Pharmaceutical Development and Technology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597289

Influence of Cellulose Ether Mixtures on Ibuprofen Release: MC25, HPC and HPMC K100M

M. L. Vueba [a]; L.A.E. Batista de Carvalho [b]; F. Veiga [a]; J. J. Sousa [a]; M. E. Pina [a]
[a] Centro de Estudos Farmacêuticos (CEF), Laboratório de Galénica e Tecnologia Farmacêutica, Faculdade de Farmácia Universidade de Coimbra, Coimbra, Portugal [b] Unidade de I&D Química Física Molecular, FCTUC, Coimbra, Portugal

Online Publication Date: 01 July 2006

To cite this Article Vueba, M. L., de Carvalho, L.A.E. Batista, Veiga, F., Sousa, J. J. and Pina, M. E.(2006)'Influence of Cellulose Ether Mixtures on Ibuprofen Release: MC25, HPC and HPMC K100M',Pharmaceutical Development and Technology,11:2,213 — 228
To link to this Article: DOI: 10.1080/10837450600561349
URL: http://dx.doi.org/10.1080/10837450600561349

Pharmaceutical Development and Technology, 11:213–228, 2006

ISSN: 1083-7450 print / 1097-9867 online
DOI: 10.1080/10837450600561349

Influence of Cellulose Ether Mixtures on Ibuprofen Release: MC25, HPC and HPMC K100M

M.L. Vueba
Centro de Estudos Farmacêuticos (CEF), Laboratório de Galénica e Tecnologia Farmacêutica, Faculdade de Farmácia Universidade de Coimbra, Coimbra, Portugal

L.A.E. Batista de Carvalho
Unidade de I&D Química Física Molecular, FCTUC, Coimbra, Portugal

F. Veiga, J.J. Sousa, and M.E. Pina
Centro de Estudos Farmacêuticos (CEF), Laboratório de Galénica e Tecnologia Farmacêutica, Faculdade de Farmácia Universidade de Coimbra, Coimbra, Portugal

The influence of cellulose ether derivatives on ibuprofen release from matrix tablets was investigated. Raman spectroscopy and differential scanning calorimetry (DSC) experiments were used, in order to examine the compatibility between the matrix components: both excipients and ibuprofen. While both the DSC and Raman results did not detect any incompatibilities, DSC revealed the existence of some drug:excipient interactions, reflected by variations in the hydration/dehydration processes. Formulations containing mixtures of polymers with both low and high viscosity grades—methylcellulose (MC25) or hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC K100M), respectively—were prepared by a direct compression method (using 20, 25, and 30% of either MC25 or HPC). The tablets were evaluated for their drug content, weight uniformity, hardness, thickness, tensile strength, friability, porosity, surface area, and volume. Parameters such as the mean dissolution time (MDT) and the dissolution efficiency (DE) were calculated in all cases. The solid formulations presently studied demonstrated a predominantly Fickian diffusion release mechanism.

Keywords ibuprofen, cellulose ether polymers, polymer mixture, drug release, matrix tablets, release mechanism

Received 2 June 2005, Accepted 6 January 2006.

Address correspondence to Prof. Maria Eugénia Pina, Laboratório de Galénica e Tecnologia Farmacêutica, Faculdade de Farmácia da Universidade de Coimbra, Rua do Norte, 3000-295 Coimbra, Portugal; E-mail: epina@ci.uc.pt

INTRODUCTION

Ibuprofen is a well known nonsteroidal anti-inflammatory drug (NSAID), which was the first phenylalkanoic acid approved by the United States Food and Drug Administration (FDA) for general analgesic use. Its mode of action, while similar to that of other nonsteroidal anti-inflammatory agents, is not yet completely understood, but may be related to prostaglandin synthesis inhibition. Ibuprofen, which is available in 200, 400, 600, and 800 mg tablets for oral administration, is rapidly absorbed when conventional formulations are used and its peak serum concentration is generally attained 1–2 hours after administration.[1]

The most frequent adverse effects associated with ibuprofen include peptic ulceration and gastrointestinal disturbances (e.g., bleeding).[1] Therefore, the quest for a controlled release dosage form of this drug seems to be one rational approach in order to achieve a reduction of adverse effects of drug administration, a lower plasma peak, and an improvement of patient compliance.[2,3]

Numerous polymers can be used for the preparation of oral controlled release dosage forms, in view of modulating the kinetic drug release process.[4] Cellulose derivatives, for instance, have been successfully used with this objective.[5,6] The choice of the polymer viscosity grade is of the utmost importance, as the drug release mechanism can be altered by combining different polymers with distinct viscosity grades.[7] In fact, these polymer mixtures have been used more and more in the last few years.[8–13] On the other hand, previous studies developed by Vueba

et al.,[14,15] dealing with drug release from tablets containing polymers such as methylcellulose (MC25) and hydroxypropylcellulose (HPC), demonstrated that formulations using a low viscosity grade exhibited an undesired greater erosion and faster release of the drug. Consequently, polymer mixtures comprising both low viscosity and high viscosity components seem to be advantageous for obtaining appropriate modified release systems.

Several mathematical models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas) lately have been tested, in an attempt to understand the drug release mechanism from hydrophilic matrices. Baveja et al.[16] and Vázquez et al.[17] verified that one of the drawbacks of the mixtures containing hydrophilic swellable polymers is that the desirable zero-order kinetics are not usually attained. On the other hand, Bettini et al.[18] using different cellulose ether derivatives, reported that matrix tablets prepared with low viscosity grade HPMC were more erodible. Moreover, according to Rodriguez et al.[19] the drug release profiles can be modified by optimizing the erosion rate.

The present study is focused on the use of cellulose ether polymer mixtures in ibuprofen formulations: either methylcellulose (MC25) or hydroxypropylcellulose (HPC), with hydroxypropylmethylcellulose (HPMC K100M). The influence of the diluent—lactose monohydrate (LAC) or β-cyclodextrin (β-CD)—is also considered. In the near future, studies on mixtures comprising MC25 or HPC, with HPMC K15M will be described. Hopefully, this will contribute to an elucidation of the role of the most commonly used cellulose ethers on ibuprofen release or similar drugs from matrix tablets.

MATERIALS AND METHODS

Chemicals

Ibuprofen (IBP) (Lot no. 9907257) was purchased from Knoll, Nottingham, England and used as a model drug. Flurbiprofen (FNP) (Lot No 91K3452) was supplied by Sigma-Aldrich, Chemie Gmbh, Steinheim, Germany and employed as an internal standard. Three different viscosity grades of cellulose ether polymers were used in the formulations (Table 1). Diluents included lactose monohydrate (LAC) (Granulac® 200, Meggle, Wasserburg, Germany) and β-cyclodextrin (β-CD) (Kleptose®, Roquette, Lestrem, France). Lubricants were talc and magnesium stearate (Mg S), of analytical grade. Indium (99.98%) was obtained from Aldrich®, Milwaukee, USA. Acetonitrile (ACN) and methanol were HPLC grade purchased from Merck KgaA, Darmstadt, Germany. Water was obtained by a Millipore Elix system.

Raman Spectroscopy

The Raman spectra were obtained on a triple monochromator Jobin-Yvon T64000 Raman system (focal distance 0.640 m, aperture f/7.5) equipped with holographic gratings of 1800 grooves.mm^{-1}. The premonochromator stage was used in the subtractive mode. The detection system was a liquid nitrogen cooled, nonintensified 578 × 385 pixel (1/2") Charge Coupled Device (CCD). A Coherent (model Innova 300–05) Ar^+ laser was used as the light source, the output of which, at 514.5 nm, was adjusted to provide 35 mW at the sample position. A 90° geometry between the incident radiation and the collecting system was employed. The entrance slit was set to 200 μm, and the slit between the premonochromator and the spectrograph was opened to 12 mm. An integration time of 3 s and 10–15 scans were used in all experiments.

Samples were sealed in Kimax glass capillary tubes of 0.8 mm inner diameter. Under the previously mentioned conditions, the error in wavenumbers was estimated to be within 1 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Thermal analysis was carried out using a Shimadzu DSC-50 calorimeter, coupled to a Shimadzu TA-50 analyzer. The samples were heated in sealed aluminium pans under a nitrogen flow (20 mL/min). 3 mg of either pure drug or pure

Table 1
Cellulose ether polymers grades[a]

Polymer	Methoxyl %	Hydroxypropoxyl %	Viscosity (mPa.s)[b]	Brand®	Lot number
MC25	27.5–32	0	10–25	Methocel A	MFCD00081763
HPC	0	53.4–77.5	1500–3000[c]	Klucel HF	8174
HPMC K100M	19–24	7–12	16922–19267	Methocel K 100M	OB12012N11

[a]According to the supplier.
[b]Apparent viscosity, 2% aqueous solution at 20°C, mPa.s according to the supplier.
[c]Apparent viscosity, 1% aqueous solution at 20°C, mPa.s according to the supplier.

polymer, and 9 mg of the drug/polymer mixture 1:1:1 (w/w) were analyzed, from 25 to 250°C at a heating rate of 10°C/min. An empty sealed pan was used as a reference. The apparatus was calibrated with indium (m.p. 156.65°C).

