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Compaction properties, drug release kinetics and fronts movement studies of matrices combining mixtures of swellable and inert polymers. III: Effect of polymer substitution type

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ABSTRACT

Theophylline radial release from cellulose derivatives with different substitution type (HPMC K4M, HPC H, MC A4M) matrix tablets has been modulated by the introduction of a new inert polymeric excipient, at different proportions (75, 50, 25%). The new polymer was hydroxypropylcellulose-methyl methacrylate (HCMMA), which was dried either in a vacuum oven (OD-HCMMA) or freeze-dried (FD-HCMMA). MC A4M and its mixtures presented the best compaction properties results, especially mixed with FD-HCMMA, according to 100% mixtures. Only high levels of HCMMA (75%) in the matrices showed interesting differences to drug release modulation. Also, at this proportion (75:25), the HPC H mixtures presented the highest differences in relation with OD or FD HCMMA respect to the other cellulose polymers. HPMC K4M and HPC H mixtures showed a combination of diffusion and erosion release mechanisms. The last one was nearly negligible in MC A4M mixtures, according with its highest diffusion rate constant values, and the absence of hydroxypropyl substituents. Only HPMC K4M mixtures presented a diffusion front that moves outwards, while HPC H and MC A4M moves inwards. The modulation of theophylline radial release was obtained using a high percentage of HCMMA, and the use of two cellulosic ethers, one of them with just one type of substituent (MC A4M or HPC H) and the other with two types of substituent (HPMC K4M). Another possibility is changing the HCMMA copolymer (OD or FD) in the 75/25 mixture with HPC.

1. Introduction

Cellulose derivatives are widely used to control the release of drugs from matrix formulations. However, according to the different characteristics of the polymer used, the drug delivery systems exhibit different release kinetics and swelling behaviour (Bettini et al., 1994). Also, the drug release from cellulose-tablets can be modified by the addition of other hydrophilic polymers. So Pérez-Marcos et al. (1994) indicated that combining propanolol hydrochloride with carpobol® 974 and HPMC K4M, these ingredients are capable of interacting to some extent with each other to control drug release (Pérez-Marcos et al., 1996).

Bonferoni et al. (1994) demonstrated that salbutamol sulphate and chlorpheniramine maleate release profiles can be modified by the mixture of λ-carrageenan and HPMC K4M due to the combination of different release mechanisms (Bonferoni et al., 1998). Nerurkar et al. (2005) indicated that lambda and iota carrageenan can be used in combination with cellulose ethers for the formulation of controlled-release ibuprofen tablets. Traconis et al. (1997) and Conti et al. (2007) studied the effect of addition of CMCNa to HPMC in the controlled release of metronidazole and diltiazem HCl, respectively. Juárez et al. (2001) related that the addition of CMC to HPMC matrices to get zero-order release kinetics could only be obtained by restricting the dissolution process. Also, the polymer's degree of substitution, position of the hydroxyl groups and viscosity grade contributes to the strength of interpolymer interactions non-ionic and ionic polymers.

The dissolution profiles obtained for atenolol tablets made with HPMC K100LV/K100M mixtures showed that the use of these polymers permits an efficient control of the release (Vázquez et al., 1996). It has been shown that the methacrylate acid polymer (Eudragit® L100-55) can significantly enhance the release of weakly basic drugs (papaverine HCl or propanolol HCl) from HPMC based hydrophilic matrices (Takka et al., 2001; Tatavarti et al., 2004; Tatavarti and Hoag, 2006).

Also, the drug release from HPMC matrix tablets has been modified for various purposes through the addition of anionic surfactants, ion-exchange resins (Feely and Davis, 1998; Sriwongjanya and Bodmeier, 1998; Takka et al., 2001), poly(ethyloxazoline)

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(Shenouda et al., 1990) and hydrogenated vegetable oil (Kiortsis et al., 2005).

Recently, Escudero et al. (2010, 2008) demonstrated the possibility of modulation of theophylline release. They mixed a new generation of copolymers – hydroxypropylcellulose-methyl methacrylate (HCMMA) – with HPMC of different viscosity grades or with different degrees of substitution (Castellano et al., 1997; Ferrero et al., 2003; Ferrero and Jiménez-Castellanos, 2002). So, they combined the porosity, tortuosity and water uptake capacity from inert matrices as well as the influence of swelling rate from hydrophilic matrices. On another hand, it is known that cellulose polymers of different substitution types (HPMC, MC, HPC) possess different degrees of hydrophilic and hydrophobic substitution. This influences the way water attaches itself to the polymer (McCrystal et al., 1999) and, subsequently the formation of the barrier gel layer and water diffusion that determine the rate and mechanism of drug release (Rajabi-Siahboomi et al., 1996).

For the above reasons, the aim of this paper is to evaluate the influence of different mixtures on technological characteristics and drug release from matrix tablets. These will contain hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) or methylcellulose (MC) of same viscosity grade, 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 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 type on cellulose derivative.

2. Materials and methods

2.1. Materials

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 –. The OD product was crushed in a knives mill (Retsch, Haan, Germany) to obtain powdery samples.

