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Directly Compressed Mini Matrix Tablets Containing Ibuprofen: Preparation and Evaluation of Sustained Release

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ABSTRACT Directly compressed mini tablets were produced containing either hydroxypropylmethylcellulose (HPMC) or ethylcellulose (EC) as release controlling agent. The dynamics of water uptake and erosion degree of polymer were investigated. By changing the polymer concentration, the ibuprofen release was modified. In identical quantities, EC produced a greater sustaining release effect than HPMC. Different grades of viscosity of HPMC did not modify ibuprofen release. For EC formulations, the contribution of diffusion was predominant in the ibuprofen release process. For HPMC preparations, the drug release approached zero-order during a period of 8 h. For comparative purposes, tablets with 10 mm diameter were produced.

KEYWORDS Mini matrix tablets, Ibuprofen, Sustained release, HPMC, Ethylcellulose

INTRODUCTION

The development of mini matrices is a new and promising area in pharmaceutical research which has attracted some attention to control the release of a drug (Colombo et al., 1985; Sujja-areevath et al., 1998; Cox et al., 1999; De Brabander, 2000a). The mini matrices, as multiple unit dosage forms, present several advantages over conventional single unit dosage forms, namely, dose flexibility, high degree of dispersion in the gastrointestinal tract, and thus minimizing irritation due to high local drug concentrations, reproducible bioavailability (Graffner et al., 1986), and uniform plasma levels (Edgar et al., 1984).

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) widely prescribed for the treatment of inflammatory pain or rheumatism. Maximum ibuprofen plasma concentrations are achieved within 1–2 h after ingestion of the drug, but due to its short biological half-life (2h) (De Brabander et al., 2000b), therapeutic plasma concentration can only be maintained when ibuprofen is administered frequently. These drug characteristics make ibuprofen a suitable candidate for sustained drug delivery. Several studies have been carried out in order to achieve a desirable release rate of a few NSAIDs. One of the most commonly used methods of modulating drug delivery from pharmaceutical systems is to include it in a matrix system (Reddy et al., 2003). In these

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systems, the drug is embedded in a polymeric matrix and the release of the drug takes place after the partition of the drug between the forming matrix material and its environment.

Mini tablets are tablets with a diameter equal to or smaller than 2–3 mm (Lennartz & Mielck, 1998). The production of mini matrices using a tabletting technique is an attractive alternative to the production of pellets, particularly by avoiding the presence of a solvent (e.g., water) and by maintaining high production yields like the ones observed in extrusion or spheronization (a common technique to produce pellets with identical size to the mini tablets). Recently, De Bradander et al. (2003) described the in vitro behavior of mini matrices prepared by hot-melt extrusion, formulated with ibuprofen, ethylcellulose (EC), and a hydrophilic excipient, and demonstrated that the drug release rate from these mini matrices can be modified by proper selection of hydrophilic excipients at different concentrations.

No data has been published so far on mini tablet properties and mini tabletting processes, such as tensile strength, friability, release profiles, and density at diameters of 2.5 mm as compared with conventional larger tablets, produced under identical conditions. Like pellets, the mini tablets can be filled either into capsules or compacted into bigger tablets and then released intact in the gastrointestinal tract.

In matricial systems, the characteristics of the matrix forming agent play an important role in the release mechanism(s) of the drug. Hydrophilic polymers are widely used in oral controlled drug delivery due to their flexibility to produce desirable drug release profiles, cost effectiveness, and broad regulatory acceptance (Alderman, 1984). Among the hydrophilic polymers, hydroxypropylmethylcellulose (HPMC) is the most commonly used carrier for the preparation of oral controlled drug delivery systems due to its properties, such as its ability to swell upon jellification once in contact with water, and its very low toxicity and ease of manufacture. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution (Colombo et al., 2000; Kiil & Dam-Johansen, 2003). On the other hand, hydrophobic polymers, such as EC, can be alternatives to the swelling polymers by forming an inert matrix with no physiological action and stable at different pH values and moisture levels. Ethylcellulose (EC) has been extensively used as a pharmaceutical matrix-forming material for sustained release dosage forms (Shaikh et al., 1987; Sadeghi et al., 2003; Upadrashta et al., 1993; Katikaneni et al., 1995; Pather et al., 1998). When a tablet with a hydrophobic matrix is placed in the dissolution medium, the drug at the surface is released quickly, with a possible burst effect, requiring its replacement by drug from inner layers that must diffuse through the pores until it reaches the surface.

The aim of this study was to develop sustained release mini tablets (as multiple unit dosage forms) containing ibuprofen and a matrix forming material by direct compression. Ethylcellulose (EC) and HPMC were used as matricial agents to control the release of the drug. For comparative purposes, tablets with 10 mm diameter were produced under the same compression pressure and their properties were evaluated.

MATERIALS AND METHODS

Materials

Ibuprofen was supplied by Laboratórios Medinfar (Lisboa, Portugal). The polymers used were ethylcellulose (EC, 30–60 mPa.s, Ethocel®, Fluxa Biochemika, Germany) and hydroxypropylmethylcellulose in three different viscosity grades (HPMC, 4000 mPa.s, Methocel® K4M; 15000 mPa.s, Methocel® K15M, and 100000 mPa.s, Methocel® K100M, Colorcon, Orpington, UK). Sodium hydroxide and potassium dihydrogenophosphate (analytical grade, Merck, Germany), were used in the preparation of the dissolution medium (phosphate buffer, pH 7.2).

