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Research paper

Drug release behaviour from methyl methacrylate-starch matrix tablets: Effect of polymer moisture content

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Abstract

The aim of this work was to study the effect of the initial moisture content of the polymer on the tabletting and drug release behaviour of controlled release inert matrices elaborated with methyl methacrylate (MMA)-starch copolymers. The copolymers, obtained by free radical polymerisation and dried by two different methods (oven-drying or freeze-drying), were equilibrated at different relative humidities (0%, 25%, 50% and 75% RH) at room temperature. From these copolymers, matrix systems were directly compressed containing either a slightly water-soluble drug (anhydrous theophylline) or a freely water-soluble drug (salbutamol sulphate), and their compaction properties and *in vitro* dissolution profiles were evaluated. The release profiles were compared following model-independent methods, such as the Q_t parameter and the similarity factor f_2. Moreover, several kinetic models were employed to evaluate the possible changes in the release mechanism. For anhydrous theophylline, the initial moisture content of the copolymers did not affect the release characteristics from the inert matrices under study, and a typical Fickian diffusion mechanism was observed for the different formulations. However, in case of salbutamol sulphate, the presence of moisture might induce a fast drug dissolution, promoting the weakness of the matrix structure and hence, its partial disintegration. So, an ''anomalous'' mixed phenomenon of diffusion and erosion was found, influenced by the initial moisture content of the copolymer.

Keywords: Methyl methacrylate-starch copolymers; Moisture content; Matrix tablets; Drug release profiles; Model-dependent methods; Model-independent methods

1. Introduction

Controlled release systems have been developed and studied to increase the drug pharmacological action and reduce their side effects. The basic concept is that the rate of drug absorption may be adjusted through a controlled rate of drug release from the dosage form. A huge variety of such systems have been proposed over the last two decades; among them, the simplest system is the matrix device, where the drug is dispersed within a polymer network [1]. In this sense, a new generation of grafted copolymers combining-starch derivatives and methyl methacrylate (MMA) polymers [2] has been introduced as direct compression excipients [3]. These materials form, under compression, inert matrices able to control the release of the model drug (anhydrous theophylline) by a diffusion mechanism through the matrix porous structure [4].

In terms of drug release, the presence of initial moisture in inert matrices can affect their mechanical strength and porous structure and hence, the drug release profiles [5,6]. In addition, drugs themselves may undergo also changes in presence of moisture in the formulation, such as degradation, hydration, etc. [7,8]. Excipients able to protect drugs, at least partially, from moisture negative effects, may be of extreme interest from a technological point of view [9,10].

The interaction of MMA-starch copolymers with water has been already analysed at molecular level [11,12] and the

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influence of the moisture content on their mechanical behaviour (flow and compaction properties) has been already elucidated [13]. The purpose of the present work is to evaluate the effect of the initial moisture content of the copolymers on the controlled release behaviour of the inert matrices formed, using two model drugs of different solubility (anhydrous theophylline and salbutamol sulphate). Dissolution profiles obtained are compared following model-independent methods, such as the Q_t parameter and the similarity factor f_2, and model-dependent methods, such as Higuchi [14], Korsmeyer et al. [15] and Peppas and Sahlin [16] equations.

2. Materials and methods

2.1. Materials

Copolymers (batches SS02) synthesised by free radical polymerisation of methyl methacrylate (MMA) on two different potato-starch derivatives (hydroxypropylstarch HS – Perfectamyl, Avebe, Holland-, carboxymethylstarch CS – Quicksolan, Avebe, Holland-) were selected for the study [2]. The products (HSMMA, CSMMA) were dried either in a vacuum oven at 6.67–13.33 hPa and 50 °C until constant weight (OD copolymers) or freeze-dried (freezing process at −20 °C for 24 h and sublimation process at 0.13 hPa and −50 °C) (FD copolymers). OD-CSMMA was crushed in a knives mill (Retsch, Haan, Germany) to obtain powdery samples. Sieve fractions of 25–500 μm were selected for all copolymers.

Salbutamol sulphate (Roig Pharma, Terrasa, Spain, batch 3851297) and anhydrous theophylline (Sigma–Aldrich Chemie, Germany, batch 99H0870) were selected as model drugs. Salbutamol sulphate is freely soluble in water (1–10 ml/g) and the batch used has a mean particle size of 164 (120) μm and a specific surface area of 2.88 (0.36) m^2/g. Anhydrous theophylline is slightly soluble in water (100–1000 ml/g) and the batch used has a mean particle size of 285 (94) μm and a specific surface area of 1.86 (0.08) m^2/g.

Stearic acid (Estearina® L2SM, Pulcra, Barcelona, Spain, batch 0055003) was selected as lubricant.

