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Stereoselective Drug Release From Ketoprofen and Ricobendazole Matrix Tablets

COVADONGA ÁLVAREZ, JUAN J. TORRADO,* AND RAFAEL CADÓRNIGA
Departamento de Farmacia y Tecnología Farmacéutica, Universidad Complutense de Madrid, Plaza Ramón y Cajal, 28040 Madrid, Spain

ABSTRACT Crystalline characteristics of racemic, pure R and S enantiomers and physical mixtures of Ketoprofen (KET) have been studied by DSC and X-ray diffractometry. Aqueous solubilities were 182.6 ± 9.1 μg/ml for racemic KET, 259.6 ± 6.6 μg/ml for R-KET, and 304.3 ± 2.7 μg/ml for S-KET. Matrix tablets made with racemic and physical mixtures of KET show stereoselective drug release, which is faster for S-KET than for R-KET. This effect is more marked when the chiral excipient hydroxypropylmethylcellulose (HPMC) is used in place of the achiral Eudragit RL. Stereoselectivity of release is also affected by the amount of KET. Similar results were obtained when another chiral drug with low solubility, Ricobendazole (RBZ), is used. Depending on the excipient and drug dosage, more or less marked stereoselective drug release is obtained in RBZ matrix tablet formulations. *Chirality 11:611–615, 1999.*

KEY WORDS: ketoprofen; chirality; drug release; matrix tablets; ricobendazole

A large number of potent and effective therapeutic agents are administered as racemic mixtures, although in most instances only one of the stereoisomers exhibits the desired pharmacological effect.[1] This is now changing and many racemic drugs are beginning to be replaced by enantiomerically pure drugs.

Although there are many papers related to pharmacological aspects of enantiomeric drugs, there are few available data about pharmaceutical differences. If the solid structures of these products are different, this may affect many properties. Of special importance in pharmaceutics is solubility and its relation with drug release. Release of enantiomeric drugs has been studied previously for propanolol,[2] verapamil,[3] ibuprofen,[4] and salbutamol.[5] Results differ between authors and drugs. It seems that chirality has little effect, if any, on drug release. Frequently, significant enantiomeric differences on drug release formulations are produced when a chiral excipient, usually hydroxypropylmethylcellulose (HPMC), is used. The effect on drug release produced between two chiral products, drug and excipient, could be considered as a new kind of interaction.

The aim of this work is to study the effect of chirality on solubility and drug release from matrix tablets formulations. To this end two chiral drugs were chosen: Ketoprofen (KET) and Ricobendazole (RBZ). Ketoprofen is a nonsteroidal antiinflammatory drug and Ricobendazole is a benzimidazole carbamate antihelminthic drug.[6] The solid states of the different drugs used as raw materials were characterized by differential scanning calorimetry (DSC) and X-ray diffractometry. The aqueous solubilities of the different materials were also determined. Matrix tablets were produced with two different excipients: a chiral one, HPMC, and an achiral acrylic polymer, Eudragit RL. Drug release from the different formulations was assayed by spectrophotometry and HPLC and the possible effect of enantiomerism was evaluated.

MATERIALS AND METHODS

Chemicals

Racemic Ketoprofen was obtained from Roig Farma S.A. (Tarrasa, Spain), Ketoprofen enantiomers were kindly provided by Menarini (Barcelona, Spain), and racemic Ricobendazole was supplied by Chemo Iberica (Alcalá de Henares, Spain). HPMC (Pharmacoat 615) was obtained from ISISA (Barcelona, Spain) and Eudragit RL was supplied by Rhom (L'Hospitalet, Spain). All other chemicals were of analytical grade.

Differential Scanning Calorimetry

The DSC patterns from the racemates, the pure enantiomers, and physical mixtures of both enantiomers of the KET samples were determined with a Mettler 8000 thermal analyzer connected to a data station. Each sample (5 mg in aluminum pans) was heated at a heating rate of 10°C/min from 20 to 150°C.

X-ray Diffractometry

X-ray diffractograms of the racemates, the pure enantiomers, and physical mixtures of both enantiomers from KET samples were carried out with a Philips X'Pert-MPD diffractometer (C.A.I. X-ray diffraction, U.C.M.), with Ni-filtered Cu Kα radiation. The samples were analyzed over a 2θ range of 5–40° and with a step size of 0.03° and a time per step of 1 s.

