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Compaction properties, drug release kinetics and fronts movement studies from matrices combining mixtures of swellable and inert polymers. II. Effect of HPMC with different degrees of methoxy/hydroxypropyl substitution

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ABSTRACT

The aim of this paper is the modification of the release behaviour of hydrophilic HPMC-based matrices of different substitution degree (E4M, F4M, K4M) by the introduction of a new inert polymeric excipient hydroxypropylcellulose-methyl methacrylate (HCMMA) at different proportions (75:25, 50:50 and 25:75). The product (HCMMA) was dried either in a vacuum oven – OD copolymers – or freeze-dried—FD copolymers. HPMC E4M formulations showed the worst compaction properties. All mixtures presented a percentage of theophylline release between 47% and 32% at 1440 min. The drying methods employed had only influence over the drug release in E4M and K4M formulations, at higher proportions of HCMMA, showing the highest release the mixtures containing OD-HCMMA. Combinations of diffusion and erosion release mechanisms were found to matrix tablets. All mixtures with F4M did not modify relaxation rate constant values of Peppas and Shalin equation (k_r) respect to F4M 100%. However, all mixtures with K4M showed the highest k_r values, which decreased when HCMMA proportion decreased. Only K4M mixtures showed a different diffusion front movement than the other mixtures. The modulation of theophylline monoaxial release was obtained using a high percentage of HCMMA, and HPMCs with a substantial difference of hydroxypropyl groups (F4M and K4M or E4M).

1. Introduction

Hydroxypropylmethylcellulose (HPMC) are celluloses ethers which are frequently used to provide a controlled release of drugs from matrix tablets (Melia, 1991). The interaction of these polymers with water is a major factor in formulation, processing and sustaining the drug release. Thus, the ability to hydrate rapidly when in contact with liquid water and thus to form a protective gel around the tablet matrix is an essential property for drug release (Carstensen and Li Wan Po, 1992). Application of an impermeable coating that covers different surface portions of the hydrogel matrix (Colombo et al., 1987, 1990, 1992), graft the cellulose with synthetic polymers (Castellano et al., 1997), the use of ion exchange resin in the matrix (Feely and Davis, 1988), the careful control of drug particle size (Ford et al., 1985a,b), drug/cellulose ether ratio (Ford et al., 1985a,b, 1987) or even matrix shape (Ford et al., 1987), and the use of polymeric mixtures (Walker and Wells, 1982; Bonferoni et al., 1994; Traconis et al., 1997) are some examples of the changing of drug diffusion or relaxation rates for the modulation of drug release from hydrophilic matrices.

Since diffusion plays such a prominent role in controlling drug release, the release kinetics are ever changing because of the changing diffusional path length. Indeed, the release kinetics follows the kinetics of swelling (Colombo et al., 1990). In a previous paper (Escudero et al., 2008), we demonstrate the possibility of modulation of theophylline release by mixing HPMC of different viscosity grades (hydrophilic matrices) and a new generation of copolymers (Castellano et al., 1997; Ferrero and Jiménez-Castellanos, 2002; Ferrero et al., 2003) introduced as excipient for oral controlled released matrices (inert matrices), combining the influence of swelling rate from hydrophilic matrices as well as the porosity, tortuosity and water uptake capacity from inert matrices.

Following these principles, and since there is evidence that varying the degree of substitution of HPMC used may also influence drug release characteristics (Alderman, 1984), the aim of this paper is to evaluate the influence of different mixtures on technological characteristics and drug release from matrix tablets containing HPMC of same viscosity grade but different substitution degree (HPMC K4M; HPMC E4M and HPMC F4M), as hydrophilic polymer, hydroxypropylcellulose-methyl methacrylate (HCMMA), as inert polymer and theophylline as model drug. Because in a previous paper (Escudero et al., 2008) we discuss the effect that drying

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method produced on the different technological characteristics and drug release from matrices tablets containing HCMMA, in this paper the results will be focused on the influence of: (a) polymer type; (b) ratio of two polymers in the matrix tablets; (c) substitution degree of HPMC.

2. Materials and methods

2.1. Materials

2.1.1. Inert polymer

The copolymer (batch SS02) synthesised by free radical copolymerisation of methyl methacrylate (MMA) and hydroxypropylcellulose (HC) was select as inert polymer. The product (HCMMA) was dried either in a vacuum oven – OD copolymers – or freeze-dried—FD copolymers (Castellano et al., 1997). The OD product was crushed in a knives mill (Retsch, Haan, Germany) to obtain powdery samples.

2.1.2. Commercial polymers

Hydroxypropylmethylcellulose (Methocel® K4M with 19–24% methoxyl groups and 7–12% hydroxypropyl groups; E4M with 28–30% methoxyl groups and 7–12% hydroxypropyl groups; F4M with 27–30% methoxyl groups and 4–7.5% hydroxypropyl groups; Premium EP, Colorcon, England, batches KI10012N02, LB24012N11 and KB21012N81, respectively) was selected as swellable polymer.

2.1.3. Others components

Anhydrous theophylline (Theophylline BP 80, Roig Farma, Barcelona, Spain, batch 0212030) was chosen as model drug. Stearic acid (Estearina® L2SM, Pulcra, Barcelona, Spain, batch 0055003) was selected as lubricant.

Before use, the materials were stored at constant relative humidity (40%) and room temperature (20 °C).

2.2. Methods

2.2.1. Mixtures preparation

Anhydrous theophylline (24%, w/w) and mixtures (75%, w/w) of inert and swellable polymers in different proportions (100:0, 75:25, 50:50, 25:75 and 0:100 HCMMA:HPMC) were mixed for 15 min using a double cone mixer (Retsch, Haan, Germany) at 50 rpm. After addition of stearic acid (1%, w/w), the mixing procedure was continued for a further 5 min. A total of 23 mixtures were prepared. The nomenclature used for these HCMMA:HPMC mixtures was: the first two letters corresponding to the inert polymer (OD or FD), the following number is the proportion of inert polymer in the mixture (75, 50 or 25%), and the background is the variety of hydrophilic polymer (K4M, E4M or F4M).

2.2.2. Apparent particle density

The apparent particle densities of the mixtures were determined, in triplicate, by means of an air comparison pycnometer (Ultrapycnometer 1000, Quantachrome, Boyton Beach, FL, USA), using helium as an inert gas, according to European Pharmacopoeia (2007).

