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# Role of Cellulose Ether Polymers on Ibuprofen Release from Matrix Tablets

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**ABSTRACT** Cellulose derivatives are the most frequently used polymers in formulations of pharmaceutical products for controlled drug delivery. The main aim of the present work was to evaluate the effect of different cellulose substitutions on the release rate of ibuprofen (IBP) from hydrophilic matrix tablets. Thus, the release mechanism of IBP with methylcellulose (MC25), hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC K15M or K100M) was studied. In addition, the influence of the diluents lactose monohydrate (LAC) and β-cyclodextrin (β-CD) was evaluated. Distinct test formulations were prepared containing: 57.14% of IBP, 20.00% of polymer, 20.29% of diluent, 1.71% of talc lubricants, and 0.86% of magnesium stearate as lubricants. Although non-negligible drug-excipient interactions were detected from DSC studies, these were found not to constitute an incompatibility effect. Tablets were examined for their drug content, weight uniformity, hardness, thickness, tensile strength, friability, porosity, swelling, and dissolution performance. Polymers MC25 and HPC were found to be unsuitable for the preparation of this kind of solid dosage form, while HPMC K15M and K100M showed to be advantageous. Dissolution parameters such as the area under the dissolution curve (AUC), the dissolution efficiency ($DE_{20\ h}$), dissolution time (t 50%), and mean dissolution time (MDT) were calculated for all the formulations, and the highest MDT values were obtained with HPMC indicating that a higher value of MDT signifies a higher drug retarding ability of the polymer and vice-versa. The analysis of the drug release data was performed in the light of distinct kinetic mathematical models—Kosmeyer-Peppas, Higuchi, zero-, and first-order. The release process was also found to be slightly influenced by the kind of diluent used.

**KEYWORDS** Ibuprofen, Cellulose ether polymers, Drug release, Hydrophilic matrix tablets, Release mechanism

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## INTRODUCTION

Numerous types of polymers are currently employed to control the drug release from the pharmaceutical dosage forms. Among these compounds, cellulose ethers are often used in tablet formulations since most display good compression characteristics, even when directly compressed, and have adequate swelling properties that lead to a rapid formation of an external gel layer, allowing drug release modification. Furthermore, hydroxypropylmethylcellulose (HPMC), for instance, is commonly used in the development of modified release formulations on account of its properties, namely its nontoxic nature, its ability to accommodate a large percentage of drug, and its non-pH dependence (Rodriguez et al., 2000; Siepmann et al., 1999; Sung et al., 1996). These characteristics are in accordance with the main requirements of a modern pharmaceutical excipient, recently proposed by Pifferi and Restani (2003).

Several studies on the use of HPMC are found in the literature. It has been demonstrated that the viscosity grade of the polymer is a determinant of the rate of polymer hydration, taken into account the percentage of hydrophobic (methoxyl) and hydrophilic (hydroxypropoxyl) substitutions (Bettini et al., 1994; Ranga Rao et al., 1988). Rajabi-Siahboomi (1998) in turn, reported that the degree of methoxy and hydroxypropoxyl substitution influences the water mobility, and therefore the drug release process from these matrices. The effect of HPMC on the release of sodium diclofenac from matrix tablets was investigated by other authors (Velasco et al., 1999), who concluded that the most important factor affecting the rate of the release process was the drug/HPMC ratio: an increase in polymer concentration was found to lead to an increase in the gel viscosity, as well as the formation of a gel layer with a longer diffusional path, which could result in a decrease on the effective diffusion coefficient of the drug and hence, in a reduction in the drug release rate. Moreover, this study reported that drug and HPMC particle size also influence the drug release parameters, although to a lesser extent. The influence of technological variables on release modulation of theophylline from matrices was also investigated (Pina & Veiga, 2000; Veiga et al., 1997). More recently, (Salsa et al. 2003) studied the effect of HPMC K15M hydration on the kinetic release of ibuprofen and ketoprofen from matrix tablets, concluding that most of the hydration water is retained by the polymer, which pointed to the occurrence of different types of hydration water.

It is well known that other cellulose ether polymers such as methylcellulose (Alvarez-Lorenzo et al., 2000; Mitchell et al., 1993a, 1993b; Panomsuk et al., 1995) or hydroxypropylcellulose (HPC) (Alvarez-Lorenzo et al., 2000; Panomsuk et al., 1995) are not currently used to control drug release from pharmaceutical systems, because of their low swelling capacity. However, it is important to clarify the role these formulations may have on the drug release process, namely in association with HPMC (Ebube & Jones, 2004).

In this work, a poorly water-soluble drug was chosen. Ibuprofen (IBP) [2-(4-isobutylphenyl) propionic acid] belongs to the arylpropionic acids family, which is a class of nonsteroidal anti-inflammatory drugs (NSAIDs) widely employed in the treatment of arthropathies due to their high anti-inflammatory and analgesic activity. When this drug is administered as a conventional dosage form, it displays a very short half-life (2 to 4 hours) (Martindale, 1999). These properties have justified its selection as a model drug for the present study.

The aim of this investigation was to study the role of the referred cellulose polymers on modified pharmaceutical solid dosage formulations and drug release kinetics (by fitting to several models, either zero-order, first-order, or Higuchi and Korsmeyer-Peppas). IBP was used as a model drug. In addition, the influence of the diluent on the drug release from matrix tablets was also assessed.