*Correspondence to: J.J. Torrado.
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Table 1. Composition of different Ketoprofen tablet formulations

	K_1 (mg)	K_2 (mg)	K_3 (mg)	K_4 (mg)	K_5 (mg)	K_6 (mg)	K_7 (mg)	K_8 (mg)
Racemic KET	200							
R-KET		100		100	100	50	25	12,5
S-KET		100	100	500	100	50	25	12,5
HPMC15	400	400	500			200	100	50
Eudragit RL					400			

Solubility Studies

The solubilities of KET and RBZ were determined at 37°C to quantify differences in the solubility of the racemate and pure enantiomers. To this end, excess drug was added to distilled water and shaken at 37°C. After equilibrium was attained, the supernatant was filtered (0.45 μm) and assayed by spectrophotometry or HPLC.

Matrix Tablet Formulations

Several types of matrix tablets were prepared: The composition of each formulation is listed in Tables 1 and 2. Ingredients of each formulation were mixed in a mortar and sieved through a 500-μm sieve. The final mixtures were formed into tablets by direct compression with an eccentric tablet press machine (Bonals).

Dissolution Rate Studies

The dissolution tests were performed in 900 ml of phosphate buffer at pH 7.2, at 37°C and stirred at 150 rpm, using a modified USP XXIII apparatus 1 (rotating baskets; six replicates). Samples of 5 ml were collected at 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, and 1440 min, filtered, analyzed by spectrophotometry, and immediately stored until a second HPLC analysis was performed.

Analytical Procedures

Spectrophotometry assay. Samples collected during the solubility and the dissolution rate tests were assayed by UV spectrophotometry (UV–vis spectrophotometer, Beckman DU-7), at 260 nm for the KET and at 290 nm for the RBZ samples. Calibration solutions of KET and RBZ were prepared over the range 1–20 μg/ml. This analytical technique proved to be sensitive, selective, accurate, and reproducible for the determination of KET and RBZ under the conditions described.

Chromatographic assay. In order to isolate and quantify KET and RBZ enantiomers, a modular HPLC (Gilson, USA) equipped with a 306 piston pump, 116 UV–vis detector, SP-4270 integrator, and 231 XL sampling injector was employed.

KET was analyzed according to Menzel-Soglowek et al.[7] A chiral AGP column (ChromTech AB, Sweden, 100 mm × 4.0 mm ID) was used. A mixture of 0.5% 2-propanol in 0.02 *M* aqueous phosphate buffer with 5 m*M* DMOA and 0.1 *M* NaCl at pH 6.8 was used as mobile phase, at 0.9 ml/min flow rate. The injection volume was 20 μl. The UV detection was performed at 260 nm.

The procedure for RBZ analysis was that according to Lienne et al.[8] A mobile phase of 8 m*M* phosphate buffer, pH 7.0, containing 1% 2-propanol was used, flow rate 0.9 ml/min. The UV detection was performed at 290 nm.

Table 2. Composition of different Ricobendazole tablets

	R_1 (mg)	R_2 (mg)	R_3 (mg)	R_4 (mg)
RBZ	200	200	50	20
HPMC 15	400			
Eudragit RL		400	100	40

Statistical Analysis

According to Duddu et al.[2] we have used the paired *t*-test ($P < 0.05$) because this method allows us to compare the concentrations of the two enantiomers in a given experiment and is not affected by variations between experiments.

RESULTS AND DISCUSSION

Figure 1 shows the DSC results for the KET. Pure R- and S-KET have lower melting points than racemic KET. When a physical mixture of R- and S-KET is prepared at a ratio 1:1, its thermal behavior is different from the pure enantiomers and racemic samples.