2.2.3. Preparation of tablets

The different mixtures were compacted into tablets using an instrumented (Muñoz-Ruiz et al., 1995) single punch tablet machine (Bonals AMT 300, Barcelona, Spain) running at 30 cycles/min. To investigate the compaction characteristics of mixtures, a quantity of powder (500 mg) was preweighed and manually fed into the die (12 mm) and flat-faced compacts were prepared to have a constant breaking force of 70–80 N. Typical compaction parameters (maximum upper pressure – Psup –, apparent net work – Wan –, expansion work – We –, plasticity—Pl) describe by Doelker (1978) and Järvinen and Juslin (1981) were collected from four tableting cycles.

Also, in order to produce a sufficient number of tablets for physical testing, the mixtures were tableted in the same conditions outlined before (500 mg weight, 12 mm diameter, 70–80 N breaking force).

The values obtained from the different mixtures were statistically analysed by one-way analysis of variance (ANOVA) using SPSS® 14.0 software. Post-ANOVA analysis was carried out according to Bonferroni's multiple comparison tests. Results were quoted is significant when $p < 0.05$.

2.2.4. Standard physical test of tablets

The physical testing of tablets was performed after relaxation period of at least 24 h.

The tablet average weight and the standard deviation were obtained from 20 individually weighed (Sartorius CP224S, Gottingen, Germany) tablets according to European Pharmacopoeia (2007). The thickness of 10 tablets was measured individually placing them in and parallel to the face of an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan). The breaking force (European Pharmacopoeia, 2007) of 10 tablets was determined by diametrical loading with a Schleuninger-2E tester (Greifensee, Switzerland). Tablet friability (European Pharmacopoeia, 2007) was calculated as the percentage weight loss of 20 tablets after 4 min at 25 rpm in an Erweka TA (Heusenstamm, Germany) friability tester.

2.2.5. Mercury porosimetry measurements

Mercury porosimetry runs were undertaken using an Autopore IV 9510 (Micromeritics, Madrid, Spain) porosimeter with a 3 cm^3 penetrometer. An adequate number of tablets per formulation tested was used according to obtain a stem volume between 20% and 90% of the penetrometer capacity. Working pressures covered the range of 0.1–60000 psi and the mercury solid contact angle and surface tension were considered to be 130° and 485 nM m^{-1}, respectively. Total porosity was determined, in duplicate, for each tablet tested.

2.2.6. Drug release study

A special device (Bettini et al., 1994) was used in order to obtain 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 centre. The assembled devices (three replicates) were introduced into the vessels of the dissolution apparatus 2 (Aidec, Barcelona, Spain) (European Pharmacopoeia, 2007) and tested for 24 h. Distilled water (900 ml) maintained at 37 ± 0.5 °C was used as dissolution medium and tablets were tested with a paddle rotation speed of 50 rpm. Filtered samples (2.8 ml) were withdrawn at specified time intervals via a peristaltic pump (Hewlett-Packard 8452a diode-array UV–vis spectrophotometer, Waldbronn, Germany). Theophylline release was monitored continuously at 272 nm on a Hewlett-Packard 8452a diode-array UV–vis spectrophotometer.

Drug release data ($M_t/M_\infty \leq 0.6$) were analysed according to Higuchi (1963) (Eq. (1)), Korsmeyer et al. (1983) (Eq. (2)) and Peppas and Sahlin (1989) (Eq. (3)) equations:

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

$$\frac{M_t}{M_\infty} = k'\,t^{n} \quad (2)$$

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

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), k, k' are kinetic constants characteristic of the drug/polymer system, t is the release time, n is the release exponent that depends on the release mechanism and the shape of the matrix tested (Ritger and Peppas, 1987), k_d, k_r are the diffusion and relaxation rate constants, respectively, m is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release.

The optimum values for the present parameters in each equation were determined by linear or non-linear least-squares fitting methods with SPSS® 14.0 software. The determination coefficient (r^2) and the F-ratio probability were used to test the applicability of the release models.

Release profiles were compared using similarity factor, f_2, calculated by the following equation:

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} 100 \right\} \quad (4)$$

where R_t and T_t are the percentages released at each time point. An f_2 value between 50 and 100 implies similarity between two release profiles (Losi et al., 2006).

2.2.7. Fronts movement study

Fronts movement measurements were effected as described elsewhere (Ferrero et al., 2000). Methylene blue (0.004%, w/v) was added to the dissolution medium (900 ml distilled water) in order to improve the visualisation of the different fronts. The experiment was carried out, in duplicate, in the same conditions as the radial release studies (37° C and 50 rpm). At defined time intervals (0, 10, 30, 60, 90, 120, 180, 240, 360, 480, 600, and 720 min), the devices were removed from the dissolution apparatus and photographed by means of a camera (Sony® DSC-F717). Focal distance was kept constant during all measurements. The photographs analysed by computer using Corel Draw® X3 Software (Ferrero et al., 2003). The concentric circles carved on the top of the devices were taken as reference to adjust the photograph to the rulers. The initial diameter of the tablet, as well as the position of the different fronts, were obtained by placing tangent lines to these boundaries and seeing the corresponding values in the rulers. Four measurements at the two equatorial axes were made to allow precise measurement of fronts positions versus time. The interface between the matrix and the dissolution medium at the beginning of the experiment (initial diameter) was referred as position 0. The inward fronts movement was represented by a negative value, while the outward movement was indicated by a positive one.

3. Results and discussion

3.1. Apparent particle density

Table 1 shows the apparent densities of mixtures containing different proportions of HCMMA (OD or FD) and HPMC (K4M, E4M and F4M). Apparent particle density values were statistically lower ($p < 0.05$) for HCMMA than HPMC mixtures at the 100% proportions. The packing of the HPMC polymers is more effective than in case of the HCMMA materials, due to the markedly bigger size of the poly(methyl methacrylate) – PMMA – moiety compared to the methoxyl and hydroxypropyl groups.

The apparent density values of mixtures at different proportions and same substitution degree were between the values of mixtures with only one polymer, and these increased with decreased proportions of HCMMA (OD or FD) in the mixture.

