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Ketoprofen pulsatile absorption from 'multiple unit' hydrophilic matrices

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Summary

Ketoprofen is an analgesic and non-steroidal anti-inflammatory drug (NSAID) usually employed in the therapy of rheumatic disorders, and is rapidly eliminated from the blood after dosing (plasma half-life 1–3 h). Therefore, extended release dosage forms of this drug may be beneficial, but constant drug release is not always the optimal choice for its administration, since, owing to circadian rhythms, some pathologies (such as rheumatoid disorders) may require different, consecutive pulses of drug. In this work, an extended-release oral formulation of ketoprofen was prepared. It is a 'multiple-unit' formulation constituted by four hydrophilic matrices of identical composition, prepared with hydroxypropylmethylcellulose (Methocel®) and placed in a gelatin capsule. Each unit contains 50 mg of drug. In vivo tests carried out on 12 healthy volunteers demonstrated that pulsatile plasma levels (two peaks at second and eighth hours after dosing) correspond to an in vitro fairly constant drug release. In vitro and in vivo test results were also compared with those obtained from a commercial ketoprofen oral modified release formulation (capsule containing pellets).

Introduction

Ketoprofen (2-arylpropionic acid derivative) is an important analgesic and non-steroidal anti-inflammatory drug, also with antipyretic properties, whose mechanism of action is the inhibition of prostaglandin synthetase (Avouac et al., 1988).

This drug is used in the therapy of rheumatic disorders, such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, and is also used to relieve pains of non-rheumatoid origin (Avouac et al., 1988).

Its usual dose is from 50 to 100 mg twice daily, orally (Martindale, 1989), and among anti-rheumatic agents it is one of the most well tolerated.

Like other non-steroidal anti-inflammatory agents (such as ibuprofen, diclofenac and indomethacin), ketoprofen is rapidly eliminated from the blood after dosing (Houghton et al., 1984), its plasma elimination half-life being 1–3 h (Jamali and Brocks, 1990), and in order to maintain therapeutic plasma levels the drug must be administered at least twice daily.

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Thus, in certain therapies, extended-release preparations can be considered desirable, since they would allow once-daily administration of the drug, with consequent improvement in patient compliance.

Some extended-release preparations that permit constant blood levels of ketoprofen to be maintained over 8–12 h after dosing, are already known (Borsa et al., 1983; Drugs of Today, 1983).

However, constant drug release is not always the optimal choice for controlled drug administration, since some therapeutic situations could require that extended drug release is not constant, but is given in different consecutive pulses, for example, in relation to the course of painful symptoms of rheumatoid pathologies. Consecutive drug pulses could also be helpful in maintaining constant drug levels in the case of variability of drug absorption throughout the GI tract.

In a previous work (Conte et al., 1989), an ibuprofen pulsed release dosage form, constituted by a three-layer tablet (two doses of the drug and an intermediate gelling layer) was prepared. This formulation showed bimodal drug release both in vitro and in vivo.

In addition, certain types of hydroxypropylmethylcellulose ethers (HPMCs), such as Metolose®, have recently been proposed and used as polymeric materials able to give bimodal drug release profiles when mixed with drugs and compressed into tablets (Shah et al., 1989).

The aim of this work was the design and preparation of an oral extended-release therapeutic system. It is a multiple-unit formulation consisting of four hydrophilic matrices of identical composition, prepared with hydroxypropylmethylcellulose (Methocel® K4M), each containing 50 mg of drug and placed in a gelatin capsule.

In vitro and in vivo tests of the multiple-unit formulation were carried out and the results obtained were compared with those of a commercial ketoprofen oral modified release formulation (Oruvail®, capsule containing pellets), with a drug content of 200 mg.

Oruvail® capsules contain ketoprofen controlled-release pellets, with a ketoprofen layer deposited onto a central core coated with a dialyzing membrane (Drugs of Today, 1983).

