Carbohydrate Polymers 80 (2010) 71–77

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Graft tapioca starch copolymers as novel excipients for controlled-release matrix tablets

Marta Casas, Carmen Ferrero, Mª Rosa Jiménez-Castellanos *

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/Profesor García González, 41012 Sevilla, Spain

ARTICLE INFO

Article history:
Received 1 October 2009
Received in revised form 27 October 2009
Accepted 28 October 2009
Available online 30 October 2009

Keywords:
Tapioca starch
Graft copolymers
Breaking force
Drying methods
Matrix tablets
Release kinetic
Fronts movement

ABSTRACT

This paper studies new graft tapioca copolymers as an alternative for the formulation of controlled-release matrix tablets, using anhydrous theophylline as model drug. Copolymers were synthesised by free radical copolymerisation of ethyl methacrylate with tapioca starch (TS) or hydroxypropyl starch (THS), being alternatively dried by two methods: oven or freeze-drying. The influence of carbohydrate nature, drying process and breaking force on drug release was evaluated. Radial drug release and fronts movement were also studied using special devices consisting of two Plexiglass® discs. The paper demonstrates the use of these new copolymers as excipients for controlled drug release. All tablets behave as inert matrices controlling drug release mainly by diffusion. However, TSEMA matrices demonstrated to have better binding properties with lower release than THSEMA tablets. Drying process and breaking force had a significant influence on dissolution behaviour only in THSEMA matrices. Porosity and tortuosity values explained the higher drug release observed for THSEMA matrices with low crushing force and for freeze-dried copolymer tablets.

1. Introduction

Among the different approaches for oral prolonged-release dosage forms, matrix tablets have been the most widely used because of the simple and low-cost manufacturing process (Ferrero & Jiménez-Castellanos, 2002). A variety of polymers is employed as matrix-forming excipients whose characteristics may play a key role and significantly influence the behaviour of these devices.

Starches are natural biopolymers widely used as fillers, binders and disintegrants in the pharmaceutical fields as they are cost-effective, non-toxic and can be metabolised by the human body (Demirgöz et al., 2000; Dumoulin, Cartilier, & Mateescu, 1999; Pifferi, Santoro, & Pedrani, 1999). However, native starches are not suitable for controlled drug delivery systems due to poor flow and compressibility and, most notably, fast release properties in physiological fluids (Dumoulin et al., 1999; Kost & Shefer, 1990). In spite of this, it has been demonstrated that compression force can be used to obtain slower release of drug in starch matrices (Weyenberg, Vermeire, Remon, & Ludwig, 2003). Depends on the variety of starch its chemical composition changes and this also change its physical properties, which means that the different starches may not be interchangeable as regards a specific pharmaceutical use (Pifferi et al., 1999). Tapioca starch is differentiated from other starches by its low level of residual materials, lower amylose content (17%) and high molecular weights of amylose and amylopectin. These properties make tapioca a good native starch for direct use in industrial applications and a starting material for physical and chemical modifications (BeMiller & Whistler, 2009).

Recently, it has been introduced a new generation of graft copolymers combining natural or semi-synthetic (tapioca starch derivatives) and synthetic (ethyl methacrylate – EMA) polymers. The products tapioca starch–ethylmethacrylate (TSEMA) and hydroxypropyl tapioca starch–ethylmethacrylate (THSEMA) were synthesised and dried by two different methods: drying in a vacuum oven (OD copolymers) or freeze-drying (FD copolymers) (Casas, Ferrero, & Jiménez-Castellanos, 2009).

These polymers were thoroughly characterised physicochemical and technologically by NMR, IR spectrophotometry, X-ray diffraction and compression properties studies. One of the technological improvements of the new copolymers was the possibility to obtain an adequate crushing strength of TSEMA and THSEMA tablets using lower compression force and lower ejection force than for raw commercial starches (Casas et al., 2009). It was also remarkable the longer disintegration time values observed, similar to Preflo®, a commercial direct compression diluent for sustained released tablets (Sanghvi, Collins, & Shukla, 1993). Concerning the drying methods, FD products showed different compaction properties, with higher plasticity and lower elasticity than OD copolymers, but similar disintegration times.

* Corresponding author. Tel.: +34 954556836; fax: +34 954556085.
E-mail address: mrosa@us.es (M.R. Jiménez-Castellanos).

0144-8617/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2009.10.065

Due to the good results obtained with the tapioca starch graft copolymers described, the aim of this work was to study the drug release of systems prepared with EMA copolymers as matrix-forming materials and anhydrous theophylline as model drug. Raw materials (tapioca or hydroxypropyl tapioca starch) were used as reference. Also, this paper evaluated the influence of carbohydrate nature, drying process (freeze-dried and oven-dried) and compression force (70–80 N and 140–150 N) on the mechanistic aspects of drug release from these matrices. Drug release phenomena were studied using Higuchi (1963), Korsmeyer, Gurny, Doelker, Buri, and Peppas (1983) and Peppas and Sahlin (1989) kinetic equations because of its major appliance. Fronts movement were evaluated according to Ferrero, Muñoz-Ruiz, and Jiménez-Castellanos, (2000) in order to understand in greater detail the internal processes controlling drug release. Finally, in order to relate drug release and fronts movement data, radial drug release (Bettini, Colombo, Massimo, Catellani, & Vitali, 1994) was also evaluated.

