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Release of ketoprofen enantiomers from HPMC K100M matrices—diffusion studies

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Abstract

Sustained release formulations of ketoprofen elaborated with HPMC K100M were studied to test the hypothesis that chiral excipients can stereoselectively affect the release of the racemic drug. The differences observed in the percentage released between enantiomers show the existence of a chiral interaction between ketoprofen and HPMC K100M. HPMC interacts preferably with the *S*-enantiomer, although the enantioselectivity observed was not relevant from biopharmaceutical and clinical points of view. Diffusion studies were carried out in membrane diffusion cells to simplify the excipient–drug system and hence to analyze only the influence of diffusion process on the stereoselectivity. The results obtained show that the absence of the erosion process strengthens the enantiomeric differences observed in the drug release from tablets. Another objective of this work was to study the influence of formulation pH on the 'in vitro' release profile of ketoprofen. The amount and the release mechanism of ketoprofen from formulations elaborated are conditioned mainly by the pH of the matrix.

Keywords: Chiral excipient; Drug diffusion; Stereoselective dissolution; Ketoprofen; Hydroxypropylmethylcellulose K100M

1. Introduction

Approximately 75% of all drugs in therapeutic use have a chiral center and hence exhibit stereoisomerism (Ariens et al., 1988). Most of those which are produced by chemical synthesis are only available as racemates. The FDA current specifications make it clear that the development of only one enantiomer form of a chiral drug is preferred, although the development of a racemic mixture may continue to be appropriate in certain situations (Tomaszenski and Rumore, 1994). Ketoprofen is a potent non-steroidal anti-inflammatory drug. The biological activity of ketoprofen is due mainly to the *S*-enantiomer while *R*-ketoprofen is therapeutically inactive or less active (Jamali and Brocks, 1990).

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Previous research has studied the effect of chirality on the release or dissolution of enantiomers of several drugs such as salbutamol (Solinís et al., 1998; Srichana and Suedee, 2001), ketoprofen (Álvarez et al., 1999), propranolol (Duddu et al., 1993; Suedee et al., 1997, 2000), and verapamil (Maggi et al., 1996) from matrix formulations. It has been hypothesized that chiral excipients may interact preferentially with one enantiomer leading to stereoselective release from a formulation containing a racemate (Duddu et al., 1993). The composition of the analyzed matrices vary from chiral excipients used commonly in pharmaceutical formulations, such as cellulose polymers and cyclodextrins, to the use of cellulose derivatives used in chromatography, or molecularly imprinted polymers. Hydroxypropylmethylcellulose (HPMC) K100M is a chiral excipient derived from cellulose and widely used in oral and topical pharmaceutical formulations. Moreover, it is one of the excipients that has been studied more in the works about stereoselective release (Duddu et al., 1993; Maggi et al., 1996; Solinís et al., 1998; Álvarez et al., 1999; Srichana and Suedee, 2001). HPMC K100M is used as the main component of the formulations or in combination with other excipients.

In the present work sustained release formulations of racemic ketoprofen elaborated with HPMC K100M were studied in order to test the hypothesis that chiral excipients can stereoselectively affect the release of the drug. Moreover, diffusion studies of ketoprofen from HPMC K100M gels were carried out using membrane diffusion cells. The objective of the latter studies was to simplify the excipient–drug system and to analyze only the influence of the diffusion process on a possible stereoselective interaction or lack of it in absence of erosion process.

On the other hand, formulation buffers can be incorporated to modify the microenvironmental pH in order to control the solubility of the drug in the diffusion layer and, hence, the concentration gradient with subsequent effects on the dissolution rate (Doherty and York, 1989). For this reason, the last objective of this work was to study the influence of formulation pH on the 'in vitro' release profiles of ketoprofen enantiomers.

2. Materials and methods

2.1. Materials

Racemic ketoprofen was obtained from Sigma chemical company (St. Louis, MO, USA). Hydroxypropylmethylcellulose (HPMC) K100M was a gift from Colorcon (Kent, UK). All other chemicals were of analytical grade.

2.2. Preparation of tablets

Three types of HPMC K100M tablets were elaborated. The compositions of formulations are listed in Table 1. Ketoprofen was mixed with HPMC K100M and the remaining additives (mannitol, magnesium stearate and buffering agents). Formulation 1 was unbuffered, its pH value was around 6; formulation 2 was internally buffered at pH 2.5 (with citric acid and disodium phosphate), and formulation 3 at pH 10 (with sodium carbonate and disodium bicarbonate). The mixture of all components was tabletted by direct compression with a reciprocating tablet press machine (BONALS, Barcelona, Spain) equipped with cylindrical punches of 12 mm in diameter and biconvex profile.

