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Compaction properties, drug release kinetics and fronts movement studies from matrices combining mixtures of swellable and inert polymers: Effect of HPMC of different viscosity grades

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Abstract

The aim of this paper is the modification of the release behaviour of hydrophilic HPMC-based matrices of different viscosity grade by the introduction of a new inert polymeric excipient hydroxypropylcellulose-methyl methacrylate (HCMMA). The drug released could be control by both mechanisms, the swelling rate from the hydrophilic matrices, and the porosity, tortuosity and water uptake capacity from inert matrices. The effects of drying methods, presence or absence of viscosity (HCMMA in relation with HPMC), proportion of two polymers and different viscosity grade of HPMC were studied. It was observed that the mixtures with FD-HCMMA needed less pressure, presented higher plasticity and their tablets were easier to obtain compared with OD-HCMMA mixtures. Only FD-HCMMA:K100M mixtures did not show any differences in the percentage of theophylline released when FD-HCMMA proportion changed ($f_2 > 95$). All mixtures show double release mechanism, diffusion and erosion from the gel layer, but with higher contribution of the relaxation factor than on HPMC tablets. For the different mixtures HCMMA–HPMC, it is possible to see fronts movement profiles similar to swellable matrices. The results demonstrate that the use of high viscosity differences of HPMC or 50% HCMMA or above was required to produce modifications on theophylline monoaxial release modulation.

Keywords: Hydroxypropyl methylcellulose; Hydroxypropylcellulose-methyl methacrylate; Viscosity; Release modulation; Drug delivery system; Theophylline

1. Introduction

In many therapies, it is necessary to adapt the release mechanism of the system to special biological characteristics. Monolithic devices or matrices represent a substantial part of the drug delivery systems. For oral administration, they are commonly manufactured as tablets by compaction of microparticulate powders. Generally, their release rate modulation is achieved using different types of polymers, distinguishing the most frequently, matrices containing swellable polymers or inert polymers. HPMC is the most commonly used hydrophilic polymer. The drug release mechanism of these hydrophilic systems occurs by water absorption, matrix swelling and, finally, drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer (Colombo et al., 1996). In order to improve the control of drug release kinetics from hydrophilic matrices, many attempts to manipulate the relative influence of the two mechanisms of diffusion and relaxation have been made. 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 ionic-exchange resin in the matrix (Feely and Davis, 1988), 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 design of drug release from hydrophilic matrices.

Following these principles, the aim of this paper is to modify the release behaviour of these hydrophilic matrices by the introduction of a new inert polymeric excipient which possesses different release mechanism, combining the influence of swelling rate from hydrophilic matrices as well as the porosity, tortuosity and water uptake capacity from inert matrices.

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Recently, a new generation of copolymers combining semi-synthetic (cellulose and starch derivatives) and synthetic (methacrylates) polymers (Castellano et al., 1997) have been introduced as excipients for oral controlled-release matrices. Technological characteristics (Ferrero and Jiménez-Castellanos, 2002) and drug release kinetics (Ferrero et al., 2003) of these new polymers have been studied.

This paper evaluates the influence of different mixtures on technological characteristics and drug release from matrix tablets containing HPMC of different viscosity grades (HPMC K4M; HPMC K15M and HPMC K100M), as hydrophilic polymer, hydroxypropylcellulose-methyl methacrylate (HCMMA), as inert polymer and theophylline as model drug. The results will be focused in four points that will be compared and discussed: (a) effect of drying method (HCMMA was dried by two methods: vacuum oven and freeze dried); (b) effect of presence or absence of viscosity (inert polymers in relation with hydrophilic polymers); (c) effect of different proportion of two polymers in the matrix tablets; (d) effect of different viscosity grade of HPMC.

2. Materials and methods

2.1. Materials

Hydroxypropylmethylcellulose (Methocel® K4M -4000 cP-, K15M -15000 cP- and K100M -100000 cP-, Premium EP., Colorcon, England, batches KI10012N02, LA07012N01 and KJ07012N02, respectively) was selected as swellable polymer. The copolymer (batch SS02) synthesised by free radical copolymerisation of methyl methacrylate (MMA) and hydroxypropylcellulose (HC) was selected 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.

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, the following number is the proportion of inert polymer in the mixture, and the background is the variety of hydrophilic polymer.

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 (2004).

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. Compaction data 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).

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, the standard deviation (S.D.) and the relative standard deviation (R.S.D.) were obtained from 20 individually weighed (Sartorius CP224S, Gottingen, Germany) tablets according to European Pharmacopoeia (2004).

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, 2004) of 10 tablets was determined by diametrical loading with a Schleuninger-2E tester (Greifensee, Switzerland).

Tablet friability (European Pharmacopoeia, 2004) 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. The volume of sample was roughly 20–90% of the penetrometer capacity. Working pressures covered the range 0.1–60000 psi and the mercury solid contact angle and surface tension were considered to be 130° and 485 erg/cm^3, respectively. Total porosity and pore size distribution were 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, 2004) 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) (1), Korsmeyer et al. (1983) (2) and Peppas and Sahlin (1989) (3) equation:

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

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

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

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 parameters present 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:

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

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.

2.2.8. Statistical analysis

Density values and compaction data 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 $p < 0.05$.

3. Results and discussion

3.1. Apparent density

Table 1 shows the apparent densities of mixtures containing different proportions of HCMMA (OD or FD) and HPMC (K4M, K15M or K100M). Apparent particle density values were statistically higher ($p < 0.05$) for FD than OD mixture (100:0) in agreement with Ferrero and Jiménez-Castellanos (2002), but lower ($p < 0.05$) than HPMC mixtures at the same proportions (0:100).

Table 1
Apparent density values 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) CV = 0.14%	OD75K4M	1.296 (0.002) CV = 0.19%	FD75K4M	1.302 (0.003) CV = 0.25%
FD-HCMMA	1.278 (0.004) CV = 0.31%	OD75K15M	1.284 (0.002) CV = 0.17%	FD75K15M	1.287 (0.004) CV = 0.32%
HPMC K4M	1.365 (0.004) CV = 0.26%	OD75K100M	1.293 (0.002) CV = 0.17%	FD75K100M	1.300 (0.002) CV = 0.12%
HPMC K15M	1.365 (0.002) CV = 0.12%	OD50K4M	1.310 (0.003) CV = 0.24%	FD50K4M	1.315 (0.002) CV = 0.14%
HPMC K100M	1.360 (0.002) CV = 0.13%	OD50K15M	1.306 (0.002) CV = 0.12%	FD50K15M	1.313 (0.006) CV = 0.44%
		OD50K100M	1.315 (0.003) CV = 0.19%	FD50K100M	1.310 (0.001) CV = 0.08%
		OD25K4M	1.339 (0.004) CV = 0.27%	FD25K4M	1.341 (0.005) CV = 0.37%
		OD25K15M	1.336 (0.004) CV = 0.31%	FD25K15M	1.343 (0.003) CV = 0.20%
		OD25K100M	1.340 (0.004) CV = 0.30%	FD25K100M	1.338 (0.001) CV = 0.09%

The apparent density values of mixtures at different proportions and similar viscosity were between the values of mixtures with only one polymer, and these increase when decrease the proportion of HCMMA (OD or FD) in the mixture.