2. Materials and methods

2.1. Materials

Tapioca starch (TS) (Tapioca Starch, batch MCB 3053) (±17% of amylose) and hydroxypropyl tapioca starch (THS) (Tapioca Textra, Batch KCB 8010) were kindly supplied by National Starch & Chemical (Manchester, UK) as natural and semi-synthetic polymers.

Ethyl methacrylate (EMA) (Merck, Hohenbrunn, Germany) was chosen as acrylic monomer for graft copolymerisation.

Anhydrous theophylline (Theophylline BP 80, Roig Farma, Barcelona, Spain, batch 0212030) was chosen as model drug.

Stearic acid (Estearina, Roig Farma, Barcelona, Spain, batch 90003410) was selected as lubricant.

All the reagents used for the synthetic process were of analytical grade.

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

2.2. Methods

2.2.1. Synthesis of graft copolymers

Copolymers were synthesised by free radical copolymerisation of EMA and different starches (tapioca starch – TS and hydroxypropyl tapioca starch – THS) following the procedure described by Echeverría, Silva, Goñi, and Gurruchaga (2005). The carbohydrate (40 g), either tapioca starch or hydroxypropyl tapioca starch, was dispersed in 550 ml of bidistilled water into a four-necked round bottom flask (1 L). The medium was purged with purified nitrogen and the bath temperature was maintained at 30 °C. Next, 118 mL of EMA was added, followed by the initiator solution (50 ml of 0.1 M ceric ammonium nitrate in 1 N nitric acid) 15 min later. Grafting was allowed to proceed for 4 h under a constant light source (two lamps of 100 W in the vis wavelength range). Thus, the synthesised TSEMA and THSEMA were filtered off and washed with diluted nitric acid and bidistilled water until neutral pH was reached. A noteworthy aspect to mention is that the use of water as reaction solvent guarantees, not only an effective dispersion of all the reactants and reagents, but also the absence of toxic substances in the final product (Echeverría et al., 2005).

The solids obtained were dried using two different methods: drying in a vacuum oven (Vacucell 22, Gräfelting, Germany) at 50 °C (0.5 Pa) until constant weight (OD copolymers) or freeze-drying (at −80 °C for 48 h and 0.1 Pa) in a Cryodos-80 apparatus (Terrasa, Spain) until powdered product was got (FD copolymers). Finally, the starch-based copolymers (TSEMA) were crushed at 10,000 rpm in a knives mill (Retsch ZM 200, Haan, Germany) to obtain powdery samples.

2.2.2. Mixtures preparation

Anhydrous theophylline (24%, w/w) and polymer (TS, THS or graft copolymers) (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 a further 5 min.

2.2.3. Powder and particle characterisation of mixtures

2.2.3.1. Apparent particle density. The apparent particle density of the products were determined, in triplicated, by means of an air comparison pycnometer (Ultrapycnometer 1000, Quantachrome, Boyton Beach, FL, USA), using helium as an inert gas, according to European Pharmacopoeia (2007). Due to the high diffusivity of helium, this method was considered to give the closest approximation to the true density (Viana, Jouannin, Pontier, & Chulia, 2002).

2.2.3.2. Flow properties. An automated flowmeter system developed by Muñoz-Ruiz and Jiménez-Castellanos (1993) was used to estimate the flow rate of the different samples. A glass funnel with an internal diameter of 10 mm and an angle of 30° with respect to the vertical was selected as vessel (European Pharmacopoeia, 2007). Weight data were acquired by means of a balance (Mettler AE50, Zürich, Switzerland) connected to a personal computer, using adequate software. The results are shown as the mean value (g/s) of three replicates.

2.2.4. Preparation of tablets

The different mixtures were compacted into tablets using an instrumented (Muñoz-Ruiz, Gallego, del Pozo, Jiménez-Castellanos, & Domínguez-Abascal, 1995) single punch tablet machine (Bonals AMT 300, Barcelona, Spain) running at 30 cycles/min. To investigate the compression 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 at two different breaking forces: 70–80 N and 140–150 N. In the case of the mixtures based on raw materials, TS or THS, the tablets were manufactured only at 70–80 N, due to the impossibility to make them at higher pressures. Typical compaction parameters (maximum upper pressure – P, expansion work – W_e, apparent net work – W_{an}, plasticity – Pl) described by Doelker (1978) and Järvinen and Juslin (1981) were collected from four tableting cycles.

In order to produce a sufficient number of tablets for physical testing, the machine was equipped with a forced feeding system and the mixtures were tableted in the same conditions outlined before (500 mg weight, 12 mm diameter, 70–80 N or 140–150 N breaking force).

Apparent particle density and compression data from the different mixtures were statistically analysed by one way analysis of variance (ANOVA) using the SPSS® program version 14.0. Post-ANOVA analysis was carried out according to Bonferroni's multiple comparison tests. Results were quoted as significant when $p < 0.05$.

2.2.5. Standard physical test of tablets

The physical testing of tablets was performed after a relaxation period of at least 24 h. The tablet average weight and the standard deviation (SD) were obtained from 20 individually weighed (Sartorius CP224S, Göttingen, Germany) tablets according to European Pharmacopoeia (2007).

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

The breaking force (European Pharmacopoeia, 2007) of 10 tablets was determined by diametrical loading with a Schleuninger-2E tester (Greifensee, Switzerland).