Preparation of Mini Tablets

Ethylcellulose (EC) was milled (IKA, Electric Mill, Model A10, Staufen, Germany) before use. All materials were sieved and the fractions below 63 μm were used to minimize the lag time observed during drug release when coarse fractions are used. Tablets were prepared from binary mixtures of ibuprofen and matrix forming agent (HPMC or EC). Table 1 and Table 2 provide an overview of all formulations evaluated during this study. The formulations prepared contained 85% or 50% (w/w) of ibuprofen for HPMC K100M mini tablets (formulations 1 and 2, respectively) and 85% or 60% (w/w) of ibuprofen for EC mini tablets (formulations 5 and 6, respectively). Furthermore, the influence of the HPMC chain length

TABLE 1 **Physical Properties of Ibuprofen Mini Matrix Tablets (2.5 mm)**

Formulation	Polymer type	Polymer content (%)	Weight (mg) mean ± sd	Thickness (mm) mean ± sd	True density (g/cm^3) mean ± sd	Surface area (S) (mm^2)	S/V (mm^2/mm^3)	Crushing strength (*N*) mean ± sd	Friability (%)
0	—	0	13.0 ± 0.4	2.53 ± 0.01	1.1154 ± 0.0009	29.69	2.39	7.39 ± 0.09	1.92
1	HPMC K100M	15	12.3 ± 0.4	2.35 ± 0.04	1.2019 ± 0.0018	28.27	2.45	15.65 ± 0.31	0.85
2		50	12.1 ± 0.3	2.22 ± 0.04	1.2614 ± 0.0002	27.25	2.50	23.47 ± 0.33	0.51
3	HPMC K15M	50	12.4 ± 0.2	2.28 ± 0.02	1.2972 ± 0.0016	27.72	2.48	28.45 ± 0.13	0.43
4	HPMC K4M	50	12.3 ± 0.3	2.26 ± 0.03	1.2965 ± 0.0021	27.57	2.49	30.64 ± 0.18	0.38
5	EC	15	11.7 ± 0.2	2.26 ± 0.04	1.1599 ± 0.0004	27.57	2.49	17.25 ± 0.19	0.83
6		40	11.8 ± 0.3	2.32 ± 0.04	1.1820 ± 0.0004	28.04	2.46	17.79 ± 0.07	0.50

TABLE 2 **Physical Properties of Ibuprofen Matrix Tablets (10 mm)**

Formulation	Polymer type	Polymer content (%)	Weight (mg) mean ± sd	Thickness (mm) mean ± sd	True density (g/cm^3) mean ± sd	Surface area (S) (mm^2)	S/V (mm^2/mm^3)	Crushing strength (*N*) mean ± sd	Friability (%)
7	HPMC K100M	15	399.7 ± 1.0	4.78 ± 0.01	1.1707 ± 0.0007	307.25	0.82	95.65 ± 4.72	1.13
8		50	401.1 ± 0.7	4.64 ± 0.01	1.2359 ± 0.0006	302.85	0.83	159.41 ± 5.32	0.18
9	EC	15	400.8 ± 0.7	4.88 ± 0.01	1.1362 ± 0.0004	310.39	0.81	100.55 ± 6.27	1.10
10		40	400.8 ± 0.7	4.86 ± 0.00	1.1603 ± 0.0014	309.76	0.8	145.19 ± 5.63	0.18

on the properties of the tablets, particularly in vitro, was also investigated for formulations containing 50% of each component (formulations 2, 3, and 4). Mini tablets containing ibuprofen only were prepared to be used as a reference formulation (formulation 0).

Mini tablets, weighing 12.0 ± 1.0 mg, were prepared by direct compression with flat tip punches and dies with 2.5 mm diameter. The punches and dies were fit to an instrumented mechanical press machine (Lloyd Instruments LR 50K, Fareham, UK) that controlled the pressure (100 ± 5 N/mm^2) and the displacement of the punches. For comparative purposes, tablets with 10 mm diameter were prepared under the same pressure and compression speed.

Characterization of the Mini Tablets and Tablets

Tablets were characterized for weight variation (n = 20, balance METTLER AE 200, Mettler Toledo, Greifensee, Switzerland), thickness (n = 20, electronic digital micrometer, Palmer), crushing strength (n = 6, CT5, Engineering Systems, Nottingham, UK), friability (n = 20, Roche type friabilometer, 25 rpm for 4 minutes, Sotax model F1 Friabilator, Basel, Switzerland), density (n = 3, by helium pycnometry, Accupyc 1330, Mycromeritics, Norcross, GA, USA), water uptake ability, and release of the drug. The surface, S, and the volume, V, of the tablets were also calculated for each formulation by measuring the tablets' diameter and thickness.

Comparisons of the crushing strength values between the different formulations were made with analysis of variance (ANOVA) followed by post hoc multiple comparisons (Tukey) (α = 0.05). All statistical analyses were performed with the SPSS software package (SPSS for Windows 12.0, SPSS, Chicago, IL, USA).