Liquid Chromatographic Analysis

Instrumentation

The HPLC consisted of a quaternary pump Hewlett Packard (Waldbram, Germany) model 1050, equipped with a variable wavelength Hewlett Packard 1050 detector, a Hewlett Packard 3396A recorder/integration, and an injector with a 20 μL loop (model 7125, Rheodyne, Cotati, U.S.A.).

Chromatographic Conditions

The following conditions were based on the proposed method by Shah and Jung.[20] A reversed-phase column RP-18 LiChroCart® Purospher® star (250 × 4.6 mm i.d) 5 μm (Merck, Darmstadt, Germany) was used at room temperature (20–23°C). The detector was set at 229 nm. Analysis were carried out isocratically using a four component mobile phase, ACN:water:methanol:phosphoric acid (58:37:5:0.05, v/v). The mobile phase was filtered using a 0.45 μm membrane filter PVDF, Tracer®, Teknokroma, Barcelona, Spain (Lot no 103527) and was degassed prior to use. The injection volume was 20 μL and the flow rate was 1.5 mL/min.

Validation Study

Stock solutions of IBP (500 μg/mL) and FNP (300 μg/mL; internal standard) were prepared by their dissolution in ACN. Five standard solutions corresponding to IBP (5–50 μg/mL) containing 300 μg/mL of FNP were prepared. A 20 μL volume was then injected into the chromatograph and the calibration curve was calculated by linear regression of peak area ratios of IBP to internal standard vs. concentration. Unknown IBP concentrations were determined from the following regression equation:

$$Y = 0.0180\ X + 0.0062 \quad (1)$$

where Y is the peak area ratio and X is the concentration of IBP in μg/mL. The correlation coefficient of 0.9999 proved excellent linearity.

The repeatability (intra-assay precision) and intermediate (interday precision) were calculated by analysis of three standard solutions on five different days. The relative standard deviations obtained were between 0.38%–0.71% (n = 10) and 0.16%–0.68% (n = 5) respectively, demonstrating acceptable precision.

The accuracy of solutions with known IBP concentrations (10, 20, 40 μg/mL) added to the correspondent amount of excipients was analyzed. The results for recovery varied between 99.17%–101.42%, which indicates good effectiveness.

Preparation of the Matrix Tablets

Different amounts of MC25 or HPC in the mixtures with HPMC K100M were tested: 14/56, 17.5/52.5, and 21/49 mg (Table 2). In all cases, the drug content was kept at 200 mg, for a total tablet mass of 350 ± 2 mg. The diluent was either LAC or β-CD. Both talc and magnesium stearate were used as lubricants. The following percentage

Table 2
Matrix tablet composition (mg)

	Component							
Formulation	IBP	MC25	HPC	HPMC K100M	LAC	β-CD	Talc	Mg·S
A1	200.0	14.0	—	56.0	71.0	—	6.0	3.0
A2	200.0	14.0	—	56.0	—	71.0	6.0	3.0
A3	200.0	17.5	—	52.5	71.0	—	6.0	3.0
A4	200.0	17.5	—	52.5	—	71.0	6.0	3.0
A5	200.0	21.0	—	49.0	71.0	—	6.0	3.0
A6	200.0	21.0	—	49.0	—	71.0	6.0	3.0
B1	200.0	—	14.0	56.0	71.0	—	6.0	3.0
B2	200.0	—	14.0	56.0	—	71.0	6.0	3.0
B3	200.0	—	17.5	52.5	71.0	—	6.0	3.0
B4	200.0	—	17.5	52.5	—	71.0	6.0	3.0
B5	200.0	—	21.0	49.0	71.0	—	6.0	3.0
B6	200.0	—	21.0	49.0	—	71.0	6.0	3.0

compositions were thus considered: IBP, 57.14%; polymer mixture, 20.00%; diluent, 20.29%; talc, 1.71%; magnesium stereate, 0.86%. The tablets were prepared according to Vueba et al.,[14] using a single punch press (Specac Press, Automatic Press Ltd., England) at a compaction pressure of 624 MPa, with flat-faced punches of 10 mm diameter.

IBP Content

The sample solutions were prepared from each formulation by grinding five randomly selected tablets to a powder and transferring a weighed amount equivalent to 20 mg of IBP of the resulting powder to ACN with stirring and dilution to 100 mL with more solvent. An aliquot sample (1 mL) was removed, filtered through a 0.45 μm membrane filter, and transferred to a 10 mL volumetric flask with 1 mL of FNP (300 μg/mL), and then made to volume with ACN. This solution (20 μL) was injected into the HPLC, under previously described conditions, and analyzed.

Determination of the Weight, Hardness, and Thickness of the Tablets

A total of 20 tablets of each formulation were evaluated for weight (analytical balance KERN 770). For each formulation, a tablet breaking–strength measuring apparatus (Erweka TBH28, Erweka GmbH, Germany) was used, in order to determine the hardness of 10 tablets, in a diametric direction.

The thickness was determined using a micrometer (Roche, Switzerland), for 10 individual tablets of each formulation.

Determination of the Mechanical 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, Erweka GmbH, Germany), according to the equation:

$$T = \frac{2P}{\pi Dt} \tag{2}$$

where P is the applied load, and D and t represent the diameter and thickness of the tablet, respectively.[21]

Determination of the Friability

Twenty tablets were weighed, placed into a friability tester (Erweka TA20, Germany), and subjected to 25 rpm for 4 minutes and then reweighed in order to obtain the friability value. This process was repeated for all formulations and the percentage friability was calculated using the equation:

$$F = \frac{W_1 - W_2}{W_1} \times 100 \tag{3}$$

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

Tablets Porosity Determination

The percent porosity of the tablets was calculated using Eq. (4), according to Schreiner et al.[22]

$$\varepsilon(\%) = \left(1 - \frac{pa}{pt}\right) \times 100 \tag{4}$$

where ε is the percent of porosity, *pa* is the apparent density, *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.

Determination of the Surface Area

The tablet surface area (SA) was calculated using the following equation:

$$SA = 2\ \pi r(r + t) \tag{5}$$

where r is the radius of the 10.00 mm flat-faced round tablet, and t is the band thickness of the tablet.

Swelling Studies

Swelling studies were carried out for all formulations. Three metallic baskets were weighed with a matrix tablet of each formulation, and placed in 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 in order to remove

surface water, reweighted, 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.[23]

$$S = \frac{W_s - W_d}{W_d} \times 100 \quad (6)$$

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 of three determinations.

Drug Release Analysis

Dissolution studies were carried out according to the USP 25 paddle method.[24] Phosphate buffer was used as the dissolution medium (pH = 7.2, 1000 mL) at 37.0 ± 0.5°C, for a stirring speed of 100 rpm. A six-vessel dissolution apparatus (Vankel VK-7000 dissolution testing station) was used for this purpose, in-line with a closed flow through system coupled to a peristaltic pump, connected to a spectrophotometer (Shimadzu UV-1603). Six different tablets were tested. The 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 λ = 264 nm. The corresponding drug-release profiles were represented by plots of the cumulative percentage of drug release (calculated from the total amount of IBP contained in each matrix) vs. time.

Determination of the Mean Dissolution Time

In order to further characterize the drug release process, the mean dissolution time (*MDT*) was calculated, according to the following equation

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \, \Delta Q_1}{\sum_{j=1}^{n} \Delta Q_j} \quad (7)$$

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 ΔQ_j is the additional amount of drug dissolved between t_j and t_{j-1}.

Determination of the Dissolution Efficiency

The dissolution efficiency (DE) is defined by the area under the dissolution curve (AUC) at time, t. It is expressed as a percentage of the area of the rectangle corresponding to a 100% dissolution, for the same total time, [25,26] according to the following equation:

$$DE = \frac{\int_0^t y \times dt}{y100 \times t} \times 100 \quad (8)$$

where y is the drug percentage dissolved at time t.

Kinetic Mechanism

The kinetics of IBP release from hydrophilic cellulose matrix tablets were determined by finding the best fit (through minimization of the sum of the squared residuals) of the dissolution data (released fraction vs. time) to distinct mathematical models. The models considered only the points comprised in the interval $0.1 < Q_t/Q_\infty < 0.7$.