Materials and Methods

Materials

Ketoprofen (Società Italiana Medicinali Scandicci, Firenze, Italy; MW = 254.29, m.p. = 93–95 °C, dvs = 9.89), hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington, U.K.), mannitol (USPXXII grade, Carlo Erba, Milano, Italy), polyvinylpyrrolidone (Plasdone® K29-32, GAF Corp., Wayne, NY, U.S.A.), magnesium stearate (USP XXII grade, Carlo Erba, Milano, Italy) and colloidal silica (Syloid® 244, Grace, GmbH, Worms, Germany) were obtained from the indicated sources.

Preparation of the multiple-unit formulation (KTF system)

The hydrophilic matrices constituting the multiple-unit formulation were prepared as follows: 500 g of ketoprofen, 375 g of hydroxypropylmethylcellulose and 200 g of mannitol were mixed (Erweka LK5, Heusenstamm, Germany; mixing time: 20 min) and the resulting mixture was wetted with 375 ml of a 20% w/v polyvinylpyrrolidone alcoholic solution.

The wet mixture was forced through a 710 μm screen in order to obtain a granulate, which was partially dried in a circulating hot air oven at 40 °C, forced again through a 420 μm screen and then dried completely (residual moisture $< 2\%$).

The dried granulate was mixed in a Turbula apparatus (type T2A, Basel, Switzerland) with 5 g of magnesium stearate and 2.5 g of colloidal silica, both previously sieved (300 μm) (mixing time: 10 min).

The units were prepared tabletting the resulting mixture with a reciprocating tablet press machine (Korsch EKO, Berlin, Germany), equipped with 7 mm convex punches. The compression force was about 25 kN.

Each unit has the following composition: ketoprofen, 50 mg; hydroxypropylmethylcellulose, 37.5 mg; mannitol, 20 mg; polyvinylpyrrolidone, 7.5 mg; magnesium stearate, 0.5 mg; colloidal silica, 0.2 mg.

The multiple-unit formulation (KTF system) was prepared by placing four tablets in a gelatin capsule Coni Snap Supro A (Capsugel, Basel,

Switzerland). Total ketoprofen content of the formulation was 200 mg.

In vitro release tests

The release tests of the KTF system and Oruvail® capsules were performed in 1000 ml of simulated intestinal fluid (pH 7.5) without enzymes, at 37 °C, using the USPXXII dissolution test apparatus 2 (six replicates), with the paddle rotating at 100 rpm.

The capsules containing either the four ketoprofen units or the pellets were placed directly in the dissolution medium, and after a few minutes the capsule shells dissolved.

An automatic sampling and analysis system was used and the ketoprofen concentration was spectrophotometrically determined at 262 nm (Spectracomp 602, Advanced Products, Milano, Italy).

In vivo studies

The study involved 12 healthy, adult, volunteers (4 males and 8 females; age range 24–42 years).

The subjects, after fasting, received no medications in the week preceding the administration of ketoprofen.

The study was designed as a cross-over evaluation with wash-out of 15 days, with each subject receiving a single oral administration of the following dosage forms: (a) KTF system (four units each containing 50 mg of drug, in a gelatin capsule). (b) Oruvail® (gelatin capsule containing pellets and corresponding to 200 mg of drug).

Blood samples (5 ml) were collected at 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, and 24 h after the administration of the dose.

Ketoprofen content was determined by an HPLC method (Upton et al., 1980).

Results

In vitro release tests

In Fig. 1 the release profile of the KTF system is compared with that of commercial Oruvail®. For each system, six determinations were made, with the results being highly reproducible; thus, only mean values are reported.

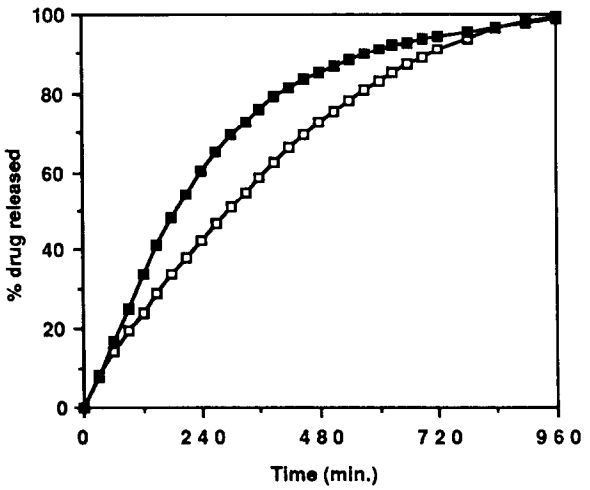

Fig. 1. Mean ($n = 6$) release profiles of (□) KTF system and (■) Oruvail®.