Hydrophilic cellulose ethers: hydroxypropylmethylcellulose (Methocel® K4M – 4000 mPa s –, with 19–24% methoxyl groups and 7–12% hydroxypropyl groups, Premium EP, Colorcon, England, batch KI10012N02), methyl cellulose (MC A4M – 4000 mPa s – with 27.5–31.5% methoxyl groups, Premium EP, Colorcon, England, batch OC11012 N02), and hydroxypropylcellulose (HPC H-1000 – 4000 mPa s – with 53.4–77.5% hydroxypropyl groups, Nisso®, Isiza, Spain, batch NAE-3601) were selected as swellable polymers.

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 or MC or HPC) 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:swelling polymer 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, 25%), and the background is the variety of hydrophilic polymer (K4M, A4M, HPC).

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 (2010).

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) described 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 (2010).

The thickness of 10 tablets was measured individually placing them in and parallel to the face of an electronic micrometre (Mitutoyo MDC-M293, Tokyo, Japan).

The breaking force (European Pharmacopoeia, 2010) of 10 tablets was determined by diametrical loading with a Schleuninger-2E tester (Greifensee, Switzerland).

Tablet friability (European Pharmacopoeia, 2010) 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 0.1–60,000 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, 2010) 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 were analysed according to Baker and Lonsdale (1974) ($M_t/M_\infty \leq 0.4$) (1) and Peppas and Sahlin (1989) ($M_t/M_\infty \leq 0.6$) (2) equations:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi r^2}\right)^{1/2} - \left(\frac{Dt}{r^2}\right) \quad (1)$$

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

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), D is the diffusion coefficient, r is cylinder radius, t is the release time, 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 parameters present in each equation were determined by linear or non-linear least-squares fitting methods with SPSS® 14.0 software. The corrected determination coefficient (r^2) was used to test the applicability of the release models.

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

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

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, 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

Only OD-HCMMA did not show statistical apparent densities differences with HPC ($p > 0.05$) at 100% ratio (Table 1). This is due to the similar particle size determined on a vibratory sieve shaker (Retsch Vibro, Haan, Germany) (154 μm and 168 μm, respectively).

In general, the apparent density values of mixtures at different proportions and similar substitution type were between the values found for 100% formulations. Moreover, the densities increase when the proportion of HCMMA (OD or FD) in the mixture decreased, except to the FD-HCMMA and HPC H mixtures. A more similar particle size distribution (skewness coefficient 0.46 and 0.66 to FD-HCMMA and HPC H, respectively), and the lack of particle sizes lower than 54 μm for both polymers, explain these results.

Finally, respect to the substitution type factor, the HPC H mixtures display lower apparent density values than the other ones at the same proportion ($p < 0.05$), according to the 100% ratio. These results agree with the different particle size distribution between HPC H and the other two celluloses derivatives (skewness coefficient: 0.66 to HPC H, 1.62 to HPMC K4M and 2.46 to MC A4M). Moreover, only HPC H show lack of particle sizes lower than 54 μm.

3.2. Compaction parameters of tablets

Taking into account that theophylline is a plastic drug (Picker, 1999; Vachon and Chulia, 1999), we found good compaction properties for hydrophilic cellulose ethers in agreement with others authors (Doelker, 1987; Nerurkar et al., 2005; Vueba et al., 2004) (Table 2). So, these cellulose derivatives showed higher plasticity, lower elastic expansion and easier tablet elaboration (lower W_{an}) than HCMMA matrices. In consequence, in the mixtures of two polymers, the necessary pressure to obtain the tablets decreased and the plasticity increased when HCMMA percentage decreased in the mixtures (Table 3). We also observed that mixtures with FD-HCMMA needed less pressure, exhibited lower expansion work, and higher plasticity and hence, higher facility to obtain the tablets, than OD-HCMMA mixtures. These results agree with the parameters corresponding to 100% formulations.

At same percentage in the formulations, MC A4M mixtures showed lower applied pressure, elastic expansion and apparent net work than HPMC K4M and HPC H mixtures, in agreement with 100% formulations.

We observed that the lubrication ratio values (data not shown) obtained from all formulations (0.8–0.6) 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 (436–132 N) that were lower than 750 N (Bolhuis and Lerk, 1973).

3.3. Physical characteristics of tablets

The breaking force test confirmed the values of 70–80 N for all tablets (European Pharmacopoeia, 2010) (Tables 2 and 4). Although, all tablets fulfilled the guidelines specified in European Pharmacopoeia (2010) related to weight uniformity test, comparing OD and FD tablets, we can observe different values in the other parameters. In general, FD-HCMMA tablets displayed higher thickness and friability than OD tablets. These results might be related to a more porous structure in FD matrices.

Table 1
Apparent particle density values ($n = 3$) from HCMMA:swellable polymer 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	OD75A4M	1.303 ± 0.005	FD75A4M	1.302 ± 0.002
HPMC K4M	1.365 ± 0.004	OD75HPC	1.271 ± 0.004	FD75HPC	1.281 ± 0.001
MC A4M	1.360 ± 0.002	OD50K4M	1.310 ± 0.003	FD50K4M	1.315 ± 0.002
HPC H	1.259 ± 0.001	OD50A4M	1.306 ± 0.002	FD50A4M	1.305 ± 0.001
		OD50HPC	1.261 ± 0.003	FD50HPC	1.268 ± 0.001
		OD25K4M	1.339 ± 0.004	FD25K4M	1.341 ± 0.005
		OD25A4M	1.332 ± 0.002	FD25A4M	1.336 ± 0.001
		OD25HPC	1.271 ± 0.004	FD25HPC	1.278 ± 0.001

[a]OD/FD-HCMMA and K4M mixtures were published (Escudero et al., 2008). Not statistical differences were found between: OD-HCMMA 100% and ODHCMMA-HPC H 25:75 and ODHCMMA-HPC H 75:25; FD-HCMMA 100% and FDHCMMA-HPC H 75:25.