## MATERIALS AND METHODS

### Materials

Ibuprofen (IBP) (batch no. 9907257) was purchased from Knoll, Nottingham, England. Polymers: methylcellulose, Methocel® MC25 (batch no. MFCD00081763), Fluka, Switzerland; hydroxypropylcellulose, HPC (batch no. 8174), Klucel, HF, USA; hydroxypropylmethylcellulose, Methocel® K15M (batch no. OG20012N31) and Methocel® K100M (batch no. OB12012N11), Colorcon, England. Diluents: β-cyclodextrin (β-CD), Kleptose®, Roquette, Lestrem, France; lactose monohydrate

(LAC), Granulac® 200, Meggle, Wasserburg, Germany. Talc and magnesium stearate (analytical grade).

## Differential Scanning Calorimetry Measurements

Differential scanning calorimetry (DSC) measurements were performed using a Shimadzu DSC-50 with a thermal analyser (Shimadzu TA-50, Tokyo, Japan). About 2.5 mg of either pure drug or pure excipient, or 5 mg of the drug/excipient (1:1 w/w) mixture were analyzed in sealed aluminium pans under nitrogen flow (20 mL/min), at a heating rate of 10°C/min, from 25 to 250°C, an empty sealed pan being used as reference. The equipment was calibrated with indium (99.98%, m.p. 156.65°C, Aldrich®, Milwaukee, WI).

## Preparation of Matrix Tablets

The distinct formulations of the matrix tablets are provided in Table 1. The tablets were prepared containing 57.14% of drug (IBP), 20.00% of polymer (MC25, HPC, HPMC K15M, or HPMC K100M), 20.29% of diluent (lactose or β-cyclodextrin), 1.71% of talc, and 0.86% of magnesium sterate as lubricants. The drug, polymer, and diluent were passed through a 100-μm sieve and thoroughly mixed in a plastic bag for 10 min. Talc and magnesium stearate were sieved through a 500-μm sieve, added to the previous mix, and blended again for 5 min. 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.

## Characterization of the Matrix Tablets

### *Assay of IBP Tablets*

For each formulation tested, five randomly chosen tablets were thinly minced in a mortar and 17.5 mg of the resulting powder was solubilized in phosphate buffer (pH 7.2, USP25) (The United States Pharmacopeia 25/The National Formulary 20, 2002), up to a final volume of 100 mL. Several aliquots were then filtered and assayed spectrophotometrically at 264 nm, in a Shimadzu UV-1603 spectrophotometer. Each measurement was carried out in triplicate and the results were averaged. A blank solution (containing all the components with the exception of the drug) was used, which yielded no interferences.

### *Weight, Hardness, and Thickness*

A total of 20 tablets of each formulation were evaluated for weight uniformity (analytical balance KERN 770). For each formulation, the hardness of 10 tablets was examined using an Erweka hardness tester TBH28 in a diametric direction. The results were given by the mean value and are expressed in Newtons (N).

The thickness was determined using a micrometer (Roche, Switzerland). Ten individual tablets of each formulation were used per experiment. The results are expressed as mean values±standard deviation.

**TABLE 1** Matrix Tablets Composition (mg)

| | Formulation | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Component | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| IBP | 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-cyclodextrin | – | 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 |

### 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), according to the following equation:

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

where $P$ is the applied load, and $D$ and $t$ represent the diameter and thickness of the tablet, respectively (Fell & Newton, 1970).

### Friability

Twenty tablets were weighed and placed into a friabilator (Erweka TA20). The tablets underwent 25 rotations per minute for 4 minutes and were then reweighed. 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.

### Tablets' Porosity Determination

The percent porosity of the tablets was calculated using Eq. 3, according to Schreiner et al. (2005).

$$\varepsilon(\%) = \left(1 - \frac{pa}{pt}\right) \times 100 \quad (3)$$

where $\varepsilon$ is the percent of porosity, $pa$ is the apparent density, and $pt$ is the true density. The true density of the tablet was measured by means of a helium pycnometer (AccuPyc TM-1330, England) as the test gas. The apparent density of the tablet was calculated using the dimensions, and the mass of 10 tablets was determined with a micrometer (Roche, Switzerland) and an analytical balance KERN 770. All measurements were performed in triplicate, for 10 tablets of each formulation.

## Polymer Swelling or Water Uptake Studies

Water uptake studies were carried out for all formulations. Three metallic baskets were weighed with a matrix tablet of each formulation, and placed into 1000 mL of phosphate buffer pH=7.2 at 37.0°±0.5°C. At hourly intervals, the previously weighed baskets containing the tablet were removed, gently wiped with a tissue to remove surface water, reweighed, and then placed back into the vessel as quickly as possible. The mean weights were determined for each formulation, and the percent of water uptake, i.e., the degree of the swelling ($S$) due to absorbed test liquid, was calculated at each time point according to the relationship (Efentakis et al., 1997).

$$S = \frac{W_s - W_d}{W_d} \times 100 \quad (4)$$

where $W_d$ and $W_s$ are the dry and swollen matrix weights, respectively, at immersion time ($t$) in the buffer. The polymer swelling degree or water uptake data are the mean of three determinations.

## Drug Release Analysis

Dissolution studies were carried out according to the USP 25 paddle method (The United States Pharmacopeia 25/The National Formulary 20, 2002). 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. Six vessel dissolution apparatus (Vankel VK 7000 dissolution testing station), in-line with a closed flow-through system using a peristaltic pump, connected to a spectrophotometer (Shimadzu UV-1603), were used for this purpose. Six different tablets were tested. Progress of the dissolution was monitored by withdrawing filtered samples every 5 min, for a total of 1200 min. The amount of IBP present in each sample was determined spectrophotometrically, at $\lambda$=264 nm. The corresponding drug-release profiles were represented through plots of the cumulative percentage of drug release (calculated from the total amount of IBP contained in each matrix) vs. time.