Quantification of the Water Uptake and Erosion Determinations

Mini tablets were placed in a dissolution vessel for the dissolution test (see following section). At time intervals of 30, 60, 120, 240, 360, and 480 min, the mini tablets from each batch were withdrawn from the medium and weighed after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at 40°C up to constant weight. The increases on weight of the tablets reflect the weight of the liquid uptake. It was estimated according equation, $Q = 100(W_i - W_w)/W_i$, where Q is the percentage of liquid uptake, W_w and W_i are the masses of the hydrated samples before drying and the initial starting dry weight, respectively.

The degree of erosion (expressed as % erosion of the polymer content, E) was determined using equation $E = 100(W_i - W_f)/W_i$, where W_f is the final mass of the same dried and partially eroded sample.

In Vitro Drug Release and Data Analysis

The release of ibuprofen was assessed by dissolution tests according to the followed conditions: n = 3, paddle method at 150 rpm in 900 mL of phosphate buffer at pH 7.2 and kept at 37 ± 0.5°C. In each dissolution vessel, an equivalent number of mini tablets to 36 mg of drug were evaluated in a dissolution apparatus (Sotax model AT7, Basel, Switzerland) with on-line evaluation of the drug release with time by a flow-through UV/VIS spectrophotometer (λ = 265 nm, Jasco model V-530, Tokyo, Japan) connected to a pump.

The suitability of several equations, which are reported in the literature to define drug release mechanism(s) (Costa & Sousa Lobo, 2001), was tested with respect to the release data. Some diffusion models (Korsmeyer-Peppas) are expected to be valid only up to approximately 60% cumulative drug released (Ritger & Peppas, 1987), and the data for analysis was therefore restricted to that range and not considered the lag time. To analyze the mechanism of drug release from the matrix mini tablets, the data obtained from the drug release studies was analyzed according to the following equations of the Zero-order model (Donbrow & Samuelov, 1980), Higuchi model (Higuchi, 1961, 1963), and the Korsmeyer-Peppas model (Korsmeyer et al., 1983; Peppas, 1985), respectively:

$$M_t = M_0 + K_0 t$$

$$M_t = M_0 + K_H t^{0.5}$$

$$M_t = M_0 + K_K t^n$$

In all mathematical expressions, M_t is the amount of drug dissolved in time t, M_0 is the initial amount of drug

in the solution, K_0 is the zero order release constant, K_H is the Higuchi rate constant, K_K is a release constant, and n is the release exponent, which characterizes the mechanism of drug release. The magnitude of the exponent n allows the general indication of the release mechanism of Fickian diffusion, case II transport, or anomalous transport. In the present study (cylindrical shape), the limits considered were $n = 0.45$ (indicates a classical Fickian diffusion-controlled drug release) and $n = 0.89$ (indicates a case II relaxational release transport: non Fickian, zero-order release). Values of n between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and polymer relaxation) commonly called anomalous transport.

RESULTS AND DISCUSSION

Physical Properties

The mixtures considered were successfully compressed into mini tablets with small weight variations (coefficient of variation <5%) and identical dimensions (diameter and thickness) assuring the suitability of the formulations to produce mini tablets. Table 1 lists the physical properties (weight, thickness, true density, surface area (S), surface area/volume ratio (S/V), crushing strength, and friability) of the mini tablets. The mini tablets containing ibuprofen only (formulation 0) presented low crushing strengths and unacceptable friability, higher than 1% due to the poor binding properties of the particles of ibuprofen, anticipating problems with their handling. The presence of HPMC and EC in the formulations resulted in tablets with more adequate physical properties. This suggests that HPMC and EC have the ability to establish larger and stronger bonds between the particles improving cohesion during compression, thus turning the production of the mini tablets more acceptable (Ho et al., 1997; Desai et al., 2001; Sánchez-Lafuente et al., 2002). The proportion of HPMC and EC in the tablets affected their physical properties. It was observed that decreasing the amount of polymer in the formulations resulted in an increase of the friability and a reduction of the crushing strength values. The apparent reason for this is that the increased proportion of drug would further spatially separate the particles of the polymer from each other. This would weaken the interparticulate adhesive forces between the polymer particles, resulting therefore, in a larger crushing strength value. Comparisons of the crushing strength values between the different formulations based on ANOVA analysis revealed no statistical differences between the crushing strength values of mini tablets formulations containing EC ($p > 0.05$). However, ANOVA has shown significant differences between the formulations containing 15% and 50% of HPMC K 100M tested ($p < 0.001$). On the other hand, the mini tablets containing different types of HPMC revealed no statistical differences between the HPMC K15M and HPMC K4M and significant differences between these two types and the HPMC K100M. The results show that for mini tablets, with similar weight and thickness, the crushing strength and the friability are more favorable as the size of the HPMC molecule decreases as a consequence of a higher bonding ability. The higher flexibility of the chains of the polymer may provide an explanation to the observation.

