Research paper

Graft copolymers of ethyl methacrylate on waxy maize starch derivatives as novel excipients for matrix tablets: Drug release and fronts movement kinetics

J.A. Marinich, C. Ferrero *, M.R. Jiménez-Castellanos

Departamento de Farmacia y Tecnología Farmacéutica, Universidad de Sevilla, Sevilla, Spain

ABSTRACT

A previous paper [1] deals with the physicochemical and technological characterization of novel graft copolymers of ethyl methacrylate (EMA) on waxy maize starch (MS) and hydroxypropylstarch (MHS). The results obtained suggested the potential application of these copolymers as excipients for compressed non-disintegrating matrix tablets. Therefore, the purpose of the present study was to investigate the mechanism governing drug release from matrix systems prepared with the new copolymers and anhydrous theophylline or diltiazem HCl as model drugs with different solubility. The influence of the carbohydrate nature, drying procedure and initial pore network on drug release kinetics was also evaluated. Drug release experiments were performed from free tablets. Radial drug release and fronts movement kinetics were also analysed, and several mathematical models were employed to ascertain the drug release mechanisms. The drug release markedly depends on the drug solubility and the carbohydrate nature but is practically not affected by the drying process and the initial matrix porosity. A faster drug release is observed for matrices containing diltiazem HCl compared with those containing anhydrous theophylline, in accordance with the higher drug solubility and the higher friability of diltiazem matrices. In fact, although diffusion is the prevailing drug release mechanism for all matrices, the erosion mechanism seems to have some contribution in several formulations containing diltiazem. A reduction in the surface exposed to the dissolution medium (radial release studies) leads to a decrease in the drug release rate, but the release mechanism is not essentially modified. The nearly constant erosion front movement confirms the behaviour of these systems as inert matrices where the drugs are released mainly by diffusion through the porous structure.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Among the different approaches experimented for obtaining sustained-release delivery systems, matrix tablets, particularly if obtained by direct compression, still appear as one of the most efficient and interesting from both the economic and the process development points of view [2].

A variety of polymers is employed as matrix-forming excipients whose nature and characteristics may play an important role and significantly influence the behaviour of these devices. The controlling effect of a polymer material on drug release depends on its physicochemical properties and the way it is mixed during the manufacture of the system. To be more specific, the effect is due to the polymer molecular properties, such as the nature of the monomer, type and degree of substitution and whether the polymer is mixed dry or dissolved [3,4].

Three main types of polymers may be used as drug delivery modulators: natural, synthetic and semi-synthetic. Among semi-synthetic polymers, modified starches have been proposed as direct compression excipients for controlled release matrices [5–9]. For instance, substituted amylose leads to hydrophilic matrix systems resistant to biodegradation [10] whereas starch acetate and graft copolymers with vinyl monomers yield hydrophobic matrices [8,11]. Therefore, native starch properties are substantially modified, and the mechanism involved on drug release differs depending on the type of polymer used.

In a previous work [1], a novel generation of copolymers combining waxy maize starch (amylose content < 1%) derivatives (MS, MHS) and ethyl methacrylate (EMA) were synthesised by free-radical polymerization and alternatively dried by vacuum oven (OD) or freeze-drying (FD) techniques. The physicochemical and technological properties of these materials were thoroughly evaluated and their performance compared with the raw starches. The grafting of EMA on the carbohydrates backbone introduced hydrophobicity and leaded to amorphization and changes in particle size and morphology that affected the densification behaviour of the original carbohydrates. Graft copolymerization also improved the

* Corresponding author. Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, C/Profesor García González No. 2, 41012 Sevilla, Spain. Tel.: +34 954557218; fax: +34 954556085.

E-mail address: cferrero@us.es (C. Ferrero).

compactibility and mechanical resistance of native starches, suggesting the potential value of these copolymers as excipients for compressed non-disintegrating matrix tablets.

In addition to the polymer nature, drug properties such as polymorphism, degree of crystallinity, particle size, solubility and amount in the pharmaceutical dosage form can influence the release kinetic [12]. From all these variables, the solubility characteristics of the active are particularly important when designing extended-release dosage forms, as they can strongly influence the overall release profile. In fact, an excessively high or an extremely low solubility may give rise to formulation problems. Indeed, it is widely accepted that for both inert and swellable systems, diffusion, preceded by dissolution, may represent the key parameter for controlling drug release [13]. Thus, in the present study, two model drugs were selected, anhydrous theophylline and diltiazem HCl, because both are suitable candidates for controlled release formulations [2,14] and have different solubility.

For the above reasons, the aim of this work was to identify the mechanism governing drug release from matrix systems prepared with the novel copolymers of ethyl methacrylate and waxy maize starch derivatives, using as model drugs anhydrous theophylline (a slightly water soluble drug) and diltiazem hydrochloride (a freely water soluble drug). Attention has also been focused on the influence of the carbohydrate nature, drying process and matrix porosity on the mechanistic aspects of drug release from the tested matrices.

2. Materials and methods

2.1. Materials

Copolymers synthesised by free radical copolymerization of ethyl methacrylate (EMA) and waxy maize starch (MS) or waxy maize hydroxypropylstarch (MHS) were selected for the study. The preparation of the grafted copolymers has been described in detail by Marinich et al. [1]. The products obtained (waxy maize starch–ethyl metacrylate – MSEMA and waxy maize hydroxypropylstarch–ethyl methacrylate – MHSEMA) were dried either in a vacuum oven (OD copolymers) or freeze dried (FD copolymers). The starch-based copolymers (MSEMA) were crushed at 10,000 rpm in a knives mill (Retsch ZM 200, Haan, Germany) to obtain powdery samples.

Anhydrous theophylline (T) (Roig Farma, Barcelona, Spain, batch 0212030) and diltiazem HCl (D) (Roig Farma, Barcelona, Spain, batch 05F1704) were selected as model drugs. Anhydrous theophylline is slightly soluble in water (100–1000 ml/g), and diltiazem HCl is freely soluble in water (1–10 ml/g) [15]. The batches used have a mean particle size of 162 (96) μm for T and 202 (129) μm for D (determined by sieve analysis).