Finally, the viscosity factor does not affect statistically ($p < 0.05$) the apparent density values, except in the case of OD75K15M and FD75K15M that present lower density values than the other mixtures at the same proportion. The differences in particle size distribution between HCMMA and HPMC, could explain this behaviour. To incorporate a small proportion (25%) of HPMC K15M (82 μm) to HCMMA (OD 154 μm; FD 305 μm) could difficult helium penetration, that would lead to higher volumes and, hence, lower density values than the same mixtures with K4M (125 μm) and K100M (122 μm). These differences decrease when increase HPMC proportion, as the final properties of the mixtures are determined by the main component.

3.2. Preparation of tablets

Typical compaction parameters (Doelker, 1978; Järvinen and Juslin, 1981) are summarised in Tables 2 and 3. The applied pressure (P) necessary to obtain tablets with a breaking force of 70–80 N was significantly larger ($p < 0.05$) for OD-HCMMA 100% than FD-HCMMA 100% matrices, according to Ferrero et al. (2003). The last mixture also presented higher plasticity (Pl) and lower expansion work (W_e) and apparent net work (W_{an}) values. Apparent net work is defined by the equation:

$$W_{an} = W_{superior} - W_{expansion} - W_{friction}$$

We, therefore, confirm that the drying process can modify the physico-mechanical characteristics of copolymers as has been mentioned in previous studies (Ferrero and Jiménez-Castellanos, 2002).

In relation with the applied pressure, HPMC 100% mixtures presented significant differences ($p < 0.05$) respect to HCMMA 100%. The first ones showed higher capacity to accept applied energy from the tablet machine (higher plasticity), lower elastic expansion during decompression (W_e) and an easier tablet elaboration (lower W_{an}) than HCMMA.

The incorporation of two polymers into the mixtures reduced the necessary pressure to obtain the tablets and increased the plasticity values compared to the HCMMA mixtures (100%). At similar viscosity grade, as HCMMA percentage decreases in the mixtures, the applied pressure, expansion work and apparent net work decreased. However, the plasticity parameters increase their values until 50:50 ratio, keeping then constant. We also observed that mixtures with FD-HCMMA needed less pressure, presented a higher facility to obtain the tablets, and higher plasticity than OD-HCMMA mixtures. These results agree with values showed for 100% formulations.

The viscosity factor has low influence in compaction parameter, and no tendency was possible to see.

We observed that the lubrication ratio values (data not showed) obtained from all formulations (0.881–0.746) did not fulfil the requirements (0.9) proposed by Bolhuis and Lerk (1973); in contrast with the values found for the ejection force (348–163 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 (2004) related to weight uniformity test.

The tablet thickness varied between 4 and 4.6 mm. In agreement with Ferrero et al. (2003), FD-HCMMA 100% obtained a higher value than OD-HCMMA 100%. This characteristic was

Table 2
Compaction parameters and physical tests from 100% matrices

Mixture	P_{sup} (MPa)	W_{an} (J)	W_e (J)	Pl (%)	Weight (mg)	Thickness (mm)	BF (N)	F (%)
OD-HCMMA	369.42 (5.26)	18.833 (0.188)	5.111 (0.373)	78.67 (1.18)	499.2 (1.7), R.S.D. = 0.35%	4.092 (0.013)	80 (3)	1.47
FD-HCMMA	160.92 (1.81)	12.290 (0.104)	1.147 (0.099)	91.47 (0.60)	497.9 (1.4), R.S.D. = 0.29%	4.227 (0.005)	82 (2)	0.48
HPMC K4M	43.64 (1.41)	4.282 (0.133)	0.134 (0.021)	97.00 (0.43)	498.8 (1.6), R.S.D. = 0.33%	4.513 (0.018)	74 (4)	1.58
HPMC K15M	35.13 (0.94)	3.480 (0.145)	0.107 (0.021)	97.05 (0.67)	498.4 (2.1), R.S.D. = 0.42%	4.571 (0.014)	71 (4)	1.44
HPMC K100M	39.31 (0.49)	3.805 (0.079)	0.094 (0.006)	97.59 (0.20)	503.1 (1.9), R.S.D. = 0.37%	4.480 (0.038)	79 (2)	1.39

Table 3
Compaction parameters from HCMMA:HPMC matrices in the proportions 75:25, 50:50 and 25:75

Mixture	P_{sup} (MPa)	W_{an} (J)	W_e (J)	Pl (%)	Mixture	P_{sup} (MPa)	W_{an} (J)	W_e (J)	Pl (%)
OD75K4M	174.80 (5.59)	11.648 (0.411)	1.213 (0.194)	90.604 (1.108)	FD75K4M	109.40 (0.52)	9.292 (0.075)	0.655 (0.034)	93.417 (0.302)
OD75K15M	200.45 (1.65)	12.039 (0.119)	1.434 (0.102)	89.363 (0.650)	FD75K15M	120.40 (0.54)	9.743 (0.140)	0.732 (0.132)	93.017 (1.232)
OD75K100M	199.86 (3.13)	11.327 (0.212)	1.582 (0.085)	87.742 (0.604)	FD75K100M	109.30 (1.51)	8.960 (0.176)	0.596 (0.062)	93.760 (0.679)
OD50K4M	99.65 (2.25)	7.726 (0.065)	0.459 (0.110)	94.411 (1.238)	FD50K4M	83.25 (0.32)	7.495 (0.036)	0.282 (0.023)	96.375 (0.288)
OD50K15M	97.77 (2.10)	7.340 (0.149)	0.456 (0.036)	94.154 (0.356)	FD50K15M	79.48 (1.62)	6.968 (0.146)	0.290 (0.046)	96.010 (0.582)
OD50K100M	104.13 (0.67)	7.938 (0.079)	0.350 (0.017)	95.778 (0.226)	FD50K100M	90.62 (2.89)	7.961 (0.233)	0.456 (0.049)	94.599 (0.411)
OD25K4M	59.85 (1.36)	5.414 (0.099)	0.396 (0.044)	93.195 (0.671)	FD25K4M	48.93 (0.66)	4.771 (0.091)	0.141 (0.028)	97.046 (0.354)
OD25K15M	53.44 (0.51)	4.849 (0.044)	0.262 (0.051)	94.886 (0.941)	FD25K15M	47.46 (0.51)	4.479 (0.077)	0.166 (0.032)	96.441 (0.662)
OD25K100M	61.58 (2.91)	5.016 (0.235)	0.246 (0.014)	95.323 (0.352)	FD25K100M	57.55 (1.25)	5.230 (0.152)	0.187 (0.017)	96.290 (0.479)

