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Research paper

Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets

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Abstract

The present work reports the study of different ketoprofen:excipient formulations, in order to determine the effect of the polymer substitution and type of diluent on the drug-release mechanism. Substituted cellulose—methylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose were used as polymers, while lactose monohydrate and β-cyclodextrin were tested as diluents. Distinct test formulations were prepared, containing 57.14% of ketoprofen, 20.00% of polymer, 20.29% of diluent, and 1.71% of talc/0.86% of magnesium stearate as lubricants. The tablets were tested for their drug content, weight variation, hardness, thickness, tensile strength, friability, swelling and release ratio. Polymers MC25 and HPC were found not to be appropriate for the preparation of modified release ketoprofen hydrophilic matrix tablets, while HPMC K15M and K100M showed to be advantageous. The analysis of the release profiles in the light of distinct kinetic models (zero-order, first-order, Higuchi and Korsmeyer–Peppas) led to the conclusion that the type of polymer did not influence the release mechanism of the drug. The mean dissolution time (MDT) was determined, the highest MDT value being obtained for HPMC formulations. Moreover, the drug-release process was found to be slightly influenced by the type of diluent, either lactose or β-cyclodextrin.

Keywords: Ketoprofen; Hydrophilic cellulose tablets; Controlled release; Matrix tablets; Cellulose polymers

1. Introduction

Ketoprofen [2-(3-benzoylphenyl)propionic acid] is a non-steroidal anti-inflammatory drug (NSAID), widely used in order to reduce pain, inflammation and stiffness caused by several conditions such as osteorarthritis, rheumatoid arthritis, ankylosing spondylitis or abdominal cramps associated with menstruation. The mechanism of action of ketoprofen is mainly associated to the inhibition of the body's ability to synthesise prostaglandins. Ketoprofen is usually formulated and administered as a racemic mixture of *R* and *S* enantiomers, which are equivalent on a per weight basis. It exhibits enantiomeric selectivity, only the *S*(+)-enantiomer displaying pharmacodynamic activity [1,2]. Conventional dosage forms of this drug, administered orally, are rapidly and almost completely absorbed from the gastro-intestinal tract, the peak plasma concentrations occurring within 1–3 h [1,3]. Ketoprofen is an appropriate model drug for formulation of controlled release dosage forms due to its short plasma elimination half-life and poor solubility in unionised water, which affects its biovailability [4,5]. Therefore, in order to maintain therapeutic plasma levels, modified release dosage forms may be beneficial, allowing only one daily administration of the drug with consequent improvement of patient compliance [6].

In recent years, the use of hydrophilic polymers, in particular cellulose derivatives, has attracted considerable attention for the development of controlled release technology in the formulation of pharmaceutical products, due to their ability to form gels in aqueous medium.

Previous studies developed by Williams et al. [7] led to the conclusion that the type and level of excipient influenced the rate and extension of drug release. Recently, Samani

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et al. [8] investigated the effect of polymer blends on release profiles of sodium diclofenac from matrices and the results showed that the drug release depends on the kind of polymer, its proportion in the formulation and its viscosity grade. Hydroxypropylmethylcellulose, is used to control drug release from several pharmaceutical systems because of its non-toxic nature, easy compression, swelling properties and accommodation to high levels of drug. This cellulose derivative excipient has been widely investigated in our laboratory [9–11]. Despite the high number of papers on this subject, few of them discuss the drug-release processes from both methylcellulose [12,13] and hydroxypropylcellulose [14,15].

The main objective of the present study is to evaluate the effect of polymers on the kinetics of the drug release, using distinct formulations, in order to understand how they rule this process. This will hopefully allow the design of more suitable cellulose matrices. The influence of the diluent is also examined. The cellulose ether polymers methylcellulose (MC), hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC), the diluents lactose monohydrate (LAC) and β-cyclodextrin (β-CD), and the lubricants talc and magnesium stearate were studied.

2. Materials and methods

2.1. Materials

Drug: ketoprofen, Sigma-Aldrich Chemie, Germany. Polymers: methylcellulose, Methocel® MC25, Fluka, Switzerland; hydroxypropylcellulose, Klucel, USA; hydroxypropylmethylcellulose, Methocel® K15M and Methocel® K100M, Colorcon, England. Diluents: β-cyclodextrin, Kleptose®, Roquette, Lestrem, France; lactose monohydrate Granulac® 200, Meggle, Wasserburg, Germany. Lubricants: talc and magnesium stearate (analytical grade). Indium: Aldrich, Milwaukee, USA.