The cumulative percentage of released drug vs. time was assessed, for a zero-order model, which results in a linear rate of drug release with time, in accordance with the equation

$$Q_t = Q_0 + k_0 t \quad (9)$$

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.

Gibaldi and Feldman,[27] in turn, applied the following relationship to drug dissolution studies, in order to describe nonconstant release from reservoir devices,

$$Q_t = 100(1 - e^{-k_1 t}) \quad (10)$$

where k_1 represents the first-order kinetic constant.

In the early 1960s, Higuchi[28,29] developed a model aimed at describing the release process of a drug incorporated in a solid or semisolid matrix,

$$Q_t = k_H t^{t/2} \quad (11)$$

where k_H is the Higuchi rate constant.

Moreover, in order to better characterize the drug release behavior, for the polymeric systems studied, the Korsmeyer-Peppas semi-empirical model was also applied.[30,31]

$$Q_t / Q_\infty = kt^n \quad (12)$$

Q_t/Q_∞ being 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) a parameter indicative of the mechanism of drug release.[32] For the particular case of cylindrical tablets,[33] $n \leq 0.45$ 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 release kinetics (case II), and $n > 0.89$ to a super case II transport.

Statistics

In order to assess statistical significance among the data, one way analysis of variance (ANOVA) was used to test variation in tablets formulations containing different polymer mixtures, MC25/HPMC K100M or HPC/HPMC K100M, at the different % w/w and in the same dissolution media. The 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 the 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

Raman Spectroscopy

The Raman spectra (in the solid state, 25°C) of the different components of the mixtures to be studied—IBP, polymers (MC25, HPC, and HPMC K100M) and diluents (β-CD and LAC)—are shown in Figure 1.

The spectrum of IBP presents intense and well-defined features, most of them directly correlatable with specific groups within the molecule. The spectrum of each of the polymers, in turn, display less intense and resolved features, as well as some background fluorescence due to their physico-chemical characteristics.

Figure 2 contains the Raman spectra of 1:1 (w/w) IBP:excipient freshly prepared physical mixtures. Despite the particular drug:excipient ratio used, these spectra reflect mostly the presence of the drug. However, a closer inspection suggests that they correspond to the superposition of the individual band patterns of IBP, and either the polymer or the diluent.

Particularly interesting and useful to this study is the 1500–1800 cm^{-1} spectral region, as none of the excipients tested gives rise to vibrational bands in this interval (Figure 1). Consequently, any change observed in the IBP signals, tentatively assigned to both C=O and ring stretching vibrational modes, should arise from intermolecular interactions between the different components in the physical mixture (mainly those involving the IBP carboxylic group).

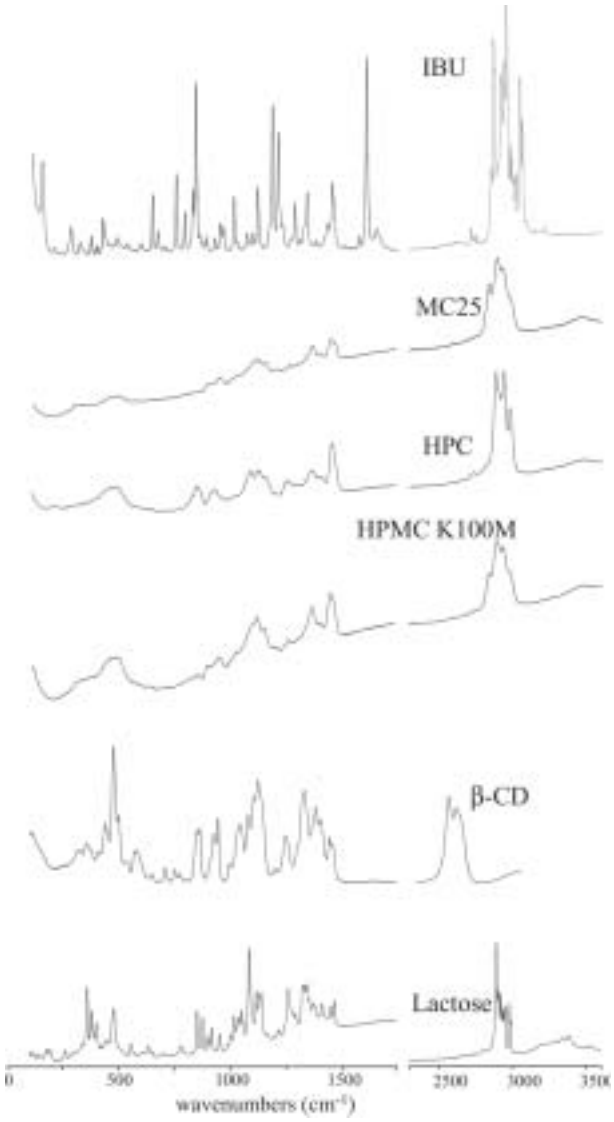

Figure 1. Raman spectra (solid state) for ibuprofen (IBP), methylcellulose (MC25), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC K100M), β-cyclodextrin (β-CD), and lactose.

Analysis of the spectra presented in Figure 2 allows one to conclude that neither new bands nor relative intensity or frequency variations were observed in the mixtures.

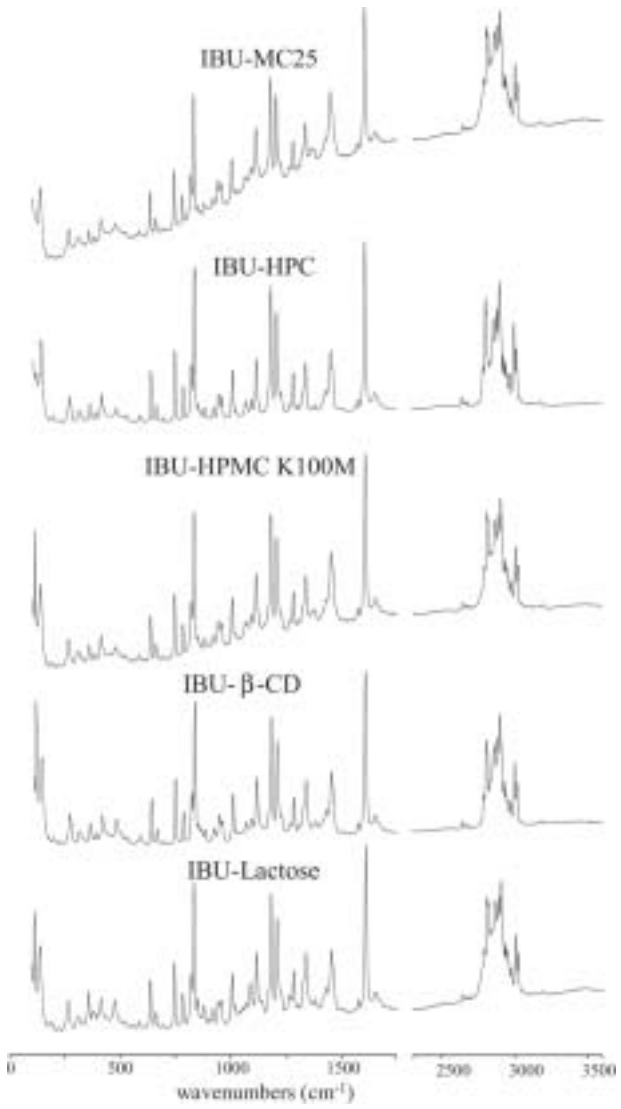

Figure 2. Raman spectra (solid state) for IBP/MC25, IBP/HPC, IBP/HPMC K100M, IBP/β-CD, and IBP/lactose, 1:1 (w/w) physical mixtures.

These spectroscopic results evidence the absence of significant intermolecular interactions between IBP and the excipients under study, in freshly prepared solid physical mixtures.

Differential Scanning Calorimetry (DSC)

The DSC was used in order to detect formulation incompatibilities resulting from possible drug:excipient interactions. The thermal curves of isolated IBP and the distinct polymers used are comprised in Figure 3a; whereas different binary and ternary mixtures are shown in Figures 3b and 3c. The results obtained for IBP were the ones expected for a crystalline anhydrous substance, displaying a sharp endothermic peak at 75.0 ± 0.5°C, which corresponds to the drug´s melting point.[34]

The DSC thermograms of IBP/β-CD, IBP/LAC, and IBP/polymer 1:1 (w/w) mixtures, were recently studied by Vueba et al.,[15] who concluded there is an absence of incompatibilities between these matrix components.