## Kinetic Mechanism

Several mathematical models can be used to describe the kinetic behavior of the drug release mechanism from matrix tablets, the most suitable being the one that best fits the experimental results. The choice of a specific model for a particular data set

depends on the shape of the plot obtained, as well as on the underlying mechanism.

The kinetics of IBP release from hydrophilic cellulose matrix tablets was determined by finding the best fitting of the dissolution data (amount of drug released vs. time) to distinct models: zero-order (5), first-order (6), and Higuchi (7) (Higuchi, 1961, 1963).

$$Q_t = Q_0 + k_0 t \tag{5}$$

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

$$Q_t = Q_\infty (1 - e^{-k_1 t}) \tag{6}$$

$Q_\infty$ being the total amount of drug in the matrix and $k_1$ is the first-order kinetic constant.

$$Q_t = k_H t^{1/2} \tag{7}$$

$k_H$ representing the Higuchi rate constant.

Moreover, to better characterize the drug release behavior for the polymeric systems under study, and particularly to gain some insight on the corresponding mechanism, the Korsmeyer-Peppas (8) semi-empirical model was applied (Korsmeyer et al., 1983).

$$Q_t/Q_\infty = kt^n \tag{8}$$

where $Q_t/Q_\infty$ is the fraction of drug released at time $t$, $k$ is a constant comprising the structural and geometric characteristics of the tablet, and $n$, the release exponent, is a parameter that depends on and is used to characterize the release mechanism (Peppas, 1985). For the case of cylindrical tablets (Ritger & Peppas, 1987), in particular, $n$=0.45 corresponds to a Fickian diffusion release (case I diffusional), 0.45<n=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.

The direct fitting of the drug release data to the nonlinear equations mentioned above is usually avoided through linear transformation of the data, followed by a linear regression analysis. However, this method may not be mathematically accurate, once it uses transformed values (logarithms) instead of the original data (Lu et al., 1996). Consequently, a direct nonlinear fitting of the experimental results was performed in the present work, for each of the mathematical models considered (through the minimization of the sum of the squared residuals). Only the points comprised in the interval $0.1 < Q_t/Q_\infty < 0.7$ were used.

## Mean Dissolution Time

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

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta Q_j}{\sum_{j=1}^{n} \Delta Q_j} \tag{9}$$

where $j$ is the sample number, $n$ is the number of dissolution sample times, $\hat{t}_j$ is the time at midpoint between $t_j$ and $t_{j-1}$, and $\Delta Q_j$ is the additional amount of drug dissolved between $t_j$ and $t_{j-1}$.

## Dissolution Efficiency

The dissolution efficiency (*DE*) is defined as the relation between the area under the dissolution curve (AUC) of dissolved percentage as a time function at an observed time and the area of a rectangle that represents 100% dissolved at the same time, and is calculated by the following equation (Khan, 1975; Khan & Rhodes, 1972):

$$D.E = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100 \tag{10}$$

where $y$ is the drug percent dissolved at time $t$.

## Statistics

In order to assess statistical significance among the data, one-way analysis of variance (ANOVA) was used to test variation in tablet formulations containing different polymers (MC25, HPC, HPMC K15M, and HPMC K100M) at the same % w/w and in the same dissolution media. ANOVA was utilized as well as to test differences in the physical characterization of the matrix tablets. The difference between variants was considered significant if $p<0.05$, followed by Bonferroni comparison t-test. The statistical work was done using Sigma Stat® for Windows version 2.03 software, 1992–1997 SPSS Inc.

## RESULTS AND DISCUSSION

### DSC

Excipients constitute the major component, in weight, of matrix tablets and they contain reactive functional groups that may give rise to chemical and physical transformations. Thus, when studying new pharmaceutical formulations, it is important to determine the possibility of occurrence of incompatibilities between the components of the tablet. The interactions between IBP and distinct polymer or diluents (50% mixtures) were then investigated along this work, by differential scanning calorimetry (DSC). A 1:1 (w/w) drug:excipient ratio was chosen, once it was known to maximize the likelihood of observing intermolecular interactions (Mura et al., 1995). DSC thermograms of free drug and excipients, as well as of the 1:1 mixtures, are presented in Figs. 1, 2. The thermal curve of IBP displays a single sharp endothermic peak at 75°C, corresponding to its melting point (Higginis et al., 2001). Polymers MC25, HPC, HPMC K15M, and HPMC K100M exhibit a large broad endothermic effect over a temperature range of 60° to 140°C, which may be due to water loss. In fact, previous studies on cellulose reported the occurrence of endotherms above 100°C, which were attributed to dehydration (Ford, 1999; Mcphillips et al., 1999).

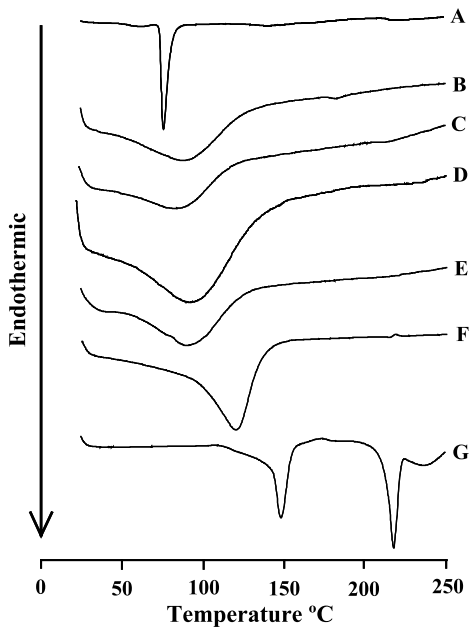


**FIGURE 1** DSC Curves for Ibuprofen and the Different Excipients Studied: IBP (A), MC25 (B), HPC (C), HPMC K15M (D), HPMC K100M (E), β-CD (F), and Lactose (G).