2.2. Differential scanning calorimetry (DSC)

Thermal analysis were carried out using a Shimadzu DSC-50 calorimeter, coupled to a Shimadzu TA-50 analyser. The samples were heated in sealed aluminium pans, under a nitrogen flow (20 ml/min). About 2.5 mg of either pure drug or pure excipient, or 5 mg of the drug:excipient mixture was analysed, at a heating rate of 10 °C/min, from 25 to 250 °C, an empty sealed pan being used as reference. The apparatus was calibrated with indium (99.98%, m.p. 156.65 °C).

2.3. Preparation of the matrix tablets

The distinct formulations of the matrix tablets analysed along this study are provided in Table 1. The tablets were prepared containing 57.14% of drug (KETO), 20.00% of polymer (MC25, HPC, HPMC K15M or HPMC K100M), 20.29% of diluent (LAC or β-CD), 1.71% of talc and 0.86% of magnesium stearate as lubricants. The drug, polymer and diluent were passed through a 100 mesh sieve and thoroughly mixed in a plastic bag for 15 min. Talc and magnesium stearate were sieved (500 mesh), added to the previous mixture and blended for 5 min more. All matrices (total mass of 350 mg) were prepared by direct compression in an automatic hydraulic press (Speca Press, England), using flat 10 mm diameter punches and a compaction pressure of 624 MPa.

2.4. Assay of ketoprofen in matrix tablets

Five randomly chosen tablets of each of the formulations tested were thinly minced in a mortar, and 17.5 mg of the resulting powder was solubilised in phosphate buffer (pH 7.2, USP25) [16], up to a final volume of 100 ml. Several aliquots were then filtered and assayed spectrophotometrically at 320 nm, in a Shimadzu UV-1603 spectrophotometer. Each measurement was carried out in triplicate and the results averaged. A blank solution (containing all the components except from the drug) was

Table 1
Composition of the distinct hydrophilic formulations of ketoprofen

Component	Formulation (mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
Ketoprofen	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0
MC25	70.0	70.0	–	–	–	–	–	–
HPC	–	–	70.0	70.0	–	–	–	–
HPMC K15M	–	–	–	–	70.0	70.0	–	–
HPMC K100M	–	–	–	–	–	–	70.0	70.0
Lactose	71.0	–	71.0	–	71.0	–	71.0	–
β-CD	–	71.0	–	71.0	–	71.0	–	71.0
Talc	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Mg stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0

also prepared. No other assay method was considered necessary since no interferences were observed at 320 nm.

2.5. Weight, hardness and thickness of tablets

A total of 20 tablets of each formulation was evaluated for weight (analytical balance KERN 770). For each formulation, the hardness of 10 tablets was examined using an Erweka hardness tester TBH28.

The thickness was determined using a micrometer (Roche, Switzerland). Ten individual tablets of each formulation were used.

2.6. Tensile strength

The tensile strength (T) was determined, for 10 matrix tablets of each formulation, from the force required to fracture the tablets by diametral compression, on a tablet hardness tester (Erweka TBH28, Germany), according to the following equation:

$$T = \frac{2P}{\pi D t} \quad (1)$$

where P is the applied load, and D and t represent the diameter and thickness of the tablet, respectively [17].

2.7. Friability

Twenty tablets were weighed and placed into a friabilitor (Erweka TA20, Germany). The samples underwent 25 rotations per minute, for 4 min, and were then re-weighed. This process was repeated for all formulations and the percentage friability was calculated using the equation:

$$F = \frac{W_1 - W_2}{W_1} \times 100 \quad (2)$$

where F represents the percentage weight loss, and W_1 and W_2 are the initial and final tablets weights, respectively.