Stearic acid (Estearina®, Roig Farma, Barcelona, Spain, batch 90003410) 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

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

2.2.2. Preparation of tablets

The different mixtures were compacted into tablets using an instrumented [16] single punch tablet machine (Bonals AMT 300, Barcelona, Spain) running at 30 cycles/min. The powders were manually fed into the die (12 mm) to obtain flat-faced compacts of 500 mg weight at a fixed crushing force (140–150 N).

Compression data were collected from four tabletting cycles and statistically analysed by one-way analysis of variance (ANOVA) using SPSS® 14 software. Post-ANOVA analysis was carried out according to Bonferroni's multiple comparison tests. Results were quoted as significant when $p < 0.05$.

2.2.3. Standard physical test of tablets

The physical testing of tablets was performed 24 h after production to allow for stress relaxation.

The tablet average weight and the standard deviation (SD) were obtained from 20 individually weighed (Sartorius CP224S, Göttingen, Germany) tablets according to European Pharmacopoeia [15].

The thickness of 10 tablets was measured individually using an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan).

The crushing force [15] of 10 tablets was determined by diametral loading with a Schleuninger-2E tester (Greifensee, Switzerland).

Tablet friability [15] was calculated as the percentage weight loss of 20 tablets after 4 min at 25 rpm in an Erweka TA (Heusenstamm, Germany) friability tester.

Disintegration testing [15] was performed at 37 °C in deionised water (800 ml), using an Erweka ZT3 (Heusenstamm, Germany) apparatus without discs. The disintegration times reported are averages of six determinations.

2.2.4. Mercury porosimetry measurements

Mercury porosimetry runs were undertaken using an Autopore IV 9510 (Micromeritics, Madrid, Spain) porosimeter with a 3 cm³ penetrometer. A quantity of sample was included in order to obtain 20–90% of mercury intrusion. Working pressures covered the range 0.1–60,000 psi, and the mercury solid contact angle and surface tension were assumed to be 130° and 485 mN/m, respectively. Blank runs were also undertaken to correct the data for compressibility effects using the same run conditions and penetrometer type than for the real sample. Total porosity and pore size distribution were determined, in duplicate, for each tablet tested.

2.2.5. Drug release study

Release experiments (six tablets) were performed in an automatic dissolution apparatus 2 (Erweka DT 600 HH, Heusenstamm, Germany) [15] as a function of time (12 h). Deionised and deaerated 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 89079AX, Böblingen, Germany). Drug release was monitored continuously on a spectrophotometer (Agilent Technologies 8453 UV–vis, China) at $\lambda = 272$ nm for theophylline and $\lambda = 235$ nm for diltiazem.

In a second series of experiments, special devices [17] were used in order to obtain a rigorous radial release. The tablets were locked between two transparent Plexiglass® discs by means of four stainless steel screws. The upper disc was carved with concentric circles (from 8 to 20 mm of diameter), so that the tablet could be placed just in the centre (Fig. 1). The assembled devices (three replicates) were introduced into the vessels of the dissolution apparatus and tested for 12 h in the same conditions as previously.

For both studies, drug release data ($M_t/M_\infty \leqslant 0.6$) were analysed according to Higuchi [18] (1), Korsmeyer et al. [19] (2) and Peppas and Sahlin [20] (3) equations:

$$\frac{M_t}{M_\infty} = k\, t^{\frac{1}{2}} \tag{1}$$

$$\frac{M_t}{M_\infty} = k'\, t^n \tag{2}$$
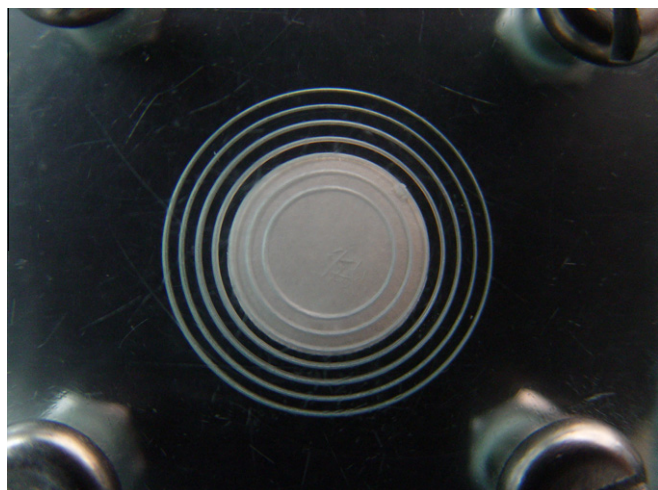
Fig. 1. Photograph of the matrix tablet (OD-MSEMAD at $t = 0$ h) fitted into the Plexiglass® device used for radial drug release and fronts movement experiments. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), k and 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 [21], k_d and k_r, are the diffusion and relaxation rate constants, respectively, m is the purely Fickian diffusion exponent for a device of any geometrical shape that exhibits controlled release.

The optimum values for the parameters present in each equation were determined by linear or nonlinear least-squares fitting methods with SPSS® 14 software. Besides the adjusted coefficient of determination $\left(r_{adj}^2\right)$, the Akaike Information Criterion (AIC) was used to test the applicability of the release models. The AIC can be defined as

$$AIC = n \times \ln\left(\frac{SSR}{n}\right) + 2 \times p \qquad (4)$$

where n is the number of dissolution data points, SSR is the sum of the squared residuals and p is the number of the parameters of the model. When comparing several models for a given set of data, the model associated with the smallest value of AIC is regarded as giving the best fit [12,22].