Tablet friability (European Pharmacopoeia, 2007) was calculated as the percentage weight loss of 20 tablets after 4 min at 25 rpm in an Erweka TA (Heusenstamm, Germany) friability tester.

Disintegration testing (European Pharmacopoeia, 2007) was performed at 37 °C in distilled water (800 ml), using an Erweka ZT3 (Heusenstamm, Germany) apparatus without discs. The disintegration times reported are averages of six determinations.

2.2.6. 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 and pore size distribution were determined, in duplicate, for each tablet tested.

2.2.7. Drug release study

Release experiments (six tablets) were performed in an automatic dissolution apparatus 2 (Erweka DT 600 HH, Heusenstamm, Germany) (European Pharmacopoeia, 2007) as a function of time (12 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 89079AX, Böblingen, Germany). Theophylline release was monitored continuously at 272 nm on an Agilent Technologies, 8453 UV–vis spectrophotometer.

In a second series of experiments, special devices (Bettini et al., 1994) were used in order to obtain a rigorous radial release. The tablets were locked between two transparent Plexiglass® discs by means of four stainless steel screws. The upper disc was carved with concentric circles (from 8 to 20 mm of diameter), so that the tablet could be placed just in the centre. 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 (1963) (1), Korsmeyer et al. (1983) (2) and Peppas and Sahlin (1989) (3) equations:

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

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

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

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), k 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 (Ritger & Peppas, 1987), 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 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 correct determination coefficient (r^2) was used to test the applicability of the release models.

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

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

where R_t and T_t are the percentages released at each time point. An f_2 value between 50 and 100 implies similarity between two release profiles (Guidance for industry, 1997).

2.2.8. Fronts movement study

Fronts movement measurements were effected as described elsewhere (Ferrero, Muñoz-Ruiz, & Jiménez-Castellanos, 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 (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 (Japan) with a 10× digital zoom. Focal distance was kept constant during all measurements. The photographs were analysed by computer using Corel Draw X3®. 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 discussions

3.1. Synthesis of graft copolymers

The choice of the polymer is an important aspect to achieve the desired release profile. To this aim, a good characterisation of products is necessary, thus, some of the physicochemical and technological properties of powders were studied in previous work (Casas et al., 2009). These new copolymers offered a high percent grafting (%*G* = percentage weight of grafted acrylic polymer with respect to grafted carbohydrate): 148.6 ± 6.2% for OD-TSEMA, 170.7 ± 4.5% for FD-TSEMA, 213.5 ± 3.5% for OD-THSEMA and 229.7 ± 6.8% for FD-THSEMA. The high %*G* indicates the strong tendency of the polymer to graft onto the carbohydrate backbone, preferably on THSEMA.

3.2. Characterisation of mixtures and compression properties

As can be seen in Table 1, apparent particle density values were statistically lower ($p < 0.05$) for copolymers mixtures than carbohydrate ones, due to the markedly big size of the poly(methyl methacrylate) – PMMA. However, no difference ($p > 0.05$) was found between drying methods or carbohydrate nature results. Besides, all the mixtures were characterised by poor flow (<10 g/s).

Also, graft copolymer mixtures required markedly lower applied pressure (P) to obtain tablets with the same breaking force (70–80 N) than carbohydrates ones ($p < 0.05$). Moreover, the maximum applied pressures were larger for OD than FD derivatives, in agreement with the results of the previously work without theophylline (Casas et al., 2009).

Respecting to the expansion work (W_e) and apparent net work (W_{an}), the lower values obtained for the copolymer mixtures indicate better compression properties than carbohydrate mixtures.

Table 1
Apparent particle density (g/cm^3) and compression parameters ($n = 4$) for the different mixtures at 70–80 N and 140–150 N: maximum applied upper punch pressure (P), expansion work (W_e), Juslin's apparent net work (W_{an}) and plasticity (Pl). Values in brackets represent the standard deviation.

Mixtures	Apparent particle density (g/cm^3)	P (MPa)	W_e (J)	W_{an} (J)	Pl (%)
TS 70–80 N	1.494 (0.005)	339.18 (7.90)	3.470 (0.931)	18.718 (0.371)	84.44 (3.79)
OD-TSEMA 70–80 N	1.285 (0.004)	92.83 (0.43)	0.604 (0.044)	11.078 (0.081)	94.84 (0.36)
140–150 N		128.61 (2.85)	0.550 (0.370)	15.504 (1.019)	96.54 (2.45)
FD-TSEMA 70–80 N	1.290 (0.007)	67.45 (1.44)	0.240 (0.075)	10.241 (0.453)	97.70 (0.78)
140–150 N		100.97 (3.07)	0.336 (0.058)	15.034 (0.599)	97.82 (0.32)
THS 70–80 N	1.481 (0.006)	310.27 (14.65)	3.639 (0.302)	17.218 (0.219)	82.57 (1.04)
OD-THSEMA 70–80 N	1.280 (0.001)	93.73 (1.06)	0.615 (0.200)	13.408 (0.674)	95.59 (1.56)
140–150 N		158.35 (2.48)	0.961 (0.057)	20.265 (0.275)	95.47 (0.24)
FD-THSEMA 70–80 N	1.274 (0.002)	80.32 (0.44)	0.269 (0.029)	13.307 (0.244)	98.02 (0.19)
140–150 N		122.83 (2.34)	0.616 (0.071)	18.190 (0.215)	96.73 (0.33)

Related to the drying method, it is also possible to see lower W_e and W_{an} values for FD mixtures.