The substitution degree factor (same proportion) affects the apparent density values. In every case, the mixtures with E4M showed the lowest density values compared to K4M and F4M mixtures, according to 100% proportions (not statistical differences were found between OD/FD50E4M and OD/FD50F4M).

3.2. Preparation of tablets

In relation with the applied pressure (Table 2), HCMMA 100% presented significant differences ($p < 0.05$) respect to HPMC 100%. The last ones showed higher capacity to accept applied energy from the tablet machine (higher plasticity), lower elastic expansion during decompresion (We) and an easier tablet elaboration (lower Wan) than HCMMA.

The existence of two polymers into the mixtures reduced the necessary pressure to obtain the tablets (Table 3), and increased the plasticity values compared to the HCMMA 100% mixtures. At identical substitution degree but different percentage, when HCMMA percentage decreases in the mixtures, the applied pressure, expansion work and apparent network decreased. In the mixtures with OD-HCMMA, the plasticity parameters increased their values from 75:25 to 50:50 ratio, keeping then constant. However, similar values were found for mixtures with FD-HCMMA, according with the more alike values found for FD-HCMMA and HPMC 100%. We also observed that mixtures with FD-HCMMA needed less pressure, presented lower expansion work, higher facility to obtain the tablets (not statistical differences were found between OD25F4M and FD25F4M), and higher plasticity than OD-HCMMA mixtures. These results agree with the parameters obtained for 100% formulations.

At same percentage in the formulations, HPMC E4M mixtures showed higher applied pressure (Psup) necessary to obtain tablets with a breaking force of 70–80 N, higher elastic expansion during decompresion (We) and higher apparent network (Wan) values than HPMC K4M and F4M, according to 100% mixtures (not statistical differences were found between OD75E4M and OD75F4M).

We observed that the lubrication ratio values (data not showed) obtained from all formulations (0.871–0.722) did not fulfil the requirements (0.9) proposed by Bolhuis and Lerk (1973) as direct compression excipients, in contrast with the values found for the ejection force (378–168 N) that were lower than 750 N (Bolhuis and Lerk, 1973).

3.3. Standard physical test of tablets

Results from the physical testing of tablets obtained from the different mixtures are compiled in Tables 2 and 4.

All tablets fulfilled the guidelines specified in European Pharmacopoeia (2007) related to weight uniformity test. The tablet thickness varied between 4 and 4.6 mm. All FD-HCMMA mixtures obtained a higher value than OD-HCMMA mixtures. These results might be related to a more porous structure in FD matrices. The breaking force test (European Pharmacopoeia, 2007) confirmed the values of 70–80 N for all tablets. Only FD-HCMMA 100% and OD50E4M presented friability values lower than 1% (European Pharmacopoeia, 2007). The high values observed for this parameter make us think about the need of increase the breaking force in a future. With exception of FD25E4M and FD25F4M, the FD mixtures presented higher friability values than OD mixtures.

3.4. Mercury porosimetry measurements

In order to evaluate the microstructure of the matrices, the pore size distributions were measured by mercury intrusion–extrusion porosimetry. HCMMA 100% presented lower porosity than K4M and F4M 100%. However, HPMC E4M only showed lower porosity than FD-HCMMA (Table 5).

Table 1
Apparent particle density values ($n = 3$) from HCMMA:HPMC mixtures (100:0, 75:25, 50:50; 25:75, 0:100).

Mixture	Density (g/cm^3)	Mixture	Density (g/cm^3)	Mixture	Density (g/cm^3)
OD-HCMMA	1.266 ± 0.002	OD75K4M	1.296 ± 0.002	FD75K4M	1.302 ± 0.003
FD-HCMMA	1.278 ± 0.004	OD75E4M	1.284 ± 0.004	FD75E4M	1.289 ± 0.005
HPMC K4M	1.365 ± 0.004	OD75F4M	1.289 ± 0.003	FD75F4M	1.295 ± 0.001
HPMC E4M	1.327 ± 0.003	OD50K4M	1.310 ± 0.003	FD50K4M	1.315 ± 0.002
HPMC F4M	1.357 ± 0.002	OD50E4M	1.306 ± 0.005	FD50E4M	1.297 ± 0.005
		OD50F4M	1.299 ± 0.001	FD50F4M	1.297 ± 0.001
		OD25K4M	1.339 ± 0.004	FD25K4M	1.341 ± 0.005
		OD25E4M	1.315 ± 0.001	FD25E4M	1.316 ± 0.001
		OD25F4M	1.333 ± 0.004	FD25F4M	1.327 ± 0.004

OD/FD-HCMMA and K4M mixtures were published in Escudero et al. (2008).

Table 2
Compaction parameters ($n = 4$) and physical tests from 100% matrices.

Mixture	Psup (MPa)	Wan (J)	We (J)	Pl (%)	Weight (mg)	Thickness (mm)	BF (N)	F (%)
OD-HCMMA	369.42 ± 5.26	18.8 ± 0.2	5.1 ± 0.4	78.7 ± 1.2	499.2 ± 1.7	4.092 ± 0.013	80 ± 3	1.47
FD-HCMMA	160.92 ± 1.81	12.3 ± 0.1	1.1 ± 0.1	91.5 ± 0.6	497.9 ± 1.4	4.227 ± 0.005	82 ± 2	0.48
HPMC K4M	43.64 ± 1.41	4.3 ± 0.1	0.1 ± 0.0	97.0 ± 0.4	498.8 ± 1.6	4.513 ± 0.018	74 ± 4	1.58
HPMC E4M	66.95 ± 0.93	5.4 ± 0.1	0.2 ± 0.0	95.2 ± 0.3	498.0 ± 1.5	4.289 ± 0.013	69 ± 1	2.05
HPMC F4M	41.07 ± 0.86	3.9 ± 0.1	0.1 ± 0.0	96.8 ± 0.4	501.4 ± 1.7	4.545 ± 0.011	76 ± 4	1.86

OD/FD-HCMMA and K4M mixtures were published in Escudero et al. (2008).

Table 3
Compaction parameters ($n = 4$) from HCMMA:HPMC matrices in the proportions 75:25, 50:50 and 25:75.

