) fronts, whose positions have been followed using different techniques:

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penetrometer measurements (Colombo et al., 1987; Konrad et al., 1998), optical microscopy or image analysis (Thomas and Windle, 1978; Lee, 1993; Pham and Lee, 1994; Colombo et al., 1995, 1996; Gao and Meury, 1996; Moussa and Cartilier, 1996; Moussa et al., 1998), NMR imaging (Weisenberg and Koenig, 1990; Rajabi-Siahboomi et al., 1994, 1996), ultrasound measurements (Konrad et al., 1998).

Colombo et al. (1995, 1996) used special devices to correlate drug release with the radial movement of these fronts. Their studies confirmed the presence of a third front (the diffusion front or undissolved-dissolved drug boundary), firstly described by Lee and Kim (1991) in matrices containing diclofenac. The authors used a coloured drug (buflomedil pyridoxal phosphate) in order to distinguish the different fronts position and pointed out the importance of the dissolved drug layer thickness (distance between erosion and diffusion fronts) in analyzing drug release.

Advantages and disadvantages from each group of techniques mentioned above are difficult to establish due to differences in the experimental conditions involved. Nevertheless, a significant drawback of some of these methods is the ex situ characterization of the gelled tablets (Colombo et al., 1987; Rajabi-Siahboomi et al., 1994; Colombo et al., 1995, 1996; Moussa and Cartilier, 1996). In this sense, Gao and Meury (1996) and Konrad et al. (1998) offer the likelihood of continuous measurements. In addition, penetrometer tests (Colombo et al., 1987; Konrad et al., 1998) have been reported as invasive techniques whereas the restriction of water penetration and matrix swelling in radial direction becomes a disadvantage in certain studies (Pham and Lee, 1994; Colombo et al., 1995, 1996).

In spite of the listed limitations, the simplicity of Colombo et al. (1995, 1996) method, the fact that it provides a well-defined geometry of the tablet, as well as the possibility of diffusion front determination, makes it very suitable for a routine analysis.

For the above reasons, the aim of our study is to modify this last method in order to widen it to uncoloured drugs and hydrophilic non-swellable matrices.

2. Materials and methods

2.1. Materials

Sodium carboxymethylcellulose (NaCMC) (NaCMC 7HF, Aqualon, USA, lot 67798) and a new graft copolymer, hydroxypropylcellulose methylmethacrylate dried by lyophilization (HCMMAL), were used as polymer carriers. NaCMC is a water-swellable cellulose ether and has been selected for comparative purposes in the development of fronts movement method. HCMMAL belongs to a group of copolymers recently obtained by graft copolymerization of methylmethacrylate on various natural substrates (hydroxypropylstarch, carboxymethylstarch, hydroxypropylcellulose) (Castellano, 1997). These polymers have been previously characterized by IR spectrophotometry and NMR techniques (Castellano, 1997) and their amorphous nature has been confirmed by X-ray diffraction (Ferrero et al., 1997). Mean particle sizes of 89 (72) μm and 282 (131) μm were obtained for NaCMC and HCMMAL powders, respectively.

Anhydrous theophylline (Theophylline BP80, Roig Farma, Barcelona, Spain, lot 1201094) with a mean particle size of 105 (63) μm was used as model drug.

Stearic acid (Estearina L2SM, Pulcra, Barcelona, Spain, lot 0055003) was also introduced in the formulation as lubricant.

2.2. Matrix tablet preparation

Theophylline (24% w/w) and polymer (75% w/w) were mixed for 15 min using a double-cone mixer (Retsch, Haan, Germany) at 50 rpm. After the addition of stearic acid (1% w/w), the mixing procedure was continued for 5 min.

The mixtures were compressed in an instrumented (Muñoz-Ruiz et al., 1995) single-punch tablet machine (Bonals, model AMT 300, Barcelona, Spain) equipped with 12 mm flat-faced punches, in order to obtain tablets weighing 500 mg and with a crushing strength around 70–80 N.

2.3. Drug release and fronts movement

The release experiments (six tablets) were performed in a USP 23 dissolution apparatus 2 (Aidec, Barcelona, Spain) as a function of time. Distilled water (900 ml) at 37°C was used as dissolution medium and the tablets were tested with a paddle rotation speed of 50 rpm. Theophylline release was monitored continuously at 272 nm on a Hewlett Packard 8452A diode-array UV-vis spectrophotometer (Waldbronn, Germany).