2.2.6. Fronts movement study

The experiment was carried out, in duplicate, in the same conditions as the radial release studies (37 °C and 50 rpm). However, in order to enhance the visual detection of the fronts, methylene blue (0.004%, w/v) was added to the dissolution medium (900 ml deionised and deaerated water). At defined time intervals (10, 30, 60, 90, 120, 180, 240, 360, 480, 600 and 720 min), the Plexiglass® devices were removed from the dissolution apparatus and photographed by means of a camera Sony® DSC-F717 (Tokyo, Japan) with a 10× digital zoom. Focal distance was kept constant during all measurements. The photographs were analysed by computer using Corel Draw X3® software as previously reported [23]. The interface between the matrix and the dissolution medium at the beginning of the experiment (initial diameter) was referred to as position 0. The inward front movement was represented by a negative value, while the outward movement was indicated by a positive one.

3. Results and discussion

3.1. Preparation of tablets

Although a thorough study on compression characteristics of the copolymers has been reported in a previous paper [1], it is known that the addition of drug and lubricant to direct compression tablet matrices could produce substantial changes in compaction profiles [8,24,25]. For this reason, some compression parameters [26,27] obtained from the different mixtures are summarised in Table 1.

Concerning the influence of the carbohydrate nature, the applied pressure (P) required to obtain tablets from the mixtures with a crushing force of 140–150 N is significantly ($p < 0.05$) larger for MHSEMA than MSEMA. Similar tendency is observed for OD products compared with FD derivatives ($p < 0.05$). This behaviour would be related with the higher ability to plastic deformation reported for MSEMA and FD derivatives [1].

On the other hand, theophylline mixtures show better compression properties than diltiazem mixtures, in agreement with the plastic deformation behaviour of theophylline [24,28]. Furthermore, the smaller theophylline particles would provide a higher total area for bonding than the larger diltiazem particles [29].

It is also important to mention that the type of drug has a remarkable influence on friction properties. As a consequence of the adhesion to the surfaces of diltiazem, their mixtures show worse lubrication ratio (R), ejection force (F_e) and apparent network (W_{an}) values than theophylline mixtures ($p < 0.05$).

3.2. Standard physical test of tablets

Results from the physical testing of tablets obtained from the different mixtures are also illustrated in Table 1.

All tablets satisfy the requirements specified in European Pharmacopoeia [15] related to weight uniformity test and the tablet thickness ranges between 4.2 and 4.3 mm, so a decrease of this dimension is found compared with tablets prepared from the pure materials [1].

The crushing force test confirms the values of 140–150 N for all tablets, and the friability percentages are lower than 1% [15]. The higher friability values obtained for mixtures containing diltiazem agree with their lower binding capacity and the higher friction suffered by these tablets during the ejection process. However, the addition of both the drug and stearic acid improves the friability compared with tablets elaborated only with copolymers [1].

None of the tablets disintegrated after 30 min. Tablets obtained from theophylline formulations and MSEMA/diltiazem mixtures maintained their physical integrity after the test whereas tablets from MHSEMA/diltiazem mixtures suffered some attrition, probably due to a combined effect of the matrix friability and the hydrophilic character of this copolymer.

3.3. Mercury porosimetry measurements

As the porous structure is a useful tool in the prediction of water and drug diffusivity [8,11,30,31], results from mercury intrusion-extrusion porosimetry are compiled in Table 2.

Matrices containing anhydrous theophylline are characterised by higher porosities and mean pore diameters than tablets containing diltiazem hydrochloride. This behaviour correlates well with the higher pressures applied to obtain tablets from diltiazem formulations.

The unimodal pore size distribution profiles (Fig. 2) resemble those reported for the copolymers [1], and according to IUPAC guidelines definitions [32], the systems under study contain mesopores.
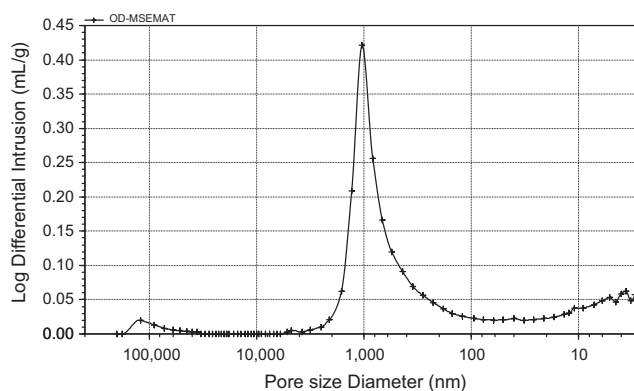
Table 1
Main compression parameters and tablet test results for the different mixtures: maximum applied upper punch pressure (P), lubrication ratio (R), maximum ejection force (F_e), Juslin's apparent network (W_{an}), average weight, thickness, crushing force (CF), friability (F) and disintegration time (t_d). Values in parentheses represent the standard deviation.

Mixtures	P (MPa)	R	F_e (N)	W_{an} (J)	Weight (mg)	Thickness (mm)	CF (N)	F (%)	t_d (min)
OD-MSEMAT	133.29 (0.63)	0.785 (0.016)	184.9 (12.5)	14.0 (0.3)	499 (1)	4.214 (0.011)	146 (6)	0.56	>30
FD-MSEMAT	108.88 (1.10)	0.786 (0.012)	186.2 (10.7)	12.5 (0.1)	500 (2)	4.246 (0.005)	149 (7)	0.57	>30
OD-MHSEMAT	147.01 (3.77)	0.745 (0.009)	201.3 (9.8)	15.7 (0.3)	500 (2)	4.302 (0.009)	150 (6)	0.46	>30
FD-MHSEMAT	125.61 (3.25)	0.772 (0.017)	154.5 (6.1)	14.0 (0.2)	499 (1)	4.281 (0.010)	150 (11)	0.48	>30
OD-MSEMAD	176.41 (5.82)	0.610 (0.006)	1739.4 (73.1)	15.9 (0.6)	500 (3)	4.212 (0.012)	147 (8)	0.66	>30
FD-MSEMAD	144.47 (1.98)	0.585 (0.008)	1562.5 (63.6)	14.6 (0.1)	501 (4)	4.323 (0.014)	147 (8)	0.90	>30
OD-MHSEMAD	202.90 (0.63)	0.635 (0.006)	1481.5 (40.5)	18.7 (0.1)	503 (2)	4.281 (0.009)	148 (7)	0.48	>30
FD-MHSEMAD	169.53 (1.72)	0.612 (0.004)	1459.4 (20.2)	17.2 (0.2)	499 (2)	4.316 (0.007)	148 (9)	0.67	>30