The higher plasticity behaviour (Pl) values from the copolymer mixtures than the carbohydrate ones were in agreement with the higher plastic character of these materials, especially for FD derivatives (Casas et al., 2009).

Respect to the breaking force, when it increases, only the applied pressure and apparent net work increased significantly ($p < 0.05$).

3.3. Physical test of tablets

Results from the physical test of tablets obtained from the different products are compiled in Table 2. All tablets fulfilled the guidelines specified in European Pharmacopoeia (2007) related to weight uniformity test. The copolymer tablets displayed higher thickness than the raw materials tablets. These results might be related to a more porous structure in copolymer tablets. The breaking force confirmed the values of 70–80 N and 140–150 N for the tablets.

Tablets from carbohydrates mixtures presented the highest friability values, according to their lower binding capacity. Besides, the friability of copolymer tablets improved with the addition of theophylline in the formulation (Casas et al., 2009). However, only at 140–150 N, this parameter is below the limit proposed by European Pharmacopoeia (2007).

Carbohydrate mixture tablets completely disintegrated before 10 min of the experiment, while none of the copolymer tablets disintegrated before 30 min. However, tablets obtained from TSEMA mixtures maintained their physical integrity after this test, whereas tablets from THSEMA mixtures suffered some attrition.

In order to evaluate the microstructure of the matrices, their pore size distribution was measured by mercury intrusion–extrusion porosimetry (Table 2).

According with the thickness results indicated before, raw materials mixtures showed lower porosity than copolymer tablets. Relating to the copolymer mixture tablets, similar values were observed between TSEMA and THSEMA. Regarding the drying method, FD mixtures show slightly higher porosity than OD mixtures. Respect to the breaking force, porosity values decreased in all cases when the breaking force increased. Other authors have also studied starch tablets compressed at different forces and have confirmed the same porosity results (Weyenberg et al., 2003).

According to IUPAC definitions the mean pore diameters revealed the presence of mesopores in the matrices from carbohydrates and FD-TSEMA, and macropores for all the other cases. The pore size distribution profiles were unimodal in all cases, similar to the copolymers tablets without drug (Casas et al., 2009).

3.4. Drug release study

Fig. 1 illustrates a pronounced faster drug release for carbohydrates matrices (TS and THS) compared with graft copolymers ($f_2 < 50$). So, TS and THS showed a 100% of drug released at the first hour with a complete disintegration, while graft copolymer matrices had not released the totally of the drug at the end of the study. On the other hand, TSEMA matrices were associated to a lower drug release than THSEMA matrices, with big differences in the case of tablets at 70–80 N ($f_2 < 50$). Besides, matrices from TSEMA copolymers remained nearly intact, while matrices containing THSEMA derivatives experimented a slight attrition of the tablet surface at the end of the dissolution process, at both compression forces. This behaviour of TSEMA matrices could be attributed to the better binding properties of these copolymers (Table 1).

Respect to the different drying method, only THSEMA showed differences between its profiles, with a faster release for FD derivatives (OD-THSEMA/FD-THSEMA at 70–80 N $f_2 = 37.9$; OD-THSEMA/FD-THSEMA at 140–150 N $f_2 = 30.0$) according with its higher porosity (Table 2).

In spite of the higher porosity showed by all mixtures at 70–80 N, only biopharmaceutical differences were found in the case of OD-THSEMA when the breaking force was increased from 70–80 N to 140–150 N. It is important to mention that drug release of TSEMA tablets has not been biopharmaceutically influenced by

Table 2
Tablet test results for the different mixtures: average weight, thickness, breaking force (BF), friability (F), disintegration time (DT), porosity values (calculated by mercury intrusion–extrusion porosimetry) and the apparent diffusion coefficients (obtained from Higuchi rate constant) for drug release studies. Values in brackets represent the standard deviation.

Mixtures	Average weight (mg)	Thickness (mm)	BF (N)	F (%)	DT (min)	Porosity (%)	$D' \times 10^{-4}$ (cm^2/min)
TS 70–80 N	496 (2)	3.369 (0.106)	80 (9)	2.39	<1	16.63 (0.04)	–
OD-TSEMA 70–80 N	500 (1)	4.729 (0.055)	81 (8)	2.10	>30	29.70 (0.51)	5.26
140–150 N	503 (1)	4.435 (0.081)	146 (12)	0.55	>30	22.97 (0.59)	8.40
FD-TSEMA 70–80 N	500 (2)	4.988 (0.037)	81 (9)	2.02	>30	33.61 (0.08)	3.76
140–150 N	500 (1)	4.536 (0.059)	148 (11)	0.95	>30	26.06 (0.23)	4.47
THS 70–80 N	495 (5)	3.428 (0.032)	77 (11)	2.43	8	17.84 (0.56)	–
OD-THSEMA 70–80 N	502 (1)	4.900 (0.052)	74 (6)	2.02	>30	32.87 (0.94)	18.38
140–150 N	500 (1)	4.401 (0.020)	149 (11)	0.70	>30	24.48 (0.21)	11.71
FD-THSEMA 70–80 N	503 (1)	5.023 (0.030)	75 (9)	1.96	>30	33.86 (0.02)	35.26
140–150 N	503 (1)	4.555 (0.027)	147 (8)	0.78	>30	27.05 (0.93)	36.31