Mixture	Psup (MPa)	Wan (J)	We (J)	Pl (%)	Mixture	Psup (MPa)	Wan (J)	We (J)	Pl (%)
OD75K4M	174.80 ± 5.59	11.6 ± 0.4	1.2 ± 0.2	90.6 ± 1.1	FD75K4M	109.40 ± 0.52	9.3 ± 0.1	0.7 ± 0.0	93.4 ± 0.3
OD75E4M	229.62 ± 2.80	12.6 ± 0.1	2.2 ± 0.1	85.5 ± 0.5	FD75E4M	141.99 ± 1.75	11.0 ± 0.1	0.7 ± 0.2	93.8 ± 1.5
OD75F4M	236.07 ± 2.19	13.4 ± 0.1	2.3 ± 0.1	85.4 ± 0.5	FD75F4M	114.29 ± 2.37	9.8 ± 0.5	0.7 ± 0.0	93.0 ± 0.5
OD50K4M	99.65 ± 2.25	7.7 ± 0.1	0.5 ± 0.1	94.4 ± 1.2	FD50K4M	83.25 ± 0.32	7.5 ± 0.0	0.3 ± 0.0	96.4 ± 0.3
OD50E4M	191.58 ± 3.02	11.5 ± 0.1	1.2 ± 0.1	90.4 ± 0.9	FD50E4M	125.11 ± 1.33	9.4 ± 0.1	0.8 ± 0.1	92.2 ± 1.0
OD50F4M	107.13 ± 1.29	8.1 ± 0.1	0.5 ± 0.0	93.9 ± 0.3	FD50F4M	86.12 ± 0.36	7.4 ± 0.1	0.4 ± 0.1	94.3 ± 1.4
OD25K4M	59.85 ± 1.36	5.4 ± 0.1	0.4 ± 0.0	93.2 ± 0.7	FD25K4M	48.93 ± 0.66	4.8 ± 0.1	0.1 ± 0.0	97.0 ± 0.4
OD25E4M	96.24 ± 1.69	6.8 ± 0.1	0.5 ± 0.1	93.5 ± 1.0	FD25E4M	80.16 ± 1.64	6.2 ± 0.5	0.4 ± 0.0	94.6 ± 0.4
OD25F4M	59.22 ± 1.67	5.1 ± 0.1	0.3 ± 0.0	94.8 ± 0.3	FD25F4M	57.74 ± 0.34	5.4 ± 0.1	0.2 ± 0.0	96.7 ± 0.4

K4M mixtures were published in Escudero et al. (2008).

Table 4
Physical tests from HCMMA:HPMC matrices in the proportions 75:25, 50:50 and 25:75.

Mixture	Weight (mg)	Thickness (mm)	BF (N)	F (%)	Mixture	Weight (mg)	Thickness (mm)	BF (N)	F (%)
OD75K4M	500.0 ± 0.8	4.153 ± 0.012	75 ± 2	1.17	FD75K4M	498.0 ± 1.0	4.358 ± 0.009	74 ± 2	1.81
OD75E4M	500.4 ± 0.5	4.006 ± 0.004	77 ± 2	1.28	FD75E4M	500.3 ± 1.2	4.207 ± 0.011	77 ± 2	1.59
OD75F4M	499.9 ± 1.4	4.117 ± 0.009	78 ± 2	1.43	FD75F4M	499.6 ± 1.0	4.350 ± 0.006	79 ± 1	1.67
OD50K4M	500.6 ± 1.5	4.312 ± 0.011	75 ± 2	1.82	FD50K4M	500.7 ± 1.2	4.475 ± 0.007	78 ± 2	3.35
OD50E4M	499.3 ± 1.3	4.040 ± 0.009	81 ± 3	0.97	FD50E4M	498.6 ± 1.0	4.232 ± 0.006	77 ± 3	1.72
OD50F4M	499.4 ± 1.3	4.212 ± 0.002	79 ± 3	1.62	FD50F4M	499.6 ± 1.0	4.496 ± 0.009	72 ± 3	2.11
OD25K4M	502.2 ± 1.4	4.383 ± 0.011	81 ± 3	1.34	FD25K4M	499.0 ± 2.0	4.555 ± 0.012	74 ± 3	1.69
OD25E4M	500.2 ± 1.4	4.141 ± 0.008	78 ± 4	1.60	FD25E4M	501.4 ± 2.0	4.226 ± 0.005	79 ± 4	1.45
OD25F4M	500.1 ± 2.0	4.397 ± 0.018	79 ± 2	1.71	FD25F4M	500.5 ± 1.2	4.513 ± 0.007	72 ± 3	1.66

K4M mixtures were published in Escudero et al. (2008).

Table 5
Porosity values ($n = 2$) from HCMMA:HPMC mixtures (100:0, 75:25, 50:50; 25:75, 0:100).

Mixture	Porosity (%)	Mixture	Porosity (%)	Mixture	Porosity (%)
OD-HCMMA	17.8 ± 1.4	OD75K4M	22.0 ± 1.8	FD75K4M	26.2 ± 0.4
FD-HCMMA	23.6 ± 0.6	OD75E4M	25.3 ± 0.3	FD75E4M	24.9 ± 0.4
HPMC K4M	31.4 ± 2.7	OD75F4M	18.1 ± 1.0	FD75F4M	22.2 ± 4.7
HPMC E4M	21.4 ± 0.3	OD50K4M	27.2 ± 0.2	FD50K4M	34.0 ± 7.4
HPMC F4M	27.5 ± 0.1	OD50E4M	24.7 ± 0.1	FD50E4M	24.2 ± 0.2
		OD50F4M	22.2 ± 4.7	FD50F4M	29.1 ± 0.1
		OD25K4M	28.5 ± 2.3	FD25K4M	32.7 ± 0.1
		OD25E4M	23.5 ± 0.1	FD25E4M	25.9 ± 0.1
		OD25F4M	27.6 ± 0.4	FD25F4M	32.2 ± 0.4

OD/FD-HCMMA and K4M mixtures were published in Escudero et al. (2008).

When two polymers were in the mixture (Table 5), the porosity values were higher than those corresponding to HCMMA 100% (not statistical differences were found between FD75F4M than FD-HCMMA 100%). If we compare OD with FD mixtures, in general, the formers showed lower porosity values, as happened in HCMMA 100% tablets.