Table 2
Parameters characterising the porous structure of the matrix systems, calculated by mercury intrusion–extrusion porosimetry. Values in parentheses represent the standard deviation (n = 2).
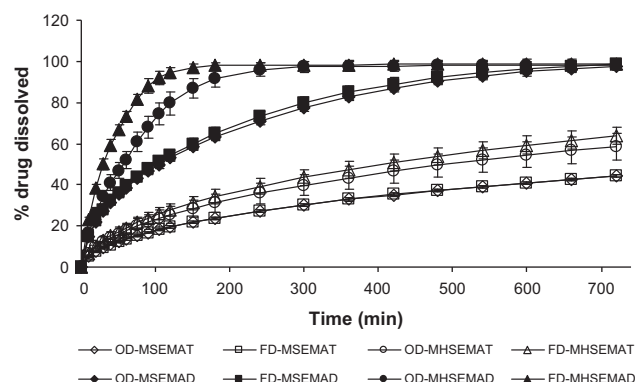
Mixtures	Porosity (%)	Mean pore diameter (nm)	Median pore diameter (nm)
OD-MSEMAT	22.4 (0.0)	33.5 (0.1)	805 (2)
FD-MSEMAT	22.8 (0.6)	30.5 (0.7)	677 (31)
OD-MHSEMAT	23.2 (0.2)	32.6 (0.0)	827 (3)
FD-MHSEMAT	23.5 (0.2)	32.2 (0.0)	826 (9)
OD-MSEMAD	18.6 (0.3)	28.4 (0.3)	563 (8)
FD-MSEMAD	20.1 (0.1)	27.7 (0.4)	507 (2)
OD-MHSEMAD	19.2 (0.2)	27.2 (0.0)	604 (2)
FD-MHSEMAD	20.2 (0.0)	28.5 (0.1)	600 (6)

Fig. 2. Pore size distribution profile for OD-MSEMAT matrices.

Fig. 3. Release profiles (over 12 h) of anhydrous theophylline (open symbols) and diltiazem hydrochloride (closed symbols) from formulated tablets of MSEMA and MHSEMA copolymers.

However, the addition of theophylline or diltiazem and stearic acid diminishes the porosity and mean pore diameter compared with tablets containing only copolymers [1]. This behaviour is in agreement with the reduction in the tablet thickness and is clearer for matrices containing diltiazem. The higher contribution of smaller pores for these tablets is also reflected in the median pore diameters shifting to smaller values.

3.4. Drug release study

Fig. 3 illustrates the drug release profiles from matrices prepared from the different mixtures. The studies are performed over a period of 12 h, and a higher percentage of drug release is observed for matrices containing MHSEMA copolymers compared with the tablets produced from MSEMA derivatives. This behaviour is noticed for both theophylline and diltiazem mixtures and could be explained on the basis of the higher hydrophilic character of MHSEMA copolymers. Echeverria et al. [3] reported also a relationship between the higher hydrophilia of HS copolymers (potato derivatives) and the faster drug release. Concerning the drying process,

differences are only found for MHSEMA-diltiazem formulations, where the matrices elaborated with the freeze-dried derivative show slightly higher drug release.

Comparison of the release profiles of diltiazem HCl and anhydrous theophylline reveals a faster drug release for diltiazem HCl formulations (complete drug release at the end of the dissolution test), attributable to the higher aqueous solubility of this drug [13,33–35]. Moreover, it is important to mention that theophylline matrices remain nearly intact after the dissolution process, while matrices containing diltiazem experiment a slight attrition of the tablet surface, according with their higher friability (Table 1).

To understand the mechanistic aspects of the drug release from the polymeric matrices, release data ($M_t/M_\infty \leqslant 0.6$) were analysed according to Higuchi [18], Korsmeyer et al. [19] and Peppas and Sahlin [20] equations and the main parameter values are listed in Table 3. For Peppas and Sahlin model, $m = 0.44$ was used as the matrices under study presented an aspect ratio (diameter/thickness) around 3.

Matrices under study provide a good fit to the different models $\left(r_{adj}^2 \geqslant 0.994\right)$, being Peppas–Sahlin equation the best suitable

Table 3
Mathematical modelling and drug release kinetics from EMA copolymers-based tablets.

| Mixtures	Higuchi equation		Korsmeyer equation			Peppas equation		
	k (min$^{-1/2}$)	Fit factors	n	k' (min^{-n})	Fit factors	k_d (min$^{-0.44}$)	k_r (min$^{-0.88}$)	Fit factors
OD-MSEMAT	0.015	$r^2_{adj} = 0.9947$ $AIC = -236.9$	0.48	0.019	$r^2_{adj} = 0.9973$ $AIC = -179.2$	0.029	1.8×10^{-4}	$r^2_{adj} = 0.9998$ $AIC = -331.1$
FD-MSEMAT	0.015	$r^2_{adj} = 0.9939$ $AIC = -232.9$	0.48	0.019	$r^2_{adj} = 0.9968$ $AIC = -174.4$	0.030	-2.0×10^{-4}	$r^2_{adj} = 0.9998$ $AIC = -322.4$
OD-MHSEMAT	0.022	$r^2_{adj} = 0.9986$ $AIC = -209.7$	0.51	0.022	$r^2_{adj} = 0.9980$ $AIC = -148.4$	0.036	-0.8×10^{-4}	$r^2_{adj} = 0.9998$ $AIC = -257.1$
FD-MHSEMAT	0.025	$r^2_{adj} = 0.9981$ $AIC = -185.4$	0.53	0.022	$r^2_{adj} = 0.9969$ $AIC = -125.8$	0.041	-1.4×10^{-4}	$r^2_{adj} = 0.9998$ $AIC = -230.7$
OD-MSEMAD	0.048	$r^2_{adj} = 0.9973$ $AIC = -107.0$	0.51	0.048	$r^2_{adj} = 0.9962$ $AIC = -78.8$	0.081	-9.4×10^{-4}	$r^2_{adj} = 0.9999$ $AIC = -151.9$
FD-MSEMAD	0.049	$r^2_{adj} = 0.9974$ $AIC = -106.8$	0.51	0.048	$r^2_{adj} = 0.9963$ $AIC = -79.0$	0.083	-9.7×10^{-4}	$r^2_{adj} = 0.9999$ $AIC = -157.9$
OD-MHSEMAD	0.079	$r^2_{adj} = 0.9996$ $AIC = -70.1$	0.65	0.037	$r^2_{adj} = 0.9995$ $AIC = -53.6$	0.080	32.9×10^{-4}	$r^2_{adj} = 0.9998$ $AIC = -73.1$
FD-MHSEMAD	0.115	$r^2_{adj} = 0.9998$ $AIC = -48.0$	0.68	0.049	$r^2_{adj} = 0.9981$ $AIC = -30.9$	0.139	23.4×10^{-4}	$r^2_{adj} = 0.9997$ $AIC = -46.3$