Extended release of ketoprofen at a fairly constant rate is obtained for about 12 h (90% of dissolved drug) and the total amount of dissolved drug (100%) is achieved within 16 h.

Comparison of the two profiles indicates that ketoprofen is released more quickly from Oruvail® capsules (about 80% of dissolved drug after 6 h), than from the KTF system (about 80% after 10 h).

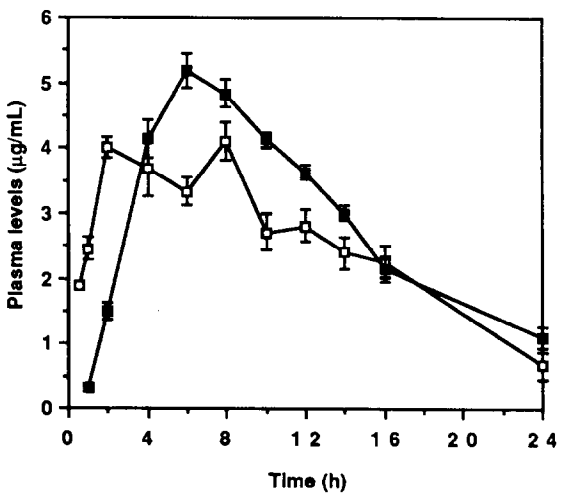

Fig. 2. Mean plasma concentration-time profiles: (±SE) ($n = 12$) of (□) KTF system and (■) Oruvail®.

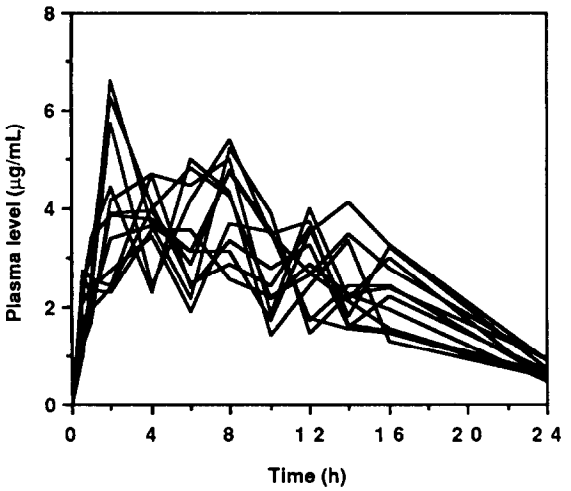

Fig. 3. Plasma concentration-time profiles of the 12 subjects after administration of KTF system.

In vivo studies

Fig. 2 shows the mean plasma profiles obtained after administration of the two formulations.

Individual plasma concentration-time profiles are given, vs time, in Figs 3 and 4, for the KTF system and for Oruvail®, respectively.

The mean plasma profile of the KTF system is characterized by two peaks, the first (4.02 μg/ml) at the second hour after dose administration and the second one (4.11 μg/ml) at the eighth hour.

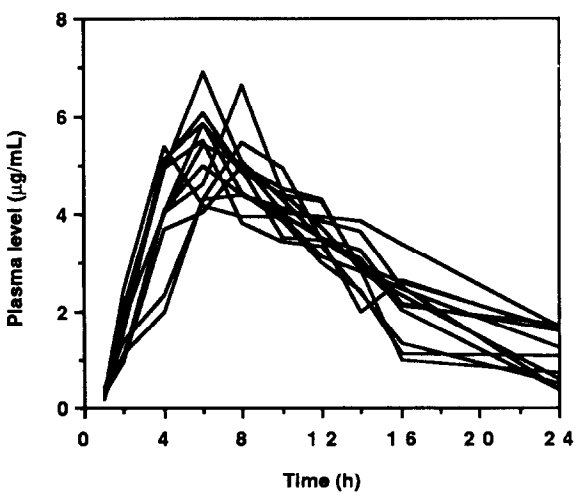

Fig. 4. Plasma concentration-time profiles of the 12 subjects after administration of Oruvail®.