When we compared HCMMA:HPMC ratios for the same substitution degree, the porosity only increased to K4M and F4M mixtures as HCMMA percentage decreased. To HPMC E4M mixtures, porosity values decreased when OD-HCMMA percentage decreased, keeping constant the porosity values with FD-HCMMA. The rough fibrous particles of F4M and K4M that constitute the compacts and the different particle size of E4M could explain the differences on porosity parameter.

Besides, respect to substitution degree (same HCMMA:HPMC ratio), the porosity did not present a clear tendency.

According to IUPAC definitions, as the pore diameter values were accomplished between 20 and 500 Å, all mixtures possessed mesopores, except to HPMC K4M 100%, OD/FD25K4M and OD/FD25F4M, that presented macropores (>500 Å).

3.5. Drug release study

Fig. 1 illustrates the drug release profiles from HCMMA and HPMC 100% matrices. Higher percentages of drug release were observed for OD-HCMMA matrices than FD tablets (f_2 = 60.3). HPMC E4M showed a release profile between OD– and FD-HCMMA, whereas HPMC K4M and HPMC F4M tablets displayed the lowest release (f_2 = 93.3).

Fig. 2 illustrates the release profiles from the matrices prepared with different mixtures of OD-HCMMA and FD-HCMMA with HPMC (K4M, E4M, F4M) in three defined proportions HCMMA:HPMC (75:25, 50:50, 25:75). All mixtures presented a percentage of theophylline release between 47% and 32% at 1440 min. As the content of HCMMA in the mixtures was reduced, the ability to control drug release increased, mainly from 75:25 to 50:50 ratios, being the liberation profiles more similars to HPMC 100%. Mitchell et al. (1993) demonstrated that only low levels of cellulose ethers in a matrix showed interesting differences between different substitution degrees. The two grades of HPMC (E4M and K4M) behaved similarly and the major differences were with F4M, that always presented the lowest theophylline release, in agreement with its lowest hidrophylicity. We could observe that the drying methods employed have influence over the drug release in E4M and K4M. Thus, we found again important differences at higher proportions of HCMMA, showing the highest release OD-HCMMA with

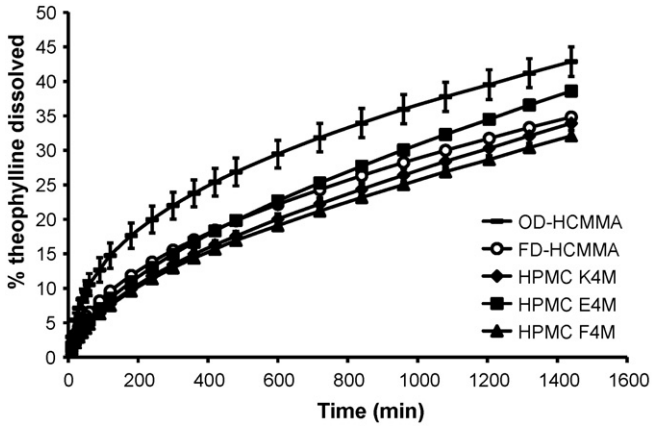

Fig. 1. Release profiles of anhydrous theophylline (over 24 h) from 100% tablets. The bars show the standard deviation.

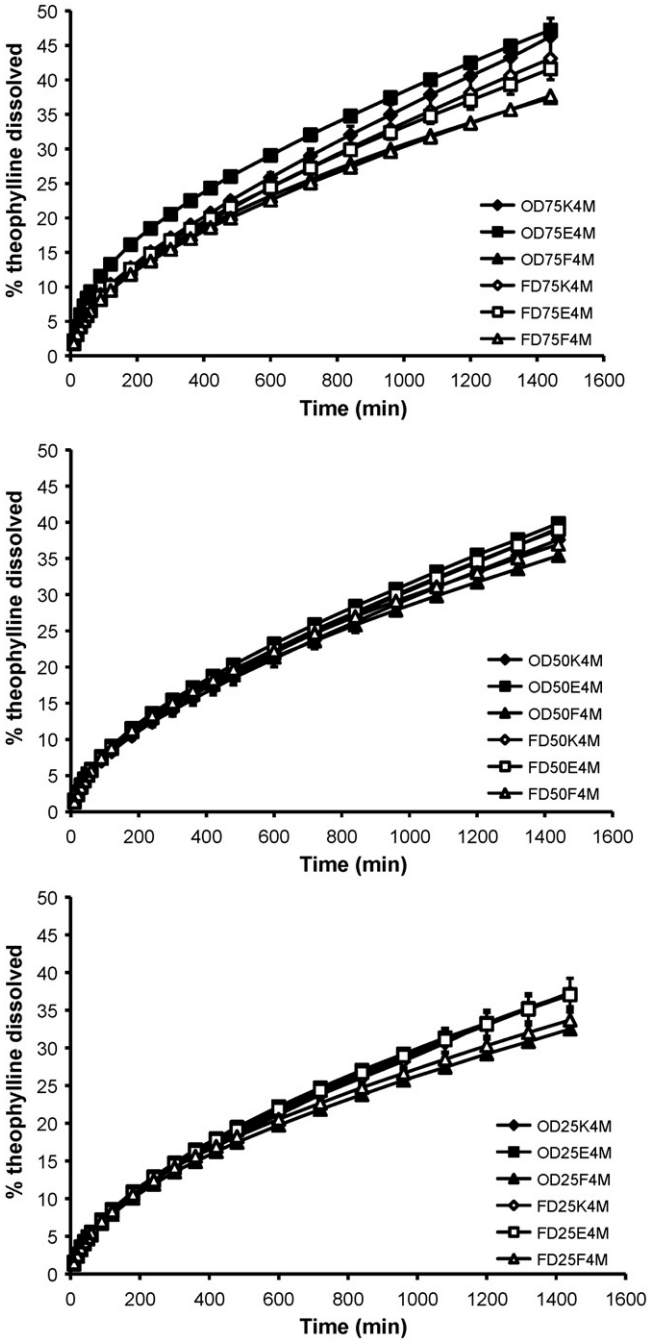

Fig. 2. Release profiles of anhydrous theophylline (over 24 h) from mixtures of HPMC with HCMMA. The bars show the standard deviation.

E4M and K4M. Not important differences were found to f_2 in the case of F4M related to either proportion or drying method used (f_2 > 86).