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), R.S.D. = 0.17%	4.153 (0.012)	75 (2)	1.17	FD75K4M	498.0 (1.0), R.S.D. = 0.20%	4.358 (0.009)	74 (2)	1.81
OD75K15M	500.6 (0.9), R.S.D. = 0.19%	4.122 (0.025)	79 (2)	1.00	FD75K15M	499.7 (1.2), R.S.D. = 0.23%	4.344 (0.007)	76 (2)	1.72
OD75K100M	499.5 (1.4), R.S.D. = 0.29%	4.084 (0.014)	80 (1)	0.89	FD75K100M	498.6 (1.1), R.S.D. = 0.23%	4.303 (0.013)	81 (1)	1.63
OD50K4M	500.6 (1.5), R.S.D. = 0.29%	4.312 (0.011)	75 (2)	1.82	FD50K4M	500.7 (1.2), R.S.D. = 0.24%	4.475 (0.007)	78 (2)	3.35
OD50K15M	499.6 (1.6), R.S.D. = 0.33%	4.201 (0.014)	75 (2)	1.54	FD50K15M	499.6 (1.1), R.S.D. = 0.23%	4.441 (0.014)	74 (2)	1.80
OD50K100M	499.2 (1.6), R.S.D. = 0.32%	4.212 (0.002)	73 (3)	1.55	FD50K100M	499.4 (1.5), R.S.D. = 0.30%	4.427 (0.012)	74 (2)	2.23
OD25K4M	502.2 (1.4), R.S.D. = 0.28%	4.383 (0.011)	81 (3)	1.34	FD25K4M	499.0 (2.0), R.S.D. = 0.40%	4.555 (0.012)	74 (3)	1.69
OD25K15M	501.9 (1.2), R.S.D. = 0.26%	4.408 (0.010)	76 (3)	1.39	FD25K15M	500.4 (1.4), R.S.D. = 0.28%	4.480 (0.013)	75 (5)	1.39
OD25K100M	499.0 (1.7), R.S.D. = 0.34%	4.316 (0.009)	76 (2)	1.49	FD25K100M	501.4 (1.5), R.S.D. = 0.30%	4.418 (0.016)	78 (3)	1.36

fulfilled by all the mixtures. This might be related to a more porous structure in FD matrices.

The breaking force test (European Pharmacopoeia, 2004) confirmed the values of 70–80 N for all tablets.

Only FD-HCMMA 100% and OD75K100M presented friability values lower than 1% (European Pharmacopoeia, 2004). Again, in accordance with Ferrero et al. (2003), FD-HCMMA 100% had lower friability values than OD-HCMMA 100%. However, with exception of FD25K15M and FD25K100M, 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 distribution was measured by mercury intrusion–extrusion porosimetry. FD-HCMMA 100% presented higher porosity and higher small pores contribution (lower median pore diameter values), and lower average pore diameter than OD-HCMMA 100% (Table 5), in agreement with their larger and smaller thickness, respectively (Ferrero et al., 2003). HPMC 100% presented higher porosity, average pore diameter and median pore diameter than HCMMA, except HPMC K100M, whose porosity was similar to FD-HCMMA 100%. It also showed lower average pore diameter and higher small pores contribution than the other HPMCs.

When two polymers were incorporated to the mixture (Table 6), the porosity and average pore diameter values were higher than those corresponding to HCMMA 100%, except to FD75K100M that were similar. Comparing OD with FD mixtures, the first ones showed in general, lower porosity values, but higher average pore diameter, like happened in HCMMA 100% tablets.

Table 5
Parameters characterising the porous structure of 100% matrices

Mixture	Porosity (%)	Median pore diameter (volume) (Å)	Average pore diameter (4V/A) (Å)
OD-HCMMA	17.8 (1.4)	22650 (4916)	268.0 (19.8)
FD-HCMMA	23.6 (0.6)	9300 (1204)	241.5 (7.8)
HPMC K4M	31.4 (2.7)	41731 (1272)	601.0 (55.2)
HPMC K15M	33.6 (0.5)	35203 (1427)	639.0 (7.1)
HPMC K100M	23.3 (0.7)	21282 (1546)	434.5 (16.3)

Table 6
Parameters characterising the porous structure of HCMMA:HPMC matrices

Mixture	Porosity (%)	Median pore diameter (volume) (Å)	Average pore diameter (4V/A) (Å)
OD75K4M	22.0 (1.8)	29899 (3458)	338.5 (23.3)
OD75K15M	21.7 (0.1)	31646 (609)	335.0 (2.8)
OD75K100M	19.7 (0.8)	25473 (2229)	302.0 (9.9)
OD50K4M	27.2 (0.2)	36123 (588)	452.5 (2.1)
OD50K15M	25.0 (0.3)	26761 (1124)	402.0 (11.3)
OD50K100M	24.1 (1.9)	27560 (3677)	388.5 (29.0)
OD25K4M	28.5 (2.3)	37016 (1692)	510.0 (35.4)
OD25K15M	27.0 (3.6)	28124 (4599)	474.5 (61.5)
OD25K100M	28.0 (0.5)	30473 (1177)	482.5 (14.8)
FD75K4M	26.2 (0.4)	18770 (1620)	299.5 (12.0)
FD75K15M	26.4 (0.1)	16748 (71)	283.0 (1.4)
FD75K100M	23.3 (2.0)	13334 (4962)	282.5 (21.9)
FD50K4M	34.0 (7.4)	27626 (797)	370.5 (6.4)
FD50K15M	28.4 (0.4)	22081 (1406)	353.5 (10.6)
FD50K100M	28.2 (0.2)	24203 (194)	354.0 (0.0)
FD25K4M	32.7 (0.1)	40703 (954)	504.0 (1.4)
FD25K15M	26.0 (2.0)	22913 (2695)	391.0 (24.0)
FD25K100M	25.8 (2.5)	24525 (1769)	385.5 (37.5)

According to HCMMA:HPMC ratio, at the same viscosity grade, as HCMMA percentage decrease, average pore diameter increased. On the other hand, as porosity values in OD mixtures increased but in FD mixtures, the higher porosity values were for 50:50 mixture. This higher porosity of 50:50 could affect the control release tendency attending to polymers ratio.