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 ± 5	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	161 ± 2	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	44 ± 1	4.3 ± 0.1	0.1 ± 0.0	97.0 ± 0.4	498.8 ± 1.6	4.513 ± 0.018	74 ± 4	1.58
MC A4M	24 ± 1	2.9 ± 0.1	0.0 ± 0.0	99.0 ± 0.1	501.3 ± 1.8	4.815 ± 0·012	80 ± 2	1.23
HPC	37 ± 1	3.6 ± 0.1	0.0 ± 0.0	98.7 ± 0.2	499.2 ± 1.5	4.368 ± 0.014	75 ± 2	1.51

[a]OD/FD-HCMMA and K4M mixtures were published (Escudero et al., 2008).

Table 3
Compaction parameters ($n = 4$) from HCMMA:swellable polymer 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	175 ± 6	11.6 ± 0.4	1.2 ± 0.2	90.6 ± 1.1	FD75K4M	109 ± 1	9.3 ± 0.1	0.7 ± 0.0	93.4 ± 0.3
OD75A4M	145 ± 2	10.5 ± 0.3	1.1 ± 0.1	90.2 ± 0.8	FD75A4M	93 ± 2	8.5 ± 0.2	0.5 ± 0.0	94.4 ± 0.5
OD75HPC	211 ± 3	11.9 ± 0.3	1.8 ± 0.1	86.4 ± 1.1	FD75HPC	113 ± 1	10.4 ± 0.1	0.8 ± 0.1	93.3 ± 1.1
OD50K4M	100 ± 2	7.7 ± 0.1	0.5 ± 0.1	94.4 ± 1.2	FD50K4M	83 ± 0	7.5 ± 0.0	0.3 ± 0.0	96.4 ± 0.3
OD50A4M	67 ± 2	5.9 ± 0.2	0.3 ± 0.0	94.9 ± 0.5	FD50A4M	65 ± 1	6.2 ± 0.1	0.2 ± 0.0	96.8 ± 0.6
OD50HPC	114 ± 2	7.6 ± 0.2	0.4 ± 0.1	94.5 ± 1.0	FD50HPC	76 ± 1	6.1 ± 0.1	0.3 ± 0.0	94.9 ± 0.4
OD25K4M	60 ± 1	5.4 ± 0.1	0.4 ± 0.0	93.2 ± 0.7	FD25K4M	49 ± 1	4.8 ± 0.1	0.1 ± 0.0	97.0 ± 0.4
OD25A4M	38 ± 1	3.8 ± 0.1	0.2 ± 0.0	96.2 ± 1.1	FD25A4M	38 ± 0	4.1 ± 0.0	0.1 ± 0.0	97.4 ± 0.4
OD25HPC	49 ± 2	3.8 ± 0.1	0.1 ± 0.0	98.0 ± 0.3	FD25HPC	47 ± 2	3.8 ± 0.1	0.1 ± 0.0	97.4 ± 0.5

[a]K4M mixtures were published (Escudero et al., 2008). Not statistical differences were found between: *Plasticity*: OD25K4M and OD50K4M; OD25HPC and FD25HPC. *Expansion work*: OD25HPC and FD25HPC. *Apparent network*: OD50A4M and FD50A4M; OD25A4M and FD25A4M; OD25HPC and FD25HPC; OD25A4M and OD25HPC; FD50A4M and FD50HPC; FD25A4M and FD25HPC. *Elastic expansion*: OD25A4M and OD25HPC; FD25A4M and FD25HPC.

Only FD-HCMMA 100%, OD75HPC, OD25HPC, FD50HPC and FD25HPC presented friability values lower than 1% (European Pharmacopoeia, 2010). The high values observed for this parameter make us think about the need of increase the breaking force in a future.

3.4. Pore size of tablets

HCMMA presented lower porosity than hydrophilic cellulose ethers 100% (Table 5), in agreement with the thickness results (Table 2). Moreover, the higher porosity of FD respect to OD tablets confirms the physical results observed. In consequence of this, in the matrices with two polymers, the porosity values increased when decreased OD-HCMMA in the mixtures. On another hand, it is possible to see a similar behaviour in FD-MC A4M mixtures due to the different porosity values of both polymers. However, porosity values do not change in the case of FD-HPC H mixtures, due to the similar values presented for both polymers in 100% ratio.

The great difference in particle size and particle size distribution along with the different porosity values of FD and HPMC K4M explain that the 50:50 mixture reaches the porosity value of HPMC K4M 100%.

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%, MC A4M 100%, OD/FD25K4M and OD/FD25A4M, that displayed macropores (>500 Å).