Release data ($M_t/M_\infty \leq 0.6$) were analysed according to Higuchi (1963), Korsmeyer et al. (1983), and Peppas and Sahlin (1989) equations. The main parameters are listed in Table 6 for 100% mixtures, and in Tables 7 and 8 for mixtures of OD-HCMMA:HPMC and FD-HCMMA:HPMC, respectively. As the matrices studied presented an aspect ratio (diameter/thickness) around 3, the m value was 0.44 (Peppas and Sahlin, 1989). The determination coefficient (r^2) and the *F*-ratio probability were used to test the applicability of the release models.

Although the matrices with two polymers (Tables 7 and 8) had a good fit to Higuchi equation, indicative of a diffusion mecha-

Table 6
Mathematical modelling and drug release kinetics from 100% matrices.

Mixture	Higuchi equation		Korsmeyer equation			Peppas equation		
	k ($min^{-1/2}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
OD-HCMMA	0.011	0.9950 (F = 4011)	0.49	0.013	0.9869 (F = 1500)	0.021	0.00011	1.0000 (F = 24393)
FD-HCMMA	0.009	0.9999 (F = 273578)	0.55	0.007	0.9957 (F = 4614)	0.013	0.00008	1.0000 (F = 457998)
HPMC K4M	0.009	0.9982 (F = 10857)	0.61	0.004	0.9990 (F = 20588)	0.010	0.00020	1.0000 (F = 292743)
HPMC E4M	0.011	0.9979 (F = 9495)	0.64	0.004	0.9986 (F = 14334)	0.011	0.00023	1.0000 (F = 323812)
HPMC F4M	0.009	0.9991 (F = 21947)	0.63	0.003	0.9953 (F = 4215)	0.010	0.00015	0.9999 (F = 118900)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis (p = 0.000).
OD/FD-HCMMA and K4M mixtures were published in Escudero et al. (2008).

Table 7
Mathematical modelling and drug release kinetics from OD-HCMMA–HPMC mixtures.

Mixture	Higuchi equation		Korsmeyer equation			Peppas equation		
	k ($min^{-1/2}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
OD75K4M	0.012	0.9937 (F = 3147)	0.60	0.006	0.9962 (F = 5285)	0.010	0.00038	0.9997 (F = 27002)
OD75E4M	0.012	0.9990 (F = 19068)	0.56	0.009	0.9879 (F = 1635)	0.016	0.00014	0.9993 (F = 13249)
OD75F4M	0.010	0.9998 (F = 92949)	0.59	0.006	0.9949 (F = 3732)	0.013	0.00013	1.0000 (F = 495932)
OD50K4M	0.010	0.9948 (F = 3834)	0.62	0.004	0.9979 (F = 9185)	0.008	0.00030	0.9998 (F = 59250)
OD50E4M	0.011	0.9974 (F = 7757)	0.62	0.004	0.9982 (F = 11287)	0.011	0.00025	1.0000 (F = 226444)
OD50F4M	0.010	0.9992 (F = 24495)	0.59	0.005	0.9971 (F = 6925)	0.011	0.00016	0.9999 (F = 130262)
OD25K4M	0.010	0.9962 (F = 6305)	0.61	0.004	0.9984 (F = 12454)	0.010	0.00025	0.9999 (F = 97685)
OD25E4M	0.010	0.9986 (F = 14351)	0.61	0.004	0.9987 (F = 14793)	0.011	0.00020	1.0000 (F = 286940)
OD25F4M	0.009	0.9996 (F = 45568)	0.61	0.004	0.9956 (F = 4469)	0.011	0.00013	1.0000 (F = 291821)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis (p = 0.000).
K4M mixtures were published in Escudero et al. (2008).

Table 8
Mathematical modelling and drug release kinetics from FD-HCMMA–HPMC mixtures.

Mixture	Higuchi equation		Korsmeyer equation			Peppas equation		
	k ($min^{-1/2}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
FD75K4M	0.012	0.9946 (F = 3660)	0.60	0.005	0.9986 (F = 14437)	0.009	0.00034	0.9998 (F = 37686)
FD75E4M	0.011	0.9981 (F = 10556)	0.60	0.005	0.9968 (F = 6235)	0.012	0.00023	0.9999 (F = 65065)
FD75F4M	0.010	0.9986 (F = 14430)	0.57	0.006	0.9971 (F = 6875)	0.011	0.00019	0.9999 (F = 73196)
FD50K4M	0.011	0.9950 (F = 3956)	0.64	0.004	0.9971 (F = 6786)	0.009	0.00030	0.9998 (F = 55770)
FD50E4M	0.011	0.9968 (F = 6313)	0.63	0.004	0.9968 (F = 6190)	0.010	0.00026	0.9999 (F = 143278)
FD50F4M	0.010	0.9995 (F = 36444)	0.63	0.004	0.9934 (F = 3020)	0.012	0.00015	0.9999 (F = 146442)
FD25K4M	0.010	0.9959 (F = 4802)	0.61	0.004	0.9990 (F = 20669)	0.009	0.00027	0.9997 (F = 33262)
FD25E4M	0.010	0.9985 (F = 12968)	0.64	0.004	0.9965 (F = 5710)	0.011	0.00021	1.0000 (F = 632458)
FD25F4M	0.009	0.9996 (F = 53599)	0.60	0.004	0.9961 (F = 5105)	0.011	0.00013	0.9999 (F = 172171)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis (p = 0.000).
K4M mixtures were published in Escudero et al. (2008).