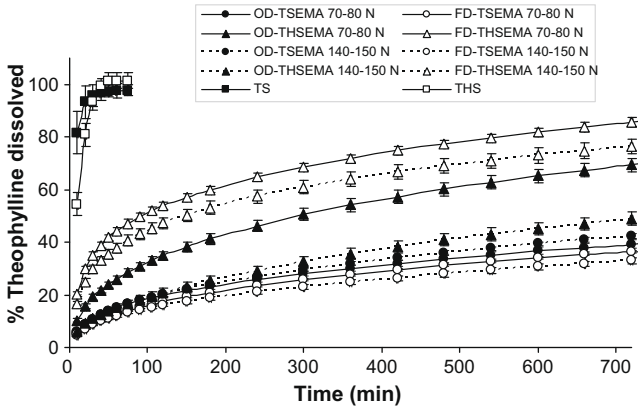

Fig. 1. Release profiles of anhydrous theophylline from formulated tablets of TS (■), THS (□), TSEMA (●) and THSEMA (▲). OD products are represented by closed symbols and FD products by open ones. Tablets at crushing force of 70–80 N are represented by continuous line and 140–150 N by discontinuous one. The bars show the standard deviation ($n = 6$).

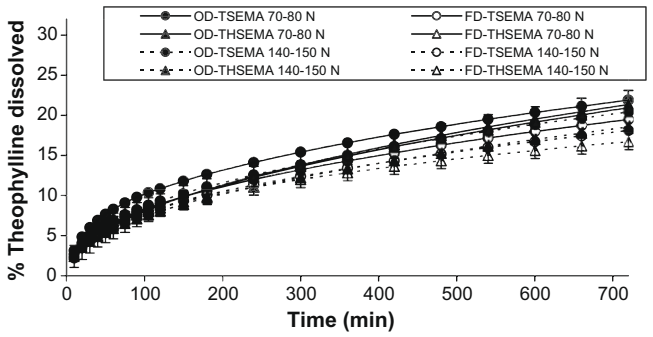

Fig. 2. Radial release profiles of anhydrous theophylline (over 24 h) from formulated tablets of TSEMA (●) and THSEMA (▲) copolymers. OD products are represented by closed symbols and FD products by open ones. Tablets at crushing force of 70–80 N are represented by continuous line and 140–150 N by discontinuous one. The bars show the standard deviation ($n = 3$).

drying process or breaking force. This could be due to the fact that TSEMA matrices have been prepared with copolymer powders exhibiting lower particle size (d_{50}OD-TSEMA = 138 μm; d_{50}FD-TSEMA = 125 μm; d_{50}OD-THSEMA = 346 μm; d_{50}FD-THSEMA = 377 μm) (Casas et al., 2009), so increasing the efficiency of the compaction level (Hüttenrauch, 1977) in making a resisting matrix for the release process.

Release data analysis was carried out according to Higuchi (1963), Korsmeyer et al. (1983) and Peppas and Sahlin (1989) equations and the main parameter values are listed in Table 3 (except to carbohydrate matrices). For Peppas model, $m = 0.44$ was used as the matrices under study presented an aspect ratio (diameter/thickness) around 3.

All matrices provide better fit to the Peppas & Sahlin model (Table 3). The n values from Korsmeyer equation lower than 0.45 (Ritger & Peppas, 1987) and the prevalence of k_d and the negative values for k_r in Peppas equation reveals a drug release mechanism controlled mainly by drug diffusion (Colombo, Bettini, Catellani, Santi, & Peppas, 1999). Different authors (Carli, Capone, & Colombo, 1984; Colombo, Conte, Caramella, Gazzaniga, & La Manna, 1985; Farhadieh, Borodkin, & Buddenhagen, 1971) have also postulated a diffusion mechanism when evaluating the drug release mechanism from matrices obtained from acrylic/methacrylic copolymers.

THSEMA tablets showed higher diffusion rate constants and k_d values than TSEMA, especially for FD-THSEMA matrix, according with the results showed in Fig. 1. Moreover, an important decrease on diffusion rate constant ($min^{-1/2}$) can be seen on OD-THSEMA when the breaking force increased, according with the results indicated before. Similar diffusion rate constants and k_d values was possible to see in the case of TSEMA tablets.

The methodology for the application of Peppas equation (1989) proposes the determination of R/F (relaxation/diffusion ratio) parameter. However, due to the negative values of k_r in all cases, this datum was not calculated. Ferrero, Bravo, and Jiménez-Castellanos (2003) have also obtained negative values for k_r in tablets prepared with methyl methacrylate copolymers with theophylline.

In order to relate drug release and fronts movement data, release studies were also performed clamping the tablets between Plexiglass discs (Bettini et al., 1994), where only radial drug release was allowed. The results of Fig. 2 indicate a drastic change compared with free tablets besides the logical decrease in the amount of drug release. Similar profiles were observed for all matrices, without differences between the type of polymer, drying method or breaking force ($f_2 > 50$). Furthermore, the Plexiglass avoided THSEMA matrices disintegration observed from the free tablets, which could explain the marked reduction in the quantity of drug release. According with Colombo et al. (1990) and Ferrero et al. (2003), these results seem to indicate that the initial amount of area exposed to the dissolution medium determines the amount of drug release.