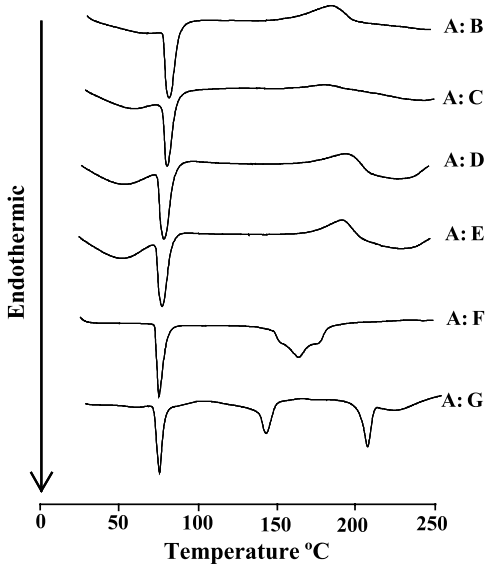


**FIGURE 2** DSC Curves for Ibuprofen and 1:1 (*w/w*) Mixtures of IBP with: MC25 (A:B), HPC (A:C), HPMC K15M (A:D), HPMC K100M (A:E), β-CD (A:F), and Lactose (A:G).

The thermograms obtained for the IBP mixtures showed that the glass transition values (Tg) measured for each of the cellulose ethers studied were clearly distinguishable (Fig. 2), and occurred over a wide temperature range, in accordance with Wade and Weller (1994). Moreover, these thermograms were found not to be a simple superposition of the ones obtained for each component separately. In fact, 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 a loosening of the water-polymer binding strength, due to a certain competition from the drug ionizable groups (e.g., carboxylates).

The DSC trace of β-CD (Fig. 1) shows a broad endothermic effect, which attained a maximum around 130°C, corresponding to a dehydration process (Mura et al., 1998). A second, very weak effect was also observed near 220°C and was assigned to a phase transition. The combination of IBP and β-CD, in turn, exhibited the typical drug melting point, but the signal corresponding to the dehydration process of β-CD was increased by ca. 50°C relative to the free cyclodextrin. Interestingly enough, this behavior is opposite to the one observed for the cellulosic polymers, and is most probably due to the hydrophobicity of IBP, which may affect the normal dehydration process of β-CD (hindering the loss of water

molecules). In fact, studies on water/β-CD interactions, performed by Steiner et al. (Steiner & Koellner, 1994; Steiner et al., 1995), concluded that water absorbed by β-CD is largely "free" and the water exchange process follows a first order kinetics. Since no other thermal event occurred, these kinds of drug/β-CD interactions do not necessarily lead to incompatibility (Nokhodchi et al., 1996).

Lactose thermogram demonstrated two sharp endothermic peaks at 147°C and 219°C (Fig. 1). When this diluent was mixed with the drug in a 1:1 ratio (w/w), the IBP endothermic peak remained unchanged, yet some downward shift coupled with broadening of the excipient melting peak were detected (Fig. 2). Even though 1:1 is not the anticipated ratio for the final dosage form, the results now obtained (no extra thermal events were found in the corresponding thermograms) allow us to conclude that no incompatibility is present between IBP and lactose.

## Characterization of the Matrix Tablets

Evaluation of the matrix tablets yielded a drug content ranging from 99.22% to 100.41% of the desired amount, which evidences an even quantity of drug in all formulations (Table 2). The differences in the mean values among the treatment groups are not great enough to exclude the possibility that the difference is due to random sampling variability; there is not a statistically significant difference ($F=1.23$; $P>0.05$).

The physical characteristic of the IBP mixtures—namely its homogeneity—allows the preparation of tablets with uniform weight (350 mg target, Table 2), as indicated by the very low relative standard deviation (RSD $<0.4\%$ in all formulations). ANOVA revealed that uniform weight of all formulations were different in the mean values among the treatment groups and are a little greater than would be expected by chance; there is a statistically significant difference ($F=28.66$; $P<0.05$). The hardness of the different formulations studied was within the range 62 N to 107 N ($F=2504.39$; $P<0.05$), corresponding to obvious variations in the tablet tensile strength from 1.02 MPa to 1.81 MPa ($F=1709.50$; $P<0.05$). The thickness of the tablets (Table 2) was found in the range of 3.77 mm to 3.88 mm ($F=10.18$; $P<0.05$), a statistical difference that may be influenced by the properties of each polymer. The tablets also passed the friability test (F $<1\%$), showing that all formulations lie within the USP 25 limits (Table 2).

Porosity represents a measure of the amount of air present in the tablets, which is responsible for their floating properties, and is related to the compression force used during their preparation (Baumgartner et al., 1998; Nokhodchi et al., 1996). The porosity percentage of the hydrophilic formulations with lactose as a diluent was found to be slightly greater than that of the tablets containing β-CD (Table 2). Bi et al. (1999) suggested that when the tablet porosity is very high, significant water absorption occurs and tablets are easily disrupted. On the other hand, for a moderate tablet porosity, disintegration will be mainly determined by the characteristics of the excipient. Despite the small porosity differences between the hydrophilic matrix tablets presently studied (Table 2), these were found to influence both the water uptake and the drug release mechanism, as will be discussed later.