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_{adj}, adjusted coefficient of determination; AIC = Akaike Information Criterion.

model according to the lower (more negative) AIC values. The accurate fit to Higuchi equation, the n values from Korsmeyer equation around 0.5 and the prevalence of k_d over k_r in Peppas equation reveal a drug release mechanism controlled mainly by Fickian diffusion for matrices containing anhydrous theophylline. On the other hand, the tablets being nearly intact, when visually inspected after drug release, confirmed the absence of erosion. Different authors [3,8,36] have also postulated a diffusion mechanism when evaluating the theophylline release mechanism from matrices obtained from methacrylic/starch copolymers.

In contrast, the behaviour of matrices containing diltiazem is not so clear. MSEMA tablets show, in general, a good fit to the different equations and Fickian diffusion seems to be the dominant mechanism controlling drug release, although the release rate is faster compared with the counterpart matrices containing theophylline. However, in case of MHSEMA tablets, the 0.5 < n < 1 values from Korsmeyer equation and the increase in k_r values from Peppas equation reveal that these matrices are more liable to erosion, although diffusion is still the predominant process. The anomalous transport detected for these tablets could be related with their higher hydrophilicity and lower mechanical integrity.

On the other hand, from the comparison of the kinetic constants, it can be concluded that the drug solubility is the main factor controlling drug release rate [3,34], followed by the hydrophilic character of the copolymer type. The initial pore structure of the formulations has not a substantial influence on the drug release rates. Although tablets with theophylline show larger porosity and mean pore diameters than tablets with diltiazem, the higher contribution of smaller pores in diltiazem matrices approximates the total pore surface areas (data not shown). Hence, the contact surface area with the dissolution media is similar for all batches, not greatly affecting matrix hydration [30].

In order to relate drug release and fronts movement data, release studies were also performed clamping the tablets between Plexiglass® discs [17], where only radial drug release was allowed. The results of Fig. 4 indicate no drastic change in the shape of the release profiles (over 12 h) compared with the free tablets for anhydrous theophylline, whereas diltiazem HCl matrices show less steep profiles. Obviously, there is a decrease in the amount of drug released (19–22% for theophylline formulations and 49–60% for diltiazem formulations), as the surface area exposed to the dissolution medium has diminished [8].
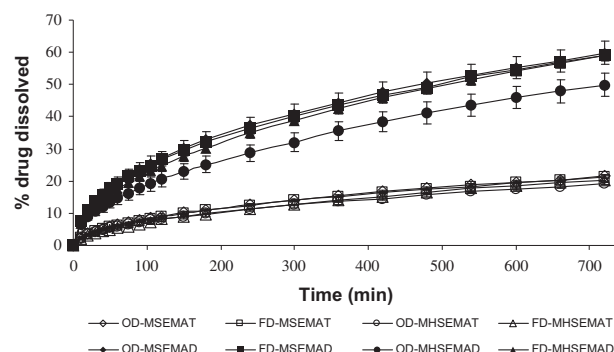
Fig. 4. Radial release profiles (over 12 h) of anhydrous theophylline (open symbols) and diltiazem hydrochloride (closed symbols) from formulated tablets of MSEMA and MHSEMA copolymers.

The radial drug release profiles fit better ($r^2_{adj} \geqslant 0.997$, lower AIC values) to the different kinetic models (Table 4) than the release profiles obtained from non-restricted tablets (Table 3). In view of AIC values, the models that statistically describe the best the experimental data are Peppas–Sahlin and Higuchi equations, demonstrating that radial drug release from matrices containing both theophylline and diltiazem are governed mainly by drug diffusion. The Plexiglass® devices prevented the attrition observed for free tablets of MHSEMA and diltiazem, so the contribution of the erosion mechanism is negligible. However, the influence of drug solubility is still noticeable since theophylline matrices have a diffusion rate around 0.008 min$^{-1/2}$ whereas diltiazem tablets have a diffusion rate around 0.02 min$^{-1/2}$ (Table 4).

3.5. Fronts movement study

With the purpose of obtaining useful information for a better understanding of the drug release mechanism from the different matrices [23], fronts movement kinetics were evaluated.