Table 4
Physical tests from HCMMA:swellable polymer 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
OD75A4M	500.6 ± 1.1	4.270 ± 0.036	72 ± 2	1.29	FD75A4M	499.3 ± 1.1	4.432 ± 0.012	75 ± 2	1.69
OD75HPC	501.1 ± 1.3	4.092 ± 0.011	79 ± 2	0.99	FD75HPC	500.1 ± 1.1	4.445 ± 0.031	78 ± 3	1.95
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
OD50A4M	499.3 ± 1.3	4.452 ± 0.003	73 ± 3	1.44	FD50A4M	501.9 ± 0.8	4.638 ± 0.007	76 ± 3	2.05
OD50HPC	499.7 ± 1.9	4.195 ± 0.008	76 ± 2	1.40	FD50HPC	500.1 ± 1.3	4.117 ± 0.013	79 ± 4	0.98
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
OD25A4M	498.7 ± 1.1	4.626 ± 0.011	73 ± 6	1.40	FD25A4M	500.7 ± 1.2	4.754 ± 0.009	76 ± 2	1.46
OD25HPC	502.6 ± 1.5	4.248 ± 0.023	80 ± 2	0.87	FD25HPC	503.2 ± 1.7	4.350 ± 0.014	80 ± 1	0.96

[a]K4M mixtures were published (Escudero et al., 2008). Not statistical differences were found in thickness between OD50HPC and FD50HPC.

Table 5
Porosity values ($n = 2$) from HCMMA:swellable polymer 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	OD75A4M	25.5 ± 0.8	FD75A4M	28.3 ± 0.5
HPMC K4M	31.4 ± 2.7	OD75HPC	19.8 ± 1.2	FD75HPC	24.6 ± 0.2
MC A4M	36.3 ± 0.3	OD50K4M	27.2 ± 0.2	FD50K4M	34.0 ± 7.4
HPC	25.8 ± 0.7	OD50A4M	26.7 ± 0.6	FD50A4M	31.7 ± 0.1
		OD50HPC	21.2 ± 0.1	FD50HPC	23.4 ± 0.3
		OD25K4M	28.5 ± 2.3	FD25K4M	32.7 ± 0.1
		OD25A4M	34.6 ± 0.3	FD25A4M	35.6 ± 0.3
		OD25HPC	23.0 ± 0.1	FD25HPC	24.8 ± 0.5

[a] OD/FD-HCMMA and K4M mixtures were published (Escudero et al., 2008). Not statistical differences were found between FD50HPC and FD-HCMMA 100%; OD25HPC and FD25HPC.

3.5. Drug release study

Fig. 1 illustrates the drug release profiles from HCMMA and ethers of cellulose 100% matrices. All tablets showed a drug release lower than 50% at 1440 min. Besides, whereas OD-HCMMA tablets show the fastest drug release, HPC H tablets displayed the lowest values. However, not biopharmaceutical relevant differences were found ($f_2 = 51.6$). On another hand, MC A4M and HPMC K4M showed similar release profiles than FD-HCMMA ($f_2 = 96.3$ and 85.2, respectively).

The mixtures of polymers presented a percentage of theophylline release between 47% and 32% at 1440 min (Fig. 2). However, only the matrices HCMMA:ethers of cellulose (75:25) showed biopharmaceutical relevant differences ($f_2 > 50$ to 50:50 and 25:75 proportions). So, respect to OD-HCMMA, the highest variations were found with MC A4M, which exhibited the lowest theophylline release, in agreement with its minor hidrophilicity (theophylline is a poor water soluble drug). However, to FD-HCMMA, the main differences were observed with HPMC K4M, which presented the highest theophylline release. Therefore, the HPC H mixtures displayed the highest differences between OD and FD HCMMA compared to the other hydrophilic cellulose ethers.

Release data were analysed according to Baker and Lonsdale (1974), and Peppas and Sahlin (1989) equations (Tables 6–8). As the cylindrical geometry is concerned with the present release device used, the m value was 0.44 (Peppas and Sahlin, 1989). The corrected determination coefficient (r^2) was used to test the applicability of the release models.

The same sequence observed for drug release profiles from 100% matrices (Fig. 1) was obtained to D values (Table 6). We found in general a combination of diffusion and erosion mechanisms.

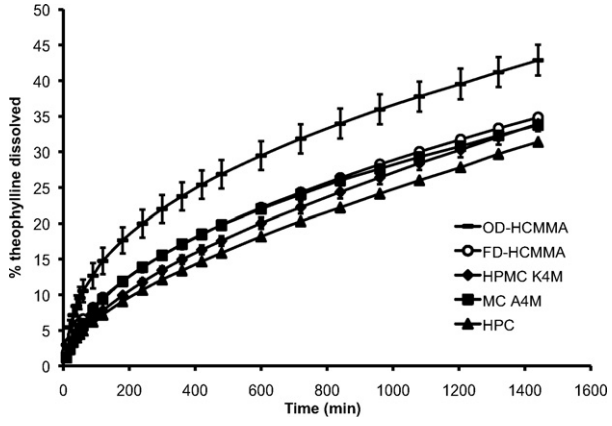

Fig. 1. Release profiles of anhydrous theophylline (over 24 h) from 100% tablets. The bars show the standard deviation.