Besides, the viscosity grade showed, in general term, that higher viscosity entailed lower porosity values and average pore diameter. This tendency was not follow by both OD25K100M, with higher porosity and average pore diameter than OD25K15M, and FD75K15M, with similar porosity than FD75K4M. Small pores contribution did not present a clear tendency in viscosity grade factor and HCMMA:HPMC ratio.

There was not a clear tendency between thickness and porosity data when we used two polymers into the mixture. It could be due to either physical interactions between the two polymers or/and some differences between the particle sizes and shapes of the two polymers.

According to IUPAC definitions, as the pore diameter values were accomplished between 20 and 500 Å, all mixtures possessed mesopores, except OD/FD25K4M, HPMC K4M and K15M 100%, that presented macropores (>500 Å).

3.5. Drug release study

Fig. 1 illustrates the drug release profiles from HCMMA 100% and HPMC 100% matrices. Higher percentage of drug release was observed for HCMMA matrices, where OD tablets exhibited a faster release than FD tablets ($f_2 = 60.3$). HPMC K100M tablets displayed the lowest release, corresponding to higher viscosity grade. This is probably due to the degree of entanglement at high molecular weights that reduced the effective molecular diffusion area (Colombo et al., 1995). Similar results were observed by Nellore et al. (1998) where the higher viscosity gel layers of Methocel® K100M matrices provided a more tortuous and resistant barrier to diffusion, resulting in slower release of metoprolol tartrate from these matrices.

No significant differences in release behaviour were observed for systems prepared with Methocel® K4M and K15M ($f_2 = 99.5$), in agreement with Colombo et al. (1995).

Fig. 2 illustrates the release profiles from the matrices prepared from different mixtures of OD-HCMMA and FD-HCMMA with HPMC (K4M, K15M, K100M) in three defined proportions HCMMA:HPMC (75:25, 50:50, 25:75).

The mixtures of HPMC with OD-HCMMA released less theophylline than the copolymer 100%, except for 75:25 OD-HCMMA-HPMC (K4M and K15M) that were similar. Likewise, the release of theophylline was lower when the viscosity grade increased (mixtures with K100M) mainly as a result of a slower diffusion and extensive swelling (Reynolds et al., 1998). Besides, the theophylline release could be increased at low percentage of HMPC (up to 50%). The f_2 values obtained comparing 75:25 and 50:50 proportions were $f_2 < 80$ and $f_2 > 97$ for 50:50 and 25:75.

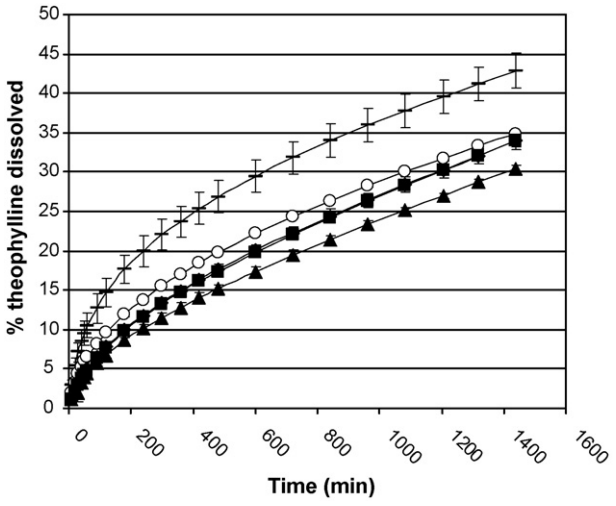

Fig. 1. Release profiles of anhydrous theophylline (over 24 h) from tablets of OD-HCMMA (–), FD-HCMMA (◯), and HPMC: K4M (♦), K15M (■), K100M (▲). The bars show the standard deviation.

As Takka et al. (2001)–HPMCK100M:Eudragit S–and Lotfipour et al. (2004)–HPMC K4M:Eudragit RSPO–, it is observed that the amount of HPMC played a dominant role, affecting the drug release in these mixtures. Kiortsis et al. (2005) showed that the release rate of indomethacin (low solubility drug) decreased as the mass fraction of HPMC increased, replacing either drug or hydrophobic component. The profiles were more similar to HCMMA or HPMC 100% mixtures in function of predominant polymer. In this sense, Nellore et al. (1998) fit the polymer charge to 40%, changing the viscosity of the materials (Methocel K100LV, K4M, K15M, K100M). The mixtures showed a similar but less dramatic effect of the viscosity on metoprolol release than mixtures where polymer level was held to 10%, particularly at higher viscosity (K4M, K15M and K100M).

Only HPMC K100M mixtures had a slower or equal release than FD-HCMMA 100%. Related to viscosity grade and percentage of HPMC, the behaviour for FD-HCMMA:HPMC mixtures were similar to OD-HCMMA:HPMC ones, except FD-HCMMA:K100M blends. They did not show any differences in the percentage of theophylline released when FD-HCMMA ratio changed ($f_2 > 95$).

These results demonstrate that changes in the amount of HCMMA from 50% can be used to produce modifications on drug release rates in monoaxial delivery, because the presence of solid particles (theophylline and HCMMA) can reduce the entanglement HPMC chains, thus lowering gel resistance (Grassi et al., 2004).

Release data ($M_t/M_\infty < 0.6$) were analysed according to Higuchi (1963), Korsmeyer et al. (1983) and Peppas and Sahlin (1989) equations. The main parameters are listed in Table 7 for 100% mixtures and in Tables 8 and 9 for mixtures of OD-HCMMA:HPMC and FD-HCMMA:HPMC, respectively. As the matrices under study 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.

In agreement with Ferrero et al. (2003), FD-HCMMA provided the best fit to the different models. Both, in OD and in FD matrices 100% (Table 7), the accurate fit to Higuchi equation, the n values from Korsmeyer equation and the prevalence of k_d over k_r in Peppas equation revealed a drug release mechanism controlled mainly by diffusion. Moreover, the different constants had lower values for FD matrices, which indicate a lower release of theophylline. Heng et al. (2001) reported that polymer powder of different size distribution, as these polymers (Ferrero and Jiménez-Castellanos, 2002), had influence on drug release rate but not on release mechanism.