2.3. Dissolution tests

The dissolution tests of the tablets were performed in 1000 ml of phosphate buffer pH 7.2, at 37 °C and 100 rpm, using the rotating basket (USP 23 apparatus I) (six replicates). Samples (2 ml) were taken at prefixed times and analyzed by HPLC.

Table 1
Formulation composition (mg)

	1	2	3
Ketoprofen	9.6	9.6	9.6
HPMC K100M	156.8	156.8	156.8
Mannitol	230.8	186.4	186.4
Magnesium stearate	2.8	2.8	2.8
Citric acid	–	37.4	–
Disodium phosphate	–	2.6	–
Sodium carbonate	–	–	32.34
Sodium bicarbonate	–	–	7.66

2.4. Preparation of gels

For the diffusion studies HPMC K100M gel at 0.2% containing ketoprofen was prepared. The corresponding amount of polymer was dispersed in 100 ml of ketoprofen solution (123 μg/ml) in phosphate buffer pH 7.2, with continuous stirring to obtain a homogeneous mixture. Drug–excipient ratio (ketoprofen–HPMC K100M) was 1:16, the same that for tablets. In order to complete the hydration of the polymer the gel was kept at rest overnight in a refrigerator (4–6 °C) and were brought back to room temperature prior to use.

2.5. Diffusion tests

The release of ketoprofen enantiomers from the HPMC gel was studied at 37 °C using Franz-Chien diffusion cells (six replicates). Gel samples of 2 ml were added to the donor compartment and 5.2 ml of phosphate buffer pH 7.2 were placed in the receptor compartment and maintained with constant stirring. Both compartments were separated by a membrane of 0.45 μm pore size cellulose acetate and 25 mm diameter being the effective area available for diffusion 0.785 cm^2. Once the assay was initiated, 0.5 ml samples were collected at prefixed times and analyzed by HPLC. In order to maintain a constant volume, 0.5 ml of fresh solution was added to the receptor compartment after sampling.

2.6. Analytical procedure

Ketoprofen enantiomers in the samples from dissolution and diffusion tests were determined by a previously reported stereospecific HPLC assay involving precolumn derivatization (Péhourcq et al., 1995).

The analyses were performed at room temperature using an analytical column (Nucleosil 120 C18, 5 μm, 250 × 0.4 mm, i.d.). The mobile phase consisted of phosphate buffer 0.06 M (60%) acetonitrile (40%) and triethylamine (0.1%). The flow rate was 1.3 ml/min and the detection wavelength was 254 nm for ketoprofen enantiomers and 225 nm for *S*-ibuprofen (internal standard). The assay was linear over the concentration range of 0.25–10 μg/ml for each enantiomer. Accuracy assay gave an error ranging from 0.25 to 4.75% for *R*-ketoprofen and from 0.50 to 4.00% for *S*-ketoprofen. The intra- and interday coefficients of variation ranged from 1.40 to 2.63% and from 1.52 to 3.32% for *R*- and *S*-ketoprofen, respectively. The limits of detection and quantification were calculated by analyzing in triplicate a calibration curve elaborated with low concentrations of analyte. The limits of detection were 0.0074 and 0.0076 μg/ml and the quantification limits were 0.023 and 0.022 μg/ml for *R*-ketoprofen and *S*-ketoprofen, respectively. No interfering peaks were noted with the assay.

2.7. Kinetic and statistical analysis

In order to characterize the drug release mode from the matrices, the data were fitted to the following power law equation (Peppas, 1985):

$$M_t/M_\infty = Kt^n$$

where M_t/M_∞ is the fraction of drug released up to time t, K is the kinetic constant and n is the release exponent indicative of the release mechanism.

The mean dissolution time (MDT) was also calculated. MDT is the mean ratio of the first to zero moments of the dissolution rate–time curve and it is expressed by the following equation:

$$\mathrm{MDT} = \mathrm{ACC}/M_\infty$$

where ACC is the complementary area under the accumulated dissolution curve and M_∞ is the maximum accumulated dissolution amount.

The data obtained from diffusion tests were fitted to the Higuchi equation (Higuchi, 1963). Drug diffusion coefficients in the gels were calculated for each enantiomer.

$$\frac{Q}{A} = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2}$$

where Q is the amount of drug released into the receptor phase per area unit of exposure (mg),

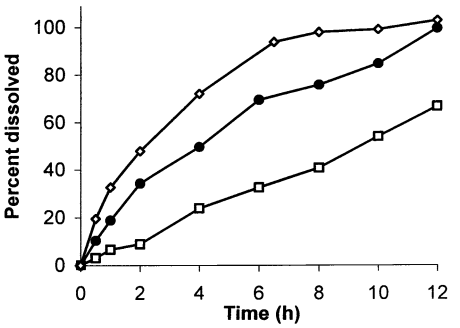

Fig. 1. Plots of cumulative percentage of dissolved racemic ketoprofen vs. time for formulations 1 (●), 2 (□), and 3 (○).