The values from Table 4 support this behaviour. So, the slower rate observed (around 0.007 $min^{-1/2}$) was due to a considerable decrease in the release surface available. According to Korsmeyer equation, the n values observed higher than 0.45 indicate an anomalous (non-Fickian) transport. However, we observed a less accurate fit to Korsmeyer equation than to binomial model. The prevalence of k_d and the small, even negative, values for k_r in Peppas equation reveals a drug release mechanism controlled mainly by drug diffusion (Colombo et al., 1999).

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

Tablets	Higuchi equation		Korsmeyer equation			Peppas equation		
	k ($min^{-0.5}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
OD-TSEMA 70–80 N	0.013	0.99251	0.414	0.0261	0.99150	0.025	-1.7×10^{-4}	0.99894
140–150 N	0.014	0.99471	0.436	0.0242	0.99680	0.027	-1.6×10^{-4}	0.99992
FD-TSEMA 70–80 N	0.012	0.99162	0.446	0.0196	0.99277	0.025	-2.0×10^{-4}	0.99991
140–150 N	0.011	0.99640	0.423	0.0205	0.99762	0.020	-7.0×10^{-5}	0.99964
OD-THSEMA 70–80 N	0.026	0.99281	0.439	0.0418	0.99447	0.051	-6.1×10^{-4}	0.99983
140–150 N	0.017	0.99824	0.475	0.0214	0.99942	0.029	-4.0×10^{-5}	0.99955
FD-THSEMA 70–80 N	0.037	0.96098	0.356	0.0998	0.97506	0.105	-4.1×10^{-3}	0.99688
140–150 N	0.032	0.96559	0.370	0.0805	0.97841	0.084	-2.7×10^{-3}	0.99755

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.

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

Tablets	Higuchi equation		Korsmeyer equation			Peppas equation		
	k ($min^{-0.5}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
OD-TSEMA 70–80 N	0.007	0.99483	0.416	0.0143	0.99436	0.013	-6.5×10^{-5}	0.99915
140–150 N	0.007	0.99842	0.451	0.0106	0.99818	0.012	-1.0×10^{-5}	0.99987
FD-TSEMA 70–80 N	0.007	0.99771	0.460	0.0096	0.99536	0.011	-2.0×10^{-5}	0.99965
140–150 N	0.006	0.99713	0.455	0.0092	0.99499	0.011	-2.6×10^{-5}	0.99951
OD-THSEMA 70–80 N	0.008	0.99994	0.501	0.0079	0.99980	0.011	5.5×10^{-5}	0.99998
140–150 N	0.007	0.99981	0.467	0.0086	0.99963	0.010	4.1×10^{-5}	0.99996
FD-THSEMA 70–80 N	0.008	0.99994	0.475	0.0092	0.99958	0.010	7.2×10^{-5}	0.99997
140–150 N	0.005	0.99363	0.395	0.0125	0.99807	0.010	-6.8×10^{-5}	0.99974

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.

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, fronts movement kinetics was evaluated. The photographs obtained from the matrices revealed the absence of swelling and gel layer formation. As a clear gel layer was not detected, a new denomination for the fronts observed in these inert matrices has been suggested (Ferrero et al., 2000). Three fronts could be clearly distinguished from the centre to the periphery of the matrix: water uptake front (between dry and 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 depicted in Fig. 3 showed a nearly constant erosion front movement for all copolymers, independent of the breaking force, which agrees with the absence of swelling in these matrices. As no swelling or erosion (the tablet diameter remained about constant) could be detected, it seems that copolymer tablets behave as matrices where the drug is released by diffusion through the porous structure.

Respect to water uptake and complete wetting fronts, it can be seen a clearly difference between the two breaking forces studied. Like this, tablets at 140–150 N experimented lower fronts movement, according with data porosity (Table 2) and lower dug release (Fig. 1 and 2). For tablets at 70–80 N, the fast initial water uptake and complete wetting fronts observed, especially for THSEMA, might be due to the water penetration through capillaries and higher size pores. Also, in general, water uptake front seemed to move faster in matrices containing FD copolymers, which would be consistent with the highest initial porosity in these matrices (Table 2).