The lower values of k and especially for k_d of K100M agreed with its lower release of theophylline. However, consistent with Salomen et al. (1979) and Ford et al. (1985), the matrices containing K4M, K15M and K100M grades of HPMC had similar Higuchi constants. This implies that viscosities of the hydrated matrices may be identical, despite the apparent differences in their viscosity grades (Ford et al., 1985). Campos-Aldrete and Villafuerte-Robles (1997) pointed out the necessity of a high

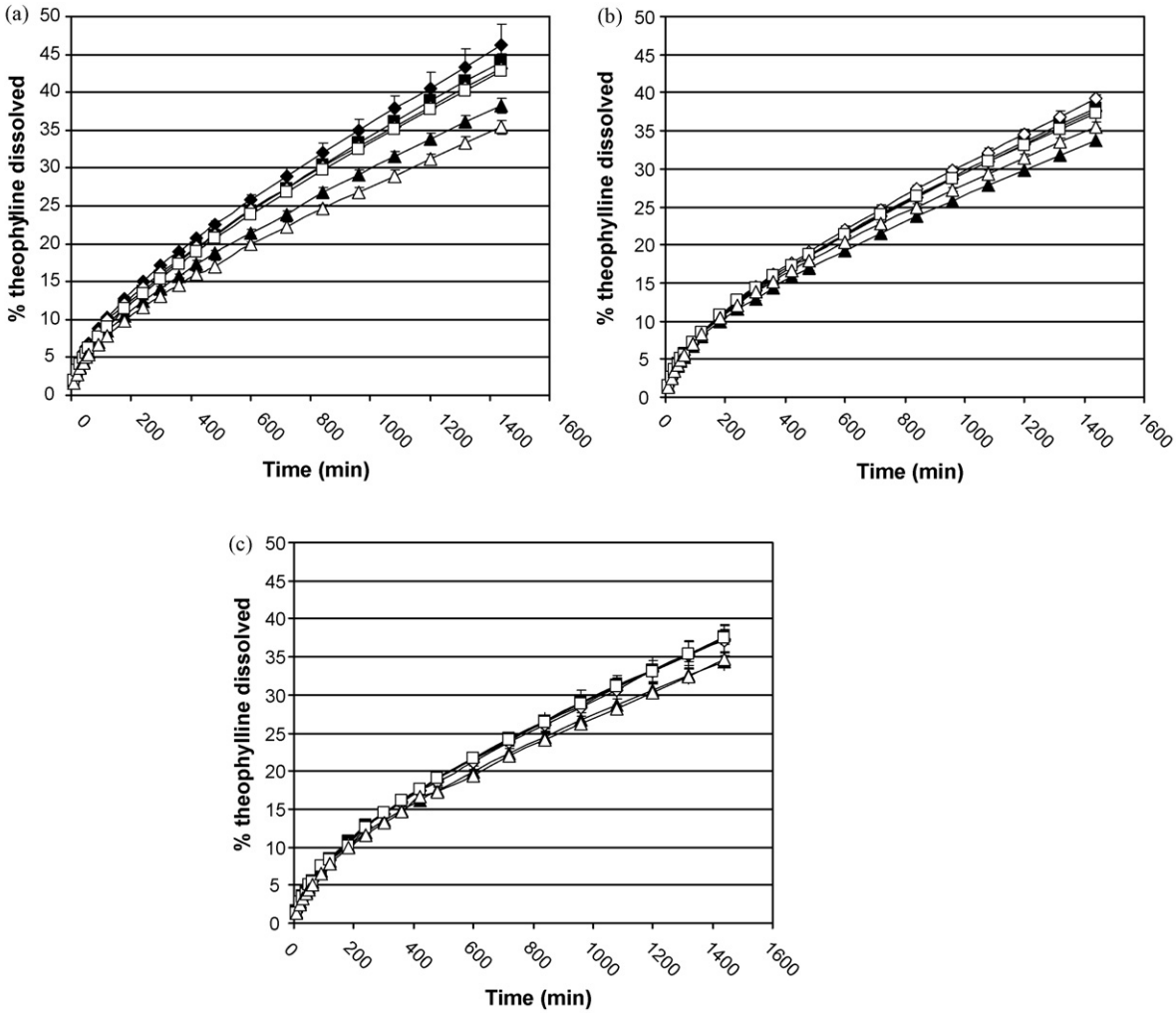

Fig. 2. Release profiles of anhydrous theophylline (over 24 h) from mixtures of HPMC with HCMMA: (a) 75% HCMMA, (b) 50% HCMMA, (c) 25% HCMMA. The mixtures are represented in function of viscosity grade of HPMC: K4M (♦), K15M (■), K100M (▲), and drying method of HCMMA: OD mixtures are represented by closed symbols and FD mixtures by opened ones. The bars show the standard deviation.

Table 7
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	0.9996 ($F = 24393$)
FD-HCMMA	0.009	0.9999 ($F = 273578$)	0.55	0.007	0.9957 ($F = 4614$)	0.013	0.00008	0.99998 ($F = 457998$)
HPMC K4M	0.009	0.9982 ($F = 10857$)	0.61	0.004	0.9990 ($F = 20588$)	0.010	0.00020	0.99997 ($F = 292743$)
HPMC K15M	0.009	0.9980 ($F = 9821$)	0.64	0.003	0.9962 ($F = 5205$)	0.010	0.00020	0.99994 ($F = 158784$)
HPMC K100M	0.008	0.9963 ($F = 5441$)	0.65	0.003	0.9932 ($F = 2940$)	0.008	0.00021	0.99958 ($F = 22657$)

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 ($p = 0.000$).

concentration of HPMC (at least 20%) to disappear the effect of the viscosity grade on the Higuchi constant. Although HPMC 100% tablets had a good fit to Higuchi equation indicative of a diffusion mechanism, however, according to n values from Korsmeyer equation higher than 0.5, and the high values of k_r in Peppas and Sahlin equation reveals a drug release mechanism that combine diffusion through the gel layer and erosion of this gel layer, due to the relaxation component (Ford et al., 1991).