In a second series of experiments, special devices (Bettini et al., 1994) were used in order to obtain a rigorous radial release. The tablets were locked between two transparent Plexiglass® discs by means of four stainless steel screws. The upper disc was carved with concentric circles (from 8 to 20 mm of diameter), so that the tablet could be placed just in the center. The assembled devices (three replicates) were introduced into the vessels of the dissolution apparatus and tested in the same conditions as previously.

Release data analysis was carried out according to Higuchi (1963), Korsmeyer et al. (1983) and Peppas and Sahlin (1989) equations using SPSS program version 7.5. Linear or non-linear least-squares fitting methods were used to determine the optimum values for the parameters present in each equation.

Finally, the measurement of the fronts movement during drug release was also performed using the previous devices. Methylene blue (0.004% w/v) was added to the water (900 ml) in order to improve the visualization of the different fronts. The experiment was carried out, in duplicate, in the same conditions as in the release studies (37°C and 50 rpm). At defined time intervals (10, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720 min), the devices were removed from the dissolution apparatus and photographed by means of a camera (Canon, EOS) provided with a macro (1:1) and an intermediate ring. The photographs were scanned (Scanrom 4E, Taiwan) and analysed by computer using the Corel Draw® 7 program. As depicted in Fig. 1A, the concentric circles carved on the top of the devices were taken as a reference to adjust the photograph to the rulers. The initial diameter of the tablet as well as the position of the different fronts (Fig. 1) was obtained by placing tangent lines to those boundaries and seeing the corresponding values in the rulers. Four measurements at the two equatorial axes were made to estimate the position of each front at each time. The interface between the matrix and the dissolution medium at the beginning of the experiment (initial diameter) was indicated by position 0. The inward movement of the fronts was represented by a negative value, while the outward movement was indicated by a positive one.

3. Results and discussion

Fig. 2 (filled symbols) illustrates the drug release profiles from matrices prepared with both polymers. A faster release was observed for matrices containing NaCMC. All the drug content was released after ten hours, while more than 40% of theophylline remained in HCMMAL matrices at that time. Furthermore, HCMMAL matrices appeared nearly intact while NaCMC matrices completely disintegrated at the end of the experiment.

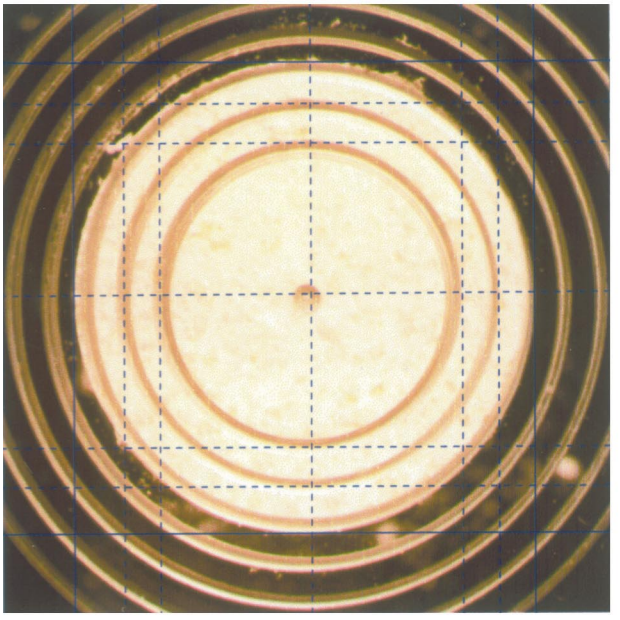
Drug release data ($M_t/M_\infty \leq 0.60$) were analysed according to Higuchi (1963), Eq. (1); Korsmeyer et al. (1983), Eq. (2); and Peppas and Sahlin (1989), Eq. (3).