The results for the 1:1 and 1:3 (w/w) binary mixtures (MC25/HPMC K100M and HPC/HPMC K100), shown in Figures 3b and 3c were not found to differ significantly from the DSC curves of isolated MC25, HPC, or HPMC K100M (Figure 3a), where a large broad endothermic effect was observed over a temperature range of 60 to 140°C, due to the dehydration process. The occurrence of a shift to lower temperatures in these endothermic events (Figures 3b and 3c) must be pointed out, reflecting a straightforward dehydration in the polymer mixtures.

Regarding the ternary systems IBP/MC25/HPMC K100M and IBP/HPC/HPMC K100M (Figures 3b and 3c), the drug signal was clearly distinguishable. Furthermore, clear downward shifts of the excipient signals, upon dehydration, were also seen. This may be related to the presence of nonnegligible drug:excipient interactions, possibly responsible for a loosening of the water-polymer binding strength, due to some degree of competition between the drug ionizable groups (e.g., carboxylates). These results are in accordance with the ones obtained for IBP:polymer binary mixtures.[15]

Moreover, the broad signal observed at about 200°C in the ternary mixtures (Figures 3b) could be attributed to either a glass transition or to polymer degradation products.[35]

The DSC results presently described suggest the existence of both polymer:polymer and IBP:polymer interactions that modulate the hydration/dehydration processes. Since no other endothermic events were observed, one can state that no incompatibilities were found between IBP and the polymers studied, whose presence could prevent their simultaneous use in pharmaceutical formulations.

Also, since the intermolecular interactions described earlier, mainly associated with the hydration/dehydration mechanisms are rather weak, they are not likely to be detected by Raman. In fact, this spectroscopic technique does not allow observation of the water vibrational modes, which are much more affected by the dehydration process, but almost inactive in Raman.

Evaluation of the Tablet Properties

The drug content and physical characteristics of the matrix tablets containing either MC25 or HPC as release

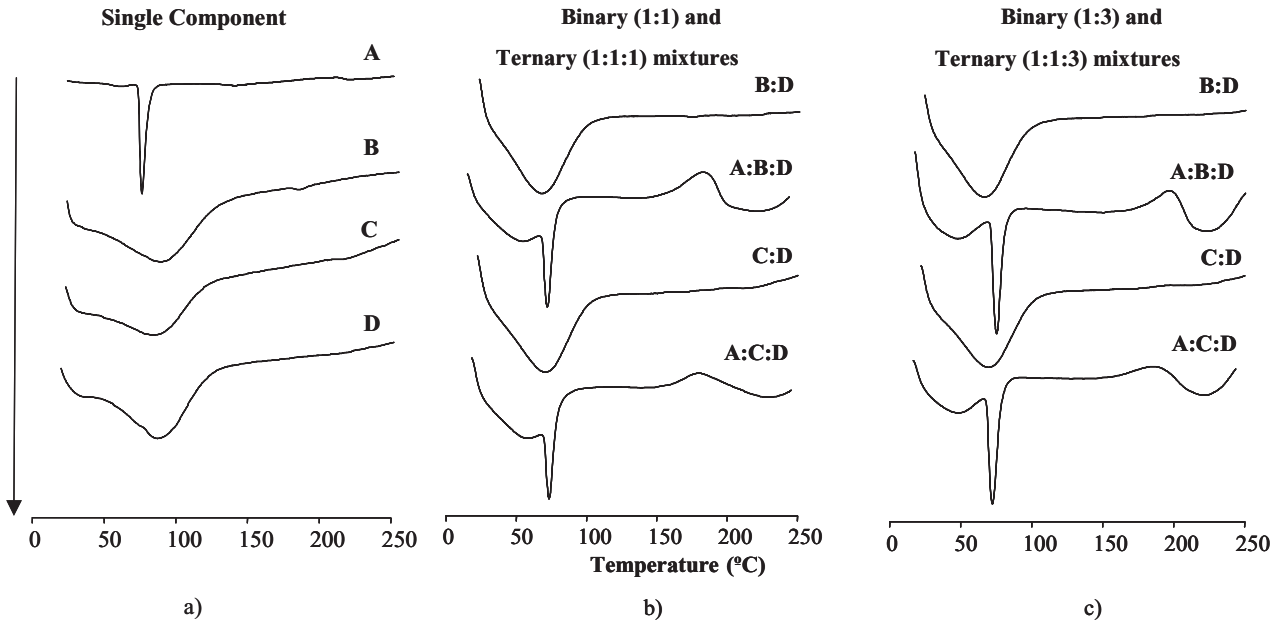

Figure 3. DSC curves for IBP (A), MC25 (B), HPC (C), HPMC K100M (D); binary and ternary physical mixtures.

modulators are shown in Tables 3 and 4, respectively. The HPLC analysis in all cases yields a drug content ranging from 99.30% to 100.45%, based on the theoretical composition, which evidences content uniformity. 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 ($F = 2.34$; $P > 0.05$).

Table 5 contains the statistical parameters corresponding to the measured data—mean values, standard deviation (SD), relative standard deviation (RSD), median, variance, and minimum and maximum values of the IBP matrix formulations relative to mass uniformity. The ANOVA revealed that uniform weight of all formulations were different in the mean values among the treatment groups are a little greater than would be expected by chance; there is a

Table 3
Physical characterization of MC25-containing IBP hydrophilic matrix tablets[a]

Formulation code	Drug content (mg) n = 3	Hardness (N) n = 10	Thickness (mm) n = 10	T. strength (MPa) n = 10	Friability (%) n = 20
A1	19.86 ± 0.05	94.03 ± 1.55	3.81 ± 0.03	1.571 ± 0.027	0.70
A2	19.87 ± 0.03	86.92 ± 1.91	3.83 ± 0.01	1.446 ± 0.030	0.89
A3	19.99 ± 0.01	97.13 ± 1.66	3.80 ± 0.01	1.626 ± 0.027	0.87
A4	19.88 ± 0.02	94.53 ± 1.90	3.83 ± 0.03	1.571 ± 0.032	0.95
A5	20.05 ± 0.21	99.47 ± 1.81	3.81± 0.04	1.661 ± 0.007	0.62
A6	20.26 ± 0.02	91.62 ± 3.25	3.83 ± 0.04	1.524 ± 0.056	0.84
	True density (g/cm^3) n = 10	Apparent density (g/cm^3)[b] n = 10	Porosity (%) n = 10	Surface area (mm^2) n = 10	
A1	1.2424 ± 0.0004	1.1652 ± 0.0018	6.21 ± 0.14	276.81 ± 0.10	
A2	1.2330 ± 0.0003	1.1593 ± 0.0028	5.98 ± 0.23	277.31 ± 0.31	
A3	1.2436 ± 0.0002	1.1640 ± 0.0021	6.40 ± 0.17	276.56 ± 0.21	
A4	1.2365 ± 0.0004	1.1629 ± 0.0024	6.00 ± 0.19	277.43 ± 0.10	
A5	1.2456 ± 0.0002	1.1638 ± 0.0030	6.57 ± 0.24	276.84 ± 0.13	
A6	1.2376 ± 0.0003	1.1629 ± 0.0025	6.03 ± 0.20	277.34 ± 0.13	

[a]Mean value ± Standard Deviation.
[b]Using the equation: density = weight (g)/volume (cm^3).

Table 4
Physical characterization of HPC-containing IBP hydrophilic matrix tablets[a]

Formulation Code	Drug content (mg) n = 3	Hardness (N) n = 10	Thickness (mm) n = 10	T. strength (MPa) n = 10	Friability (%) n = 20
B1	20.14 ± 0.15	88.12 ± 1.37	3.84 ± 0.03	1.461 ± 0.023	0.86
B2	20.30 ± 0.46	54.92 ± 1.29	3.85 ± 0.03	0.908 ± 0.021	0.94
B3	20.21 ± 0.29	86.02 ± 1.63	3.83 ± 0.05	1.428 ± 0.026	0.83
B4	20.19 ± 0.01	78.32 ± 0.95	3.84 ± 0.01	1.297 ± 0.015	0.92
B5	20.24 ± 0.01	80.45 ± 1.35	3.84 ± 0.03	1.334 ± 0.023	0.54
B6	20.29 ± 0.03	50.63 ± 1.43	3.85 ± 0.03	0.838 ± 0.023	0.76
	True density (g/cm^3) n = 3	Apparent density (g/cm^3)[b] n = 10	Porosity (%) n = 10	Surface area (mm^2) n = 10	
B1	1.2325 ± 0.0003	1.1546 ± 0.0018	6.11 ± 0.66	277.75 ± 0.10	
B2	1.2244 ± 0.0001	1.1529 ± 0.0016	5.83 ± 0.13	278.00 ± 0.10	
B3	1.2322 ± 0.0001	1.1572 ± 0.0026	6.09 ± 0.21	277.53 ± 0.16	
B4	1.2285 ± 0.0003	1.1566 ± 0.0035	5.85 ± 0.29	277.84 ± 0.26	
B5	1.2323 ± 0.0001	1.1576 ± 0.0040	6.06 ± 0.33	277.69 ± 0.10	
B6	1.2260 ± 0.0001	1.1569 ± 0.0020	5.75 ± 0.16	277.87 ± 0.50	

[a]Mean value ± Standard Deviation.
[b]Using the equation: density = weight (g)/volume (cm^3).