In all mixtures (Tables 8 and 9), the Higuchi constants were very similar, on the contrary to Vázquez et al. (1996), who indicated that the principal factor affecting the Higuchi constant, in mixtures with Methocel® K100LV and K100M, was the gelling agent composition. A drug release mechanism that combine dif-

Table 8
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 ($F=3147$)	0.6	0.006	0.9962 ($F=5285$)	0.010	0.00038	0.99965 ($F=27002$)
OD75K15M	0.012	0.9925 ($F=2644$)	0.62	0.005	0.9985 ($F=13523$)	0.008	0.00040	0.99987 ($F=75013$)
OD75K100M	0.010	0.994 ($F=3272$)	0.61	0.004	0.9982 ($F=10967$)	0.008	0.00032	0.99982 ($F=53550$)
OD50K4M	0.010	0.9948 ($F=3834$)	0.62	0.004	0.9979 ($F=9185$)	0.008	0.00030	0.99984 ($F=59250$)
OD50K15M	0.010	0.9953 ($F=4240$)	0.62	0.004	0.9968 ($F=6285$)	0.009	0.00029	0.99978 ($F=44013$)
OD50K100M	0.009	0.9963 ($F=5320$)	0.60	0.004	0.9971 ($F=6901$)	0.008	0.00023	0.99974 ($F=35879$)
OD25K4M	0.010	0.99624 ($F=6305$)	0.61	0.004	0.9984 ($F=12454$)	0.010	0.00025	0.9999 ($F=97685$)
OD25K15M	0.010	0.9973 ($F=7284$)	0.62	0.004	0.9989 ($F=17677$)	0.010	0.00024	0.9999 ($F=177177$)
OD25K100M	0.009	0.99707 ($F=6807$)	0.60	0.004	0.9981 ($F=10435$)	0.009	0.00022	0.99983 ($F=56093$)

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 ($p=0.000$).

Table 9
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 ($F=14437$)	0.0094	0.00034	0.99975 ($F=37686$)
FD75K15M	0.012	0.9926 ($F=2697$)	0.61	0.005	0.9989 ($F=17681$)	0.0081	0.00038	0.99993 ($F=145695$)
FD75K100M	0.009	0.9932 ($F=2936$)	0.59	0.005	0.9984 ($F=12225$)	0.0070	0.00030	0.9997 ($F=31936$)
FD50K4M	0.011	0.9950 ($F=3956$)	0.64	0.004	0.9971 ($F=6786$)	0.0088	0.00030	0.99983 ($F=55770$)
FD50K15M	0.010	0.9964 ($F=5575$)	0.61	0.004	0.9979 ($F=9374$)	0.0092	0.00026	0.99986 ($F=68805$)
FD50K100M	0.010	0.9968 ($F=6313$)	0.62	0.004	0.9945 ($F=3627$)	0.0092	0.00023	0.99971 ($F=32563$)
FD25K4M	0.010	0.99585 ($F=4802$)	0.61	0.004	0.999 ($F=20669$)	0.0090	0.00027	0.99971 ($F=33262$)
FD25K15M	0.010	0.99683 ($F=6286$)	0.63	0.004	0.9946 ($F=3700$)	0.0097	0.00025	0.99966 ($F=28270$)
FD25K100M	0.009	0.99622 ($F=5277$)	0.62	0.004	0.9968 ($F=6302$)	0.0087	0.00023	0.99939 ($F=15553$)

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 ($p=0.000$).

fusion and erosion is supported by the n values from Korsmeyer equation indicative of an anomalous drug release (Catellani et al., 1988), similar to obtain by Takka et al. (2001) in mixtures of Eudragit-HPMC K100M, and the higher values of k_r in Peppas equation for these mixtures in relation with only one polymer matrices. According to the same ratio, important differences were only displayed for K100M in k_r values for Peppas and Sahlin equation (Tables 8 and 9). Tahara et al. (1995) reported that the selection of the viscosity grade of HPMC is an important consideration in the formulation development, for a drug with poor aqueous solubility. This parameter (k_r) decreased when the HPMC proportions in the matrix tablets increased, being more important in the 75–50% HCMMA range. As HCMMA could destabilise the gel structure, with which a lower percentage of this copolymer or a higher viscosity of gel layer (HPMC K100M) could explain the lower drug release of theophylline in these matrices.

3.6. Fronts movement study

With the purpose of obtaining useful information for a better understanding of the drug release mechanism from the different matrices, fronts movement kinetics were evaluated (Ferrero et al., 2003). According to Ferrero et al. (2003) 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).

Fronts movement kinetics (over 12 h) depicted in Fig. 3 for HCMMA 100% showed a nearly constant erosion front movement, which proved the absence of swelling in these matrices. As no swelling or erosion could be detected (the tablet diameter remained constant), it seems that copolymer tablets behave as matrices where the drug is released by diffusion through the porous structure. The fast initial water uptake observed might be due to the water penetration through capillaries and higher size pores.

Water uptake and complete wetting fronts seemed to move faster in FD-HCMMA 100% matrices, which is consistent with the highest initial porosity in these matrices (Table 5). However, this not explains the lower release of FD to OD HCMMA matrices 100%. Table 10 shows the approximate values for the apparent diffusion coefficient D', obtained from 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. D' values were smaller for matrices obtained from FD mixtures 100%, which implies higher tortuosity values and an increment in the diffusional resistance for these

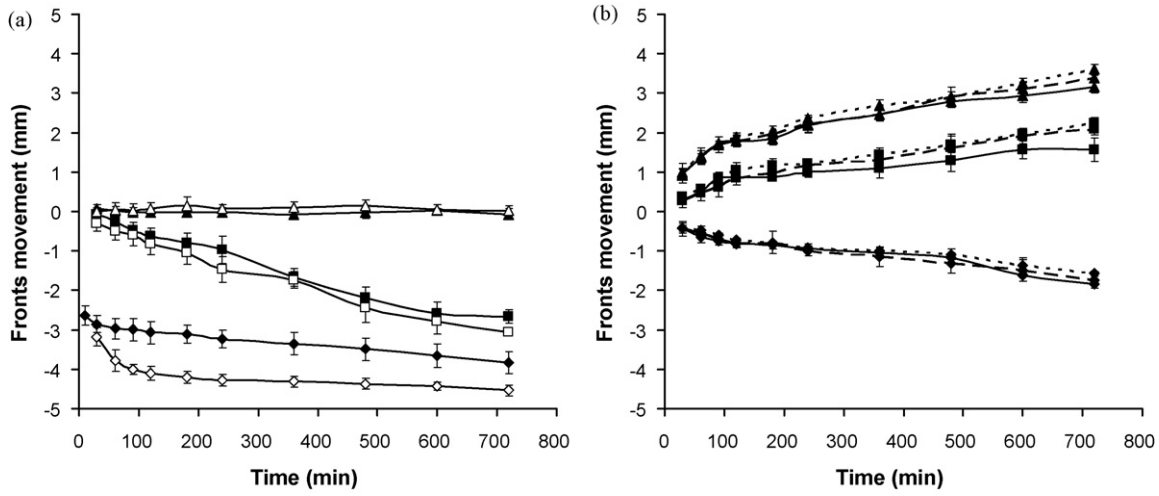

Fig. 3. Fronts movement (over 12 h) from 100% matrices. Swelling (water uptake for HCMMA) (♦), diffusion (complete wetting for HCMMA) (■) and erosion (▲) fronts from: (a) OD-HCMMA (closed symbols), FD-HCMMA (open symbols). (b) HPMC K4M (continuous line), K15M (uncontinuous line), K100M (points line).