2.8. Swelling

Swelling studies were carried out for all formulations. Three metallic baskets containing a matrix tablet of each formulation were weighed, and placed in 1000 ml of phosphate buffer (pH 7.2) at 37.0 ± 0.5 °C. At hourly intervals, the previously weighted baskets with the tablet were removed, gently wiped with a tissue to remove surface water, re-weighted and then placed back into the vessel as quickly as possible. The mean weights were determined for each formulation, and the degree of swelling (S) was calculated according to the relationship [18]:

$$S = \frac{W_s - W_d}{W_d} \times 100 \quad (3)$$

where W_d and W_s are the dry and swollen matrix weights, respectively, at immersion time t in the buffer. The swelling degree was the mean value of three measurements.

2.9. Drug release analysis

Release studies were carried out according to the USP 25 paddle method [16]. The dissolution medium was phosphate buffer (pH 7.2, 1000 ml) at 37.0 ± 0.5 °C, and a stirring speed of 100 rpm was used. A closed-flow in-line mutiple vessel dissolution apparatus (Vankel VK-7000 dissolution testing station), connected to a spectrophotometer (Shimadzu UV-1603), was used for this purpose. Six different tablets were tested. Progress of the release was monitored by withdrawing filtered samples every 5 min, for a total of 1200 min. The amount of ketoprofen present in each sample was determined spectrophotometrically, at $\lambda = 320$ nm. The corresponding drug-release profiles were represented through plots of the cumulative percentage of drug release (calculated from the total amount of ketoprofen contained in each matrix) versus time.

2.9.1. Kinetic mechanism

Different mathematical models may be applied for describing the kinetics of the drug-release process from matrix tablets, the most suited being the one which best fits the experimental results.

The kinetics of ketoprofen release from hydrophilic cellulose formulations was determined by finding the best fit of the dissolution data (drug-released fraction versus time) to distinct models: zero-order (4), first-order (5) and Higuchi (6) [19,20]:

$$Q_t = Q_0 + k_0 t \quad (4)$$

where Q_t is the amount of drug released at time t, Q_0 the amount of drug in the solution at $t = 0$, (usually, $Q_0 = 0$) and k_0 the zero-order release constant

$$Q_t = Q_\infty (1 - e^{-k_1 t}) \quad (5)$$

Q_∞ being the total amount of drug in the matrix and k_1 the first-order kinetic constant.

$$Q_t = k_H t^{1/2} \quad (6)$$

k_H representing the Higuchi rate constant.

Furthermore, in order to better characterise the drug-release behaviour for the polymeric systems studied, namely to understand the corresponding mechanism, the Korsmeyer–Peppas (7) semi-empirical model was applied [21].

$$Q_t/Q_\infty = kt^n \quad (7)$$

where Q_t/Q_∞ is the fraction of drug released at time t, k a constant comprising the structural and geometric characteristics of the tablet, and n, the release exponent, is a parameter which depends on the release mechanism and is thus used to characterise it [22]. For the case of cylindrical tablets [23], in particular, $n \leq 0.45$ corresponds to a Fickian

diffusion release (case I diffusional), $0.45 < n \leq 0.89$ to an anomalous (non-Fickian) transport, $n = 0.89$ to a zero-order (case II) release kinetics, and $n > 0.89$ to a super Case II transport.

A direct fitting of the drug-release data to the non-linear equations described above is usually avoided by performing a linear transformation of the data, followed by regression analysis. Nevertheless, this method may not be mathematically accurate, as it uses transformed values (logarithms) instead of the original data [24]. Therefore, a direct non-linear fitting of the experimental results was carried out in the present work, for each of the mathematical models considered (through minimisation of the sum of the squared residuals). Only the points within the interval $0.1 < Q_t/Q_\infty < 0.7$ were used.

2.9.2. Mean dissolution time

To further characterise the drug-release process, the mean dissolution time (MDT) was calculated according to the following equation:

$$\mathrm{MDT} = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta\, Q_j}{\sum_{j=1}^{n} \Delta Q_j} \tag{8}$$

where j is the sample number, n the number of time increments considered, $\hat{t}_j$ the time at midpoint between t_j and t_{j-1}, and ΔQ_j the additional amount of drug dissolved in the period of time t_j and t_{j-1}.

2.10. Statistics

All results were expressed as mean values ± standard deviation (SD). In order to assess the statistical significance between the data, a single-factor analysis of variance (ANOVA) was carried out, at a 5% significance level.