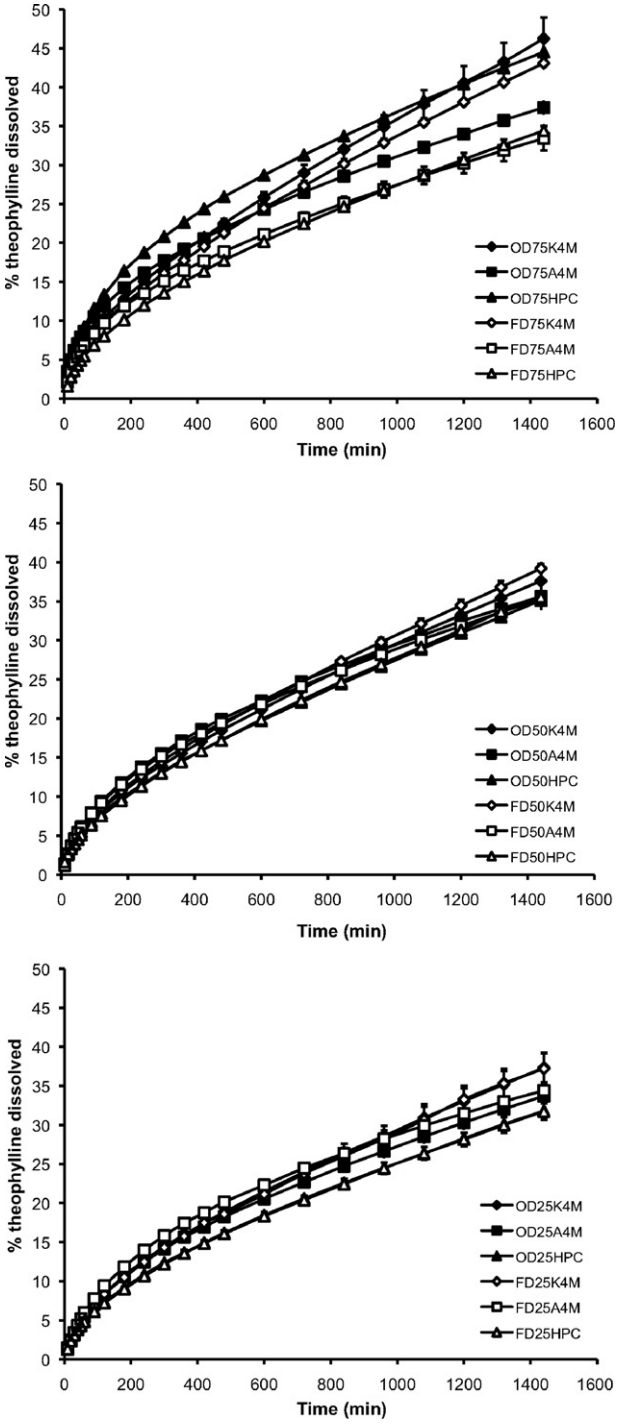

Fig. 2. Release profiles of anhydrous theophylline (over 24 h) from mixtures of swellable polymers with HCMMA. The bars show the standard deviation.

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

Mixture	Baker equation		Peppas equation		
	D (cm^2/s)	r^2	k_d (min$^{-0.44}$)	k_r (min$^{-0.88}$)	r^2
OD-HCMMA	2.50×10^{-7}	0.9991	0.021	0.00011	0.9996
FD-HCMMA	1.09×10^{-7}	0.9999	0.013	0.00008	0.9999
HPMC K4M	0.69×10^{-7}	1.0000	0.010	0.00020	0.9999
MC A4M	1.47×10^{-7}	0.9998	0.016	−0.00002	0.9999
HPC	0.43×10^{-7}	0.9999	0.007	0.00023	0.9999

[a] k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant and r^2, corrected determination coefficient to OD/FD-HCMMA and K4M mixtures were published (Escudero et al., 2008).