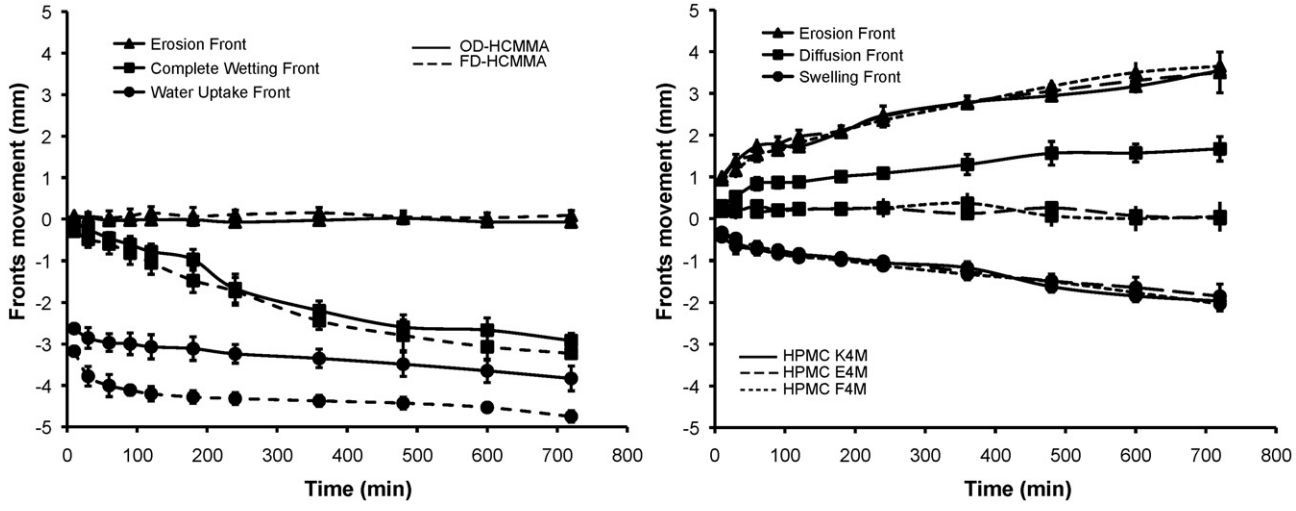

Fig. 3. Fronts movement (over 12 h) from 100% matrices.

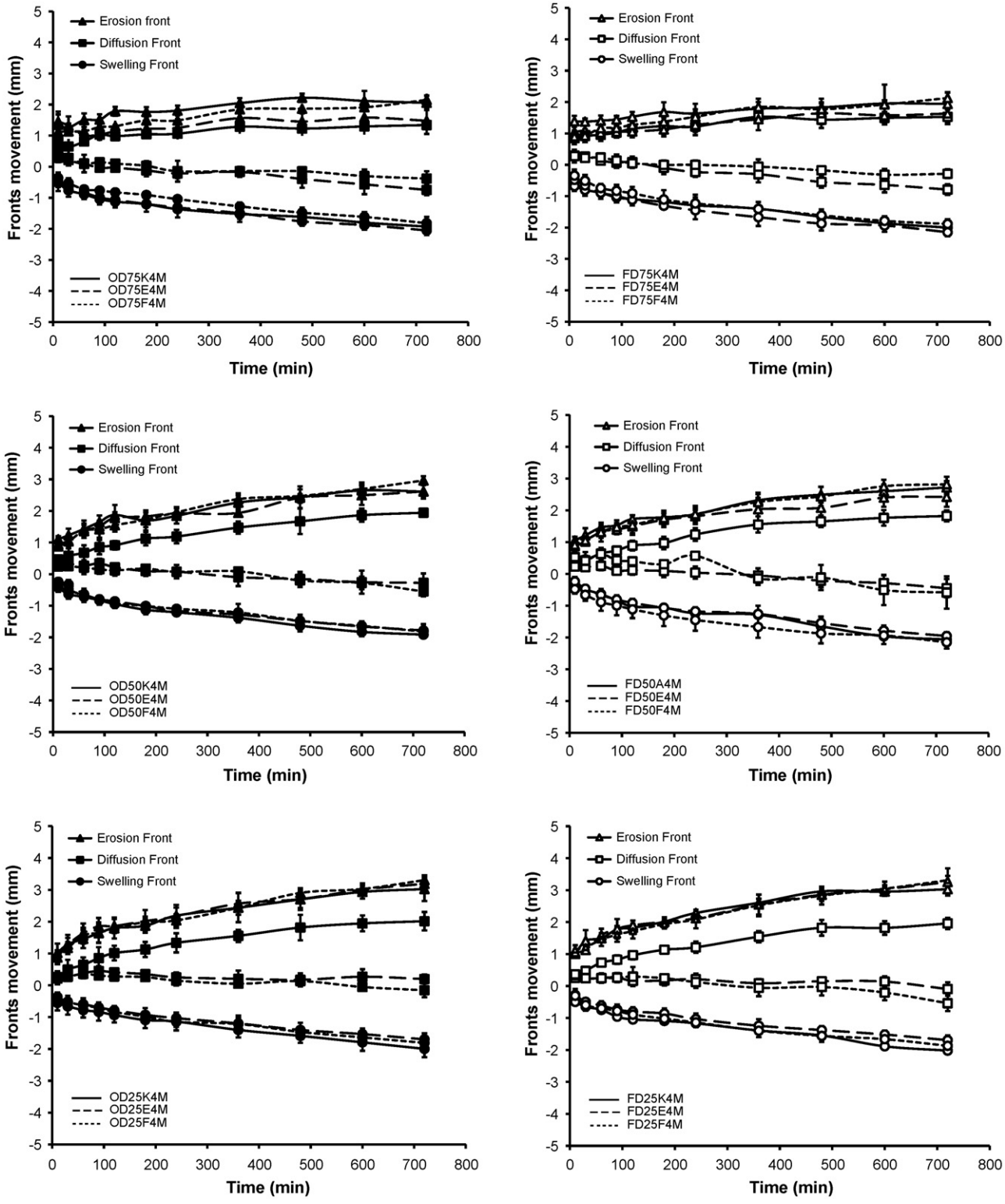

Fig. 4. Fronts movement (over 12 h) from HCMMA–HPMC mixtures.

nism, as the n values from Korsmeyer equation were higher than 0.50, and the values of k_r in Peppas and Sahlin equation were high, a combination of diffusion and erosion release mechanism were found. Their k_d values remained more or less similar to HPMC 100%, apart from OD75E4M and F4M mixtures, lightly increased k_d values. However, the most important changes were found in k_r values. In this sense, all mixtures with F4M did not modify this parameter respect to F4M 100%, in concordance with the lowest theophylline release. Likewise, all mixtures with E4M presented similar k_r values to E4M 100% proportion, except to OD75E4M, that showed the lowest k_r value, but in contrast, the highest k_d value that could justify its higher theophylline release. All mixtures with K4M showed the highest k_r values, which decreased when HCMMA proportion decreased, in concordance with the compression properties.