Table 5
Statistical parameters for the IBP matrix tablets (n = 20)

Formulation	Average (mg)	SD[a]	RSD[b] (%)	Median (mg)	Variance	Minimum (mg)	Maximum (mg)
A1	348.44	0.64	0.18	348.35	0.41	347.30	349.60
A2	348.14	0.75	0.21	348.20	0.56	347.00	349.20
A3	349.84	0.60	0.17	349.80	0.36	348.70	350.80
A4	349.83	0.90	0.26	350.00	0.81	348.20	350.90
A5	348.45	0.79	0.23	348.40	0.63	347.30	350.90
A6	349.75	0.95	0.27	350.10	0.91	348.10	350.90
B1	348.59	0.62	0.18	348.60	0.39	347.10	349.60
B2	348.76	0.75	0.21	348.90	0.56	347.20	350.50
B3	348.44	0.74	0.21	348.45	0.55	347.10	349.50
B4	349.31	0.62	0.18	349.25	0.39	348.20	350.90
B5	348.78	0.89	0.26	348.75	0.80	347.20	350.50
B6	349.40	0.79	0.22	349.30	0.62	348.00	350.80

[a]Standard variation.
[b]Relative standard variation.

statistically significant difference ($F = 13.59$; $P < 0.001$). However, when comparing formulations (A1–A6) and (B1–B6), it was possible to detect a certain uniformity, since the SD and RSD were lower than 1.0 mg and 0.3%, respectively. The variance of all formulations was below 1.0%, evidencing a homogenous distribution of the drug in the tablets. The maximum value measured for formulations (A1–A6) was 350.90 mg, while the minimum value was 347.00 mg. Like results were obtained for mixtures (B1–B6).

The hardness values of various formulation matrices were found to be different within the range of 50.63 N to 99.47 N ($F = 2504.39$; $P < 0.05$), which corresponds to obvious variations in the tablet tensile strength from 0.84 MPa to 1.66 MPa ($F = 885.77$; $P < 0.001$). Results also confirmed that the porosity of the tablets is influenced by the kind of diluent used and also has an influence on the tablet tensile strength. Tablets with higher hardness values were found to have higher porosity values, and therefore a decrease of the drug release rate, in accordance with previously reported

work.[15] It was also verified that the tablets passed the friability test (F < 1%), showing that all formulations lie within the established limits.[24] These results corroborate that a compaction pressure of 624 MPa could provide tablets that are not easy broken during transportation or handling.

Hydrophilic matrix tablets manufactured with faced punches of 10 mm diameter and equal compaction pressure present surface area values (SAs) differing only by 0.87 mm^2 and 0.47 mm^2, for MC25- and HPC-containing formulations, respectively (Tables 3 and 4). As the drug release rate is supposed to be directly proportional to the ratio between SA and the volume of the matrix (SA/Vol),[36] the very small fluctuations in the SAs (<0.3%) presently measured are not expected to have any influence on the drug release process.

Swelling Studies

An important stage for the development of a controlled-release solid dosage form is the selection of an appropriate polymer or polymer mixture, based on the disintegration mechanism and/or on the penetration degree of a liquid into the tablets (i.e., the polymer's ability to absorb water and swell). For this purpose, hydrophilic polymers of a high viscosity grade, such as HPMC K100M, are often chosen for their capacity to promptly hydrate and gelatinize. Moreover, for the high molecular weight grade of HPMC, the wetting and water uptake into the matrices are enhanced[37,38]; although, there is also a decrease of the drug release rate. Thus, in order to balance these effects, while still obtaining good water uptake profiles, the formulations presently studied comprise HPMC K100M mixed with lower viscosity grade polymers (MC25 or HPC).

Figure 4 summarizes the results obtained from the swelling experiments. All formulations were found to attain a high degree of hydration after the first hour, essential for allowing gel layer formation prior to dissolution of the tablet. A gradual decrease of the hydration was observed in the following 7 hours. This decrease was even

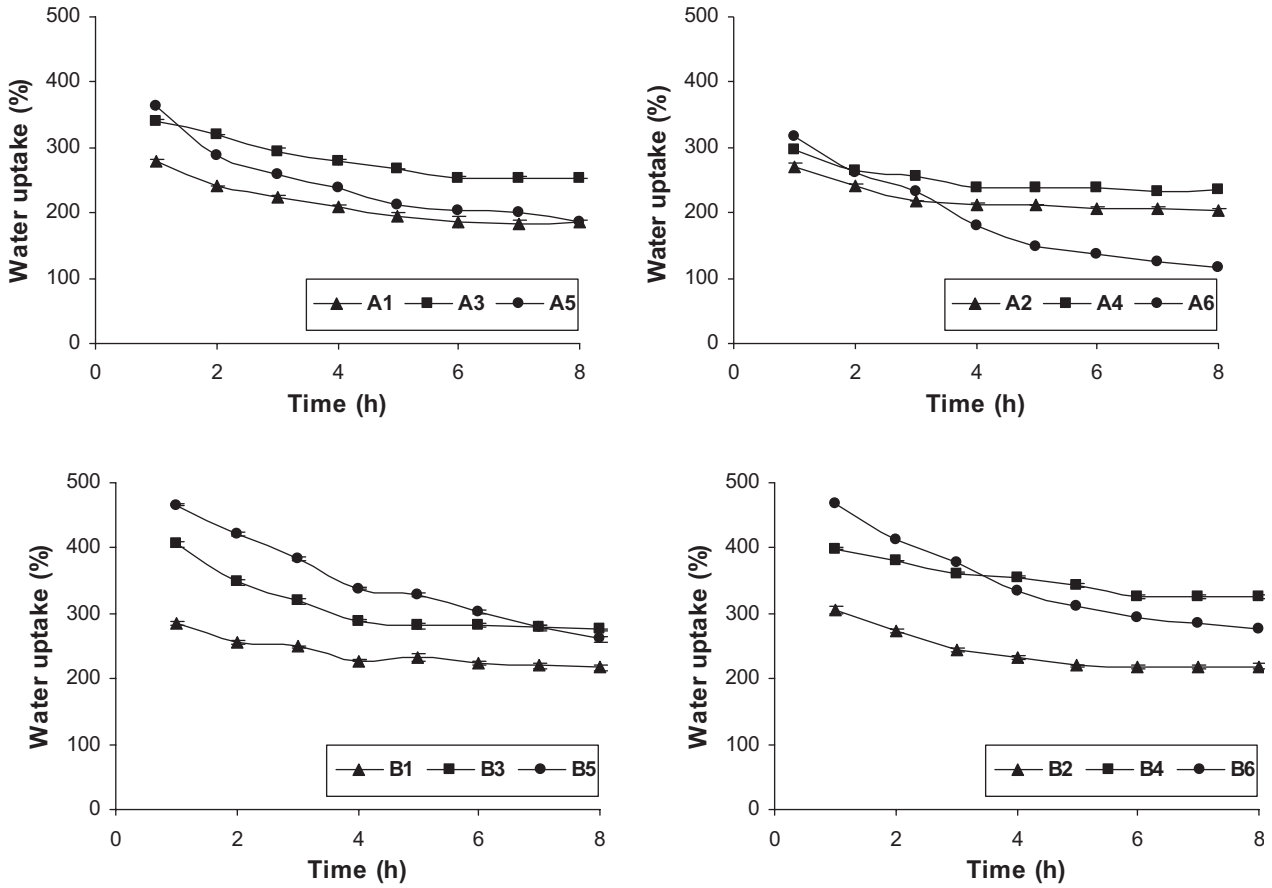

Figure 4. Graphical representation of the water uptake vs. time for several IBP matrix formulations containing either lactose (left) or β-cyclodextrin (right) and MC25 (top) or HPC (bottom).

more pronounced when either the MC25 or HPC percentage in the polymer is higher than 25%—in Fig. 4; the curves corresponding to A5, A6, B5, and B6 display higher negative gradients than the others. The time dependence of the water uptake process when HPMC K100M is mixed with either MC25 or HPC is remarkable. In fact, a steady level was attained after 1 hour of water exposure when HPMC K100M is the hydrophilic polymer present in the matrices.[15]

In a previously reported study,[15] it was verified that the absence of hydroxypropoxyl groups in the MC25 polymer, or a low hydroxyl group content, renders this polymer less hydrophilic[39,40] and contributes to an acceleration of the matrix disintegration process, despite the polymer wettability increase, which may be due to gel formation. For HPC, in turn, a low hydration level, even for long water exposures, was found.[15]

The results obtained in this work demonstrated that the swelling behavior of HPMC K100M in matrix tablets is very similar to that of the mixtures of 20% of either MC25 or HPC (i.e., formulations A1, B1, A2, B2), Figure 4. Above this percentage, increasing differences were observed up to a critical value of about 25%, above which the matrix swelling performance drastically changes, Figure 4.