**TABLE 2** **Physical Characterization of IBP Hydrophilic Matrix Tablets**[a]

| Formulation | Weight (mg) n=20 | Weight RSD (%) | Hardness (N) n=10 | Thickness (mm) n=10 | Tensile strength (MPa) n=10 | Friability (%) n=20 | Porosity (%) n=10 | Drug content (mg) n=3 |
|---|---|---|---|---|---|---|---|---|
| F1 | 348.52 (1.10) | 0.32 | 107.23 (0.98) | 3.77 (0.03) | 1.810 (0.021) | 0.95 | 6.1 | 200.82 (0.22) |
| F2 | 349.92 (1.06) | 0.30 | 105.23 (1.23) | 3.79 (0.02) | 1.768 (0.024) | 0.98 | 4.8 | 198.64 (0.34) |
| F3 | 348.61 (0.59) | 0.17 | 71.62 (0.84) | 3.86 (0.06) | 1.181 (0.024) | 0.59 | 9.5 | 198.62 (0.93) |
| F4 | 348.25 (1.26) | 0.36 | 62.12 (1.20) | 3.88 (0.03) | 1.019 (0.024) | 0.76 | 6.6 | 198.43 (1.31) |
| F5 | 348.85 (0.89) | 0.25 | 90.43 (1.08) | 3.83 (0.03) | 1.505 (0.024) | 0.90 | 7.8 | 198.57 (1.78) |
| F6 | 351.12 (0.81) | 0.23 | 68.32 (0.95) | 3.85 (0.05) | 1.130 (0.026) | 0.97 | 5.9 | 199.90 (2.64) |
| F7 | 349.62 (1.19) | 0.34 | 87.52 (1.27) | 3.81 (0.02) | 1.463 (0.027) | 0.83 | 7.0 | 198.96 (1.14) |
| F8 | 351.40 (1.00) | 0.28 | 69.72 (1.16) | 3.83 (0.03) | 1.159 (0.016) | 0.92 | 5.4 | 199.82 (0.51) |

[a]In parenthesis: standard deviation; n is the number of measurements.

## Polymer Swelling or Water Uptake Studies

Polymeric substances are known to play an important role on the rate of penetrant entry into the matrix tablets. The penetrant uptake measurement or swelling rate, and thus the formation of a continuous gel layer (through which the drug release process occurs), was found to be strongly influenced by the type, amount, hydration speed, and viscosity grade of the polymer. In fact, for a higher polymer concentration per unit area the resultant gel layer is rendered more viscous and consequently more resistant to erosion. Moreover, the hydration process of the polymer must be fast enough to allow the formation of the gel layer, in order to avoid matrix disintegration.

In the present work, polymer swelling or water uptake studies were carried out in order to investigate the effect of the distinct formulations on the swelling process. When a matrix is immersed in a dissolution medium, wetting occurs, first at the surface and then progressing into the matrix. The profiles of the liquid penetration rate into the matrix tablets have been studied by Wan et al. (1991, 1993, 1995), and their results indicate that compacts containing HPMC of higher molecular weights show a greater liquid uptake: the polymer surface swells to form a continuous gel layer and the matrix size increases.

The results of the swelling studies are gathered in Figs. 3 and 4. For matrices containing MC25 or HPC, the amount of water uptake, and consequently the degree of swelling, was found to be lower than for formulations with HPMC K15M or HPMC K100M.

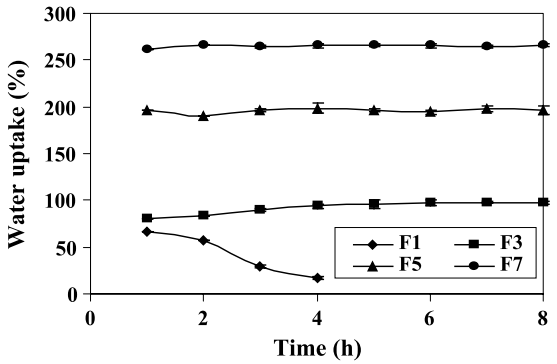


**FIGURE 3** Graphic Representation of the Water Uptake vs. Time, for Several Lactose-Containing Formulations ($F = 761.86$; $P < 0.05$).

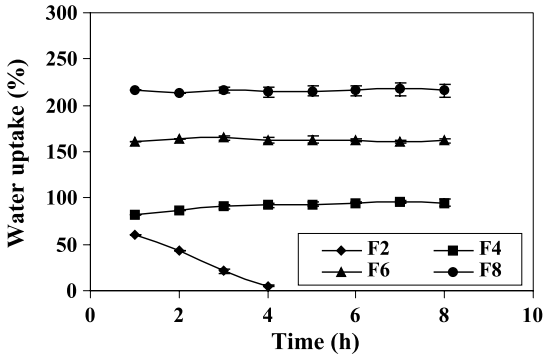


**FIGURE 4** Graphic Representation of the Water Uptake vs. Time, for Several β-Cyclodextrin-Containing Formulations ($F = 478.03$; $P < 0.05$).

In the case of MC25 these findings may be explained by the absence of hydroxypropoxyl groups in its structure, which render this polymer less hydrophilic. Moreover, at about 1 hour after the start of the experiment a gradual disintegration of the MC25-containing tablet is clearly evident (Figs. 3 and 4). This is suggested to occur on account of the very small number of hydroxyl groups, prone to interact with water molecules—consequently, few hydrogen bonds occur, and no gel-type structures are formed, as opposed to what was verified for all the other matrices studied (containing either HPC or HPMC). In fact, few water molecules are entrapped in the MC25 compared to the other polymers investigated (Kumar & Banker, 1993).