Table 9
Apparent diffusion coefficient (D') for all mixtures.

Mixture	D' (cm^2/min)	Mixture	D' (cm^2/min)	Mixture	D' (cm^2/min)
OD-HCMMA	7.24×10^{-4}	OD75K4M	6.87×10^{-4}	FD75K4M	5.51×10^{-4}
FD-HCMMA	3.54×10^{-4}	OD75E4M	6.20×10^{-4}	FD75E4M	5.04×10^{-4}
HPMC K4M	2.50×10^{-4}	OD75F4M	5.85×10^{-4}	FD75F4M	4.52×10^{-4}
HPMC E4M	5.40×10^{-4}	OD50K4M	3.72×10^{-4}	FD50K4M	3.48×10^{-4}
HPMC F4M	2.87×10^{-4}	OD50E4M	5.29×10^{-4}	FD50E4M	5.16×10^{-4}
		OD50F4M	4.67×10^{-4}	FD50F4M	3.35×10^{-4}
		OD25K4M	3.50×10^{-4}	FD25K4M	2.94×10^{-4}
		OD25E4M	4.48×10^{-4}	FD25E4M	3.99×10^{-4}
		OD25F4M	2.92×10^{-4}	FD25F4M	2.44×10^{-4}

OD/FD-HCMMA and K4M mixtures were published in Escudero et al. (2008).

3.6. Fronts movement study

Fronts movement kinetics were evaluated (Ferrero et al., 2003) in order to obtain useful information for a better understanding of the drug release mechanism from different matrices. In a previous paper (Escudero et al., 2008) we explained more extensively the different behaviour of HCMMA matrices, according to the porosity and tortuosity values of the tablets. According to Ferrero et al. (2000) for inert matrices (HCMMA, 100%), three fronts could be clearly distinguished from the centre to the periphery of the matrix: water uptake front (between dry-partial wet polymer), complete wetting front (distinguishes a partial hydrated zone from a complete wet one) and erosion front (between the external surface of the matrix and the dissolution medium).

For swellable matrix tablets, as HPMC 100%, Colombo et al. (1995) proposed three fronts: swelling front (between the still glassy polymer and its rubbery gel state), diffusion front (between the still undissolved (solid) drug and the dissolved drug in the gel layer) and erosion front (between the matrix and the dissolution medium). In Fig. 3 no important differences can be seen in the erosion and swelling fronts for the three swellable matrices tested. Similarly, Ford (1999) did not found differences in water uptake of HPMC K4M, E4M and F4M. However, the diffusion front was different for HPMC K4M. This is due to the higher hydrophilic character of K4M that leads less available water to dissolve the theophylline.

For the different mixtures HCMMA–HPMC, it is possible to see fronts movement profiles similar to swellable matrices (Fig. 4), with no changes in swelling fronts compared to HPMC 100% matrices. On the other hand, erosion fronts increased for all mixtures when the proportion of HCMMA decreased. The highest differences were observed for the 75:25 proportion related to other ratios. About the substitution degree, the lowest advance of erosion front in E4M mixtures was in agreement with its highest release.

Again only K4M mixtures showed a diffusion front that moved outwards, whereas E4M and F4M diffusion front moved lightly inwards, that implies that the formation of clear gel was quicker in the latters than in K4M mixtures. In addition, it is possible to see small differences between OD- and FD-K4M mixtures.

Lotfipour et al. (2004) explained the effect of the fillers on the release rate of atenolol, because they reduced the tortuosity of the diffusion path of the drug. We calculated the apparent diffusion coefficient (D') (Table 9), obtained from the Higuchi rate constant. D' is expressed as D/τ, where τ is the tortuosity of the matrix and D is the effective diffusion coefficient of the drug in the dissolution medium. In HCMMA:HPMC mixtures, when HPMC percentage decreased, tortuosity decreased, in agreement with Khurahashi et al. (1996). Although there was not a clear tendency in substitution degree, in general F4M mixtures had the higher tortuosity according with the lowest theophylline release.

The gel layer thickness (Colombo et al., 1995) is defined as the difference between erosion and swelling front positions. The gel layer thickness was similar to K4M, F4M and E4M 100% mixtures. Besides, it rose when decreased the proportion of HCMMA in the mixtures. In all cases, E4M mixtures showed the lowest values. In addition, it is not possible to see differences between OD and FD mixtures.

4. Conclusions

Presence of HCMMA did not provide advantages in terms of compactions performance in the mixtures. However, mixtures with FD-HCMMA showed better compression properties than OD-HCMMA mixtures. The drying method used for HCMMA only affected the theophylline release at high concentration of these polymers in the mixtures. Diffusion and erosion mechanisms, joined to tortuosity on F4M mixtures leaded to a best control of theophylline release. The higher hydrophilicity of K4M explains the different diffusion front movement observed compared to the other HPMCs.

The modulation of theophylline monoaxial release combining swellable and inert polymers is only obtained with a mixture of HCMMA:HPMC 75:25, where HCMMA plays more important role than the viscosity (Escudero et al., 2008) or different degrees of methoxy/hydroxypropyl substitution of HPMC. It is true that similar theophylline release profiles are possible to see from mixtures HCMMA/HPMC of different viscosity grades (HPMC K4M, K15M and K100M) (Escudero et al., 2008) in relation with HCMMA/HPMC of different substitution type (HPMC K4M, E4M and F4M) justify by the experimental design. However, it is interesting to mention that only the mixture OD-HCMMA/HPMC E4M showed a high diffusion constant value (k_d) from Peppas equation to the proportion 75:25. Also, important differences are found in relation with relaxation rate constant values (k_r). So, the mixtures with E4M and F4M exhibited the lowest k_r values, which indicate that HCMMA destabilize less the gel structure of these two polymers than to K HPMC series (Escudero et al., 2008). Besides, the formation of a more clear gel in E4M and F4M mixtures was made evident by the fronts movement results. However, at 75:25 proportion and from a technological point of view, K HPMC series (Escudero et al., 2008) show better compression behaviour than E4M and F4M. Therefore, a lower cost to obtain the modulation could be obtained using K HPMC series than HPMC E4M or F4M. Finally, it would be interesting to test another type of cellulose like HPC or MC which could modulate better the theophylline release with the new HCMMA copolymer.

Acknowledgements

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