3. Results and discussion

3.1. Differential scanning calorimetry (DSC)

In order to investigate the possible interactions between ketoprofen and distinct polymers and/or diluents, differential scanning calorimetry studies were carried out. The 1:1 weight ratio was chosen because it maximises the likelihood of observing any interactions. The thermal curve of ketoprofen (Fig. 1) displayed a single sharp endothermic peak at 96 °C, corresponding to the melting point of the drug [25]. A large shallow broad endothermic effect, over the temperature range 60–140 °C, was observed for the polymers MC25, HPC, HPMC K15M and HPMC K100M (Fig. 1), upon evaporation of adsorbed water. Actually, it was reported that the thermal analysis of cellulose exhibits an endothermic effect above 100 °C [26–28]. The DSC trace of β-CD showed a broad endothermic effect, which attained a maximum around 120 °C, corresponding to a dehydration process [29]. Lactose thermogram, in turn, displayed two sharp endothermic peaks, at both 147 and 219 °C.

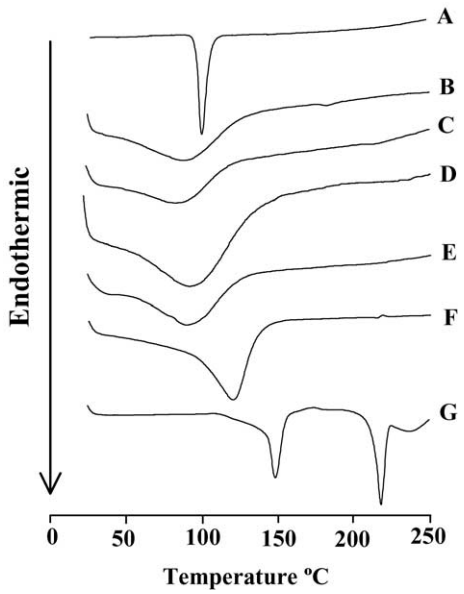

Fig. 1. DSC curves for ketoprofen and the different excipients studied. KETO (A), MC25 (B), HPC (C), HPMC K15M (D), HPMC K100M (E), β-CD (F) and lactose (G).

Regarding the (1:1) ketoprofen:excipient mixtures studied, the corresponding thermograms (Fig. 2) were found not to be a simple superposition of the ones obtained for each component separately. In fact, except in the case of MC25 (Fig. 2 (A:B)), there is a clear downward shift of the dehydration excipient signal relative to the free polymer, probably due to the presence of a non-negligible drug:excipient interaction. Actually, this could be responsible for

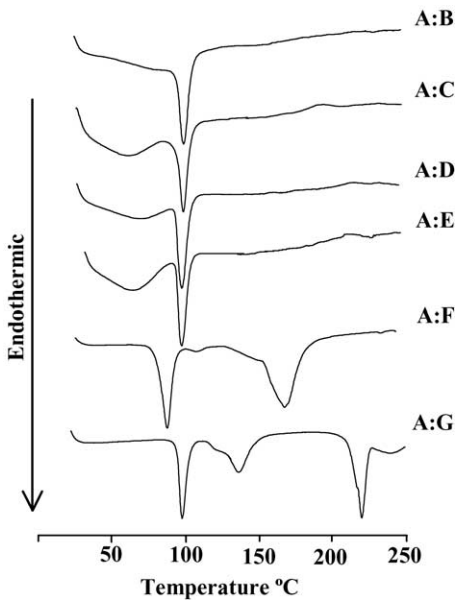

Fig. 2. DSC curves for ketoprofen and 1:1 (w/w) mixtures of ketoprofen with: MC25 (A:B), HPC (A:C), HPMC K15M (A:D), HPMC K100M (A:E), β-CD (A:F) and lactose (A:G).

a loosening of the water–polymer binding strength, due to a certain competition from the drug ionisable groups (e.g. carboxylates).

The ketoprofen:β-CD mixture exhibited the characteristic shift of the drug melting point to lower temperatures—ΔT ca. 6 °C—which is indicative of a certain loss of crystallinity (Fig. 2). The signal corresponding to the dehydration process of β-CD, in turn, is increased by ca. 50 °C. These observations reflect the existence of strong solid–solid interactions between the two components, in this formulation. Once no other thermal event occurred, these interactions do not necessarily indicate an incompatibility [30].