Formulations containing HPC evidenced a lower hydration level even for long water exposures (Figs. 3 and 4). Roy and Rodera (2002) calculated the corresponding swelling kinetic constant (k=2.47), according to the Vergnaud model (1993), and suggested that this low value could be explained by the absence of a burst effect in the polymer swelling process. The results presently obtained are in complete accordance with the ones reported by these authors, despite the use of different formulations and preparation conditions (e.g., HPC/IBP formulations did not show further hydration after 6 hours). However, the assumption of a steady swelling kinetic behavior for HPC matrices cannot be drawn, since previous studies on different drugs, using identical formulations, evidenced a clear dependence on the drug: for HPC/ketoprofen systems, for instance, a much faster water uptake was observed, the kinetic plateau being detected already 1 h after the start of the experiment (Vueba et al., 2004).

The amount of swelling obtained for the formulations containing both HPMC K15M and HPMC K100M attained its maximum hydration degree during the first hour, which was found not to change from this time on. The high degree of swelling of these formulations was attributed to the presence of the hydroxypropoxyl groups, which renders them more hydrophilic than MC25 or HPC—more water molecules are entrapped into HPMC matrices, resulting in a higher hydration and a gel-type structure. These results are in accordance with previously reported studies on polymer viscosity (Cheong et al., 1992), which concluded that the high viscosity grades of HPMC (e.g., HPMC K100M) are explained by the presence of the substituent groups that, through interaction with water molecules, lead to an increased swelling.

Furthermore, an interesting water uptake dependence on the diluent was detected. In fact, HPMC/β-cyclodextrin containing matrices evidence a lower swelling degree when compared to the HPMC/lactose ones (Figs. 3 and 4). This may be explained (among other factors) by the different porosity characteristics of the tablets (Table 2): higher values (lactose formulations) corresponding to an increase in water uptake. However, it should also be emphasized that an opposite behavior is detected when the polymer viscosity is raised—from HPMC K15M to K100M, i.e., either from F5 to F7 or from F6 to F8: a decrease in the porosity value (Table 2) corresponds to higher swelling percentages.

## Drug Release Analysis

The release profiles of IBP from matrix tablets containing the various types of hydrophilic cellulose polymers are given in Figs. 5 and 6. The type of polymer and its viscosity grade was found to have a marked effect on the drug release process, and statistical differences in the mean values among the treatment release profiles were found as expected.

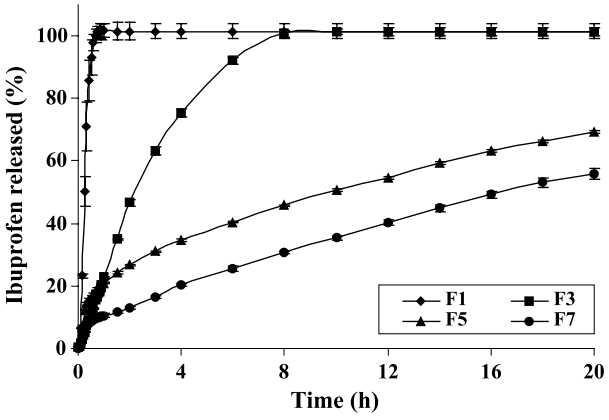


**FIGURE 5** Drug Release Profiles for Lactose-Containing Formulations ($F = 24.98$; $P < 0.05$).

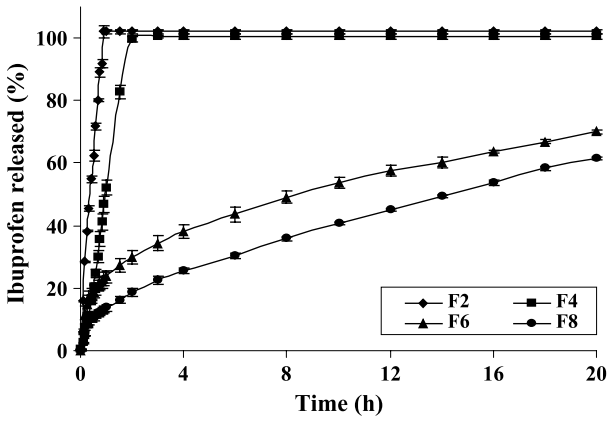


**FIGURE 6** Drug Release Profiles for β-Cyclodextrin-Containing Formulations ($F = 22.97$; $P < 0.05$).

For those formulations with MC25 (F1 and F2), a total release of the drug was observed in about 1 hour, due to tablet disintegration. On the other hand, HPC containing formulations (F3 and F4) evidenced an interesting release behavior, strongly dependent on the diluent—either lactose or β-CD. Actually, completely different release profiles were obtained for each one of these diluents: while a clear interaction was detected for lactose, hardly any interaction was evidenced for β-CD (Figs. 5 and 6). No interaction was observed with β-CD—the release was completed in ca. 2 hours (Fig. 6). However, previous studies carried out for identical formulations with ketoprofen have yielded similar results in the case of lactose, as opposed to the β-CD-containing matrices—probably an inclusion type one occurred, such as is demonstrated in Fig. 7