2.2. Methods

2.2.1. Copolymers storage

Copolymers were stored in vacuum desiccators using silica-gel as desiccant to obtain products dried to constant weight. The materials were then transferred to room-temperature (25 °C) desiccators with different sulphuric acid solutions to obtain the desired RHs (25%, 50% and 75%) [12]. The samples were regularly weighed on an analytical balance (Mettler Toledo LJ16, Zürich, Switzerland) until constant weight was reached. The equilibrium moisture content was determined on a dry weight basis of the material and the results were shown in a previous work [13] as the mean value of three replicates.

2.2.2. Mixtures preparation

For comparison purposes with previous works developed by our research group [4], a formulation containing 24% (w/w) anhydrous theophylline, 75% (w/w) copolymer and 1% (w/w) stearic acid was selected. Due to the poor compression properties observed for salbutamol sulphate in preliminary studies, the percentage of this drug was reduced, containing the formulation 15% (w/w) salbutamol sulphate, 84% (w/w) copolymer and 1% (w/w) stearic acid.

Copolymer and drug were geometrically mixed for 20 min using a double-cone mixer (Restch Vibro, Haan, Germany) at 50 r.p.m. After addition of stearic acid, the mixing procedure was continued for a further 5 min.

2.2.3. Preparation of tablets

The different mixtures were compacted into tablets using an instrumented [17] 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 (70–80 N). Compression data were collected from four tabletting cycles.

2.2.4. Standard physical test of tablets

The physical testing of tablets was performed after a relaxation period of at least 24 h stored at the same RH conditions than powders. The tablet average weight and the standard deviation (SD) were obtained from 20 individually weighed (Mettler LJ16 analytical balance, Zürich, Switzerland) tablets according to European Pharmacopeia [18].

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

The resistance to crushing [18] of ten tablets was determined by diametral loading with a texture analyser (TA-XT2i Stable Micro Systems, Surrey, UK).

Tablet friability [18] was calculated as the percentage weight loss of 20 tablets after 4 min at 25 r.p.m. in an Erweka TA (Heusenstamm, Germany) friability tester.

Disintegration testing [18] 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.

2.2.5. In vitro dissolution studies

Release experiments (six tablets) were performed in an automatic dissolution apparatus II (Aidec, Barcelona, Spain) as a function of time (8 h). Deionized and deareated 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 r.p.m. The dissolution samples (2.8 mL) were filtered and analysed spectrophotometrically (Hewlett Packard 8452A diode-array UV–vis, Waldbronn, Germany) at 272 nm for anhydrous theophylline and 282 nm for salbutamol sulphate.

2.2.6. Analysis of dissolution profiles

2.2.6.1. Model-independent methods. Dissolution data were subjected to two categories of model-independent analyses (i.e. ratio tests and pair-wise approaches) in order to determine the release profiles similarity. The ratio tests are relations between parameters obtained from the release assays of the reference and test formulations at the same time and can go from a simple ratio of percentage dissolved drug at a defined time (Q_t), to the time necessary to release a fixed percentage of drug ($t_{x\%}$), dissolution efficiency, etc. [19]. Among them, the $Q_{8\ h}$ parameter (percentage of drug dissolved at 8 h) was selected to compare the different formulations [20]. The pair-wise procedures include the Rescigno indexes (ξ_1, ξ_2) [21] and the difference (f_1) and similarity (f_2) factors [22]. Due to its simple calculation and increasingly current importance [7,23], the similarity factor (f_2) (Eq. (1)) was chosen to compare the dissolution profiles:

$$f_2 = 50 \times \mathrm{Log}\left\{\left[1 + (1/n)\sum_{t=1}^{n}|R_t - T_t|^2\right]^{-0.5} \times 100\right\} \quad (1)$$

where n is the number of experimental points in the *in vitro* dissolution assay, R_t and T_t are the mean percentages of dissolved drug from the reference and test formulations, respectively, at each time point t. No more than one sampling time point after 85% dissolution was considered [24].

The Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) [25] recommend the use of f_2 and ensure that two dissolution profiles are declared similar if f_2 is between 50 and 100, that is when two profiles show differences lower than 10% [24].

2.2.6.2. Model-dependent methods. Higuchi [14] (Eq. (2)), Korsmeyer et al. [15] (Eq. (3)) and Peppas and Sahlin [16] (Eq. (4)) equations were selected as model-dependent approaches to characterise the dissolution profiles:

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

$$M_t/M_\infty = k't^n \quad (3)$$

$$M_t/M_\infty = k_d t^m + k_r t^{2m} \quad (4)$$

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 drug release mechanism and the shape of the matrix tested [26]; 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.

M_t/M_∞ values lower than 0.6 were used for the three kinetic models evaluated and sink conditions were maintained all over the dissolution assay. The optimum values for the parameters present in each equation were determined by linear or non-linear least-squares fitting methods with SPSS® 10.0 software. The adjusted coefficient of determination (r^2_{adjusted}) was used to test the applicability of the release models.