According to Ferrero et al. [8] for inert matrices, three fronts could be 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). The water penetration

Table 4
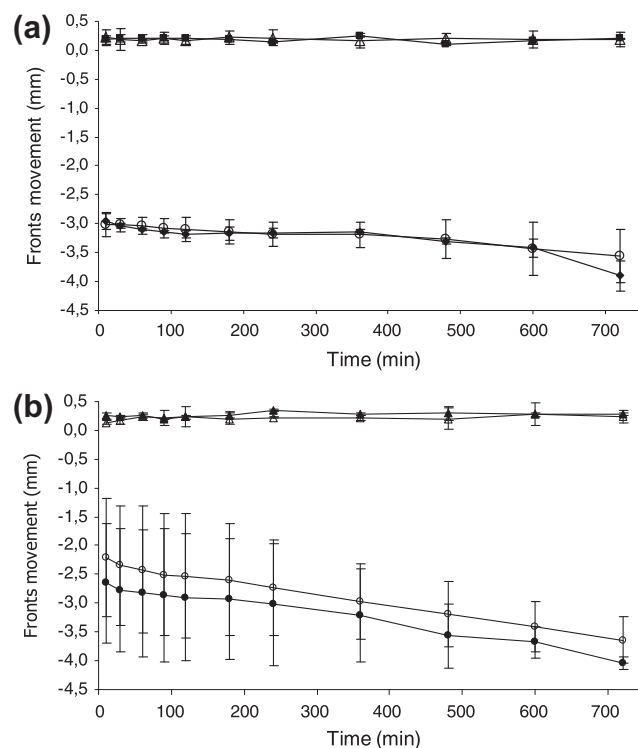Mathematical modelling and radial drug release kinetics from EMA copolymers-based tablets.

Mixtures	Higuchi equation		Korsmeyer equation			Peppas equation		
	k (min$^{-1/2}$)	Fit factors	n	k' (min^{-n})	Fit factors	k_d (min$^{-0.44}$)	k_r (min$^{-0.88}$)	Fit factors
OD-MSEMAT	0.008	$r^2_{adj} = 0.9987$ $AIC = -313.4$	0.49	0.009	$r^2_{adj} = 0.9993$ $AIC = -213.9$	0.012	-0.4×10^{-5}	$r^2_{adj} = 0.9998$ $AIC = -365.1$
FD-MSEMAT	0.008	$r^2_{adj} = 0.9992$ $AIC = -323.8$	0.50	0.008	$r^2_{adj} = 0.9990$ $AIC = -202.9$	0.012	1.1×10^{-5}	$r^2_{adj} = 0.9998$ $AIC = -368.0$
OD-MHSEMAT	0.007	$r^2_{adj} = 0.9996$ $AIC = -347.7$	0.49	0.008	$r^2_{adj} = 0.9987$ $AIC = -197.2$	0.010	4.8×10^{-5}	$r^2_{adj} = 0.9997$ $AIC = -355.1$
FD-MHSEMAT	0.008	$r^2_{adj} = 0.9997$ $AIC = -349.7$	0.54	0.006	$r^2_{adj} = 0.9993$ $AIC = -210.0$	0.010	8.1×10^{-5}	$r^2_{adj} = 0.9996$ $AIC = -343.2$
OD-MSEMAD	0.022	$r^2_{adj} = 0.9972$ $AIC = -197.3$	0.48	0.027	$r^2_{adj} = 0.9976$ $AIC = -147.2$	0.038	-20.2×10^{-5}	$r^2_{adj} = 0.9999$ $AIC = -279.6$
FD-MSEMAD	0.021	$r^2_{adj} = 0.9979$ $AIC = -203.9$	0.47	0.028	$r^2_{adj} = 0.9982$ $AIC = -153.2$	0.036	-12.4×10^{-5}	$r^2_{adj} = 0.9998$ $AIC = -252.7$
OD-MHSEMAD	0.018	$r^2_{adj} = 0.9994$ $AIC = -263.6$	0.48	0.021	$r^2_{adj} = 0.9995$ $AIC = -199.6$	0.026	12.0×10^{-5}	$r^2_{adj} = 0.9993$ $AIC = -258.8$
FD-MHSEMAD	0.022	$r^2_{adj} = 0.9997$ $AIC = -244.3$	0.50	0.023	$r^2_{adj} = 0.9997$ $AIC = -190.5$	0.032	10.0×10^{-5}	$r^2_{adj} = 0.9999$ $AIC = -275.4$

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_{adj}, adjusted coefficient of determination; AIC = Akaike Information Criterion.
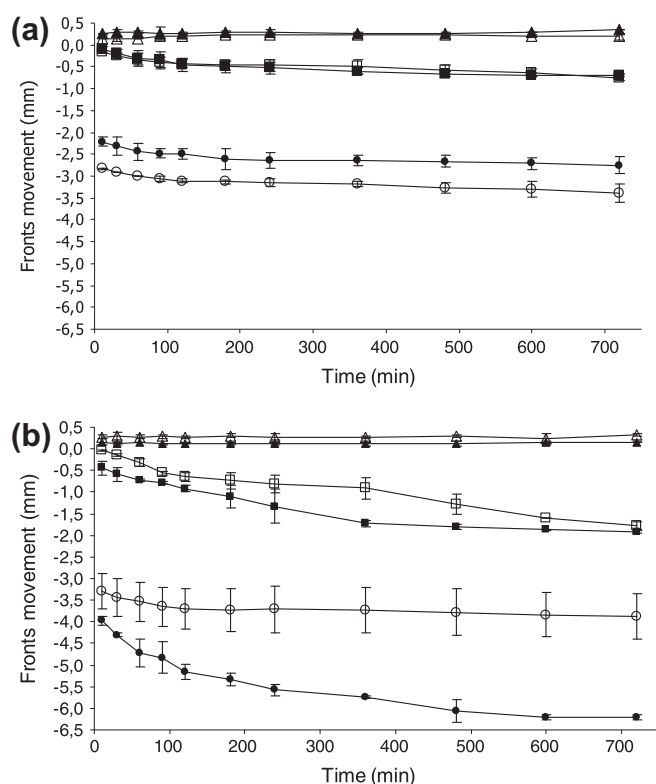
Fig. 5. Water uptake (○), complete wetting (□) and erosion (Δ) fronts positions over time for matrices containing anhydrous theophylline and MSEMA (a) or MHSEMA (b) copolymers. OD derivatives are represented by open symbols and FD derivatives by close ones.