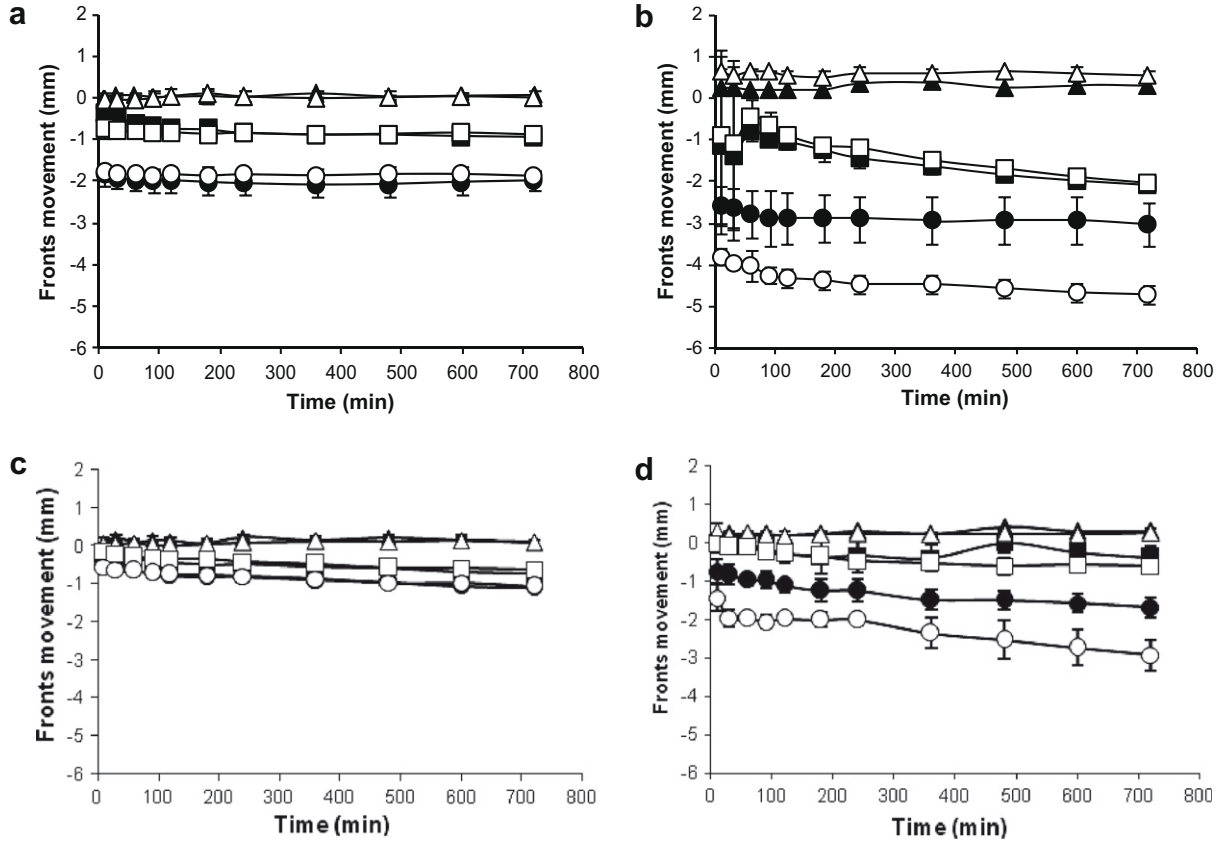

Fig. 3. Water uptake (●), complete wetting (■) and erosion (▲) fronts positions over time for matrices containing: (a) TSEMA derivatives at 70–80 N; (b) THSEMA derivatives at 70–80 N; (c) TSEMA derivatives at 140–150 N and (d) THSEMA derivatives at 140–150 N. OD products are represented by closed symbols and FD products by open ones. The bars show the standard deviation ($n = 2$).

Table 2 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 TSEMA mixtures than THSEMA ones, which implies higher tortuosity values and an increment in the diffusional resistance for these tablets. These results explain the slower diffusion rates (Table 3) and water penetration in TSEMA matrices, in spite of the similar porosity values. For TSEMA matrices, the combination of porosity and tortuosity values could explain the similar biopharmaceutical profiles without influence by drying process or breaking force. However, freeze-dried THSEMA matrices had higher D' values, which implies lower tortuosity, according with the faster drug releases (Fig. 1) and water uptake fronts (Fig. 3). Similar explanation could be give to OD-THSEMA at 70–80 N respect to 140–150 N.

4. Conclusions

Tapioca graft copolymers were shown to be a suitable material to control theophylline released, unlike the raw carbohydrates. All tablets from copolymers behave as inert matrices controlling drug release mainly by diffusion. Matrices from TSEMA have demonstrated to have better binding properties with lower release than THSEMA tablets. Drying method and breaking force had a significant influence on dissolution behaviour only in THSEMA matrices. So, it has been shown higher theophylline release for tablets at 70–80 N than 140–150 N crushing force, and for freeze-dried respect to oven-dried matrices. Moreover, porosity and tortuosity values explained the results observed. Radial drug release results demonstrated that the initial amount of area exposed to the dissolution medium determines the amount of drug release. Fronts movement data were consistent with and complementary to the drug release kinetics observed.

Acknowledgements

This work has been supported by a F.P.U. grant from the Spanish Government and is part of a project (MAT2004-01599) from Spanish Ministry of Science and Technology.

References

BeMiller, J., & Whistler, R. (2009). *Starch: Chemistry and technology* (3rd ed.). Orlando: Academic Press.

Bettini, R., Colombo, P., Massimo, G., Catellani, P. L., & Vitali, T. (1994). Swelling and drug release in hydrogel matrices: Polymer viscosity and matrix porosity effects. *European Journal of Pharmaceutical Sciences, 2*, 213–219.

Carli, F., Capone, G., & Colombo, L. (1984). Surface and transport properties of acrylic polymers influencing drug release from porous matrices. *International Journal of Pharmaceutics, 21*, 317–329.

Casas, M., Ferrero, C., & Jiménez-Castellanos, M. R. (2009). Synthesis and characterization of new copolymers of ethyl methacrylate grafted on tapioca starch as novel excipients for direct compression matrix tablets. *European Polymer Journal, 45*, 1765–1776.