2.2.7. Statistical analysis

The $Q_{8\ h}$ parameter was statistically analysed by one-way analysis of variance (ANOVA) using the SPSS® 10.0 software. Post-ANOVA was carried out according to Bonferroni's multiple comparison tests. Results were quoted as significant when $P < 0.05$.

3. Results and discussion

3.1. Preparation of tablets

A thorough study about the influence of relative humidity on the densification behaviour of MMA-starch copolymers has been presented in a previous paper [13]. However, as the incorporation of drug could produce substantial changes in compaction profiles, some compression data obtained from the different mixtures are summarised in Tables 1 and 2. As was already denoted [13], it was not possible to elaborate tablets with copolymers stored at 100% RH, due to the hydrodynamic resistance of water in the solid, joined to the surfacial contaminant effect of an excess of adsorbed water [27,28]. The maximum applied upper punch pressure (P) necessary to obtain tablets with a crushing force of 70–80 N increased at 75% RH, mainly for the OD formulations. This behaviour was already described [13] for the bulk copolymers and attributed to the surfacial contaminant effect of the high water content, that weakens the interparticle bonding. The most independent behaviour with RH was observed for FD-CSMMA mixtures. Although salbutamol sulphate was present in the formulations at lower percentage than anhydrous theophylline, the poor compressional behaviour of the soluble model drug was clearly patent in their higher requirements of maximum applied upper punch pressure.

The evaluation of the maximum ejection force (F_e) parameter (Tables 1 and 2) also revealed higher friction properties for salbutamol sulphate tablets, with values larger than 750 N [29] for several polymers and RH conditions. In contrast, anhydrous theophylline tablets (Table 2) led to F_e values similar to or even lower than the bulk copolymers [13]. As the lubricant percentage was the same for salbutamol and theophylline formulations, it seems that the type of drug has a noticeable influence on friction properties. Probably, the smaller particle size and higher surface area of salbutamol sulphate, compared with anhydrous theophylline, would increase adhesion and friction.

3.2. Standard physical test of tablets

Results from the physical testing of tablets are also illustrated in Tables 1 and 2 for sabutamol sulphate and anhydrous theophylline formulations, respectively. All batches satisfied the requirements specified in European Pharmacopeia [18] related to weight uniformity test. Similar to the

Table 1
Compression parameters and tablet test results for salbutamol sulphate formulations: maximum applied upper punch pressure (P), maximum ejection force (F_e), average weight, thickness, crushing force (CF), friability (F), disintegration time (t_d)

Formulations	RH (%)	P (MPa)	F_e (N)	Weight (mg)	Thickness (mm)	CF (N)	F (%)	t_d (min)
OD-HSMMA	0	181.5 (0.0)	1742.2 (143.9)	495 (8)	4.282 (0.020)	78.8 (1.2)	1.55	>30[a]
	25	184.3 (4.2)	1480.9 (273.7)	488 (12)	4.178 (0.081)	74.9 (2.1)	1.02	>30[b]
	50	152.1 (0.0)	1278.1 (92.6)	502 (12)	4.293 (0.022)	75.7 (4.4)	1.56	>30[a]
	75	252.6 (0.0)	973.8 (17.2)	502 (9)	4.105 (0.048)	74.6 (4.7)	0.40	>30[b]
FD-HSMMA	0	127.5 (0.0)	1363.4 (219.2)	503 (0)	4.493 (0.155)	76.6 (3.3)	1.64	>30[a]
	25	114.4 (0.0)	643.7 (179.0)	473 (20)	4.260 (0.113)	74.6 (4.3)	0.85	>30[a]
	50	110.3 (0.0)	1082.3 (64.2)	509 (11)	4.610 (0.012)	77.4 (2.3)	0.79	>30[a]
	75	123.2 (0.0)	650.3 (22.5)	506 (9)	4.284 (0.026)	75.5 (4.8)	0.87	>30[a]
OD-CSMMA	0	173.8 (0.0)	920.0 (29.6)	505 (8)	4.188 (0.035)	77.4 (3.6)	0.58	>30[a]
	25	148.5 (0.0)	1450.2 (135.5)	505 (19)	4.269 (0.076)	74.6 (3.9)	0.79	>30[b]
	50	135.1 (0.0)	923.1 (66.1)	492 (21)	4.006 (0.036)	75.8 (3.3)	0.81	>30[a]
	75	226.2 (0.0)	1739.0 (11.7)	500 (6)	3.781 (0.037)	76.2 (3.3)	0.48	>30[b]
FD-CSMMA	0	81.3 (0.0)	562.2 (79.6)	494 (7)	4.698 (0.010)	71.5 (2.2)	1.38	>30[a]
	25	73.9 (0.0)	605.2 (33.0)	499 (11)	4.669 (0.013)	74.5 (5.8)	1.12	>30[b]
	50	87.9 (0.0)	405.5 (91.5)	508 (6)	4.596 (0.041)	76.5 (2.0)	0.44	>30[a]
	75	****	****	503 (6)	4.199 (0.081)	75.7 (4.4)	0.41	>30[b]

[a] Intact tablets after the disintegration test.
[b] Partially eroded tablets after the disintegration test.
**** No parameters were recorded due to limitations in the measurement software.