Figure 2 shows X-ray diffractograms for the different

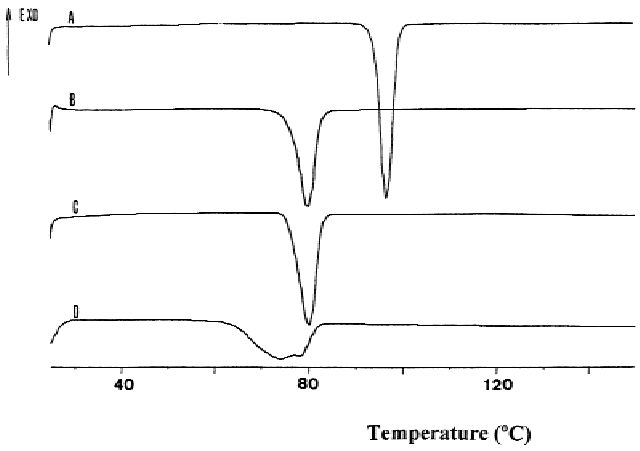

Fig. 1. DSC curves of the following KET samples: racemic KET (A), S-KET (B), R-KET (C), and physical mixture (D).

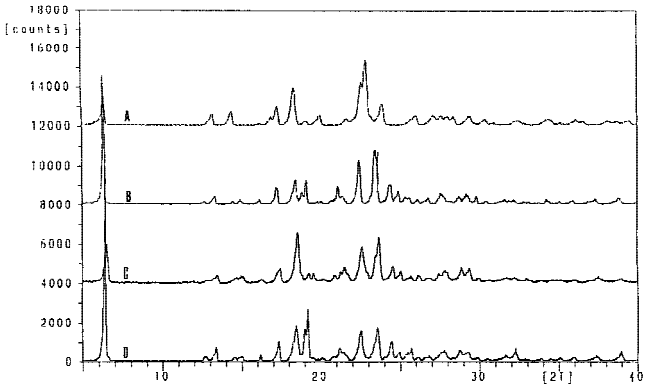

Fig. 2. X-ray diffraction patterns of the following KET samples: racemic KET (A), S-KET (B), R-KET (C), and physical mixture (D).

KET samples which can be correlated with the DSC results. X-ray diffractograms for the physical mixture are similar to those of pure R- and S-KET. However, X-ray results for the racemic sample is quite different, suggesting differences in crystalline structures. Similar results have been previously reported by other authors and are summarized by Li and Grant.[9] For many products, racemic crystals have been reported as more stable and denser than their chiral counterparts. These differences in crystalline characteristics can lead to differences in solubility.

Table 3 shows relationship between melting points obtained from DSC experiments and solubility studies. As can be seen there is a correlation between melting points and solubilities.[10] Melting points of solids are indicators of molecular cohesion and can be used as a guide to solubility in closely related products.[11] The crystalline structure of racemic KET seems to be denser and more stable than the pure enantiomers. This leads to a higher melting point than the other KET samples and, so, lower solubility.

In order to test if solubility differences can affect drug release, several controlled release formulations were produced. Figure 3 shows S/R KET ratios for two different matrix tablets. If there are no differences in drug release between R- and S-KET enantiomers, the S/R ratio should be close to unity. As can be seen there is a significant statistically ($P < 0.05$) difference. In both formulations the S-enantiomer is released faster than the *R* enantiomer. Figure 3 also shows that there are significant ($P < 0.05$) differences between S/R ratios of K_1 (formulation made with the racemate) in comparison to K_2 (formulation made with the physical mixture) K_2 being the one which shows more stereoselectivity in drug release. For the next experiments, matrix tablets were produced with physical mixtures of KET enantiomers.

Table 3. Melting point and solubility

	Melting point (°C)	Solubility (μg/ml)[a]
Racemic KET	94.1	182.6 ± 9.1
S-KET	76.5	304.3 ± 2.7
R-KET	75.8	259.6 ± 6/6

[a]Mean value of three different samples ± SD.

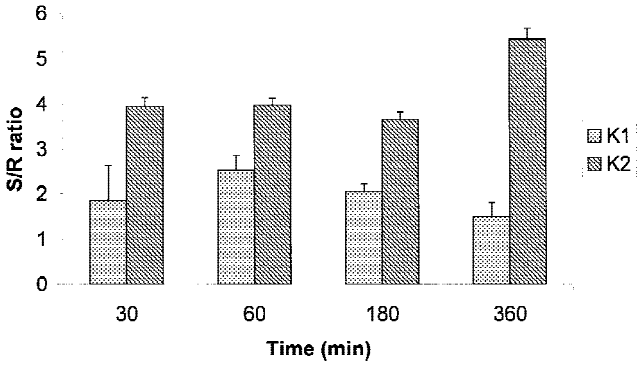

Fig. 3. S/R ratio of KET released at different times for two formulations: (dotted bars) K_1 and (hatched bars) K_2.