Once the swelling process plays an essential role on the drug release mechanism, a careful choice of the chemical characteristics (e.g., the hydroxyl group content), the viscosity and the relative amount of hydrophilic polymers used in the matrix preparation, become of utmost importance.

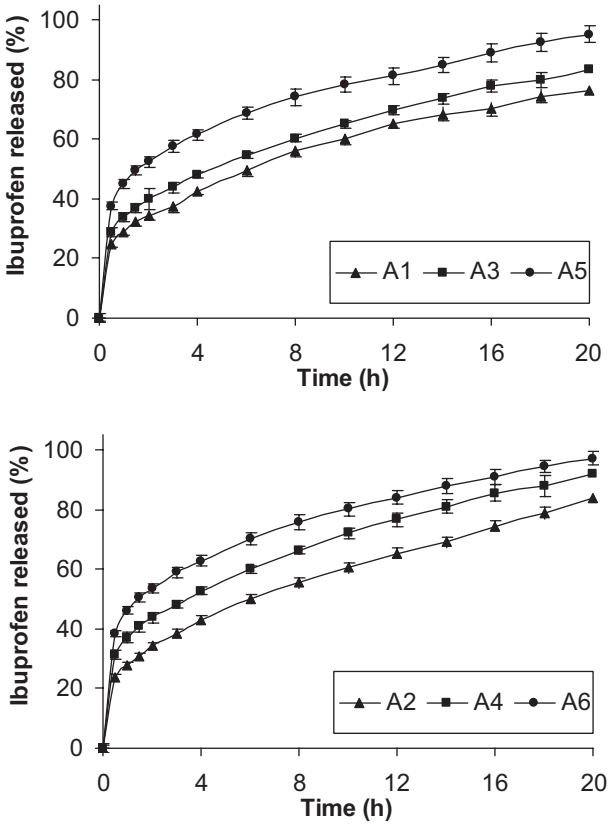

Figure 5. Drug-release profiles for IBP from MC25-containing formulations.

Release Studies

The dissolution profiles of different types of formulations in simulated intestinal fluid (pH 7.2)—in vitro experiments—are presented in Figures 5 and 6. The different relative ratios of MC25, HPC, and HPMC K100M in the MC25/HPMC K100M or HPC/HPMC K100M mixtures were found to significantly affect the profiles of IBP release. The drug release from the tablets is a result of the hydration of the polymer mixture, which swells extensively forming a pathway through which the drug can diffuse. However, a gradual disintegration of the swollen tablets is observed during the release studies, due to the presence of low viscosity grade polymers in the mixture. The percentage of drug released at 20 hours from A1, A2, B1, and B2 matrices was determined to be up to 76%–84%. For formulations A3, A4, B3, and B4 (MC25 or HPC equal to 25%), an IBP release between 83% to 93% was obtained. In turn, when HPMC K100M is reduced to 70%, coupled with a corresponding increase of the low viscosity polymers (tablets A5, A6, B5, and B6), the amount of drug released appears to be even larger than that yielded by the former mixtures, reaching values of almost 94%–98%.

These assays, combined with previous ones performed on single polymer formulations,[15] clearly show that the incorporation of either MC25 or HPC plays an important role as a release modifier from HPMC-containing tablets.

The β-CD-containing tablets were found to release IBP slightly faster than the ones having lactose as a filler. In fact, the fraction of the drug released from all β-CD formulations (A2, A4, and A6, or B2, B4, and B6) is found to be higher than for those containing the analogous lactose-containing formulations (A1, A3, and A5 or B1, B3, and B5). This observation was supported by the smaller MDT values calculated for β-CD formulations (Table 6 and Figure 7). Indeed, this parameter yields information on both the drug release process and the retarding efficacy of the polymer; larger MDT values indicating a higher drug retarding ability of the polymer (F = 1713.55; P < 0.001).

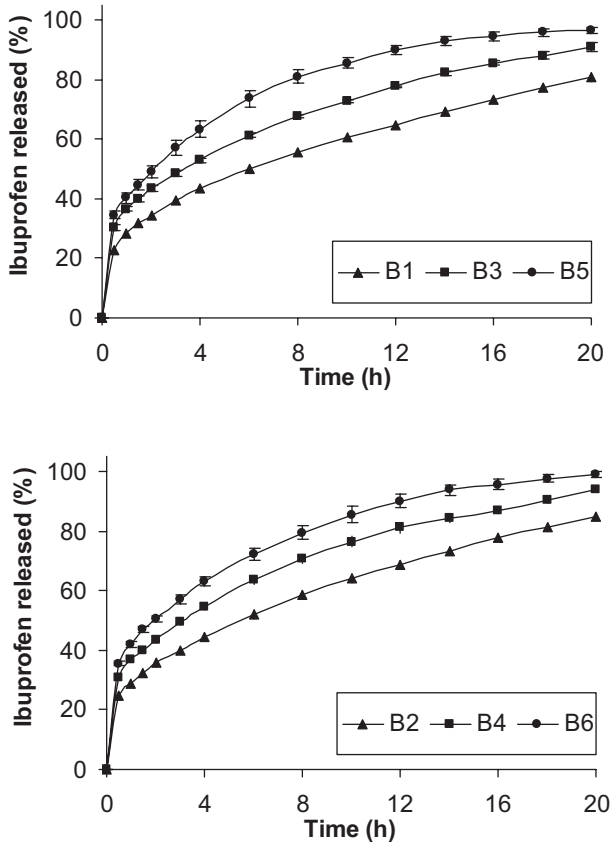

Figure 6. Drug-release profiles for IBP from HPC-containing formulations.

Table 6 also comprises several other parameters widely used for characterizing this kind of dissolution processes: $t_{50\%}$, AUC, DE, and percentage of drug dissolved at 20 hours (P_{20h}), whose variations were the ones to be expected.

Figure 7 provides a comparison of the MDT dependence on the polymer ratio composition: an increase of the low viscosity polymer MC25 content is accompanied by a decrease in the MDT values. The same occurs for the HPC-containing formulations (Table 6).

Kinetics of the Drug Release Mechanism

Either diffusion or erosion processes can contribute to the drug release process from solid matrix tablets. In fact, the release from swellable matrix systems is complex and not completely understood, as both mechanisms are sometimes present. In such cases, it is important to select a suitable mathematical model, which can be adjusted to the release profiles. The interpretation of the Korsmeyer-Peppas exponent values (*n*), in particular, provides an insight into the balance between the different mechanisms present.

The profiles of IBP release (for 10% to 70% of released drug) were fitted, and the results are summarized in (Tables 7 and 8). The reported values suggest that for this duration of the in vitro studies diffusion was the predominant process, for both the MC25 and HPC-containing formulations—exponent values (*n*) ranging between 0.235 to 0.359 (Table 7), and 0.295 to 0.360 (Table 8), respectively. This is corroborated by the good fitting obtained using Higuchi´s model. Moreover, the *n* and K values were found to be inversely related. In fact, when either MC25 or HPC matrix content was increased in the formulations, the release was markedly faster and higher values of K were obtained,

Table 6
Dissolution parameters for the IBP matrix tablets[a]

Assay	MDT (h)	$t_{50\%}$ (h)	AUC	DE (%)	P_{20h} (%)[b]
A1	5.29 ± 0.02	5.73	1132.03	56.60 ± 1.67	76.31 ± 2.14
A2	4.79 ± 0.06	5.58	1162.59	58.13 ± 1.48	83.73 ± 1.97
A3	3.46 ± 0.12	4.17	1235.13	61.76 ± 1.67	83.34 ± 3.13
A4	2.71 ± 0.13	3.07	1360.23	68.01 ± 1.32	91.64 ± 3.44
A5	1.91 ± 0.01	1.67	1475.79	73.79 ± 2.16	94.97 ± 2.76
A6	1.73 ± 0.01	1.53	1509.83	75.49 ± 1.79	97.16 ± 2.09
B1	4.95 ± 0.15	5.59	1150.71	57.54 ± 0.33	80.73 ± 1.30
B2	4.24 ± 0.10	4.86	1217.33	60.87 ± 1.03	84.56 ± 1.10
B3	2.90 ± 0.09	2.96	1378.09	68.90 ± 1.71	90.84 ± 2.11
B4	2.53 ± 0.01	2.81	1422.06	71.10 ± 1.27	93.79 ± 0.49
B5	1.81 ± 0.01	1.80	1581.90	79.09 ± 1.64	96.41 ± 1.03
B6	1.66 ± 0.01	1.81	1585.26	79.26 ± 1.78	98.84 ± 1.15

[a]Mean ± standard variation (6 measurements).
[b]P_{20} = percentage of IBP dissolved at 20 hours.