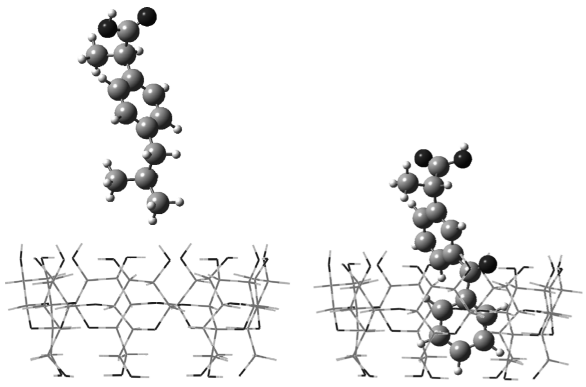

**FIGURE 7** Schematic Representation of: IBP and β-Cyclodextrin (A); Ketoprofen:β-Cyclodextrin Inclusion Complex (B).

**TABLE 3** Dissolution Parameters for the IBP Matrix Tablets[a]

| Assay | MDT (h) | $t_{50\%}$ (h) | AUC | DE (%) | $P_{20\ h}$ (%)[b] |
|---|---|---|---|---|---|
| F3 | 1.84±0.02 | 2.18 | 1750.84 | 87.55±0.70 | 101.36±1.20 |
| F4 | 0.84±0.01 | 0.97 | 1912.89 | 95.64±0.95 | 100.31±0.92 |
| F5 | 7.36±0.04 | 9.45 | 965.76 | 48.29±0.35 | 68.38±0.55 |
| F6 | 6.81±0.13 | 8.19 | 1010.98 | 50.55±1.25 | 70.02±1.29 |
| F7 | 9.36±0.02 | 16.59 | 686.91 | 34.35±0.83 | 55.89±1.82 |
| F8 | 8.66±0.13 | 14.11 | 783.93 | 39.20±0.67 | 61.48±1.02 |

[a]Mean ± standard variation (six measurements).
[b]$P_{20\ h}$ = percentage of IBP dissolved at 20 hours.

(Monti et al., 1998). This may be explained in terms of the structural characteristics of these drugs, which affect the inclusion mechanism in the solid state: in fact, once inclusion in the β-CD cavity is known to take place preferentially through the aromatic moiety of the guest molecule (Amado & Ribeiro-Claro, 2000; Monti et al., 1998), this process is prone to occur for ketoprofen, but not for IBP, which contains a bulky isobutyl ring parasubstituent group that may hinder the inclusion process (Fig. 7). Indeed, an inclusion complex displaying a 2:1 host:guest stoichiometry was recently prepared trough the reaction of β-CD with aqueous IBP (Braga et al., 2003)—it was verified that the corresponding crystal structure consisted of a head-to-head β-CD dimer with the IBP propionyl residue located at the interdimeric region.

For matrices containing HPMC K15M and K100M (F5-F8), the results showed that the drug release was influenced by the viscosity grade (Figs. 5 and 6). Drug release was slower for the HPMC polymer due to an increased gel layer viscosity, which results in a higher resistance to both dissolution and erosion (Alderman, 1984). On the other hand, these formulations were found not to allow a complete release of IBP from the matrix: after 20 hours, only up to 60–70% was released from HPMC K15M, while 56–62% was released from HPMC K100M.

Previously reported studies allowed to conclude that the presence of cyclodextrins in HPMC containing delivery systems can also influence the drug-release mechanism (Alderman, 1984). These observations are corroborated by the results presently obtained when using β-CD as a diluent: the release profiles were found to be only slightly faster than those yielded by lactose-containing matrices, despite the significant swelling and porosity decrease caused by the change in diluent (from lactose to β-CD).

These findings are supported by the MDT calculated values (Table 3). In fact, this parameter may be used to characterize both the drug release process and the retarding efficacy of the polymer—a higher value of MDT indicates a higher drug retarding ability of the polymer ($F = 4467.71$; $P < 0.05$). Dissolution efficiency (DE) is a dissolution parameter widely used as a significant index of drug dissolution performance. Actually, differences were detected between the four calculated dissolution parameters ($F = 5709.96$; $P < 0.05$) (Table 3). In effect, the dissolution efficiency and the area under the curve (AUC) increased with formulations with β-CD, as opposed to MDT and t50%, whose values were found to be decreased.

## Kinetic Mechanism

IBP (pKa = 4.4) has a very poor solubility in water and aqueous acidic conditions, which gradually increases when the pH is raised above 6, the drug becoming freely soluble for pH > 7 (Bibby et al., 2000). In the present work, the experimental conditions were established for a pH = 7.2 phosphate buffer solution, used as the dissolution medium. Thus, both diffusion and erosion could contribute to the drug release process from the matrix tablets. In fact, it is well known that in polymeric swellable hydrophilic matrices similar to the ones considered, water-soluble drugs are released mainly by diffusion across the gel layer, while barely water-soluble drugs are predominantly released by attrition mechanisms (Ghosh et al., 1998).