Table 2
Compression parameters and tablet test results for anhydrous theophylline formulations: maximum applied upper punch pressure (P), maximum ejection force (F_e), average weight, thickness, crushing force (CF), friability (F), disintegration time (t_d)

Formulations	RH (%)	P (MPa)	F_e (N)	Weight (mg)	Thickness (mm)	CF (N)	F (%)	t_d (min)
OD-HSMMA	0	100.4 (0.0)	586.0 (29.9)	512 (6)	4.511 (0.014)	74.8 (2.9)	1.84	>30[a]
	25	118.6 (3.7)	643.1 (17.4)	498 (8)	4.250 (0.010)	73.8 (3.9)	1.04	>30[a]
	50	107.0 (0.0)	517.4 (12.3)	511 (7)	4.326 (0.013)	75.6 (2.6)	0.82	>30[a]
	75	169.3 (0.0)	930.7 (54.6)	514 (8)	4.032 (0.035)	75.5 (4.0)	0.63	>30[a]
FD-HSMMA	0	80.6 (0.0)	606.4 (27.6)	502 (6)	4.538 (0.011)	76.8 (2.4)	1.09	>30[a]
	25	78.8 (0.0)	631.4 (34.5)	502 (6)	4.507 (0.014)	75.6 (4.7)	1.21	>30[a]
	50	81.9 (0.0)	538.2 (44.3)	500 (8)	4.473 (0.013)	77.8 (1.5)	1.29	>30[a]
	75	108.3 (0.0)	199.1 (16.5)	505 (9)	4.225 (0.019)	73.5 (4.1)	0.96	>30[a]
OD-CSMMA	0	111.7 (0.0)	646.2 (19.9)	508 (7)	4.187 (0.012)	76.3 (1.8)	1.20	>30[a]
	25	109.3 (0.0)	345.6 (17.5)	506 (6)	4.139 (0.021)	73.9 (2.2)	1.19	>30[b]
	50	110.6 (0.0)	479.7 (37.7)	506 (6)	4.038 (0.009)	75.4 (2.6)	1.00	>30[a]
	75	285.8 (0.0)	1663.7 (194.6)	504 (8)	3.729 (0.068)	74.3 (3.7)	0.83	>30[b]
FD-CSMMA	0	84.8 (0.0)	380.8 (26.7)	492 (7)	4.640 (0.005)	77.4 (3.8)	1.19	>30[a]
	25	72.8 (0.0)	541.6 (45.4)	509 (8)	4.663 (0.009)	74.4 (3.7)	1.07	>30[b]
	50	74.3 (0.0)	451.2 (25.6)	504 (9)	4.249 (0.038)	75.0 (4.5)	0.61	>30[a]
	75	80.4 (0.0)	701.1 (72.8)	510 (10)	3.000 (0.060)	74.9 (4.0)	0.53	>30[b]

[a] Intact tablets after the disintegration test.
[b] Partially eroded tablets after the disintegration test.

behaviour described for the bulk copolymers [13], the tablet thickness diminished with the increase in RH, mainly at 75% RH, due to the plasticising effect of water [28,30]. Moreover, FD tablets presented higher thickness values than OD ones, which might be related to a more porous structure in tablets made with FD derivatives [3,4]. The resistance to crushing test confirmed the values of 70–80 N for all batches. Friability has diminished [13] with the addition of drug and lubricant, with values around 1% [18]. The cohesive effect of water was also noticed in the lower friability percentages at 75% RH. None of the tablets disintegrated after 30 min, although some formulations (mainly at 25% and 75% RH) suffered some attrition and particle separation.

3.3. Analysis of dissolution profiles

Figs. 1 and 2 illustrate the drug release profiles from matrices prepared from the different mixtures. The studies were performed over 8 h and a higher percentage of drug release was observed for matrices containing salbutamol sulphate compared with the ones with anhydrous theophylline, in accordance with the higher solubility of the former.