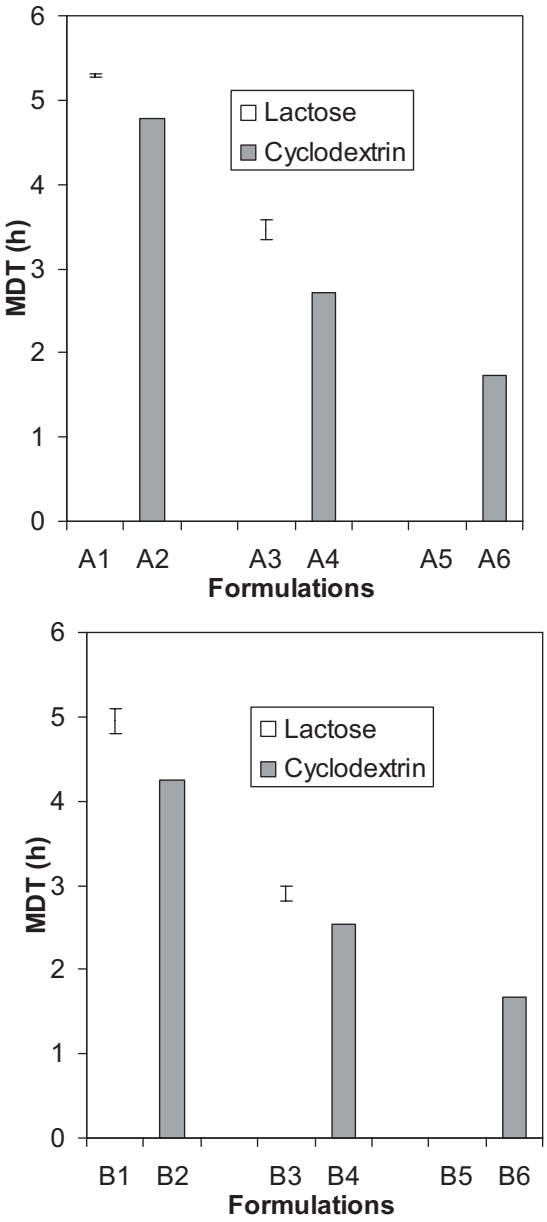

Figure 7. Graphical representation of MDT values for MC25 (top) and HPC (bottom) containing formulations.

suggesting that a small burst effect may be present. For all the formulations tested, the drug release rates were found to be higher than for those containing only HPMC K100M.[15] Given that several authors[15,41,42] have verified that the use of different HPMC viscosity grades (K4M, K15M, or K100M) for a given drug: HPMC ratio, it is not enough to alter the Higuchi-type kinetics significantly, the results obtained for both MC25 and HPC may be explained in the light of their particular chemical structure.

Thus, it is suggested that the use of polymer mixtures—using different viscosity grade polymers in order to obtain the appropriate gels—is a promising procedure for achieving optimal release properties.

CONCLUSIONS

The results obtained in the present study illustrate that both low and high viscosity grade cellulose ether polymers can be mixed uniformly, in different proportions, in order to produce matrices with modulated drug release properties. Powder mixtures compressed at a compaction pressure of 624 MPa were verified to provide suitable tablets that would not easily break during transportation or handling. The studied formulations, mainly A6, B5, and B6, suggest acceptable sustained-release performance based on the in vitro data.

While both the DSC and Raman spectroscopy experiments did not detect any incompatibilities between the IBP and the excipients under study, DSC revealed the existence of some drug:excipient interactions, reflected in changes in the hydration/dehydration processes.

The swelling experiments showed that the water uptake increases until the low viscosity polymer content reaches 25%. At higher concentrations, the swelling behavior changes drastically, suggesting a gradual degradation of the matrices.

The dissolution of IBP from mixtures of MC25/HPMC K100M or HPC/HPMC K100 matrices was found to be more effective when either the MC25 or HPC content was increased.

The solid formulations studied were far from yielding the desirable zero order kinetics, although, they allow a predominantly Fickian diffusion release mechanism.

ACKNOWLEDGMENTS

M.L. Vueba acknowledges the Ph.D. fellowship from Gabinete de Relações Internacionais da Ciência e do Ensino Superior (GRICES) and Fundação para Ciência e Tecnologia (FCT) for the financial support (Portugal). The authors thank Prof. M.P.M. Marques, University of Coimbra, for the helpful discussions.

Table 7
Fitting results of the IBP release data for several MC25-containing formulations (see Table 2)[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
A1	2.839	0.9523	0.040	0.9792	14.314	**0.9949**	27.151	0.342	0.9895
	(0.061)	(0.0017)	(0.001)	(0.0012)	(0.294)	(0.0006)	(0.997)	(0.004)	(0.0016)
A2	3.188	0.9581	0.044	0.9812	15.251	**0.9988**	26.493	0.359	0.9954
	(0.092)	(0.0009)	(0.002)	(0.0006)	(0.449)	(0.0001)	(0.999)	(0.009)	(0.0009)
A3	3.364	0.9417	0.045	0.9637	14.926	**0.9913**	32.147	0.302	0.9909
	(0.125)	(0.0067)	(0.002)	(0.0063)	(0.535)	(0.0026)	(1.300)	(0.014)	(0.0008)
A4	4.293	0.9334	0.057	0.9544	16.628	**0.9861**	35.954	0.289	0.9888
	(0.147)	(0.0085)	(0.003)	(0.0080)	(0.554)	(0.0039)	(1.323)	(0.013)	(0.0014)
A5	5.469	0.8985	0.070	0.9235	17.752	**0.9765**	44.167	0.236	0.9945
	(0.173)	(0.0006)	(0.003)	(0.0012)	(0.559)	(0.0003)	(1.650)	(0.001)	(0.0003)
A6	5.630	0.8965	0.073	0.9212	18.248	**0.9753**	45.547	0.235	0.9948
	(0.256)	(0.0017)	(0.003)	(0.0011)	(0.506)	(0.0003)	(1.304)	(0.001)	(0.0004)

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

Table 8
Fitting results of the IBP release data for several HPC-containing formulations (see Table 2)[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
B1	3.103	0.9552	0.043	0.9785	15.020	**0.9983**	27.043	0.351	0.9973
	(0.097)	(0.0065)	(0.002)	(0.0051)	(0.433)	(0.0012)	(1.160)	(0.016)	(0.0003)
B2	3.674	0.9655	0.051	0.9861	16.320	**0.9984**	27.757	0.360	0.9923
	(0.040)	(0.0030)	(0.001)	(0.0015)	(0.195)	(0.0004)	(0.967)	(0.008)	(0.0007)
B3	4.654	0.9538	0.062	0.9740	17.612	**0.9966**	35.411	0.305	0.9926
	(0.222)	(0.0062)	(0.004)	(0.0056)	(0.807)	(0.0013)	(2.144)	(0.0023)	(0.0013)
B4	5.460	0.9547	0.074	0.9740	19.365	**0.9944**	35.457	0.322	0.9911
	(0.118)	(0.0005)	(0.002)	(0.0005)	(0.417)	(0.0002)	(0.835)	(0.001)	(0.0004)
B5	8.136	0.9633	0.109	0.9800	23.299	**0.9949**	40.606	0.316	0.9881
	(0.471)	(0.0026)	(0.009)	(0.0028)	(1.334)	(0.0004)	(1.643)	(0.013)	(0.0007)
B6	7.306	0.9273	0.098	0.9516	22.055	**0.9864**	41.797	0.295	0.9932
	(0.270)	(0.0035)	(0.005)	(0.0029)	(0.811)	(0.0006)	(0.941)	(0.007)	(0.0010)