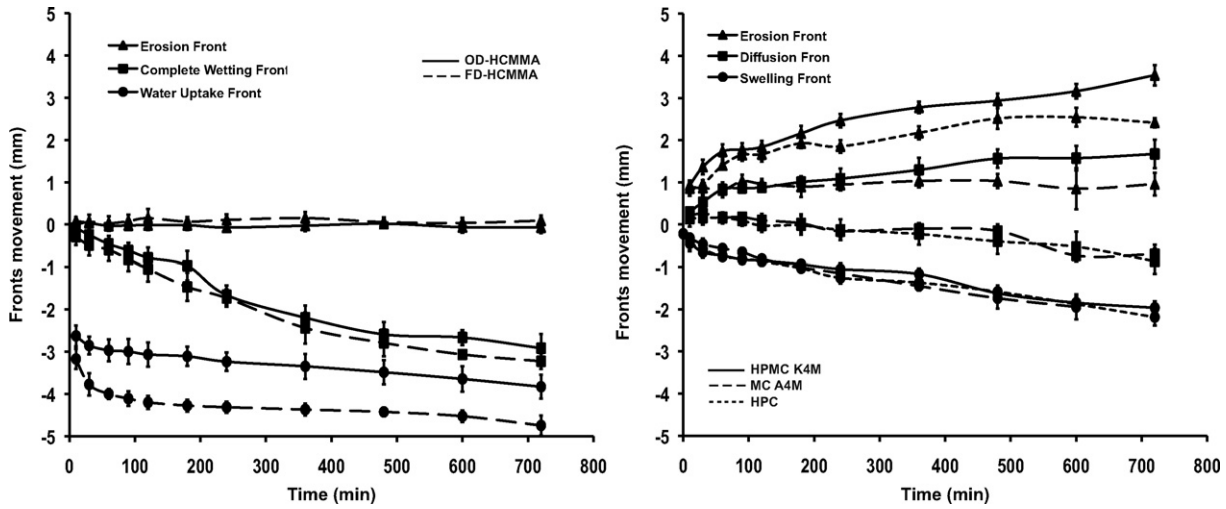

Fig. 3. Fronts movement (over 12 h) from 100% matrices.

Table 7
Mathematical modelling and drug release kinetics from OD HCMMA:swellable polymer mixtures.

Mixture	Baker equation		Peppas equation		
	D (cm^2/s)	r^2	k_d (min$^{-0.44}$)	k_r (min$^{-0.88}$)	r^2
OD75K4M	0.79×10^{-7}	0.9996	0.010	0.00038	0.9997
OD75A4M	1.18×10^{-7}	0.9995	0.014	0.00006	0.9994
OD75HPC	2.09×10^{-7}	0.9991	0.019	0.00032	0.9997
OD50K4M	0.59×10^{-7}	0.9998	0.008	0.00030	0.9999
OD50A4M	1.21×10^{-7}	0.9999	0.014	0.00008	0.9998
OD50HPC	0.42×10^{-7}	0.9998	0.007	0.00031	0.9998
OD25K4M	0.71×10^{-7}	0.9999	0.010	0.00025	0.9999
OD25A4M	0.88×10^{-7}	0.9999	0.011	0.00013	0.9999
OD25HPC	0.47×10^{-7}	0.9999	0.008	0.00022	0.9997

k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant and r^2, corrected determination coefficient to K4M mixtures were published (Escudero et al., 2008).

However, the last one was nearly negligible in 100% MC A4M and its mixtures (Tables 7 and 8). On the other side, HPC mixtures exhibited lower D values than HPMC K4M mixtures, but similar k_r values, according to 100% matrices. The exception of OD75HPC is due to a problem of particle junctions in the matrix tablets, taking into account the particle size of the polymers. So, as FD-HCMMA has high particle size, the incorporation of 25% of swelling polymer (with lower particle size) helps the junction formations among particles. This hypothesis is supported by the lower pressure data obtained for 75:25 FD-HCMMA:hydrophilic cellulose ethers mixtures (Table 3) than 100% FD-HCMMA (Escudero et al., 2008). Similar explanation could be proposed for OD75A4M. On the other hand, HPMC K4M and HPC H have similar particle size but with different particle distribution. So, while HPMC K4M has left-handed leptocurtic distribution and HPC H symmetric leptocurtic distribution, OD-HCMMA showed right-handed distribution (Staniforth, 2004). Therefore, the possibility to form particle junctions is higher in the mixture OD75K4M than in the mixture OD75HPC. The pressure values obtained for both mixtures support this conclusion (Table 3).

Table 8
Mathematical modelling and drug release kinetics from FD HCMMA:swellable polymer mixtures.

Mixture	Baker equation		Peppas equation		
	D (cm^2/s)	r^2	k_d (min$^{-0.44}$)	k_r (min$^{-0.88}$)	r^2
FD75K4M	0.75×10^{-7}	0.9997	0.009	0.00034	0.9997
FD75A4M	0.95×10^{-7}	0.9995	0.012	0.00008	0.9997
FD75HPC	0.63×10^{-7}	0.9999	0.009	0.00022	0.9999
FD50K4M	0.65×10^{-7}	0.9998	0.009	0.00030	0.9998
FD50A4M	1.12×10^{-7}	0.9998	0.013	0.00009	0.9999
FD50HPC	0.44×10^{-7}	0.9999	0.007	0.00031	0.9999
FD25K4M	0.65×10^{-7}	0.9999	0.009	0.00027	0.9997
FD25A4M	1.49×10^{-7}	0.9999	0.016	-0.00001	0.9999
FD25HPC	0.49×10^{-7}	0.9999	0.008	0.00022	0.9999

k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant and r^2, corrected determination coefficient to K4M mixtures were published (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, we explained more extensively the different behaviour of HCMMA matrices, according to the porosity and tortuosity values of the tablets (Escudero et al., 2008). 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, like 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).

We can find only remarkable differences in relation to diffusion and erosion fronts (Fig. 3). Respect to the first one, HPMC K4M presented a diffusion front that moves outwards while HPC H and MC A4M move inwards. This behaviour is justified by the amount of bound water to these polymers. So, according to McCrystal et al. (1999), HPC H and MC A4M have similar bound water content but lower than HPMC K4M. This implies more free water available to dissolve theophylline, and makes the diffusion front moves inwards. On another hand, the erosion front values ranked as followed: HPMC K4M $\geq$ HPC H > MC A4M, in agreement with the k_r values.