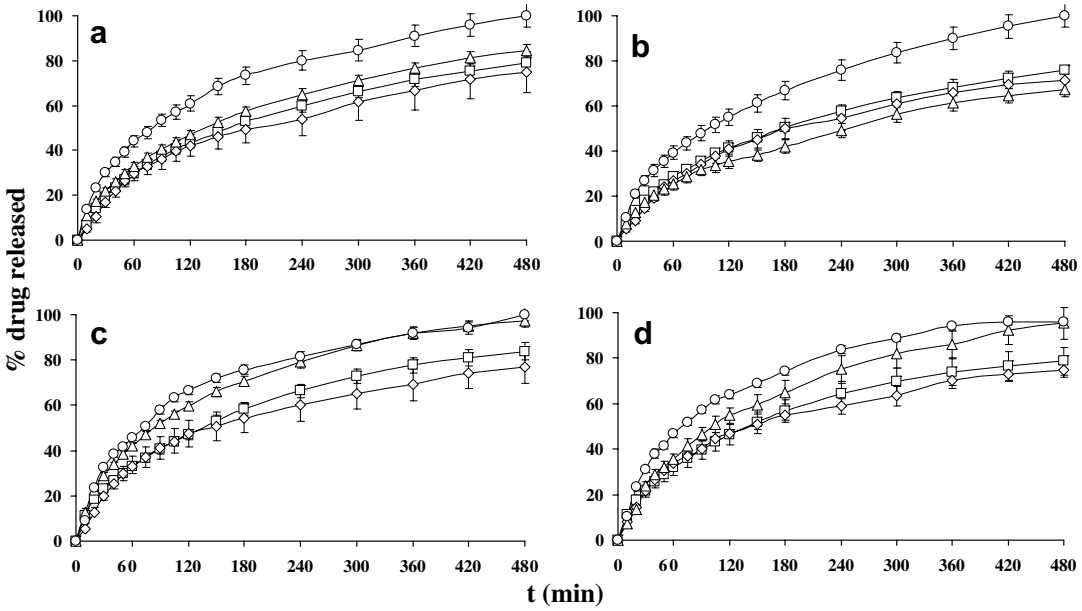

Fig. 1. Salbutamol sulphate release profiles from matrices elaborated with each copolymer (a: OD-HSMMA; b: FD-HSMMA; c: OD-CSMMA; d: FD-CSMMA) stored at different RH conditions: 0% (□); 25% (◇); 50% (Δ); 75% (○). Error bars represent the standard deviation.

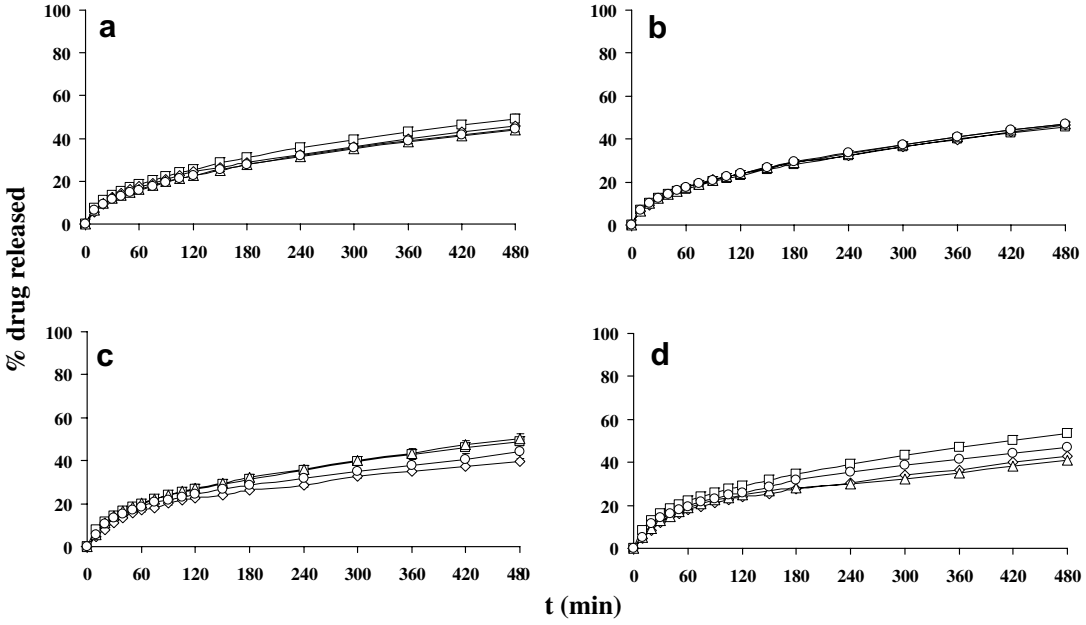

Fig. 2. Anhydrous theophylline release profiles from matrices elaborated with each copolymer (a: OD-HSMMA; b: FD-HSMMA; c: OD-CSMMA; d: FD-CSMMA) stored at different RH conditions: 0% (□); 25% (◇); 50% (Δ); 75% (○). Error bars represent the standard deviation (in some cases they are smaller than the symbol size).