On the other hand, when lactose was combined to the drug—in a (1:1) (w:w) ratio—a downward shift of the excipient melting peak was detected, coupled to a broadening effect (Fig. 2), in accordance with findings previously reported by other authors [30]. Even though 1:1 is not the anticipated ratio for the final dosage form, as no extra thermal events were found in the corresponding thermogram and the ketoprofen signal appears unaffected, the results now obtained allow us to conclude that no incompatibility is present between ketoprofen and lactose.

3.2. Physical characteristics of ketoprofen hydrophilic cellulose matrices

As summarised in Table 2, the evaluation of the prepared hydrophilic matrix tablets containing ketoprofen showed that the drug content of all formulations ranged from 98.24 to 100.75%, indicating a uniform amount of drug in the formulations. The physical characteristics of these tablets provided good weight uniformity, as indicated by the very low relative standard deviation obtained (RSD $< 1\%$ in all formulations). Each of the polymers used, with different excipients, yielded matrix tablets with a hardness value from 82.10 to 220.90 N. It was also observed that a variation in the tablet hardness was accompanied by an obvious change in tablet tensile strength, evidencing a variation of tensile strength from 1.440 to 3.995 MPa. The tablets also passed the friability test ($F < 1\%$), showing that all formulations are within the USP25 limits [16].

3.3. Swelling studies

Swelling studies were carried out, in order to investigate whether the extent of swelling varied for the different formulations. When a matrix comes into contact with an aqueous solution, wetting occurs, first at the surface and then progressing into the matrix through microscopic pores. The nature of the polymer plays an important role in this swelling process of the matrix tablets. The presence of water in the polymer causes a certain amount of stress, resulting in hydration of the polymer, which starts to swell yielding a gelatinous viscous layer [31–36].

The results obtained from these swelling studies are represented in Figs. 3 and 4. From analysis of this data, it was possible to conclude that for the MC25 and HPC-containing matrix tablets the amount of aqueous uptake absorbed (and consequently the degree of swelling) was lower than for formulations containing HPMC K15M or HPMC K100M. The MC25 matrices, in particular, displayed a quite different behaviour as compared to the other polymers tested: the absence of hydroxypropoxyl groups in its structure is responsible for a lower hydrophilicity [37] and thus for a lower water uptake; moreover, at about 1 h after the start of the experiment, a gradual disintegration process was clearly evident from the significative decrease in the water uptake.

For the HPC-containing formulations, on the other hand, a lower hydration was observed, even for long water exposure periods. Roy et al. [38] calculated the swelling kinetic constant ($k = 2.47$) for this polymer, and suggested that its low value could be explained by the absence of a burst effect during swelling. However, the swelling process was found to vary considerably from the isolated polymer to the formulations tested along the present work, as the maximum plateau value is attained after 6 h of water exposure for the former and after only 1 h for the latter.

The amount of swelling obtained for the formulations containing both HPMC K15M and HPMC K100M evidenced a high hydration degree already after the first hour of water exposure—around double the one measured for the HPC system—this water content being constant from then on. This large degree of swelling is attributed to

Table 2
Physical characterisation of ketoprofen hydrophilic matrix tablets

Formulation	Weight (mg)[a] $n = 20$	Weight RSD (%)	Hardness (N) $n = 10$	Thickness (mm) $n = 10$	Tensile strength (MPa) $n = 10$	Friability (%) $n = 20$	Drug content (mg) $n = 3$
F1	348.95 ± 1.02	0.29	220.96 ± 2.69	3.52 ± 0.03	3.995 ± 0.051	0.18	196.48 ± 0.75
F2	349.51 ± 1.37	0.39	213.86 ± 1.87	3.50 ± 0.03	3.889 ± 0.052	0.77	201.06 ± 3.04
F3	348.32 ± 0.98	0.28	88.32 ± 1.06	3.60 ± 0.03	1.562 ± 0.028	0.71	197.59 ± 1.22
F4	349.06 ± 1.43	0.41	82.12 ± 1.60	3.63 ± 0.06	1.440 ± 0.025	0.80	201.47 ± 0.42
F5	349.21 ± 0.80	0.23	205.26 ± 2.30	3.56 ± 0.02	3.675 ± 0.040	0.65	200.44 ± 1.30
F6	349.12 ± 0.62	0.18	200.26 ± 1.48	3.55 ± 0.02	3.595 ± 0.034	0.85	197.73 ± 0.50
F7	348.57 ± 0.67	0.19	210.16 ± 2.13	3.55 ± 0.02	3.768 ± 0.050	0.27	199.00 ± 2.42
F8	349.16 ± 1.46	0.42	201.16 ± 3.21	3.58 ± 0.04	3.581 ± 0.055	0.67	198.51 ± 0.30

[a] n is the number of measurements.