The results for the 10 mm diameter tablets (Table 2) followed the same pattern as for the mini tablets, which are the proportion of HPMC and EC also affected the physical properties of the large tablets. For instance, the tablets containing 15% of polymer (formulations 7 and 9) were too friable (friability > 1%) anticipating problems with their handling. The results of ANOVA indicated significant differences between the formulations containing 15% and 40% of EC and between the formulations with 15% and 50% of HPMC K100M ($p < 0.001$).

Effect of the Composition of the Mini Tablets on the Release of the Drug

Influence of the Concentration and the Viscosity of HPMC

The effect of the polymer level on the release of ibuprofen was studied by mini tablets containing 15% and 50% of HPMC K 100 M. Figure 1 shows the profiles for the release of the drug from different matrices containing ibuprofen and HPMC. Figure 1 shows that the amount of HPMC in the formulation affects the release rate of ibuprofen. The mini tablets prepared with 15% of HPMC disintegrated instantaneously on contact with the dissolution medium, leading to immediate release of the drug. In this case, the presence of 15% of HPMC was not enough to form a continuous network structure once the isolated clusters of HPMC swelled creating rupture points in the system: thus, the integrity of the matrix was destroyed quickly. At this level in the formulations,

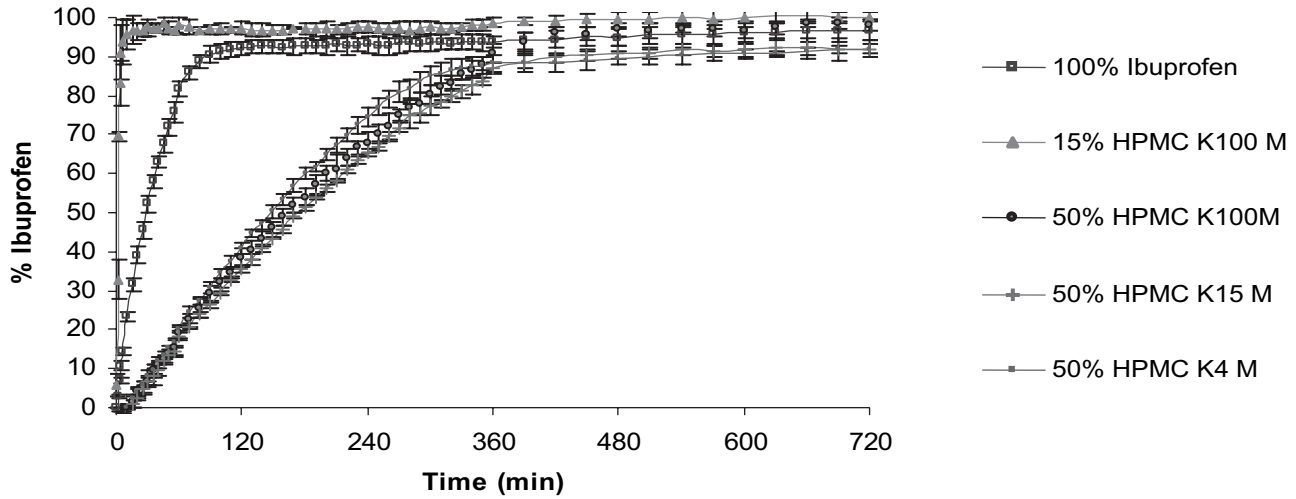

FIGURE 1 **In Vitro Ibuprofen Release Profiles of the HPMC Mini Tablets (W/W): –■– 0 HPMC/100 Ibuprofen; –▲– 15 HPMC K100M/85 Ibuprofen; –•– 50 HPMC K100M/50 Ibuprofen; –✚– 50 HPMC K15M/50 Ibuprofen; –▪– 50 HPMC K4M/50 Ibuprofen (Error Bars Represents the ± SD).**

HPMC is acting as a disintegrant. Figure 1 also shows that the disintegration from mini tablets formulated with 15% of HPMC was faster than from tablets without HPMC. This suggests that a) the interactions between particles of ibuprofen and HPMC are weaker than between particles of ibuprofen, b) the presence of particles of HPMC disrupts the structure of the ibuprofen, and c) the particles of HPMC act as disintegrant. On the other hand, by incorporating 50% of HPMC in the formulation, the complete release of the drug was not observed until the 8th hour of the test. The ability of the particles of HPMC to hydrate and form a gel layer around a core is well known and is essential to sustain and control the release of a drug from a matrix (Colombo et al., 2000). As the proportion of the polymer in the formulation was increased, the gel formed was more likely to diminish the diffusion of the drug and delay the erosion of the matrix (Ford et al., 1985). The results suggest that a threshold exists below which the release of a drug cannot be sustained with disintegration of the tablet.

Regarding the effect of the molecular weight of the polymer (Fig. 1), the drug release rates were similarly independent of the polymer considered. This result is probably due to the chemical similarity of different HPMCs. It could be expected that different grades would affect the release of the drug due to the fact that the swelling and the relaxation of the polymer are different for each grade. However, in the present work, the size of the mini tablets may be too small to show significant differences.