TABLE 1

Pharmacokinetic parameters (mean ± SE) (n = 12)

Formulation	C_{max} (μg/ml)	T_{max} (h)	AUC (μg ml^{-1} h^{-1})	$T_{1/2}$ el. (h)	MRT (h)
KTF	5.0 ± 0.3	6.0 ± 1.0	60.5 ± 1.5	9.1 ± 0.9	14.8 ± 1.1
Oruvail®	5.6 ± 0.2	6.5 ± 0.4	67.4 ± 2.1	7.2 ± 0.7	13.1 ± 1.0

The pharmacokinetic parameters (±SE) of the two formulations are listed in Table 1.

Plasma concentrations of the KTF system are significant until the twenty-fourth hour after dosing. Furthermore, the apparent plasma elimination half-life estimated for this formulation (9.1 ± 0.9 h; mean ± SE) is much higher than that quoted for the drug (1–3 h), indicating that drug absorption occurs over an extended period of time.

The estimated mean AUC from 0 to 24 h is 60.5 μg ml^{-1} h^{-1}.

From individual plasma level profiles (Fig. 3), it may be observed that all the subjects exhibited at least two concentration peaks.

For the Oruvail® system, maximum plasma concentration is observed at 6.5 h (mean value), somewhere in between the first and second peak observed for the KTF system.

The estimated mean AUC from 0 to 24 h is 67.4 μg ml^{-1} h^{-1}.

The terminal apparent plasma elimination half-life observed for Oruvail® (7.2 ± 0.7 h) is significantly greater than that quoted for the drug, thus confirming the ability of the dosage form to sustain drug release.

Individual plasma profiles (Fig. 4) confirm the presence of a single concentration peak in all subjects and provide evidence of the small inter-individual variability.

The pharmacokinetic results for Oruvail® agree with previously published data (Drugs of Today, 1983).

Discussion and Conclusions

In vivo tests demonstrate that the multiple-unit system that we prepared (KTF) determines pul-

satile plasma levels (two peaks at the second and eighth hour after dosing) and that this behaviour is not predictable by the corresponding in vitro USP test (constant drug release).

Since no enterohepatic recirculation of this drug occurs (Jamali et al., 1990), the pulsatile plasma level could be due to a progressive in vivo disintegration/erosion process of the gelled hydrophilic matrices, and consequent drug dissolution/absorption in consecutive pulses.

These results are in agreement with data previously reported by Wilson et al. (1989) who observed bimodal in vivo release patterns for hydrophilic matrices containing ibuprofen, without any evidence of such behaviour from in vitro data.

In our case (KTF system), the presence of more than two plasma peaks in a few subjects may be explained by the multiple-unit nature of the system under consideration.

The lack of multi-modal release from in vitro tests is probably due to the fact that the main factors controlling the drug release (temperature, pH, stirring rate, etc.) exert no influence on the disintegration/erosion of the gelled matrix.

The different plasma profile obtained from Oruvail® capsules, characterized by the absence of pulsatile behaviour, could be due to the fact that Oruvail® capsules contain modified release pellets that, subsequent to oral administration and rapid dissolution of the capsule, are distributed in the bowel.

Since the pellets are constituted by a core coated with the dialyzing membrane, they are not subject to erosion, and consequently allow constant drug diffusion.

The results of in vitro and in vivo tests confirm that by using hydrophilic matrices, which are generally believed to provide constant drug release, it is possible to achieve pulsatile plasma levels, and that this possibility is emphasized through the use of a system based on four units.

This observed pulsatile in vivo drug release may serve to maintain plasma levels of ketoprofen over a 24 h period, which is useful in the treatment of rheumatic diseases. Moreover, from a biopharmaceutical point of view, comparison of the pharmacokinetic parameters of the two formulations (C_{max}, T_{max}, AUC, $T_{1/2}$ el., MRT) provides evidence of the bioequivalence of the two products, as far as their extended release action is concerned.

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