Figure 4 shows the S/R ratio obtained using two different matrix tablet formulations made with the physical mixture and HPMC or Eudragit RL. HPMC is a chiral excipient which has been used previously to study possible interactions with chiral drugs.[2,5] Experiments with two different types of Eudragit, RL and RS, were previously done in order to select the one giving similar drug release to the HPMC formulation. This was achieved with Eudragit RL, classified as formulation K_5. Figure 4 shows the ratio of the enantiomer ratio for release against time. Although the ratio was found to be greater than unity for both formulations, only the formulation made using the chiral excipient HPMC showed significant ($P < 0.05$) differences in drug release.

In previous papers the effect of HPMC upon other chiral drugs have been studied. For propanolol hydrochloride,[2] significant differences were found between enantiomers. However, for salbutamol sulfate no significant differences were seen.[5] Probably, differences between authors and drugs can be related to drug solubility. Salbutamol sulfate is a very soluble drug (approximately 25%), and the effect of enantiomerism is not relevant. For other drugs, e.g. propanolol or verapamil hydrochloride, which are soluble in water (approximately 5%), significant effects were reported. KET is even less soluble (approximately 0.03%) and seems to be more affected than the other drugs. In order to check the results reported for KET, we have examined another

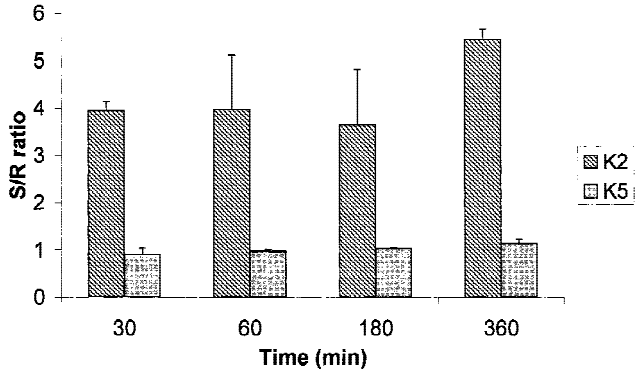

Fig. 4. S/R ratio of KET released at different times for two formulations: (hatched bars) K_2 and (shaded bars) K_5.

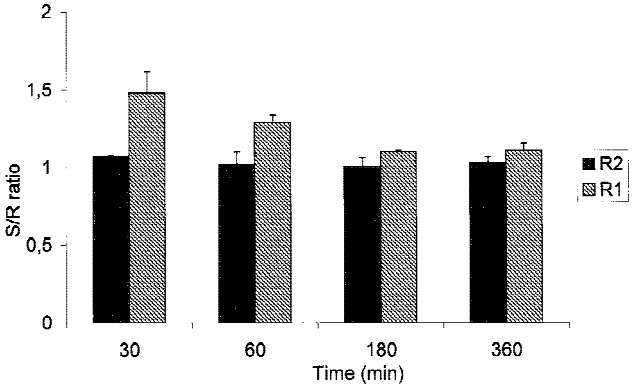

Fig. 5. (–)/(+) ratio of RBZ released at different times for two formulations: (hatched bars) R_1 and (shaded bars) R_2.

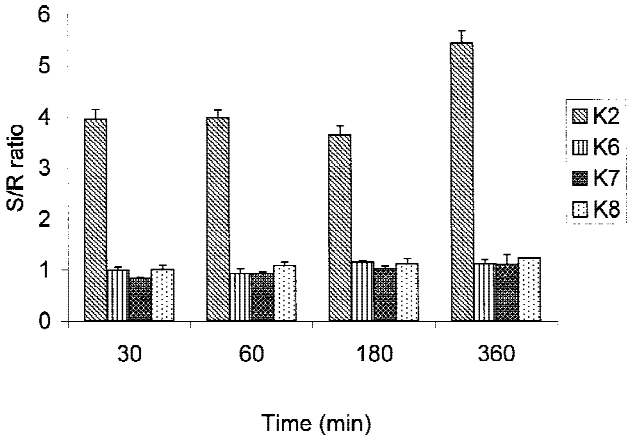

Fig. 7. S/R ratio of KET released at different times for the following KET formulations: (hatched bars) K_2, (lined bars) K_6, (dark shaded bars), K_7, and (dotted bars) K_8.

poorly soluble chiral drug, RBZ, in the same way release has been studied. Pure RBZ enantiomers were not available for our experiments, so neither DSC nor diffractometry studies were performed. Solubility studies were done with racemic RBZ. Significant ($P < 0.05$) differences in solubility were determined after HPLC chiral assay of saturated solution of racemic RBZ. The aqueous solubility was of 59.1 μg/ml for (–)-RBZ and 31.1 μg/ml for (+)-RBZ.