In HCMMA:hydrophilic cellulose ethers mixtures, the swelling front again do not depend on the type of polymer and the ratio, except to OD75HPC (Fig. 4). This last one has the fastest swelling

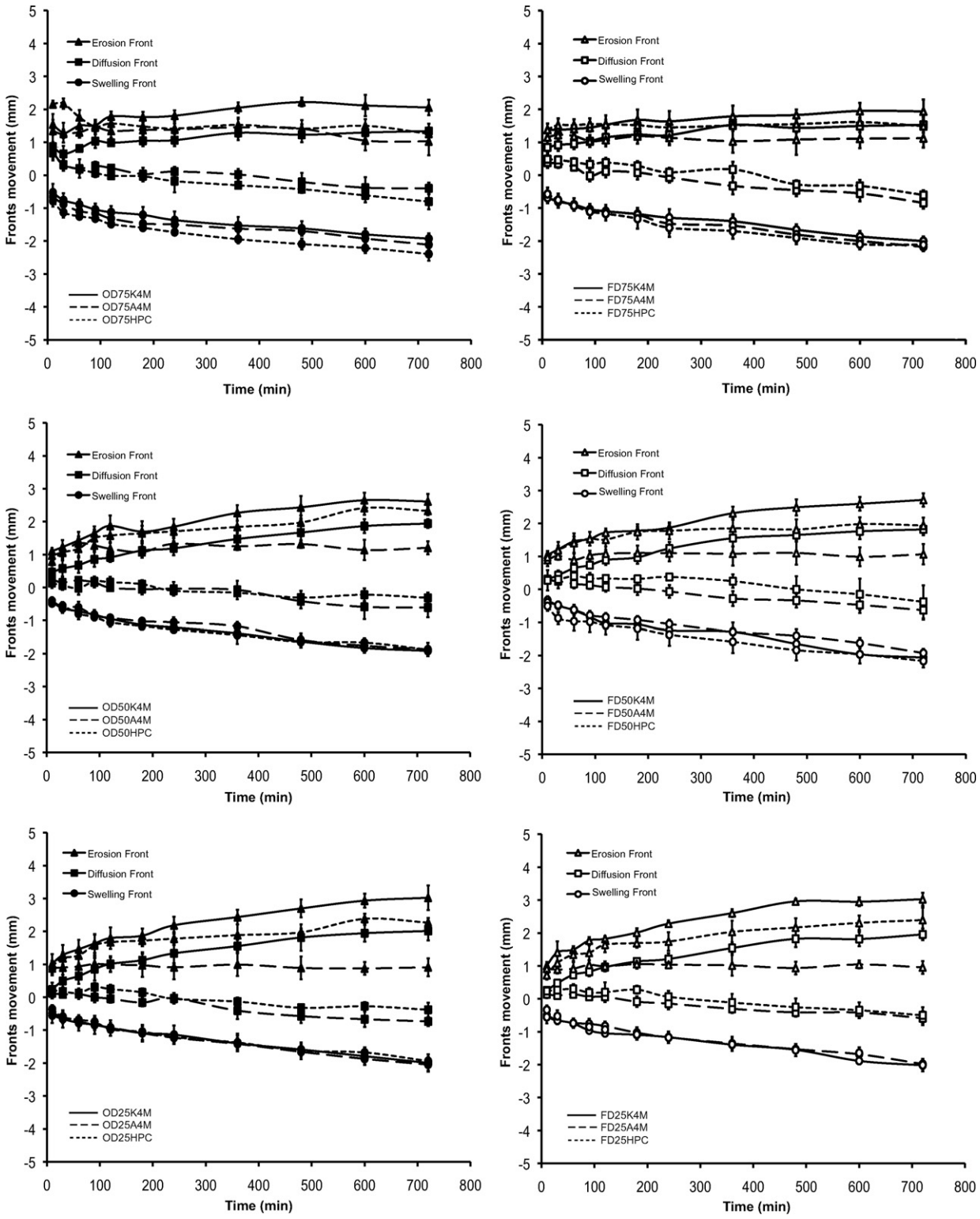

Fig. 4. Fronts movement (over 12 h) from HCMMA–swellable polymer mixtures.

front movement, in agreement with its highest D value. In relation with diffusion and erosion fronts, the 75:25 ratios displayed the lowest differences between these two front movements. Also, the erosion front movements were in agreement with the k_r values, due to the presence of inert polymer, which destabilises the gel structure. Thus, when HCMMA fraction decreases, this front movement increases.

The gel layer thickness (Colombo et al., 1995) is defined as the difference between erosion and swelling front positions (Fig. 5). OD and FD mixtures did not show remarkable differences in their behaviour. Moreover, these polymers governed the release control, reducing the gel thickness differences when HCMMA ratio increased in the mixtures. Respect to OD75HPC, it is possible to see a higher initial gel layer thickness (Fig. 5). This rapid growth