Influence of the Amount / Percentage of EC

The different amounts of EC in the formulations produced significant differences on the release profiles of ibuprofen (Fig. 2). From the figure it is clear that an increase on the content of EC in the formulation caused a delay on the release of the drug. For the same content of ibuprofen in the formulation (85%), the presence of EC in the formulation has shown a larger impact over the release of ibuprofen compared to the HPMC. When 15% of EC in the formulation was considered, it resulted in a faster release of the drug (complete release within 8 h) probably due to the higher ratio between the drug and the EC, when compared with the 40% EC in the formulation. When the amount of polymer increased from 15% to 40%, the ibuprofen release from the mini tablets was retarded dramatically. After 8 h of dissolution, the drug was completely released from the formulation containing 15% of EC, whereas the formulation with 40% of EC released only 69% of ibuprofen. These experiments suggest that different formulations can provide reasonably spread dissolution profiles by varying the amount of polymer in the formulation from 15% to 40%. Using a different technology, a comparison between the release profiles of ibuprofen released from the pellets prepared by De Brabander et al. (2003) and from the mini tablets (60:40 w/w), revealed that the hot melt extrusion process had a strong sustained effect on the ibuprofen release when compared with a direct compression. Despite the objective to control the release of ibuprofen from pellets with EC, the actual release was too slow (20% in 24 h). In

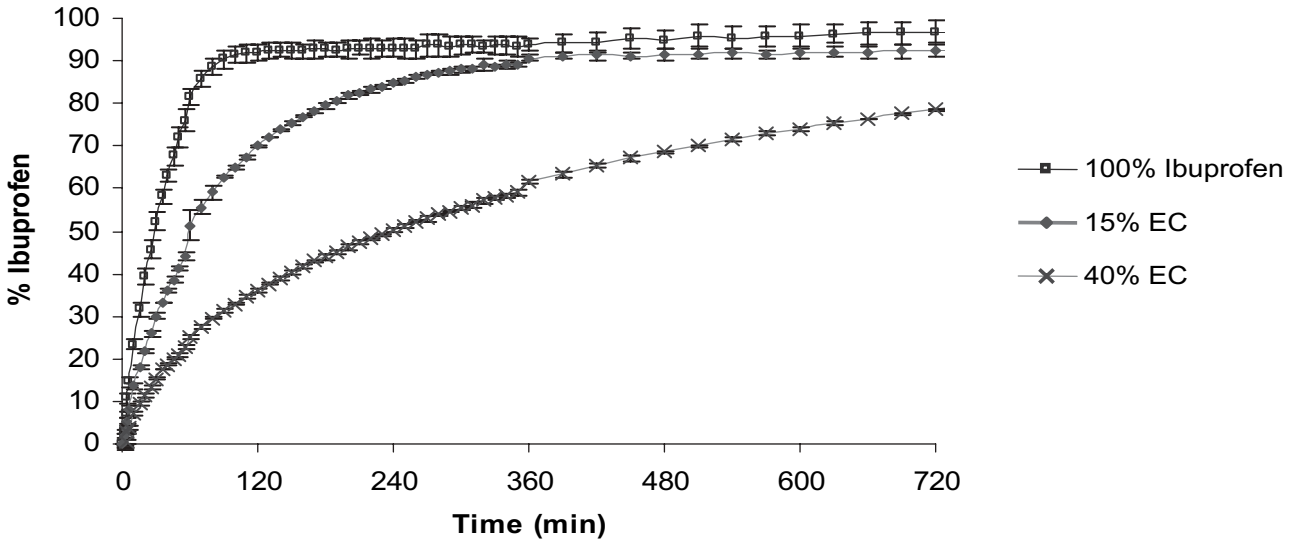

FIGURE 2 **In Vitro Ibuprofen Release Profiles of the EC Mini Tablets (W/W): –■– 0 EC/100 Ibuprofen; –•–15 EC/85 Ibuprofen; –✘– 40 EC/60 Ibuprofen (Error Bars Represents the ±SD).**

order to enhance release, it was necessary to add another excipient (HPMC or xanthan gum). In this situation, the melt extrusion provides a compact mass of EC and ibuprofen whereby the EC forms a continuous and compact barrier that sustains the release of ibuprofen. In the case of mini tablets prepared by direct compression, the particles of EC cover the particles of ibuprofen forming a porous matrix of EC that can release the drug more easily than the molten system.

Effect of the Size of the Tablets on the Release of the Drug

As seen in Figs. 3 and 4, the release rate of ibuprofen increased with increasing the S/V ratios. This result is consistent with previous research carried out with cylindrical tablets (Siepmann et al., 2000), whereby smaller cylindrical tablets have shown faster releases due to a higher specific surface area exposed to the dissolution medium. In the present study, the S/V ratio for the mini tablets is about three times larger than the ones for the larger tablets.