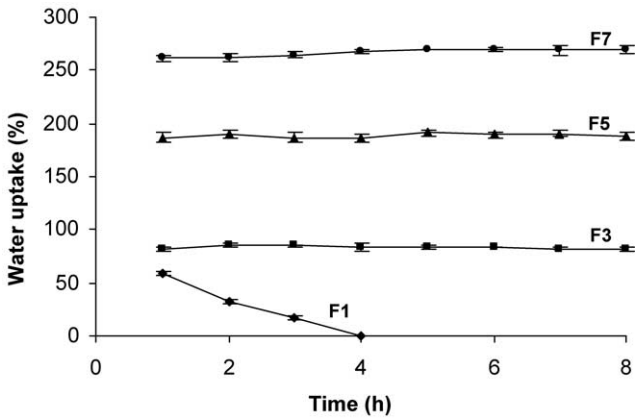

Fig. 3. Graphical representation of the water uptake versus time for several lactose-containing formulations (Table 1) of ketoprofen.

the presence of the highly hydrophilic hydroxypropoxyl groups in these polymers.

Cheong et al. [39] reported studies on polymer viscosity—which influences the drug-release process from a matrix system—having concluded that the high viscosity grades of HPMC (e.g. HPMC K100M) are explained by

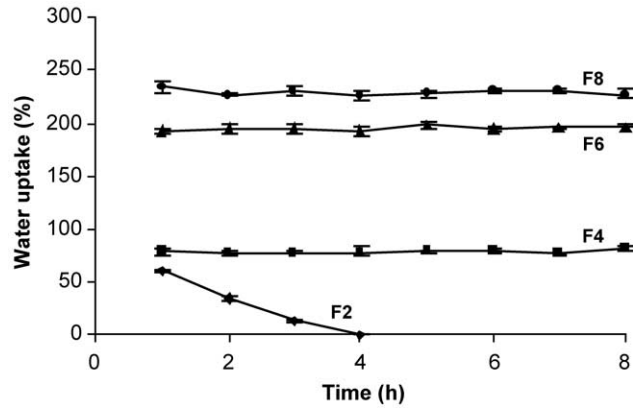

Fig. 4. Graphical representation of the water uptake versus time for several β-cyclodextrin-containing formulations (Table 1) of ketoprofen.

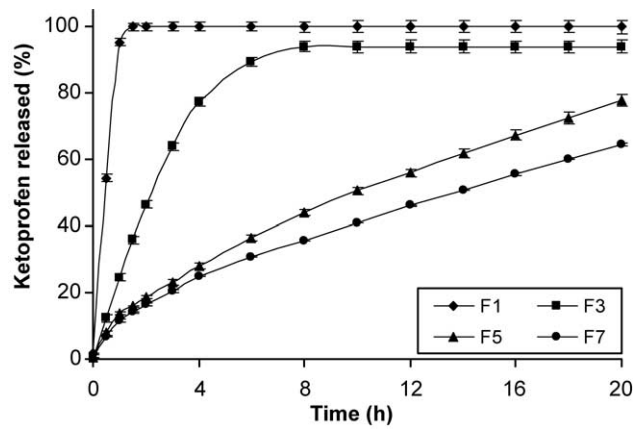

Fig. 5. Drug-release profiles for ketoprofen from lactose-containing formulations (Table 1).