C_0 is the initial drug concentration in the vehicle (mg/ml), D is the (apparent) diffusion coefficient of drug (cm^2/s), and t is the time elapsed since the start of drug release.

According to the Higuchi theory, this equation is valid if (a) the percentage released is less than 30% of the total drug in the vehicle, (b) only a single drug species is present in the vehicle, (c) the diffusion coefficient is invariant with respect to time or position within the vehicle layer, (d) only the drug diffuses out of the vehicle, and (e) the drug reaching the receptor is removed rapidly. The experimental conditions in our study match the above assumptions.

Experimental data were fitted to the Peppas and Higuchi equations by using the WINNONLIN program (Scientific Consulting, Inc., PCnonlin, 1995). MDT calculations were done with the same program.

The paired Student's t-test was used to compare the kinetics parameters and the release of the two enantiomers in every experiment by using the statistical program SPSS® 8.0 (SPSS Inc., 1998). The significance level was set at $P < 0.05$.

3. Results and discussion

3.1. Release of racemic ketoprofen from matrix tablets

Fig. 1 shows the dissolution profiles of racemic ketoprofen for formulations 1, 2 and 3. As can be seen, there are differences between the dissolution profiles of the three matrices. Formulations 1 and 3 release practically 100% of the drug at 12 h, while formulation 2, which buffered at pH 2.5, at this time releases only 70% of the drug. Ketoprofen is a weak acid ($pK_a = 5.02$), mainly non-ionized at acidic medium, and, subsequently, its solubility in the dissolution media inside the matrix is lesser than at basic pH. This leads to a retardation in the release of the drug from formulation 2.

On the other hand, when the dissolution media penetrates into swellable matrices, the particles of the polymer swell, modifying the matrix volume and the behavior according to the solubility of the loaded drug and the characteristics of excipients. Soluble material can produce greater increases in the matrix swelling than the less soluble and show faster release rates (Efentakis et al., 1997). Ketoprofen in formulation 3 (buffered at pH 10) shows a high degree of ionization and hence a high solubility, this is the reason why its release is faster than from formulation 1.

The values of the kinetic parameters of racemic ketoprofen obtained from the data fitting to the power law equation and MDT are listed in Table 2. Hydrosolubility of the drug plays an important role in the release mechanism. The release of a substance from a matrix system is produced by two simultaneous mechanisms: erosion or diffusion, the mechanism dominating is directly related with the hydrosolubility of that substance. When

Table 2
Values of the kinetic parameters obtained for racemic ketoprofen (mean ± SD)

Formulation		K (%/h)	n	MDT (h)
1 (unbuffered)	*RS*-ketoprofen	20.62 ± 2.39	0.64 ± 0.06	4.55 ± 0.44
2 (buffered pH 2.5)	*RS*-ketoprofen	5.05 ± 2.09	1.07 ± 0.20	6.20 ± 0.54
3 (buffered pH 10)	*RS*-ketoprofen	31.45 ± 3.16	0.60 ± 0.11	2.86 ± 0.42

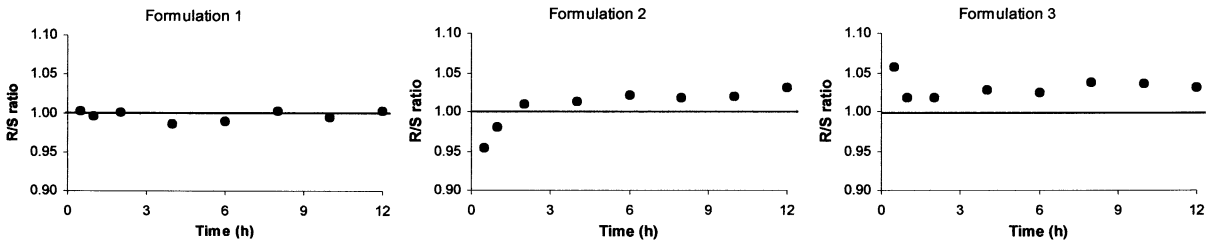

Fig. 2. R/S ratio of ketoprofen enantiomers released vs. time for formulations 1, 2, and 3.

hydrosolubility is very low the possibility of release by diffusion will be practically zero and release will take place mainly by surface erosion, giving characteristic profiles of zero-order kinetics. Conversely, if the drug is moderately or highly hydrosoluble the mechanism governing release will be diffusion (Vázquez et al., 1992). The exponent n gives an indication of the release mechanism. When n takes a value of 0.5, the drug diffuses through and is released from the polymer following a quasi-Fickian diffusion mechanism. For $n > 0.5$, an anomalous, non-Fickian solute diffusion mechanism is observed. The special case of $n = 1$ has gained importance due to its potential application in the development of swelling-controlled drug delivery systems with zero-order kinetics. This mechanism of solute transport is known as pseudo-case-II solute transport (Peppas, 1985).