Liquid Uptake and Erosion by the Mini Tablets

Since the rate of swelling and erosion is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated mini tablets were determined. The

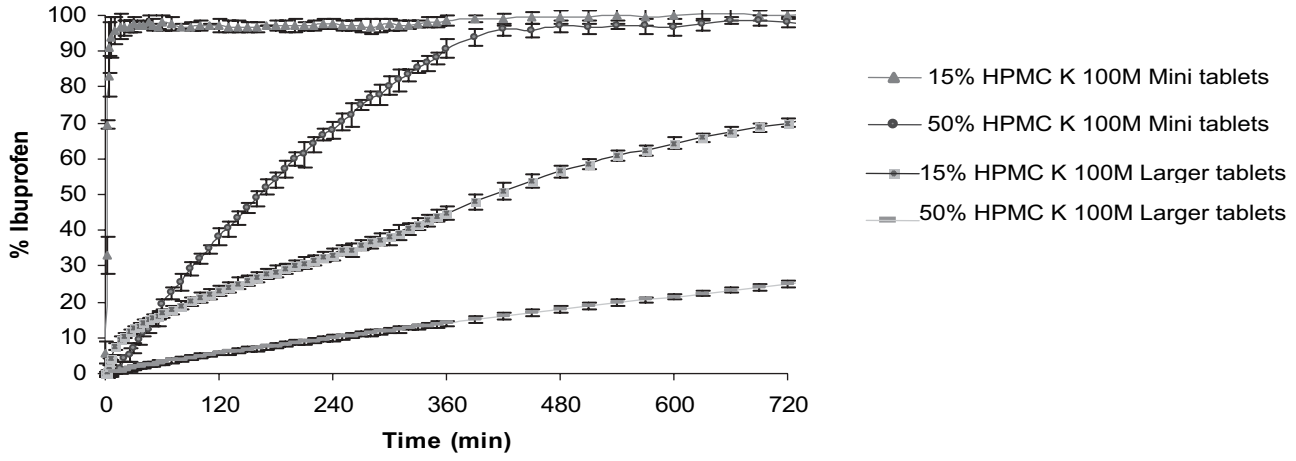

FIGURE 3 **In Vitro Release Profiles of the Matrix Tablets Containing HPMC/Ibuprofen (W/W) in Different Ratio Demonstrating the Effects of the Tablets Dimensions: –▲– 15/85 Mini Tablets; –•– 50/50 Mini Tablets; –■– 15/85 Large Tablets; ▬–50/50 Large Tablets (Error Bars Represents the ± SD).**

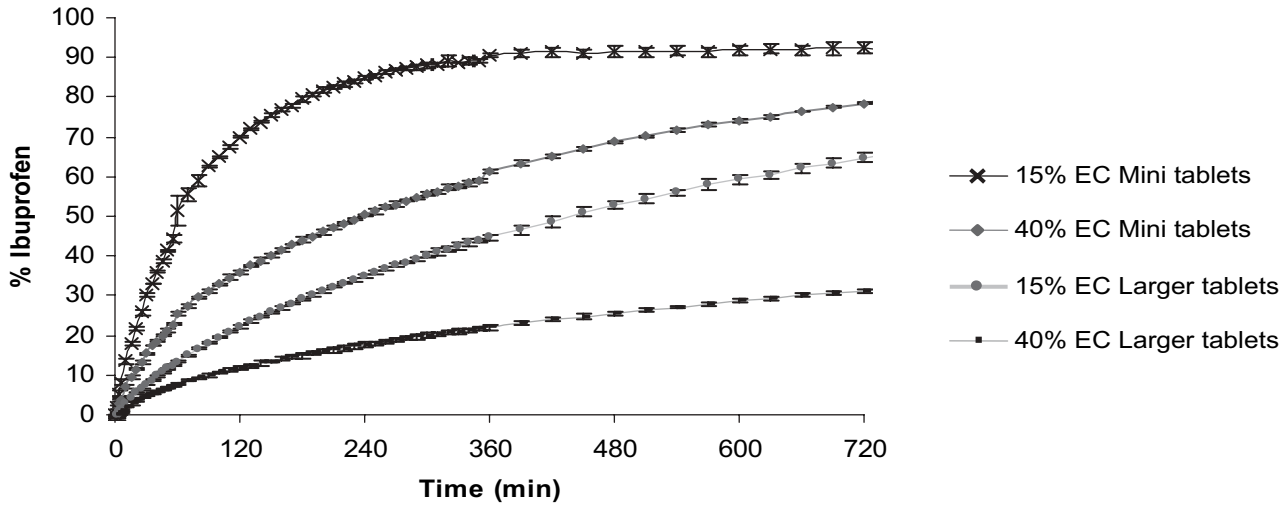

FIGURE 4 **In Vitro Release Profiles of the Matrix Tablets Containing EC/Ibuprofen (W/W) in Different Ratio Demonstrating the Effects of the Tablets Dimensions: –•– 15/85 Mini Tablets; –✘– 40/60 Mini Tablets; –■– 15/85 Large Tablets; ▬–40/60 Large Tablets (Error Bars Represents the ±SD).**

percentage increase in weight of the hydrated mini tablets containing HPMC at various time intervals up to 8 h are shown in Fig. 5. Simultaneously with the penetration liquid study, the degree of polymer erosion was measured (Fig. 6). The degree of swelling is dependent on the concentration and type of HPMC presented in the matrix: a higher viscosity grade and higher concentration (in relation to the drug load) resulted in a higher degree of swelling. The order of swelling observed in these polymers could indicate the rates at which the preparations are able to absorb water and swell. In the case of mini tablets containing 15% of HPMC K100M (formulation 1), the results are not shown in Fig. 6 because the mini tablets disintegrated instantaneously on contact with the dissolution medium. The lowest liquid uptake (and swelling) was observed for the formulation containing the lower viscosity grade HPMC (K 4M). In this formulation, the maximum liquid uptake was reached within 2 h (≈302% weight increase), while in the other formulations uptake was reached within 4 h (≈473% and 509% weight increase for HPMC K15M and HPMC K100M, respectively). After 480 min, the formulations containing these last two polymers present a liquid uptake that reaches up to 150% and simultaneous erosion closer to 95%. After this wetting period, the systems were only in gel form with a higher volume of water. Then the samples were dried, the water evaporated, and the systems presented only a film of solid residue.