The effect of matrix excipient (HPMC or Eudragit) on drug release was studied with RBZ formulations. As can be seen in Fig. 5, both formulations give a (–)/(+) RBZ ratio higher than unity. These differences are more important for the formulation made with HPMC. These results agree with those described for the KET formulations and plotted on Fig. 4.

Figure 6 shows the drug release profiles for three different KET matrix tablet formulations made with a physical mixture (K_2), S enantiomer (K_3), and R enantiomer (K_4). Drug released from the different HPMC tablets was assayed by spectrophotometry. As can be seen, a typical sigmoid release is shown for each formulation. Similar profiles were reported previously with HPMC matrix tablets.[2] The formulation with highest solubility is K_3 (only the S enantiomer) followed by K_4 (only the R enantiomer) and the formulation with the lowest solubility is K_2, made with the physical mixture. These results correlate with solubility, showing the same rank order. In conclusion, in our experimental conditions the S enantiomer always significant ($P < 0.05$) greater release profiles than the R enantiomer. Due to the low solubility of KET and RBZ, drug release tests at therapeutic dosages cannot be made. In order to elucidate the possible effect of drug saturation during the dissolution test, more matrix formulations were produced. To this end different formulations of KET and RBZ at lower dosages than those previously reported were elaborated. Matrix tablets were made maintaining the proportions of dosage to available tablet surface. The results of the dosage on drug release ratio are shown in Figs. 7 and 8. When dosage is decreased and drug release conditions are closer to sink conditions, the effect of enantiomerism on drug release is less important. For each of the RBZ formulations tested, (–)-RBZ dissolved at a significantly ($P < 0.05$) faster rate than (+)-RBZ. At low RBZ dosages (50 and 20 mg) a smaller effect of enantiomerism on drug release was observed.

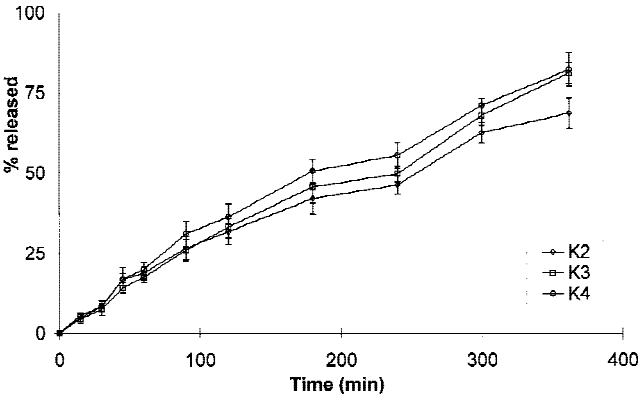

Fig. 6. Drug release profiles from three different KET formulations: (◇) K_2, (□) K_3, and (○) K_4.

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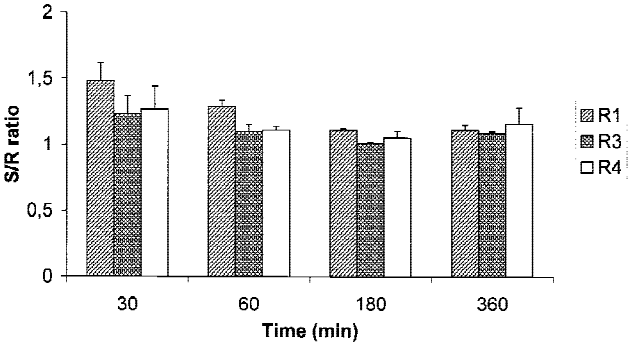

Fig. 8. (–)/(+) ratio of RBZ released at different times for different RBZ formulations: (hatched bars) R_1, (cross-hatched bars) R_3, and (open bars) R_4.

Picornel (Chemo Ibérica) for providing us with racemic RBZ.

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