The dissolution profiles obtained were analysed following model-independent and model-dependent methods. While model-independent approaches make no assumptions regarding the shape of the dissolution curves, the model-dependent methods involve the use of defined equations in which parameters defining the curve shape are optimised [23]. As specified in Section 2.2.6, $Q_{8\,h}$ and f_2 parameters were selected as model-independent methods and Higuchi [14], Korsmeyer et al. [15] and Peppas and Sahlin [16] equations were used as model-dependent methods. For Peppas model, $m = 0.44$ was used as the matrices under study presented an aspect ratio (diameter/thickness) around 2.8.

3.3.1. Salbutamol sulphate release profiles

According to Fig. 1, the release of salbutamol sulphate from the matrices seemed to depend on the copolymer storage conditions. In fact, the statistical analysis of the percentage of drug released at 8 h ($Q_{8\,h}$) (Table 3) revealed a significant increase ($P < 0.05$) in this parameter for

Table 3
Percentage of drug dissolved at 8 h ($Q_{8\,h}$) obtained from salbutamol sulphate (S) and anhydrous theophylline (T) formulations

RH (%)	0	25	50	75
OD-HSMMA-S	78.8 (3.2)	75.0 (4.9)	84.6 (4.9)	100.3 (1.9)
FD-HSMMA-S	75.9 (1.9)	71.4 (5.4)	67.2 (2.9)	100.1 (2.1)
OD-CSMMA-S	83.9 (2.9)	77.0 (7.6)	97.3 (2.6)	100.4 (2.8)
FD-CSMMA-S	78.7 (6.2)	74.9 (3.1)	95.4 (4.1)	96.0 (1.5)
OD-HSMMA-T	49.1 (2.1)	45.8 (0.7)	44.0 (1.1)	44.4 (1.3)
FD-HSMMA-T	45.8 (1.5)	46.3 (1.2)	47.2 (1.1)	47.0 (0.9)
OD-CSMMA-T	48.9 (1.0)	39.7 (3.8)	50.4 (2.3)	44.2 (2.9)
FD-CSMMA-T	53.3 (0.7)	43.0 (1.1)	41.1 (1.1)	46.8 (3.1)

HSMMA formulations at 75% RH and for CSMMA systems at RH $\geqslant$ 50%.

The similarity factor (f_2) resulting from the comparison of whole release profiles is collected in Table 4, taking as reference the profile corresponding to 0% RH. The higher the f_2 values, the more similar the dissolution profiles, so that $f_2 < 50$ represents non-similar profiles, while $f_2 > 65$ denotes a similarity between profiles higher than 95% [24]. According to the data, it was clearly observed that the increase in RH led to a progressive lack of similarity, being the dissimilarity demonstrated for all formulations at 75% RH. f_2 values were larger than 50 for formulations at RH $\leqslant$ 50%, although a higher similarity was observed for HSMMA tablets. Hence, it can be concluded that the water content of the copolymers influenced the salbutamol sulphate release in the following order: OD-CSMMA > FD-CSMMA > OD-HSMMA $\geqslant$ FD-HSMMA.

In general, the increase in water content in the matrices evaluated accelerated the drug release. These results would not agree with the decrease of the capillarity phenomenon postulated in presence of an initial amount of water in the tablet [31] or with the lower porosity usually promoted by the plasticising effect of absorbed water. The high solubility of the drug in the residual water present in the copolymer matrix might overcome those events dealing with a higher drug release. It is known that salbutamol sulphate does not present any kind of polymorph [32] or the formation of hydrates, but water molecules might condense in the cracks of crystal surface [33]. It is assumed that, after tablet elaboration, a slight amount of water might transfer from the copolymer to the crystal surface, probably promoting its partial solution, which might increase the dissolution rate. This hypothesis might be consistent with the higher effect of moisture on the release profiles of CSMMA formulations, with a larger water content and quantity of adsorbed water than HSMMA ones [13].

Table 4
Similarity factor (f_2) values for salbutamol sulphate (S) and anhydrous theophylline (T) release profiles (the drug release profile at 0% RH was taken as reference)

RH (%)	0	25	50	75
OD-HSMMA-S	100	73.66[b]	69.47[b]	41.24[a]
FD-HSMMA-S	100	77.59[b]	62.54	45.18[a]
OD-CSMMA-S	100	64.93	50.80	42.75[a]
FD-CSMMA-S	100	72.09[b]	58.42	42.22[a]
OD-HSMMA-T	100	81.48[b]	74.21[b]	74.18[b]
FD-HSMMA-T	100	92.40[b]	94.82[b]	94.37[b]
OD-CSMMA-T	100	62.73	94.32[b]	75.17[b]
FD-CSMMA-T	100	58.51	58.12	71.63[b]

[a] Dissimilar drug release profiles ($f_2 < 50$).
[b] Similarity between drug release profiles higher than 95% ($f_2 > 65$).