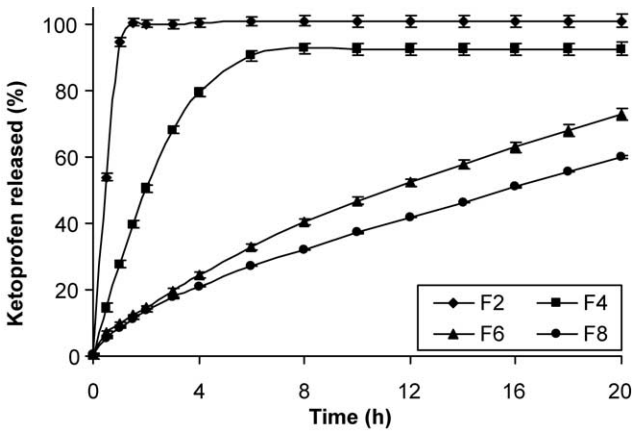

Fig. 6. Drug-release profiles for ketoprofen from β-cyclodextrin-containing formulations (Table 1).

the presence of substituent groups which, by interacting with water, lead to an increase of swelling.

3.4. Drug release analysis

Figs. 5 and 6 comprise the release profiles of ketoprofen from the distinct types of hydrophilic matrices studied. The MC25-containing tablet disintegrated, leading to a rapid release of the drug (in about 1 h). This is an indication that

Table 3
Calculated MDT values

Formulation	MDT (h)
F3	1.58 ± 0.02
F4	1.80 ± 0.02
F5	7.62 ± 0.07
F6	8.63 ± 0.18
F7	9.11 ± 0.04
F8	9.58 ± 0.07

Mean ± SD (six measurements).

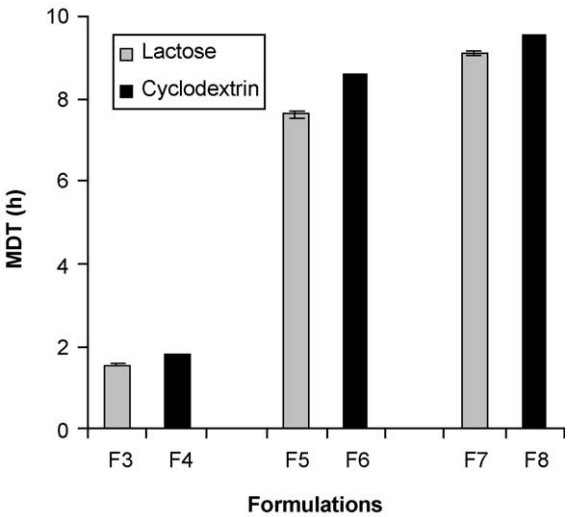

Fig. 7. Maximal MDT values (Table 3).

Table 4
Fitting results of the experimental ketoprofen release data to different kinetic equations, for several formulations

Formulation	Zero-order		First-order		Higuchi		Korsmeyer–Peppas		
	K_0 (% h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H (% $h^{-1/2}$)	R^2	K_{KP} (h^{-n})	n	R^2
F3	21.356 (0.917)	0.9904 (0.0032)	0.408 (0.035)	**0.9952** (0.0023)	52.532 (2.279)	**0.9962** (0.0019)	28.203 (1.251)	0.816 (0.013)	0.9966 (0.0015)
F4	19.752 (0.676)	0.9924 (0.0011)	0.390 (0.024)	**0.9941** (0.0021)	51.675 (1.755)	**0.9971** (0.0011)	25.453 (1.230)	0.842 (0.007)	0.9974 (0.0005)
F5	3.502 (0.089)	0.9871 (0.0007)	0.056 (0.002)	**0.9991** (0.0002)	18.609 (0.483)	0.9958 (0.0009)	12.047 (0.414)	0.621 (0.011)	0.9990 (0.0004)
F6	3.257 (0.070)	0.9817 (0.0066)	0.056 (0.002)	**0.9987** (0.0008)	19.084 (0.395)	**0.9988** (0.0007)	9.884 (0.480)	0.671 (0.018)	0.9977 (0.0020)
F7	2.718 (0.032)	0.9933 (0.0002)	0.040 (0.001)	**0.9985** (0.0001)	15.463 (0.181)	0.9918 (0.0002)	9.926 (0.209)	0.621 (0.009)	0.9978 (0.0011)
F8	2.524 (0.058)	0.9928 (0.0018)	0.037 (0.001)	**0.9985** (0.0003)	14.974 (0.322)	0.9947 (0.0015)	8.446 (0.370)	0.651 (0.017)	0.9989 (0.0005)

Values in parenthesis mean SD; R^2 is the coefficient of determination; best results in bold.

dissolution from MC25 formulations cannot be controlled. In turn, ketoprofen release from HPC was not as immediate. Different authors reported identical data [40] for other drugs. Regarding the formulations containing HPMC, the results showed that, after 20 h, 70–80% of the drug was released from F5 and F6 matrices (K15M), and 60–65% from formulations F7 and F8 (K100M).