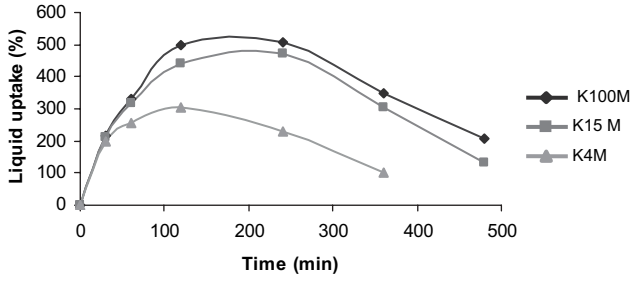

FIGURE 5 **Percentage Increase in Weight Resulting from Water Uptake by HPMC/Drug Mini Tablets at Various Time Intervals (Min) After Contact with Aqueous Medium.**

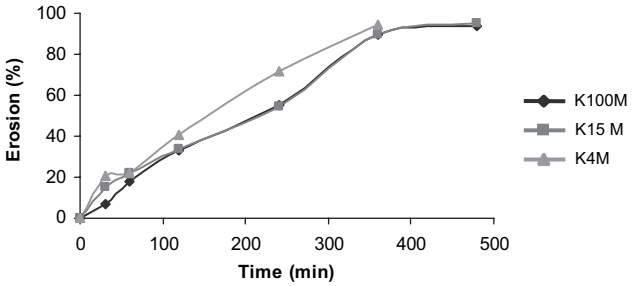

FIGURE 6 **Percentage of Weight Loss Resulting from HPMC Erosion by HPMC/Drug Mini Tablets at Various Time Intervals (Min) After Contact with Aqueous Medium.**

During the swelling of the HPMC mini tablets, an anisotropic swelling phenomena (i.e., more swelling in the axial direction than in the radial direction on exposure to water) was seen for all the formulations. Similar phenomena was observed by Papadimitriou et al. (1993) who related the predominantly axial relaxation of the HPMC compacts to the relief of stress induced during compaction and unidirectional

swelling to the orientation of molecules during compression. The reason for such preferential swelling in axial direction must be due to the need for directional stresses, imposed in HPMC during tabletting, to relax. It follows that the area change in the swollen system is directly related to the area exposed to water access.

Liquid uptake and erosion degree of mini tablets containing EC are shown in Figs. 7 and 8, respectively. In these cases, the percentage of liquid uptake by the formulation was practically negligible during the dissolution period (≈0% and ≈2% weight increased for 15% and 40% of EC, respectively). This is expected due to the nature of polymer which is water insoluble. The rate of EC erosion was greatly influenced by the polymer concentration.

Identification of the Mechanism by Which the Drug is Released

The parameters of dissolution that allow the clarification of the release of the ibuprofen from the mini tablets and tablets are presented in Tables 3 and 4, respectively. The correlation coefficient (R^2) was used as indicator of the best fitting for each of the models considered. For the mini tablets containing HPMC, the model that best describes the release of the drug was the K-P model ($R^2 > 0.997$). For these preparations, the zero order model showed good results also ($R^2 > 0.990$). From the release exponent in the K-P model ($n \cong 0.8$), it can be suggested that the mechanism that led to the release of ibuprofen (formulations 2, 3, and 4), was an anomalous transport with a constant release rate adequate for a sustained release dosage form. For the mini tablets containing EC, the models that best describe the release of the drug were the K-P and the Higuchi models ($R^2 > 0.997$). For these mini tablets, the K-P release exponent ($n \cong 0.5$) suggests that the Higuchi model can be accepted; thus, the mechanism controlling the release was a Fickian diffusion of the drug through the matrices in the EC mini tablets. However, the release data analysis applying these mathematical models is purely empirical and no definitive conclusion can be drawn concerning the dominating mass transport mechanisms.

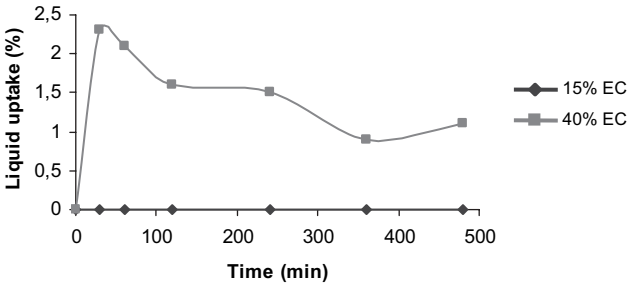

FIGURE 7 **Percentage Increase in Weight Resulting from Water Uptake by EC/Drug Mini Tablets at Various Time Intervals (Min) After Contact with Aqueous Medium.**