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

REFERENCES

1. Parfitt, K. Ed.; *Martindale: The Complete Drug Reference*, 32th Ed.; The Pharmaceutical Press: London, UK, 1999, 48–49.
2. Leo, E.; Forni, F.; Bernabei, M.T. Surface drug removal ibuprofen-loaded PLA miscrospheres. Int. J. Pharm. **2000**, *196*, 1–9.
3. Ilango, R.; Kavimani, S.; Jaykar, B. Dissolution studies on tablets of ibuprofen using chitosan. Indian J. Experim. Biol. **1999**, *37*, 505–508.
4. Salsa, T.; Veiga, F.; Pina, M.E. Oral controlled-release dosage forms. I. Cellulose ether polymers in hydrophilic matrices. Drug Dev. Ind. Pharm. **1997**, *23* (9), 929–938.
5. Veiga, F.; Salsa, T.; Pina, M.E. Influence of technological variables on the release of theophylline from hydrophilic matrix tablets. Drug Dev. Ind. Pharm. **1997**, *23*, 547–551.
6. Pina, M.E.; Veiga, F. The influence of diluent on the release of theophylline from hydrophilic matrix tablets. Drug Dev. Ind. Pharm. **2000**, *26*, 1125–1128.
7. Khanvilkar, K.H.; Huang, Y.; Moore, A.D. Influence of hydroxypropylmethylcellulose mixture, apparent viscosity,

and tablet hardness on drug release using a 2^3 full factorial design. Drug Dev. Ind. Pharm. **2000**, *28* (5), 601–608.
8. Vázquez, M.J.; Perez-Marcos, B.; Gomes-Amoza, J.L.; Martinez-Pacheco, R.; Souto, C.; Concheiro, A. Influence of technological variables on release of drugs from hydrophilic matrices. Drug Dev. Ind. Pharm. **1992**, *18* (11&12), 1355–1375.
9. Halsas, M.; Simelius, R.; Kiviniemi, A.; Veski, P.; Jurjenson, H.; Marvola, M. Effect of different combinations of hydropropylmethylcelluose on bioavailability of ibuprofen from press-coated time-controlled tablets. STP Pharma Sci. **1998**, *8* (3), 155–161.
10. Nokhodchi, A.; Rubinstein, M.H. The effect of moisture on the compaction properties of the binary mixture of hydropropylmethylcelluose K4M/ibuprofen. STP Pharma Sci. **1998**, *8* (6), 349–356.
11. Nokhodchi, A.; Khaseh, P.; Ghafourian, T.; Siahi-Shabad, M.H. The Role of various surfactants and fillers in controlling the release rate of theophylline from HPMC matrices. STP Pharma Sci. **1999**, *9* (6), 555–560.
12. Eyjofsson, R. Hydropropylmethylcelluose mixtures: effects and kinetics of release of an insoluble drug. Drug Dev. Ind. Pharm. **1999**, *25* (5), 667–669.
13. Dabbagh, M.A.; Ford, J.L.; Rubinstein, M.H.; Hogan, J.E.; Rajabi-Siahboomi, A.R. Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and hydroxypropylmethylcellulose. Pharm. Dev. Tech. **1999**, *4* (3), 313–324.
14. Vueba, M.L.; Batista de Carvalho, L.A.E.; Veiga, F.; Sousa, J.J.; Pina, M.E. Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets. Eur. J. Pharm. Biopharm. **2004**, *58* (1), 51–59.
15. Vueba, M.L.; Batista de Carvalho, L.A.E.; Veiga, F.; Sousa, J.J.; Pina, M.E. Role of cellulose ether polymers on ibuprofen release from matrix tablets. Drug Dev. Ind. Pharm. **2005**, *31*, 653–665.
16. Baveja, S.K.; Ranga Rao, K.V.; Padmalatha Devi, K. Zero-order release hydrophilic matrix tablets of β-adrenergic blockers. Int. J. Pharm. **1987**, *39*, 39–45.
17. Vázquez, M.J.; Gomes-Amoza, J.L.; Martinez-Pacheco, R.; Souto, C.; Concheiro, A. Relationships between drug dissolution profile and gelling agent viscosity in tablets prepared with hydropropylmethylcelluose (HPMC) and sodium carboxymethylcellulose (NaCMC) mixtures. Drug Dev. Ind. Pharm. **1995**, *21* (16), 1859–1874.
18. Bettini, R.; Colombo, P.; Massimo, G.; Catellani, P.L.; Vitali, T. Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects. Eur. J. Pharm. Sci. **1994**, *2*, 213–219.
19. Rodriguez, C.F.; Bruneau, N.; Barra, J.; Alfonso, D.; Doeker, E. Hydrophilic cellulose derivatives as drug delivery carriers: Influence of substitution type on the properties of compressed matrix tablets. In *Handbook of Pharmaceutical Controlled Release Technology*; Wise, D.L. Ed.; Marcel Dekker, Inc: New York/Basel, 2000, 1–30.
20. Shah, A.; Jung, D. Improved high-performance liquid chromatographic assay of ibuprofen in plasma. J. Chromatogra. **1985**, *344*, 408–411.
21. Fell, J.T.; Newton, J.M. Determination of tablet strength by diametral-compression test. J. Pharm. Sci. **1970**, *59*, 688–691.
22. Schreiner, T.; Schaefer, U.F.; Loth, H. Immediate drug release from solid oral dosage forms. J. Pharm. Sci. **2005**, *94* (1), 120–133.
23. Efentakis, M.; Vlachou, M.; Choulis, N.H. Effects of excipients on swelling and drug release from compressed matrices. Drug Dev. Ind. Pharm. **1997**, *23* (1), 107–112.
24. United States Pharmacopeia 26/The National Formulary 21. U.S.P Convention, Rockville, MD, 2003.
25. Khan, K.A.; Rhodes, C.T. Effect of compaction pressure on the dissolution efficiency of some direct compression systems. Pharm. Acta Helv. **1972**, *47*, 594–607.
26. Khan, K.A. The concept of dissolution efficiency. J. Pharm. Pharmacol. **1975**, *27*, 48–49.
27. Gibaldi, M.; Feldman, S. Establishment of sink conditions in dissolution rate determinations-theoretical considerations and application nondisintegrating dosage forms. J. Pharm. Sci. **1967**, *56*, 1238–1242.
28. Higuchi, T. Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci. **1961**, *50*, 874–875.
29. Higuchi, T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. **1963**, *52*, 1145–1149.
30. Korsmeyer, R.W.; Peppas, N.A. Swelling-controlled delivery systems for pharmaceutical applications: macromolecular and modelling considerations. In *Controlled Release Delivery Systems*; Mansdorf, S.Z.; Roseman, T.J. Eds.; Dekker: New York, 1983, 77–90.
31. Korsmeyer, R.W.; Gurny, R.; Doelker, E.M.; Buri, P.; Peppas, N.A. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm. **1983**, *15*, 25–35.
32. Peppas, N.A. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. **1985**, *60* (4), 110–111.
33. Ritger, P.L.; Peppas, N.A. A simple equation for description of solute release. II Fickian and anomalous release from swellable devices. J. Control. Release **1987**, *5*, 37–42.
34. Higginis, J.D.; Gilmor, T.P.; Martellucci, S.A.; Bruce, R.D.; Brittain, H.G.; ibuprofen. In *Analytical Profiles of Drug Substances*; Florey, K. Ed.; Vol. 27, Academic Press: New York, 2001, 265–299.
35. Wade, A.; Weller, P.J. *Handbook of Excipients*, 2nd Ed.; The American Pharmaceutical Association (USA) and the Pharmaceutical Press: London, England 1994, 306, 223–229.
36. Reynolds, T.D.; Mitchell, S.A.; Balwinski, K.M. Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets. Drug Dev. Ind. Pharm. **2002**, *28* (4), 457–466.
37. Davidson, G.W.R.; Peppas, N.A. Solute and penetrant diffusion in swellable polymers V. Relaxation-controlled transport in p (HEMA-co-MMA) copolymers. J. Control. Release **1986**, *3*, 243–258.

38. Wan, L.S.C.; Heng, P.W.S.; Wong, L.F. The effect of hydroxypropylmethylcellulose on water penetration into matrix system. Int. J. Pharm. **1991**, *73*, 111–116.
39. Siepmann, J.; Podual, K.; Sriwongjanya, M.; Peppas, N.A.; Bodmeier, R. A new model describing the swelling and drug release kinetics from hydroxypropylmethylcellulose tablets. J. Pharm. Sci. **1999**, *88* (1), 65–72.
40. Kumar, V.; Banker, G.S. Chemically modified cellulosic polymers. Drug Dev. Ind. Pharm. **1993**, *19*, 1–31.
41. Ford, J.L.; Rubinstein, M.H.; Hogan, J.E. Formulation of sustained release promethazine hydrochloride tablets using hydropropylmethlycellulose matrices. Int. J. Pharm. **1985**, *24*, 327–338.
42. Huber, H.E.; Christenson, G.L. Utilization of hydrophilic gums for the control of drug substance release from tablet formulations II. Influence of tablet hardness and density on dissolution behavior. J. Pharm. Sci. **1968**, *57* (1), 164–166.