It was verified that the presence of cyclodextrins into polymeric drug delivery systems can also influence the drug-release mechanism by Bibby et al. [41]. In the present study, β-CD was tested as a diluent in the ketoprofen matrix tablets, and the results evidenced that release profiles of these formulations were only slightly slower than those containing lactose. This is probably due to an inclusion process of the ketoprofen molecule in β-cyclodextrin, which may be considered energetically favoured when compared to inclusion of similar drugs, namely ibuprofen [42,43]. The MDT-calculated values for all the matrices investigated (Table 3, Fig. 7) corroborate these findings, once this parameter reflects the drug-release process—larger values indicating higher drug retarding ability of the formulation. In fact, it was verified that all formulations containing β-CD as a diluent yielded higher MDT values.

On the other hand, the polymer type (e.g. its viscosity) was also found to influence MDT. Thus, larger values (by ca. 7–8 h) were determined for HPMC (either K15M or K100M) as compared to HPC, the highest values having been obtained for K100M (Fig. 7).

3.4.1. Kinetic mechanism

The drug release mechanism from swellable matrices is complex and not yet completely understood. Although some processes may be classified as either purely diffusional or purely erosion controlled, many others can only be interpreted as being governed by both. The analysis of experimental data in the light of the Korsmeyer–Peppas equation (7), as well as the interpretation of the corresponding release exponent values (n), leads to a better understanding of the balance between these mechanisms.

This kind of analysis was performed for all the formulations under study, with the exception of F1 and F2 once, in these cases, more than 70% of the drug was already released during the first hour of the experiment (Figs. 5 and 6).

For F3 and F4 formulations, n was determined to be equal to 0.816 and 0.842, respectively (Table 4). Notwithstanding these values pointing to an anomalous (non-Fickian) diffusional mechanism, both Higuchi's model (Fickian) and first-order kinetics yielded similarly good quality adjustments. High values of K_{KP} found for these formulations (Table 4), in turn, suggest the possibility of occurrence of a burst effect for the HPC-containing matrices. Moreover, it is also known that HPC may yield mesophases [44], which certainly influence the kinetic behaviour of this polymer.

For HPMC-containing formulations, F5–F8, the diffusional exponent value (n) ranged from 0.621 to 0.671 (Table 4), indicating that the release mechanism of ketoprofen from these matrices is an anomalous (non-Fickian) transport, which suggests that both diffusion of the drug in the hydrated matrix and its own erosion modulate drug release. For these systems, the first-order kinetic model yielded remarkably good adjustment ($R^2 > 0.999$). These results are in agreement with those reported by Rodriguez et al. [45].

4. Conclusions

From the DSC thermograms alone, it is possible to conclude that the selected excipients are likely to be suitable for the preparation of tablet formulations, since no significative incompatibilities were detected. In fact, even when drug:excipient interactions were detected, they were not found to affect the drug bioavailability. The swelling experiments, in turn, showed that the water uptake increases with the polymer viscosity, which is a rather important factor to consider when preparing hydrophilic matrix tablets. According to the release studies, polymers MC25 and HPC are not appropriate for the preparation of modified ketoprofen hydrophilic matrix tablets, in the conditions under study, while HPMC K15M and K100M may be advantageous. On the other hand, despite no substantial differences were found when lactose or β-CD was used as diluents, it must be emphasised that for β-CD a slight decrease on the dissolution of the tablets was observed, probably due to the occurrence of an inclusion process between the ketoprofen and the cyclodextrin.

The release mechanism of ketoprofen from each formulation tested was evaluated in the light of zero-order, first-order, Higuchi's and Korsmeyer–Peppas kinetic models. Non-Fickian (anomalous) transport was observed for all cellulose ethers. Neither the effect of cellulose substitution nor the type of diluent was determined to have a significant impact on the release mechanism of ketoprofen from the hydrophilic matrix tablets investigated.

The present results provide useful information on the type of polymers and additives that should be employed on the formulation of hydrophilic matrix tablets, namely of those containing ketoprofen or similar drugs.

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