$$M_t/M_\infty = k\ t^{1/2} \quad (1)$$

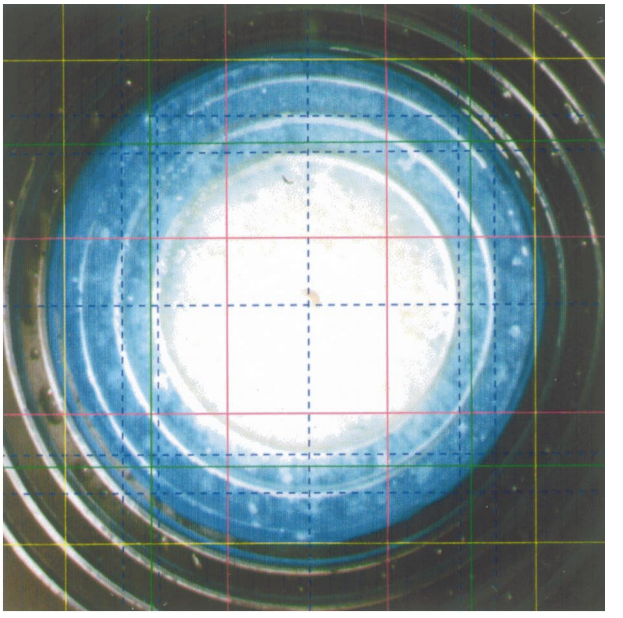
$$M_t/M_\infty = k'\ t^n \quad (2)$$

$$M_t/M_\infty = k_d\ t^m + k_r\ t^{2m} \quad (3)$$

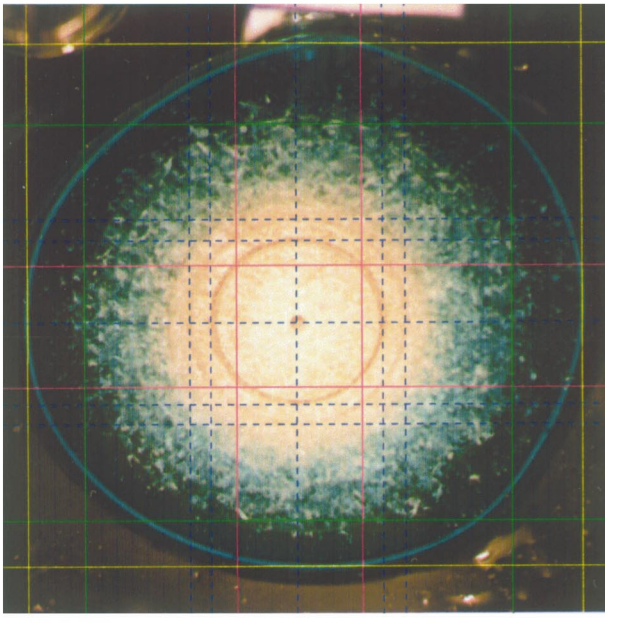
Fig. 1. Photographs obtained from the fronts movement study: (A) HCMMAL matrix at $t = 0$ h; (B) NaCMC matrix at $t = 6$ h; (C) HCMMAL matrix at $t = 6$ h. The dotted blue lines are the reference lines used to adjust the photograph. The continuous blue lines represent the initial position of the tablet. Swelling (water uptake for HCMMAL), diffusion (complete wetting for HCMMAL) and erosion fronts are represented by pink, green and yellow lines, respectively.



A



C



B

Fig. 1.

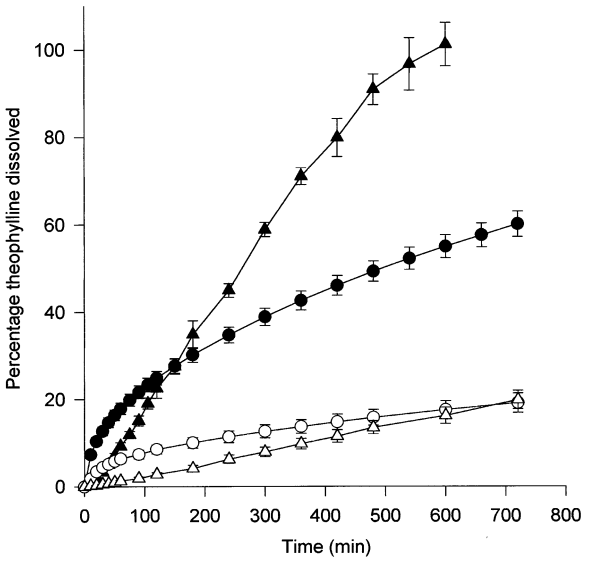


Fig. 2. Release profiles (over 12 h) from matrices containing HCMMAL (●), NaCMC (▲), $HCMMAL_{radial}$ (○), $NaCMC_{radial}$ (△).

M_t/M_∞, fractional release of the drug (the drug loading was considered as M_∞); k, k', kinetic constants characteristic of the drug/polymer system; t, release time; n, diffusional exponent that depends on the release mechanism and the shape of the matrix tested (Ritger and Peppas, 1987); k_d, diffusion rate constant; k_r, relaxation rate constant; m, purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release. In our case, HCMMAL and NaCMC matrices presented an aspect ratio around 3, which corresponded to $m = 0.44$ (Peppas and Sahlin, 1989).