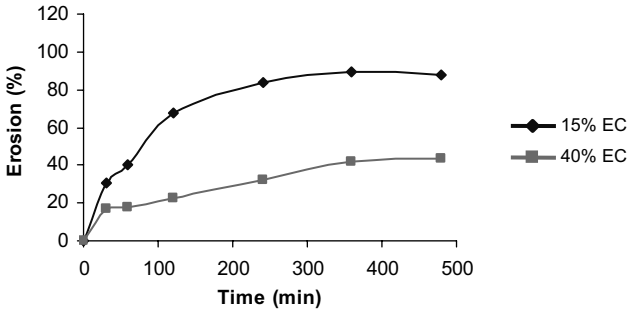

FIGURE 8 **Percentage of Weight Loss Resulting from EC Erosion by EC/Drug Mini Tablets at Various Time Intervals (Min) After Contact with Aqueous Medium.**

As can be seen in Table 4, the values for n and R^2, calculated from the results obtained for the large and small tablets, led to the same conclusions. For formulations containing EC, the release rate of ibuprofen from the tablets (2.7×10^{-2} mg/ml.min$^{0.5}$ and 1.2×10^{-2} mg/ml.min$^{0.5}$ for formulations 9 and 10, respectively) was about three times lower than the release rate observed for the mini tablets (7.5×10^{-2} mg/ml.min$^{0.5}$ and 3.4×10^{-2} mg/ml.min$^{0.5}$ for formulations 5 and 6, respectively). As anticipated, these results support the direct relationship between S/V ratio and the release rate of the ibuprofen in tablets with EC. There seems to be a direct relationship between the S/V ratio and the release rate of ibuprofen for EC. However, for tablets containing HPMC, this relationship was not verified; this may be due to the different S/V ratios exhibited by both the dry tablets and the swelled tablets.

CONCLUSIONS

The preparation of mini tablets has proved a large potential to control the release of drugs while maintaining the advantages of multi-unit dosage forms. The mini tablets offer some advantages compared to pellets even from a technological perspective. Like pellets, the mini tablets can be either filled into capsules or compacted into bigger tablets and then

TABLE 3 **Dissolution Parameters for Ibuprofen Release from Mini Matrix Tablets (2.5 mm)**

			K-P equation		*Zero order equation*		*Higuchi equation*	
Formulation	Polymer content (%)	$t_{50\%}$ (min)	*n*	R^2	K_0	R^2	K_H	R^2
0	—	28	0.5554	0.9985	1.6250	0.9811	11.9772	0.9980
1	15HPMC K100M	1–2	a	a	a	a	a	a
2	50HPMCK100M	164	0.7760	0.9978	0.3154	0.9939	5.7739	0.9905
3	50 HPMC K15M	175	0.7673	0.9990	0.2998	0.9951	5.6187	0.9927
4	50 HPMC K4M	149	0.8420	0.9989	0.3534	0.9970	6.1236	0.9880
5	15 EC	62	0.6815	0.9948	0.7481	0.9794	7.5144	0.9892
6	40 EC	239	0.3938	0.9988	0.1538	0.9280	3.4223	0.9956

a, could not be determined.

TABLE 4 **Dissolution Parameters for Ibuprofen Release from Matrix Tablets (10 mm)**

			K-P equation		*Zero order equation*		*Higuchi equation*	
Formulation	Polymer content (%)	$t_{50\%}$ (min)	*n*	R^2	K_0	R^2	K_H	R^2
7	15HPMC K100M	430	0.6812	0.9892	0.0662	0.7314	2.0999	0.8729
8	50HPMCK100M	>720	0.8103	0.9999	0.0303	0.9949	1.2829	0.9791
9	15 EC	455	0.4969	0.9983	0.1011	0.9525	2.6693	0.9977
10	40 EC	>720	0.4541	0.9997	0.0331	0.9310	1.2181	0.9991

released intact in the gastrointestinal tract. Ibuprofen mini tablets can be produced by direct compression with HPMC or EC as the controlling release agents. The tabletting of the powders produced mini tablets with identical masses for the different batches considered, suggesting a fairly good precision of the technique. The binding ability of HPMC and EC resulted in a stronger adhesion between particles and an improvement of the physical properties. In the same amount, EC produced a larger sustaining effect on the release of ibuprofen than HPMC. This difference in release characteristics results from the different behavior of the polymers relating to water. The applied mathematical models suggested that the drug released from EC mini tablets was probably controlled by diffusion. For mini tablets containing 50% of HPMC, the swelling phenomena played an important role and it was dominant throughout the dissolution time period. Hydroxypropylmethylcellulose (HPMC) was particularly suitable with release exponents approaching to zero-order (constant) release over 8 h time periods in the in vitro study. The different formulations containing HPMCs with different viscosity grades have shown no difference in drug release profiles, probably due to their similarly in chemical structure. A simple, but very effective tool for modifying the release kinetics from matrix tablets, is to vary their geometry; for example, varying the initial radius and height of cylindrical tablets strongly affects the drug release rate. In the case of mini tablets, greater surface area produces a higher number of drug molecules at the surface ready for faster release compared with the larger tablets.

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