Table 10
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}	OD75K15M	7.02×10^{-4}	FD75K15M	5.48×10^{-4}
HPMC K4M	2.50×10^{-4}	OD75K100M	5.42×10^{-4}	FD75K100M	3.53×10^{-4}
HPMC K15M	2.31×10^{-4}	OD50K4M	3.72×10^{-4}	FD50K4M	3.48×10^{-4}
HPMC K100M	2.68×10^{-4}	OD50K15M	4.16×10^{-4}	FD50K15M	3.46×10^{-4}
		OD50K100M	3.48×10^{-4}	FD50K100M	3.50×10^{-4}
		OD25K4M	3.50×10^{-4}	FD25K4M	2.94×10^{-4}
		OD25K15M	3.67×10^{-4}	FD25K15M	3.75×10^{-4}
		OD25K100M	2.93×10^{-4}	FD25K100M	3.10×10^{-4}

tablets. These results explain the slower diffusion rate in these matrices in spite of their higher porosity (Table 5) and quicker water penetration.

In the opposite, for swellable matrix tablets, as HPMC 100%, Colombo et al. (1995) proposed these three fronts: swelling front (between dry–wet polymer able to swell), diffusion front (between wet polymer–clear gel) and erosion front (between clear gel–solvent). In Fig. 3 not important differences can be seen for the three matrices compared with the different fronts. In agreement with Colombo et al. (1995), the rates of movement of the diffusion fronts were only slightly different for the three Methocel® grade formulations.

For the different mixtures HCMMA–HPMC, it is possible to see similar fronts movement profiles to swellable matrices (Fig. 4), with no changes in swelling front respect to HPMC 100% matrices. Respect to viscosity grade (Methocel® K4M, K15M and K100M) the diffusion and erosion fronts increased with viscosity (K100M), being very similar for the other ones (K4M and K15M). The diffusion front dynamics indicate the transport of solid drug particles in the gel layer, as a consequence of polymer swelling (Bettini et al., 2001). If we consider that the penetration speed of water in all matrices are similar (similar swelling front), the K100M matrices will need more time to form the clear gel and become more viscous. According to Bettini et al. (2001), for poor water soluble drugs, the diffusion front moved very close to the erosion front and, therefore, the dissolved drug gel layer thickness, which represents the drug diffusive pathway, should extremely thin, especially for K4M and K15M. Thus, a high probability existed for drug solid particles to escape from these matrices.

About the percentage of HPMC, erosion and diffusion fronts increased when decreased the proportion of HCMMA, so the fronts movement profiles resembled to HPMC 100% matrices, with the highest differences for 75% of HCMMA related to other ratios. Lotfipour et al. (2004) explain the effect of the fillers on the release rate of atenolol because they reduced the tortuosity of the diffusion path of the drug.

Table 10 shows that when HCMMA decrease from 75 to 25%, the tortuosity of the diffusion path increases, being more important in the 75–50% intervals of HCMMA. This tortuosity was usually higher for K100M mixtures.

The relative movement of either the erosion and swelling fronts or erosion and diffusion fronts indicated the tendency to move in the same way. This phenomenon can be represented in terms of gel layer thickness (Colombo et al., 1995), which is defined as the difference between erosion and swelling front positions. As shown in Fig. 5, the gel layer thickness was similar to Methocel K4M and K15M and higher to Methocel K100M. Besides, it raised when increased the proportion of