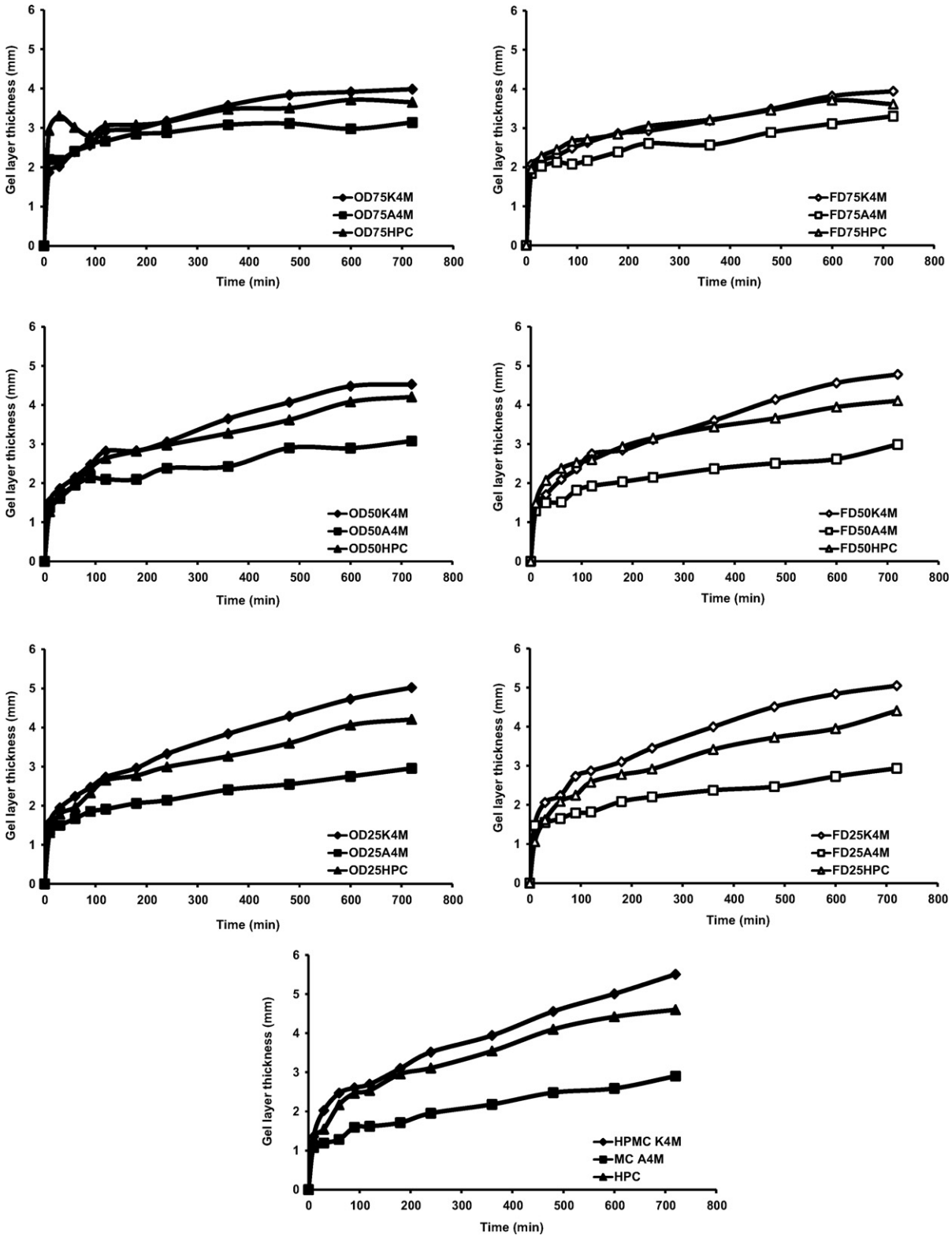

Fig. 5. Gel layer thickness from mixtures of swellable polymers with HCMMA and swellable polymers 100%.

provided a weak gel layer that could release the drug rapidly by diffusion, in agreement with its highest *D* value.

4. Conclusions

In this paper, we demonstrate the effect of polymer substitution type in the technological characteristics and controlled drug release in the mixtures studied. So, the absence of hydrophobic substitute (HPC H mixtures) implies lower density values than the other mixtures at the same ratio. However, the absence of hydrophilic substitute (MC A4M mixtures) showed the best compaction properties.

Respect to drug release profiles, the absence of hydrophobic or hydrophilic substituent in the cellulose ether polymers

(MC A4M and HPC H) means lower release profiles according to the inward movement of the diffusion front. Besides, the absence of hydrophilic substituent in the commercial polymer revealed just a diffusion mechanism, not diffusion and erosion like in the other cellulosic polymers. Also, the inert polymer hydroxypropylcellulose-methyl methacrylate (HCMMA) played a more relevant role than in the other two papers. So, in mixtures with 25% of HPC, the modulation was obtained just changing our inert polymer (OD or FD).

From these researches, we can conclude that in order to modulate the theophylline radial release we can use two mixtures containing: 75% of inert polymer (OD or FD-HCMMA) and 25% of two commercial polymers. Related to the commercial polymer there are three options: 1. The use of two HPMCs with markedly different viscosity grades (HPMC K4M or K15M and K100M) (Escudero et al., 2008); or 2. The use of HPMC F4M and another HPMC with a different substitution degree (HPMC E4M or HPMC K4M) (Escudero et al., 2010); or 3. The use of two cellulosic ethers, one of them with just one type of substituent (MC A4M or HPC H) and the other with two types of substituent (HPMC K4M).

Acknowledgements

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