When the salbutamol sulphate dissolution profiles were fitted to different kinetic models (Table 5), the better adjustment was obtained for Peppas equation, which was indicative, along with the n values from Korsmeyer equation, of the possible presence of a release mechanism more complex than Fickian diffusion. This might be particularly important in case of 25% and 75% RH batches, where some attrition was observed in the disintegration test (Table 1). San Vicente et al. [32] also found n values of 0.53–0.72 when evaluating the salbutamol sulphate release mechanism from erosionable lipid matrices. The n values obtained were consistent with the laxe and porous matrix structure visually inspected after drug release and attributed to the rapid dissolution of salbutamol sulphate, as was also reported by Gren and Nyström [34] for other soluble drug.

Although the n values predicted an anomalous transport, the small and even negative values for k_r parameter in Peppas equation revealed an insignificant contribution of the relaxation mechanism compared to Fickian diffusion [4,35]. This could be due to the fact that matrices suffered a disintegration process more than a relaxation of polymeric chains.

Relating drug diffusion, the evaluation of k and k_d rate constants confirmed the higher dissolution rate described for HSMMA batches at 75% RH and for CSMMA ones at RH $\geqslant$ 50%. The improvement in drug diffusion would be consistent with the partial drug dissolution promoted by the presence of water in the matrices.

3.3.2. Anhydrous theophylline release profiles

The anhydrous theophylline release profiles (Fig. 2) showed a more independent behaviour with RH than those of salbutamol sulphate (Fig. 1), in agreement with the behaviour described for other poor soluble drug [36]. The analysis of $Q_{8\,h}$ parameter (Table 3) revealed that drug release from FD-HSMMA matrices did not depend on RH while, for OD-HSMMA tablets, a statistical decrease ($P < 0.05$) of $Q_{8\,h}$ was found for RH $\geqslant$ 25% compared with the dried batch. Concerning CSMMA tablets, the influence of RH was more noticeable, with statistical differences ($P < 0.05$) for the profiles at 25% and 75% RHs in case of OD-CSMMA and for the profile at 50% RH in case of FD-CSMMA.

On the other hand, when the whole release profiles were analysed by means of f_2, no differences were detected among the different profiles of each copolymer, resulting in all cases values above 50 (Table 4). The marked similarity found in FD-HSMMA profiles was also evident in the high values of this model-independent parameter. In the

Table 5
Mathematical modelling and drug release kinetics from matrices containing MMA copolymers and salbutamol sulphate (S) or anhydrous theophylline (T)

Formulations	RH (%)	Higuchi equation		Korsmeyer equation			Peppas equation		
		k ($min^{-0.5}$)	r^2_{adj}	n	k' (min^{-n})	r^2_{adj}	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2_{adj}
OD-HSMMA-S	0	0.044	0.966	0.67	0.017	0.974	0.079	$-12.1\ 10^{-4}$	0.999
	25	0.041	0.972	0.72	0.013	0.943	0.105	$-32.2\ 10^{-4}$	0.997
	50	0.045	0.998	0.56	0.031	0.997	0.070	$-3.3\ 10^{-4}$	0.999
	75	0.060	0.997	0.59	0.038	0.989	0.104	$-17.3\ 10^{-4}$	0.999
FD-HSMMA-S	0	0.041	0.997	0.62	0.021	0.986	0.069	$-6.2\ 10^{-4}$	0.999
	25	0.042	0.989	0.75	0.011	0.973	0.081	$-13.1\ 10^{-4}$	0.994
	50	0.033	0.994	0.55	0.025	0.987	0.053	$-2.7\ 10^{-4}$	0.995
	75	0.055	0.994	0.63	0.029	0.973	0.102	$-20.9\ 10^{-4}$	0.998
OD-CSMMA-S	0	0.046	1.000	0.55	0.035	0.997	0.061	$3.4\ 10^{-4}$	0.999
	25	0.048	0.976	0.76	0.013	0.938	0.124	$-43.4\ 10^{-4}$	0.999
	50	0.060	0.997	0.61	0.034	0.988	0.105	$-18.4\ 10^{-4}$	0.999
	75	0.073	0.978	0.79	0.018	0.925	0.182	$-77.8\ 10^{-4}$	0.991
FD-CSMMA-S	0	0.044	1.000	0.55	0.033	0.998	0.060	$4.5\ 10^{-4}$	0.999
	25	0.044	0.971	0.61	0.025	0.959	0.109	$-34.0\ 10^{-4}$	0.997
	50	0.061	0.994	0.79	0.014	0.972	0.095	$-6.4\ 10^{-4}$	0.994
	75	0.073	0.988	0.75	0.022	0.958	0.168	$-6.4\ 10^{-4}$	0.999
OD-HSMMA-T	0	0.022	0.998	0.48	0.026	0.998	0.033	$0.2\ 10^{-4}$	0.999
	25	0.021	0.995	0.51	0.020	0.986	0.035	$-1.5\ 10^{-4}$	0.997
	50	0.020	0.998	0.49	0.022	0.998	0.029	$0.5\ 10^{-4}$	0.999
	75	0.020	0.999	0.49	0.021	1.000	0.030	$0.3\ 10^{-4}$	0.999
FD-HSMMA-T	0	0.021	0.999	0.48	0.024	0.999	0.025	$3.3\ 10^{-4}$	0.999
	25	0.021	0.998	0.49	0.023	0.997	0.031	$0.3\ 10^{-4}$	0.998
	50	0.021	1.000	0.49	0.022	0.998	0.028	$2.1\ 10^{-4}$	0.999
	75	0.021	0.999	0.49	0.023	0.999	0.028	$1.9\ 10^{-4}$	0.999
OD-CSMMA-T	0	0.021	0.997	0.45	0.030	0.996	0.035	$-1.4\ 10^{-4}$	0.999
	25	0.018	0.985	0.51	0.018	0.966	0.037	$-5.8\ 10^{-4}$	0.994
	50	0.022	0.991	0.51	0.023	0.967	0.041	$-4.0\ 10^{-4}$	0.995
	75	0.019	0.989	0.47	0.025	0.973	0.036	$-4.0\ 10^{-4}$	0.995
FD-CSMMA-T	0	0.023	0.997	0.45	0.033	0.995	0.038	$-2.0\ 10^{-4}$	0.999
	25	0.019	0.948	0.51	0.007	0.961	0.020	$-8.5\ 10^{-4}$	0.991
	50	0.017	0.959	0.47	0.023	0.949	0.045	$-9.9\ 10^{-4}$	0.984
	75	0.021	0.986	0.50	0.023	0.956	0.044	$-6.7\ 10^{-4}$	0.997