Fig. 6. Water uptake (○) and erosion (Δ) fronts positions over time for matrices containing diltiazem hydrochloride and MSEMA (a) or MHSEMA (b) copolymers. OD derivatives are represented by open symbols and FD derivatives by close ones.

through capillaries and higher size pores determines the position of the water uptake front. As the whole polymer structure (smaller pores and intraparticle permeation) is participating in water up-take, a dark blue layer (due to methylene blue diffusion) progresses towards the centre of the tablet, indicating the position of the complete wetting front [23].

Fronts movement kinetics (over 12 h) depicted in Figs. 5 and 6 show a nearly constant erosion front movement, which agrees with the complete absence of swelling in matrices elaborated with both drugs. The introduction of EMA changes the nature of starch from hydrophilic to more hydrophobic. This modification consequently inhibits the characteristic swelling and gel layer formation of native

starches. As no swelling or erosion can be detected (the tablet diameter remains constant), the copolymer tablets behave as inert matrices where drug is released by diffusion through the porous structure.

For theophylline matrices (Fig. 5), the water uptake and complete wetting fronts exhibit a sudden initial inward displacement then followed by a linear movement. These two fronts seem to move faster in tablets containing MHSEMA derivatives, which would be consistent with the higher hydrophilic character of these copolymers. The fastest hydration of matrices containing MHSEMA copolymers is in agreement with their slightly higher drug release rates (Table 3). As for the effect of the drying method, differences are mainly noticeable for the water uptake front, exhibiting FD-MHSEMA matrices the fastest water penetration.

For diltiazem matrices (Fig. 6), no great differences are seen in the water uptake front movement concerning the effect of the carbohydrate nature and the drying method. This is due to less reproducible water uptake profiles, more evident when this freely soluble drug is combined with the most hydrophilic polymer (MHSEMA). It is also noteworthy to mention the impossibility of identification of the complete wetting front, probably due to the rapid diffusion of diltiazem hydrochloride that blocked the channels into the tablets preventing the methylene blue diffusion.

4. Conclusions

The present study signifies the potential of the novel graft copolymers as directly compressible tabletting excipients for sustained release purposes. The grafting of EMA introduces hydrophobicity and steric bulkiness that considerably protect the starch and prolong drug release. This behaviour is more noticeable when a slightly water soluble drug is included in the formulation. If a freely water soluble drug is selected, the combination with MSEMA derivatives (more hydrophobic than MHSEMA copolymers) is required to prevent attrition of the system.

The influence of the drug solubility and carbohydrate nature on the drug release behaviour is then clearly demonstrated. Nevertheless, no definite trend can be established between drug release kinetics and parameters such as the dehydration method of the copolymer and the initial pore structure of the matrix.

Although Fickian diffusion is the principal mechanism for drug release in most formulations, an anomalous transport can be detected for tablets containing MHSEMA and diltiazem. However, the contribution of the erosion mechanism is mainly due to the attrition of the tablet surface, as this process is prevented when the tablets are locked between Plexiglass® discs.

The nearly constant erosion front movement and the absence of swelling confirm that the copolymer tablets behave as inert matrix systems where the drug is released by diffusion through the porous structure. In general, water uptake and complete wetting fronts seem to move faster in matrices containing MHSEMA derivatives, which would be consistent with their highest hydrophilic character.

Although experiments to test the enzymatic resistance of the copolymers under study have not been carried out yet, other authors [37] have shown that the grafting chains (ethyl methacrylate) create an acrylic cover around the carbohydrate particles (high-amylose starch), which prevents the penetration of the enzyme α-amylase. However, the authors demonstrated that the carbohydrate part of the copolymers was susceptible to colonic fermentation, so future investigations will be designed to test the applicability of these materials for effective colon-targeted drug delivery.

Acknowledgements

References

[1] J.A. Marinich, C. Ferrero, M.R. Jiménez-Castellanos, Graft copolymers of ethyl methacrylate on waxy maize starch derivatives as novel excipients for matrix tablets: physicochemical and technological characterization, Eur. J. Pharm. Biopharm. 72 (2009) 138–147.

[2] A. Ceballos, M. Cirri, F. Maestrelli, G. Corti, P. Mura, Influence of formulation and process variables on in vitro release of theophylline from directly-compressed Eudragit matrix tablets, Il Farmaco 60 (2005) 913–918.

[3] I. Echeverria, I. Silva, I. Goñi, M. Gurruchaga, Ethyl methacrylate grafted on two starches as polymeric matrices for drug delivery, J. Appl. Polym. Sci. 96 (2005) 523–536.

[4] M. Efentakis, S. Politis, Comparative evaluation of various structures in polymer controlled drug delivery systems and the effect of their morphology and characteristics on drug release, Eur. Polym. J. 42 (2006) 1183–1195.

[5] J. Herman, J.P. Remon, Modified starches as hydrophilic matrices for controlled oral delivery. II. In vitro drug release evaluation of thermally modified starches, Int. J. Pharm. 56 (1989) 65–70.

[6] G.H.P. Te Wierik, J. Bergsma, A.W. Arends-Scholte, T. Boersma, A.C. Eissens, C.F. Lerk, A new generation of starch products as excipient in pharmaceutical tablets. I. Preparation and binding properties of high surface area potato starch products, Int. J. Pharm. 134 (1996) 27–36.

[7] G.H.P. Te Wierik, A.C. Eissens, J. Bergsma, A.W. Arends-Scholte, G.K. Bolhuis, A new generation starch product as excipient in pharmaceutical tablets. III. Parameters affecting controlled drug release from tablets based on high surface area retrograded pregelatinized potato starch, Int. J. Pharm. 157 (1997) 181–187.

[8] C. Ferrero, I. Bravo, M.R. Jiménez-Castellanos, Drug release kinetics and fronts movement studies from methyl methacrylate (MMA) copolymer matrix tablets: effect of copolymer type and matrix porosity, J. Control. Release 92 (2003) 69–82.