The main parameter values from the different equations are summarised in Table 1. Matrices containing HCMMAL showed the best fit to the different equations. The accurate fit to Higuchi equation, the higher k_d in Peppas equation and the n value from Korsmeyer equation equal to 0.49 revealed a drug release mechanism controlled mainly by drug diffusion. All the equations yielded a diffusion rate constant around 0.02 $min^{-1/2}$.

Matrices containing NaCMC were related with a poorer fit to these equations, particularly to the Higuchi one. According to Korsmeyer ($n = 1.28$) and Peppas ($K_r > K_d$) equations, drug release seemed to be controlled by polymer relaxation. The n value higher than 1 would reveal a Super Case II transport, that could result from an increased plasticization at the relaxing boundary (Hopfenberg and Hsu, 1978). This type of transport has also been reported by other authors (Ranga Rao et al., 1988) for matrices containing NaCMC.

In order to relate drug release and fronts movement data, release studies were also performed using Plexiglass® discs (Bettini et al., 1994), where only radial swelling and drug release were allowed. The results of Fig. 2 (open symbols) indicate that drug release profiles were similar to the ones obtained from the whole tablets, although a slower rate could be noticed.

Table 1
Analysis of release data from hydrophilic matrix tablets using Eqs. (1–3)

Polymer type	Higuchi equation[a]		Korsmeyer equation[a]			Peppas equation[a]		
	k ($min^{-1/2}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
NaCMC	0.041	0.9501	1.28	4×10^{-4}	0.9964	−0.021*	0.005	0.9988
HCMMAL	0.022	0.9999	0.49	0.024	0.9999	0.029	3×10^{-4}	0.9999
NaCMC (radial)	0.012	0.9344	1.12	1×10^{-4}	0.9988	−0.008*	0.001	0.9990
HCMMAL (radial)	0.007	0.9981	0.50	0.007	0.9897	0.009	9×10^{-5}	0.9987

[a] k, Higuchi kinetic constant; k', Korsmeyer kinetic constant; k_d, diffusional constant; k_r, relaxational constant; r^2, determination coefficient.

* The negative values obtained for k_d in NaCMC matrices should be interpreted in terms of a diffusion process insignificant compared to the relaxation mechanism.

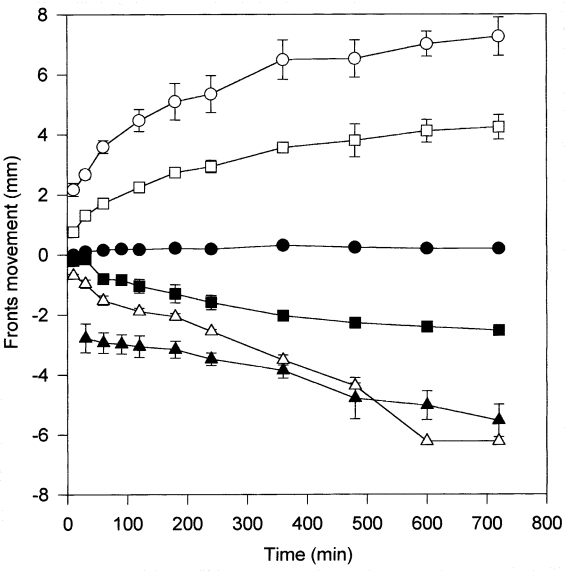


Fig. 3. Fronts movement (over 12 h) from matrices containing HCMMAL (erosion ●, complete wetting ■, water uptake ▲ fronts) and NaCMC (erosion ○, diffusion □, swelling △ fronts).

The values from Table 1 support this behaviour. Radial drug release from matrices containing HCMMAL was mainly governed by drug diffusion; however, a poorer fit could be distinguished compared to the whole tablet, probably because of the reduced release range considered. The slower rate observed (around 0.007 $min^{-1/2}$) was due to a considerable decrease in the surface exposed to the dissolution medium (388 → 162 mm^2).

Radial drug release from NaCMC matrices showed a clear dependence on the macromolecular relaxation of the polymer. A slower relaxation rate constant was obtained compared to the whole tablet, in agreement with the reduction in the release surface (367 → 141 mm^2).