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.

same sense, OD-CSMMA profiles at 25% RH and FD-CSMMA profiles at 25–50% RH revealed the less similar behaviour to the reference curves (0% RH).

During powder mixing, tablet compression and tablet storage for 24 h before the dissolution assay, anhydrous theophylline might undergo partial hydration to the monohydrate form, diminishing its water solubility [37]. However, this event seemed to be little probable, since no direct relation was found between the amount of water in the copolymer and the drug release decrease (Fig. 2). In this sense, Álvarez-Lorenzo et al. [38] found no transition after storage of HPC (60% w/w) and anhydrous theophylline (40% w/w) tablets at 70.4% RH for 6 months. Quite steady theophylline release profiles were also observed by Jannin et al. [39] and Young et al. [40] after storage for several months at accelerated conditions (40 °C/75% RH) of different controlled drug release devices elaborated with anhydrous theophylline and mixtures of hydrophilic and hydrophobic polymers.

Previous studies [13] demonstrated that 25–50% RH were the best storage conditions for these copolymers as the plasticisation effect of internally absorbed water and the lubricant effect of externally adsorbed water were maximized. At these conditions, the more dense structure of the tablets might contribute to the slower drug release profile observed.

Finally, the anhydrous theophylline dissolution profiles were also fitted to the different kinetic equations, showing a better adjustment than in the case of salbutamol sulphate matrices, as the higher values of r^2_{adj} revealed (Table 5). The good fitting to Higuchi equation and the n values of 0.45–0.51 in Korsmeyer equation indicated a drug release mechanism controlled mainly by Fickian diffusion, with a dissolution rate around 0.02 $min^{-0.5}$, as was already detected for these formulations elaborated at room conditions [4]. Many other authors [40–42] have also reported a drug diffusion mechanism from acrylic/methacrylic matrices.

4. Conclusions

Both the water content of the copolymer and the type of drug influenced the compaction characteristics of the mixtures. Although the plasticising effect of water improved the binding properties at 25–50% RH conditions, the surfacial contaminant effect of multilayer adsorbed water makes difficult the union formation at 75% RH, being necessary to apply higher maximum upper punch pressures to obtain the desired crushing force (70–80 N), especially for OD formulations. Concerning the drug, the incorporation of salbutamol sulphate led to worse compression and friction properties than the addition of anhydrous theophylline in the formulations.

The drug dissolution rate and drug release mechanism from the matrices evaluated were clearly conditioned by the type of drug, so that lower dissolution rates and a Fickian diffusion mechanism were identified for anhydrous theophylline formulations while faster dissolution rates and an anomalous transport were postulated for matrices containing salbutamol sulphate. In case of anhydrous theophylline, a slightly water-soluble drug, the moisture content of the copolymers did not seem to influence the drug diffusion rate from these inert matrices. However, the presence of moisture in the formulations containing salbutamol sulphate, a water-soluble drug, might induce its rapid dissolution, promoting the weakness of the matrix structure and hence, improving its partial disintegration and drug diffusion, especially at 75% RH for HSMMA copolymers and at RH $\geqslant$ 50% for CSMMA ones. It seems that the influence of moisture in the release profile from these systems depends on the total amount and distribution of water into the solid, characteristic of each copolymer derivative.

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