Colombo, P., Bettini, R., Catellani, P. L., Santi, P., & Peppas, N. A. (1999). Drug volume fraction profile in the gel phase and drug release kinetics in hydroxy propylmethyl cellulose matrices containing a soluble drug. *European Journal of Pharmaceutical Sciences, 9*, 33–40.

Colombo, P., Conte, U., Caramella, C., Gazzaniga, A., & La Manna, A. (1985). Compressed polymeric mini-matrices for drug release control. *Journal of Controlled Release, 1*, 283–289.

Colombo, P., Conte, U., Gazzaniga, A., Maggi, L., Sangalli, M. E., Peppas, N. A., et al. (1990). Drug release modulation by physical restrictions of matrix swelling. *International Journal of Pharmaceutics, 63*, 43–48.

Demirgöz, D., Elvira, C., Mano, J. F., Cunha, A. M., Piskin, E., & Reis, R. L. (2000). Chemical modification of starch based biodegradable polymeric blends: Effect on water uptake, degradation behaviour and mechanical properties. *Polymer Degradation and Stability, 70*, 161–170.

Doelker, E. (1978). Physique de la compression. Intérêt et limite des machines instrumentées pour loptimisation de la formulation. *Pharmaceutica Acta Helvetiae, 53*, 1–7.

Dumoulin, Y., Cartilier, L. H., & Mateescu, M. A. (1999). Cross-linked amylase tablets containing α-amylase: An enzymatically-controlled drug release systems. *Journal of Controlled Release, 60*, 161–170.

Echeverría, I., Silva, I., Goñi, I., & Gurruchaga, M. (2005). Ethyl methacrylate grafted on two starches as polymeric matrices for drug delivery. *Journal of Applied Polymer Science, 96*, 523–536.

European Pharmacopoeia (2007). 6th ed. Strasbourg, France: Council of Europe.

Farhadieh, B., Borodkin, S., & Buddenhagen, J. D. (1971). Drug release from methyl acrylate–methyl methacrylate copolymer matrix. I. Kinetics of release. *Journal of Pharmaceutical Sciences, 60*(2), 209–212.

Ferrero, C., Bravo, I., & Jiménez-Castellanos, M. R. (2003). Drug release kinetics and fronts movement studies from methyl methacrylate (MMA) copolymers matrix tablets: Effect of copolymer type and matrix porosity. *Journal of Controlled Release, 92*, 69–82.

Ferrero, C., & Jiménez-Castellanos, M. R. (2002). The influence of carbohydrate nature and drying methods on the compaction properties and pore structure of new methyl methacrylate copolymers. *International Journal of Pharmaceutics, 248*, 157–171.

Ferrero, C., Muñoz-Ruiz, A., & Jiménez-Castellanos, M. R. (2000). Fronts movement as a useful tool for hydrophilic matrix release mechanism elucidation. *International Journal of Pharmaceutics, 202*, 21–28.

Guidance for industry (1997). Dissolution testing of immediate release solid oral dosage forms. US Department of Health and Human Services, CDER.

Higuchi, T. (1963). Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of Pharmaceutical Sciences, 52*(12), 1145–1149.

Hüttenrauch, R. (1977). Uber den mechanismus des korngrossen effekts in der tablettierung. *Pharmazie, 32*, 130–131.

Järvinen, M. J., & Juslin, M. J. (1981). Evaluation of force-displacement measurements during one-sided powder compaction in a die: The influence of friction with the die wall and of the diameter of punches and die on upper and lower punch pressure. *Powder Technology, 28*, 115.

Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. *International Journal of Pharmaceutics, 15*, 25–35.

Kost, J., & Shefer, S. (1990). Chemically-modified polysaccharides for enzymatically-controlled oral drug delivery. *Biomaterials, 11*, 695–698.

Muñoz-Ruiz, A., Gallego, R., del Pozo, M., Jiménez-Castellanos, M. R., & Domínguez-Abascal, J. (1995). A comparison of three methods of estimating displacement on an instrumented single punch tablet machine. *Drug Development and Industrial Pharmacy, 21*, 215–227.

Muñoz-Ruiz, A., & Jiménez-Castellanos, M. R. (1993). Integrated system of data acquisition for measure of flow rate. *Pharmaceutical Technology & International Biopharmaceutics, 8*(4), 21–29.

Peppas, N. A., & Sahlin, J. J. (1989). A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. *International Journal of Pharmaceutics, 57*, 169–172.

Pifferi, G., Santoro, P., & Pedrani, M. (1999). Quality and functionality of excipients. *Farmaco, 54*, 1–14.

Ritger, P. L., & Peppas, N. A. (1987). 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. *Journal of Controlled Release, 5*, 23–26.

Sanghvi, P. P., Collins, C. C., & Shukla, A. J. (1993). Evaluation of Preflo® modified starches as new direct compression excipients. I. Tabletting characteristics. *Pharmacological Research, 10*, 1597–1603.

Viana, M., Jouannin, P., Pontier, C., & Chulia, D. (2002). About pycnometric density measurements. *Talanta, 57*, 583–593.

Weyenberg, W., Vermeire, A., Remon, J. P., & Ludwig, A. (2003). Characterization and in vivo evaluation of ocular bioadhesive minitablets compressed at different forces. *Journal of Controlled Release, 89*, 329–340.