The release of ketoprofen from formulations 1 and 3 is controlled by both diffusion of the drug through the hydrated matrix and the erosion of the matrix itself, because the values of n were 0.64 and 0.60, respectively. In these two formulations, ketoprofen is more soluble in the hydrated matrix and therefore may be released by diffusion, although the erosion mechanism may contribute too. These results are similar to those obtained by Efentakis et al. for flurbiprofen (Efentakis et al., 1997). Formulation 2 shows an n value of 1.07 (zero-order kinetics) which means that ketoprofen release is controlled mainly by polymer erosion due to the lesser solubility of the drug at pH 2.5.

The MDT value is different for the three formulations, with formulation 3 MDT showing the lesser value followed by that of formulation 1. The largest MDT is featured by formulation 2. These differences can be due to two factors, the different solubility of ketoprofen in the hydrated matrix and the presence of soluble material (buffering agents) in the tablets that can modify the matrix swelling and the release rates (Efentakis et al., 1997).

3.2. Release of ketoprofen enantiomers from matrix tablets

Fig. 2 shows the R/S ratio of percentage released of ketoprofen enantiomers for the three formulations. This R/S ratio shows significant differences versus unity ($P < 0.05$) for buffered formulations (2 and 3) practically at all times studied. The R-enantiomer released amount is larger than that released by the S-enantiomer for both formulations, which indicates that there is a major chiral interaction between the S-enantiomer and the excipient, and hence this enantiomer stays longer in the formulation. These results suggest that the chiral interaction between ketoprofen and HPMC may be influenced by formulation pH.

Table 3 shows the values of the kinetic parameters obtained for ketoprofen R and S-enantiomers for all formulations. The kinetic constant, K, shows significant differences ($P < 0.05$) between enantiomers only for the formulation 3. Formulation 2 shows statistical differences ($P < 0.05$) between enantiomers in the value of n and MDT.

Álvarez et al. (1999) studied the release of ketoprofen enantiomers form matrices elaborated with HPMC 15. They found larger differences in the percentage released between enantiomers, the S/R ratio at 60 min being around 3. These differences disappear when loaded drug is decreased

and drug release conditions are closed to sink conditions. Our results show the existence of a small chiral interaction between ketoprofen and HPMC. Stereoselective release depends presumably only on diffusion process (Duddu et al., 1993), although the erosion mechanism is present in the release of ketoprofen from all formulations studied. For this reason we have performed diffusion studies using gels containing only the drug and HPMC K100M. In this way we can eliminate the erosion process present in the release of ketoprofen from tablets and study only the influence of the diffusion on the stereoselectivity.

3.3. Diffusion study

Fig. 3 shows the amount of ketoprofen released (%) from the gel formulation versus the square root of time. According to the Higuchi equation (Higuchi, 1963) if the percentage of drug release is not too large ($< 30\%$) and if the membrane is not a rate limiting membrane, a plot of the cumulated quantity versus the square root of time should be linear. When the percentage release data of ketoprofen from the gels were plotted versus the square of time, straight lines were obtained and an excellent linear relationship ($r > 0.99$) was observed. This suggests that the data followed the criteria of Higuchi's equation, and the membrane is not a rate limiting membrane.

Diffusion coefficients of racemic ketoprofen and its enantiomers were calculated according to the Higuchi diffusion model and they are presented in Table 4. There are significant differences ($P < 0.05$) in the value of diffusion coefficient between ketoprofen enantiomers. The diffusion coefficient of *R*-ketoprofen is higher than that from *S*-ketoprofen indicating that this last enantiomer presents a larger interaction with HPMC K100M. This result is in agreement with that obtained in the matrices dissolution study. Fig. 4 shows the R/S ratio of ketoprofen released from the gel in comparison with formulation 1 (unbuffered tablet). The ratio of percentage released from tablets is close to unity for all times while the R/S ratio obtained from gel ranged from 1.07 to 1.29. The higher stereoselectivity found in the diffusion study confirms the existence of a chiral interaction between ketoprofen and HPMC K100M and that enantioselectivity increases in absence of erosion process. Drug–excipients diffusion studies are simple and fast tests that could be used to confirm or discover the existence of chiral interactions between drugs and excipients avoiding the influence of any other factor in the chiral interaction.