The mechanism of release from swellable matrix systems is complex and is not completely understood. Even if some processes could be characterized as either purely diffusional or purely erosion controlled, several others could only be rationalized as being due to a

**TABLE 4** Results of Fitting the IBP Release Data for Several Formulations to Different Kinetic Equations[a]

| | Zero order | | First order | | Higuchi | | Korsmeyer-Peppas | | |
|---|---|---|---|---|---|---|---|---|---|
| Formulation | $K_0$ (% $h^{-1}$) | $R^2$ | $K_1$ ($h^{-1}$) | $R^2$ | $K_H$ (% $h^{-1/2}$) | $R^2$ | $K_{KP}$ ($h^{-n}$) | $n$ | $R^2$ |
| F3 | 19.801 | 0.9846 | 0.433 | 0.9946 | 53.480 | **0.9965** | 25.505 | 0.865 | 0.9905 |
| | (0.519) | (0.0031) | (0.029) | (0.0003) | (1.470) | (0.0005) | (0.638) | (0.003) | (0.0023) |
| F4 | 61.729 | **0.9991** | 1.191 | 0.9721 | 107.786 | 0.9897 | 51.721 | 1.242 | 0.9975 |
| | (1.505) | (0.0001) | (0.015) | (0.0010) | (2.675) | (0.0009) | (2.084) | (0.027) | (0.0003) |
| F5 | 2.513 | 0.9690 | 0.036 | 0.9903 | 14.060 | **0.9990** | 19.335 | 0.423 | 0.9970 |
| | (0.031) | (0.0005) | (0.001) | (0.0005) | (0.174) | (0.0001) | (0.314) | (0.006) | (0.0002) |
| F6 | 2.534 | 0.9606 | 0.037 | 0.9858 | 14.207 | **0.9987** | 20.153 | 0.415 | 0.9976 |
| | (0.066) | (0.0054) | (0.001) | (0.0020) | (0.133) | (0.0003) | (0.317) | (0.005) | (0.0008) |
| F7 | 2.424 | 0.9926 | 0.034 | **0.9991** | 14.097 | 0.9923 | 8.056 | 0.650 | 0.9982 |
| | (0.119) | (0.0010) | (0.002) | (0.0002) | (0.683) | (0.0008) | (0.399) | (0.024) | (0.0002) |
| F8 | 2.506 | 0.9903 | 0.035 | **0.9982** | 14.070 | 0.9930 | 11.081 | 0.567 | 0.9965 |
| | (0.022) | (0.0019) | (0.001) | (0.0003) | (0.104) | (0.0013) | (0.183) | (0.004) | (0.0009) |

$R^2$ is the coefficient of determination; best results in bold.
[a]Values in parenthesis mean standard deviation.

coupling of both. The use of the Korsmeyer-Peppas equation (8), and particularly the interpretation of the release exponent values ($n$), allows to get insight into the balance between these mechanisms.

This kind of analysis was carried out for all the formulations studied except for F1 and F2 due to their extremely fast drug release kinetics (Figs. 5 and 6).

For both F3 and F4 formulations, $n$ was determined to be equal to 0.865 and 1.242, respectively (Table 4). These values confirm the previously mentioned dependence of IBP release mechanism on the diluent, for HPC containing matrices. Nevertheless, for these systems some contradictory fitting results were obtained: for F3, although $n$=0.865 pointed to an anomalous (non-Fickian) diffusional mechanism, Higuchi's model (Fickian) yielded a rather good adjustment ($R^2$=0.9965). For F4, in turn, the release exponent value (1.242) indicates a super-Case II transport; however, zero-order kinetics also led to a remarkably good fitting ($R^2$=0.9991). These discrepancies are probably due to a burst drug release from the matrices, which is suggested by the high values of $K_{KP}$ found for these formulations (Table 4). The fact that HPC is known to form mesophases (Vazquez et al., 1992) may also be responsible for this unorthodox behavior.

The diffusional exponent value ($n$) found for both F5 and F6 matrices ranged from 0.415 to 0.423, indicating a Fickian diffusion-type release mechanism for IBP from the HPMC K15M containing formulations now investigated. These results are largely corroborated by the good fitting obtained with Higuchi's model (Table 4).

In turn, for F7 and F8—HPMC K100M formulations—$n$ was equal to 0.650 and 0.550, respectively (Table 4), which evidences a coupling of diffusion and macromolecular relaxation mechanisms (the so-called anomalous diffusion). For these systems, all the tested kinetic models were well fitted ($R^2$>0.99), in particular the first-order one.

## CONCLUSIONS

Matrix formulations containing IBP and different cellulose derivatives—MC25, HPC, HPMC K15M, and HPMC K100M—were assessed for their drug content, weight uniformity, hardness, thickness, tensile strength, friability, porosity, swelling, and drug release performance.

From the DSC thermograms of the mixtures studied it was possible to detect some drug-excipient interactions that were found to affect mainly the corresponding hydration/dehydration processes. However, no significative incompatibilities were observed, which allowed to conclude that the selected excipients are suitable for the preparation of tablet formulations.

The swelling experiments, on the other hand, showed that the water uptake increases with the polymer viscosity, which leads to the conclusion that this is a rather important factor to consider when preparing hydrophilic matrix tablets.

Regarding the release of IBP from matrix formulations, the results presently obtained indicate that dissolution from MC25 or HPC matrices are not controllable, these polymers thus being unsuitable for these formulations. HPMC K15M and K100M, in turn, were found to be quite adequate for this purpose. Moreover, a slight diluent effect was detected, for the systems under study: when β-CD was used, a small increase on drug release was observed.

The release mechanism of IBP from each formulation investigated was evaluated in the light of several kinetic mathematical models: zero-order, first-order, Higuchi's, and Korsmeyer-Peppas. Only for HPMC containing polymers, either K15M or K100M, could a clear fitting be obtained, reflecting a Fickian diffusion and an anomalous transport mechanism, respectively. Thus, an increase in the polymer viscosity was found to lead to a marked change in the drug release characteristics of the corresponding formulation.

The results obtained along this study provide useful information on the type of polymer and additives that should be employed on this type of pharmaceutical formulation, as well as on the preparation of tablets containing IBP or other similar drugs. Future studies will be developed in order to improve the drug release process in this kind of formulation, in accordance with the established requirements for this dosage form.

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