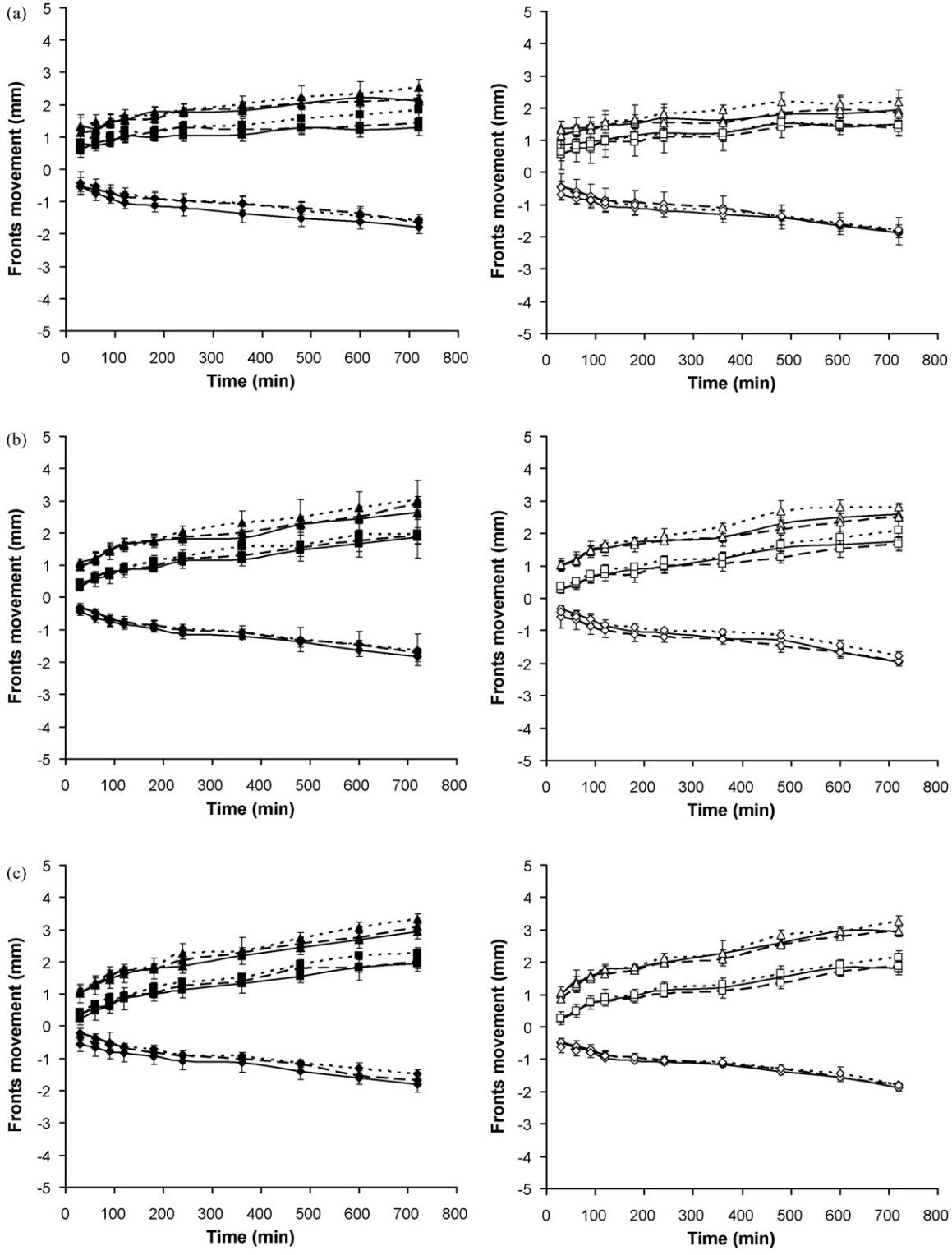

Fig. 4. Fronts movement (over 12 h) from HCMMA–HPMC mixtures: (a) 75–25%; (b) 50–50%; (c) 25–75%. Swelling (♦), diffusion (■) and erosion (▲) fronts from mixtures of: OD-HCMMA (closed symbols) or FD-HCMMA (open symbols) with HPMC K4M (continuous line), K15M (uncontinuous line) or K100M (points line).

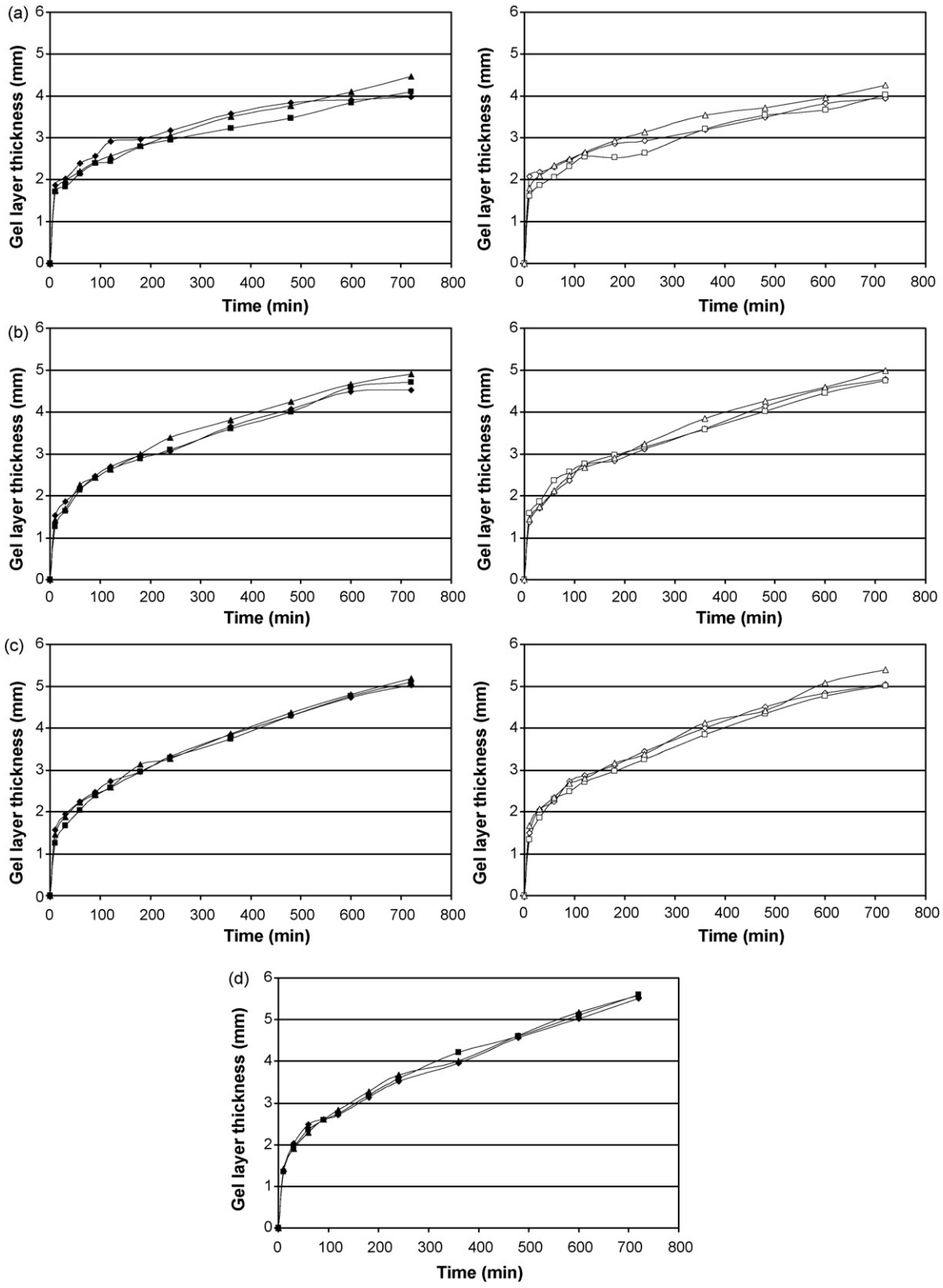

Fig. 5. Gel layer thickness from mixtures of HPMC with HCMMA: (a) 75% HCMMA, (b) 50% HCMMA, (c) 25% HCMMA, (d) 0% HCMMA. The mixtures are represented in function of viscosity grade of HPMC: K4M (♦), K15M (■), K100M (▲), and drying method of HCMMA: OD mixtures are represented by closed symbols and FD mixtures by opened ones.

HMPC in the mixtures, being very similar in 50:50 and 25:75 HCMMA:HPMC.

4. Conclusion

In conclusion, the results of this study confirm the possibility of modulation of theophylline release by mixing two polymers with different release mechanism. FD-HCMMA releases theophylline slower than OD-HCMMA, both by diffusion mechanism, but never below the control exerted by HPMC tablets. HPMC matrices show double release mechanism, diffusion and erosion of the gel layer, being predominant the diffusion pathway, affected by the viscosity grade. The different mixture of polymers studied also displayed this double mechanism, but in this case, with higher contribution of the relaxation factor. These mixtures need, for the modulation of theophylline monoaxial release, either above 50% of HCMMA or high viscosity differences of HPMC in the mixture.

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