4. Conclusions

The amount and the mechanism of the release of racemic ketoprofen from formulations elaborated are conditioned mainly by the pH of the matrix. When individual enantiomers are evaluated, a major chiral interaction is observed between the *S*-enantiomer and the HPMC K100M compared with the *R*-enantiomer, which depends on the pH formulation. This fact implies a higher amount released of *R*-ketoprofen from matrices elaborated with the racemic drug.

The results obtained in the diffusion studies with ketoprofen show that a chiral interaction

Table 3
Values of the kinetic parameters obtained for ketoprofen enantiomers (mean ± SD)

Formulation		K (%/h)	n	MDT (h)
1 (unbuffered)	*R*-ketoprofen	20.50 ± 2.47	0.64 ± 0.06	4.57 ± 0.44*
	S-ketoprofen	20.74 ± 2.32	0.64 ± 0.06	4.52 ± 0.43*
2 (buffered pH 2.5)	*R*-ketoprofen	5.03 ± 2.06	1.07 ± 0.20*	6.22 ± 0.54*
	S-ketoprofen	5.06 ± 2.12	1.06 ± 0.20*	6.17 ± 0.53*
3 (buffered pH 10)	*R*-ketoprofen	31.85 ± 3.19*	0.60 ± 0.10	2.88 ± 0.42
	S-ketoprofen	31.04 ± 3.13*	0.60 ± 0.11	2.85 ± 0.42

*Significant statistical differences between both enantiomers ($P < 0.05$).

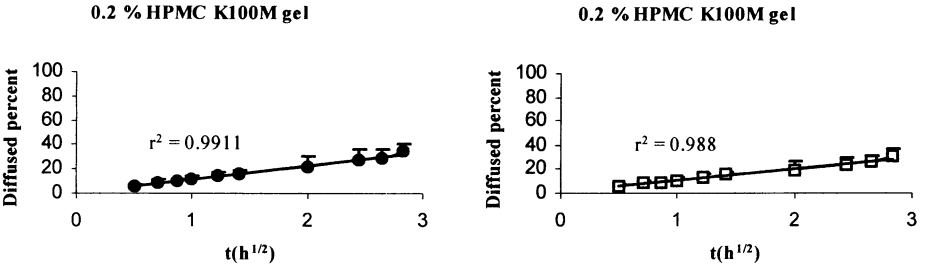

Fig. 3. Diffusion plots of (●) *S*-ketoprofen and (□) *R*-ketoprofen from 0.2% HPMC gels (mean ± SD).

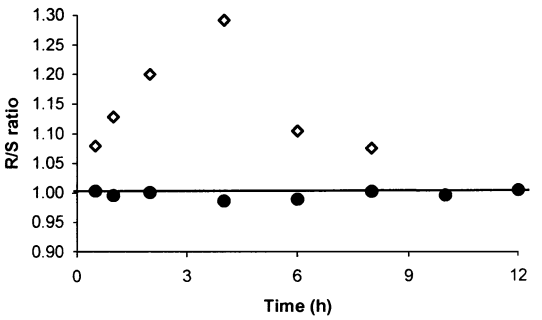

Fig. 4. *R*/*S* ratio of ketoprofen enantiomers released vs. time for (●) formulation 1 (unbuffered tablet) and (□) gel.

Table 4
Values of ketoprofen diffusion coefficients (mean ± SD) from 0.2% HPMC K100M gels

Gel		Diffusion coefficients ($10^{-3} \times cm^2/min$)
0.2% HPMC K100M	*R*-ketoprofen	6.435 ± 1.501*
	S-ketoprofen	5.730 ± 1.050*
	RS-ketoprofen	6.083 ± 1.228

*Significant statistical differences between both enantiomers ($P < 0.05$).

drug–excipient was established and that the absence of the erosion process strengthens the enantiomeric differences observed in the release from tablets. Thus, cell diffusion is an interesting system to study the enantioselective interaction between drugs and excipients.

Although the differences between both enantiomers in the studies were not relevant from biopharmaceutical and clinical points of view, they turned out to be significant ($P < 0.05$). Pharmaceutical dosage forms designed to obtain a stereoselective release, should focus on the achievement of formulations delivering the drug only by a diffusion mechanism. Moreover, the pH of formulations is another parameter that should be considered important in the development of this kind of formulations.

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