Although the release mechanism was markedly different (Table 1, Fig. 2) for both matrices, the quantity of drug released in radial direction at the end of the experiment was more or less the same. It seems that the initial amount of area exposed to the dissolution medium determines the amount of drug released, whereas the drug release kinetic is controlled by the kinetic of releasing area modification (Colombo et al., 1990). On the other hand, the comparison of radial and complete release profiles shows that the same area reduction (226 mm^2) affected more drastically to NaCMC matrices.

The different behaviour for both matrices was confirmed by means of the photographs obtained by our fronts movement method. As expected, NaCMC matrices (Fig. 1B) behaved as swellable matrix tablets, where the three fronts proposed by Colombo et al. (1995, 1996) could be distinguished: swelling front (between dry-wet polymer able to swell, represented by the pink line), diffusion front (between wet polymer–clear gel, represented by the green line) and erosion front (between clear gel–solvent, represented by the yellow line). Fronts movement kinetics depicted in Fig. 3 showed a quick outward movement of the erosion front, in agreement with the considerable swelling postulated for these matrices. In fact, the outward movement of the diffusion front was due to the swelling overcoming the drug diffusion.

For matrices containing HCMMAL, the diffusion front (Fig. 1C) could not be determined, as a clear gel layer was not observed. However, water uptake (pink line) and erosion (yellow line) fronts could be clearly distinguished. In spite of the quick water uptake (Fig. 3), the nearly constant erosion front movement and the kinetic studies revealed the absence of swelling in these matrices. It seems that HCMMAL behaved as an hydrophilic but water-insoluble matrix, where the drug is released by diffusion through the porous structure. The fast water uptake observed might be due to the water penetration through capillaries and higher size pores. The dark blue layer (Fig. 1C, green line) growing up over time might be the result of complete wetting, i.e. the whole polymer structure was participating in water uptake (smaller pores and intraparticle permeation). Carli et al. (1984) also observed an initial interparticle capillary penetration followed by an intraparticle permeation in matrices containing Eudragit® with quaternary ammonium groups (strong permeability).

These studies provide an explanation to the differences observed in radial and complete drug release. The reduction in the releasing surface in

HCMMAL matrices yielded a diminution of the porous structure in contact with the solvent medium. Then, the water uptake and particle permeation were slower and, consequently, the drug diffusion rate diminished. In matrices containing NaCMC, the smallest area in the radial experiments allowed a more controlled expansion of the tablet. The preferential swelling in the axial direction because of the stresses imposed during tabletting has been pointed out by many authors (Mitchell et al., 1993; Papadimitriou et al., 1993; Rajabi-Siahboomi et al., 1994; Moussa and Cartilier, 1996). Furthermore, the Plexiglass® devices avoided the matrix disintegration observed from the whole tablets, what could explain the marked reduction in the quantity of drug released.

Several physico–chemical properties of the polymers can have a substantial effect on the different behaviour noticed for NaCMC and HCMMAL matrices. NaCMC has been shown as a more hydrophilic polymer than hydroxypropylcellulose (HPC) (Doelker, 1990). Moreover, the copolymerization of HPC with methylmethacrylate (MMA) has made this polymer more hydrophobic (Castellano, 1997).

On the other hand, the glass transition temperature (T_g) of NaCMC has been referred as 78°C (Conte et al., 1988) while 110°C was the corresponding to HCMMAL (Ferrero et al., 1999).

The higher hydrophilicity and lower T_g for NaCMC improves the polymer plastification and its swelling characteristics whereas HCMMAL behaves as an insoluble matrix under the same conditions.

Although an increase in polymer particle size has been generally related to an increase in water uptake and drug release rate, this relationship could not be found for the matrices under study. In spite of the smaller particle size of NaCMC compared to HCMMAL, NaCMC tablets yielded higher theophylline release rate and matrix disintegration could not be avoided for the whole tablets. These findings support the presence of a different drug release mechanism and the contribution of other factors than polymer particle size over drug release from these matrices.

We can conclude that fronts movement analysis provides useful information for a better understanding of the release mechanism from hydrophilic matrices. A variation from Colombo et al. (1995, 1996) method has been introduced with the purpose of applying it to non-swellable matrices and uncoloured drugs. A new denomination for the fronts observed in matrices containing a new graft copolymer (HCMMAL) has been suggested: water uptake front (similar to the swelling front, but the name is more adequate as this matrix does not swell), complete wetting front (matrix particles are completely wet) and erosion front. Further studies must be performed in order to determine if the complete wetting front is related in some manner with the drug release.

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