[9] T. Nabais, F. Brouillet, S. Kyriacos, M. Mroueh, P. Amores Da Silva, B. Bataille, C. Chebli, L. Cartilier, High-amylose carboxymethyl starch matrices for oral sustained drug-release: in vitro and in vivo evaluation, Eur. J. Pharm. Biopharm. 65 (2007) 371–378.

[10] C. Chebli, L. Cartilier, N.G. Hartman, Substituted amylose as a matrix for sustained-drug release: a biodegradation study, Int. J. Pharm. 222 (2001) 183–189.

[11] B. van Veen, J. Pajander, K. Zuurman, R. Lappalainen, A. Poso, H.W. Frijlink, J. Ketolainen, The effect of powder blend and tablet structure on drug release mechanisms of hydrophobic starch acetate matrix tablets, Eur. J. Pharm. Biopharm. 61 (2005) 149–157.

[12] P. Costa, J.M. Sousa Lobo, Modeling and comparison of dissolution profiles, Eur. J. Pharm. Sci. 13 (2001) 123–133.

[13] P. Colombo, R. Bettini, P. Santi, A. De Ascentiis, N.A. Peppas, Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport, J. Control Release 39 (1996) 231–237.

[14] O. Korhonen, H. Kanerva, M. Vidgren, A. Urtti, J. Ketolainen, Evaluation of novel starch acetate-diltiazem controlled release tablets in healthy human volunteers, J. Control. Release 95 (2004) 515–520.

[15] European Pharmacopoeia, sixth ed., Council of Europe, Strasbourg, France, 2007.

[16] A. Muñoz-Ruiz, R. Gallego, M. del Pozo, M.R. Jiménez-Castellanos, J. Domínguez-Abascal, A comparison of three methods of estimating displacement on an instrumented single punch machine, Drug Dev. Ind. Pharm. 21 (1995) 215–227.

[17] R. Bettini, P. Colombo, G. Massimo, P.L. Catellani, T. Vitali, Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects, Eur. J. Pharm. Sci. 2 (1994) 213–219.

[18] T. Higuchi, Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52 (1963) 1145–1149.

[19] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N.A. Peppas, Mechanisms of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35.

[20] N.A. Peppas, J.J. Sahlin, A simple equation for the description of solute release. III. Coupling of diffusion and relaxation, Int. J. Pharm. 57 (1989) 169–172.

[21] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs, J. Control. Release 5 (1987) 23–26.

[22] SPSS Base 14.0 User's Guide, SPSS Inc., Chicago, IL, 2005.

[23] C. Ferrero, A. Muñoz-Ruiz, M.R. Jiménez-Castellanos, Fronts movement as a useful tool for hydrophilic matrix release mechanism elucidation, Int. J. Pharm. 202 (2000) 21–28.

[24] M.G. Vachon, D. Chulia, The use of energy indices in estimating powder compaction functionality of mixtures in pharmaceutical tableting, Int. J. Pharm. 177 (1999) 183–200.

[25] P. Di Martino, E. Joiris, S. Martelli, Particle interaction of lubricated or unlubricated binary mixtures according to their particle size and densification mechanism, Il Farmaco 59 (2004) 747–758.

[26] E. Doelker, Physique de la compression. Intérêt et limite des machines instrumentées pour l'optimisation de la formulation, Pharm. Acta Helv. 53 (1978) 1–7.

[27] M.J. Järvinen, M.J. Juslin, Evaluation of force–displacement measurements during one-sided powder compaction in a die; the influence of friction with die wall and of the diameter of punches and die on upper and lower punch pressure, Powder Technol. 28 (1981) 115.

[28] K.M. Picker, The use of carrageenan in mixture with microcrystalline cellulose and its functionality for making tablets, Eur. J. Pharm. Biopharm. 48 (1999) 27–36.

[29] C. Sun, D.J.W. Grant, Effects of initial particle size on the tableting properties of L-lysine monohydrochloride dihydrate powder, Int. J. Pharm. 215 (2001) 221–228.

[30] K.A. Mehta, M.S. Kislalioglu, W. Phuapradit, A.W. Malick, N.H. Shah, Effect of formulation and process variables on porosity parameters and release rates from a multi unit erosion matrix of a poorly soluble drug, J. Control. Release 63 (2000) 201–211.

[31] J. Pajander, B. Van Veen, O. Korhonen, R. Lappalainen, J. Ketolainen, Liquid boundary movements in cylindrical and convex hydrophobic matrix tablets: effects on tablet cracking and drug release, Eur. J. Pharm. Biopharm. 64 (2006) 167–172.

[32] B.D. Zdravkov, J.J. Čermák, M. Šefara, J. Janků, Pore classification in the characterization of porous materials: a perspective, Cent. Eur. J. Chem. 5 (2007) 385–395.

[33] X.C. Fu, G.P. Wang, W.Q. Liang, M.S.S. Chow, Prediction of drug release from HPMC matrices: effect of physicochemical properties of drug and polymer concentration, J. Control. Release 95 (2004) 209–216.

[34] I. Bravo-Osuna, C. Ferrero, M.R. Jiménez-Castellanos, Drug release behaviour from methyl methacrylate-starch matrix tablets: effect of polymer moisture content, Eur. J. Pharm. Biopharm. 69 (2008) 285–293.

[35] H. Kojima, K. Yoshihara, T. Sawada, H. Kondo, K. Sako, Extended release of a large amount of highly water-soluble diltiazem hydrochloride by utilizing counter polymer in polyethylene oxides (PEO)/polyethylene glycol (PEG) matrix tablets, Eur. J. Pharm. Biopharm. 70 (2008) 556–562.

[36] M. Casas, C. Ferrero, M.R. Jiménez-Castellanos, Graft tapioca starch copolymers as novel excipients for controlled-release matrix tablets, Carbohyd. Polym. 80 (2010) 71–77.

[37] J. Alias, I. Goñi, M. Gurruchaga, Enzymatic and anaerobic degradation of amylose based acrylic polymers, for use as matrices for drug release, Polym. Degrad. Stabil. 92 (2007) 658–666.