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(54) Oral ketoprofen formulation

(57) Delayed release ketoprofen formulations are in the form of microcapsules and comprise a core containing: 20–60% by weight of ketoprofen; 10–40% by weight of a sphere-forming binder; and 20–70% of a non-toxic, inert inorganic material having a specific gravity in the range 1.5–3.5 and less than 5% moisture; and an enteric coating.

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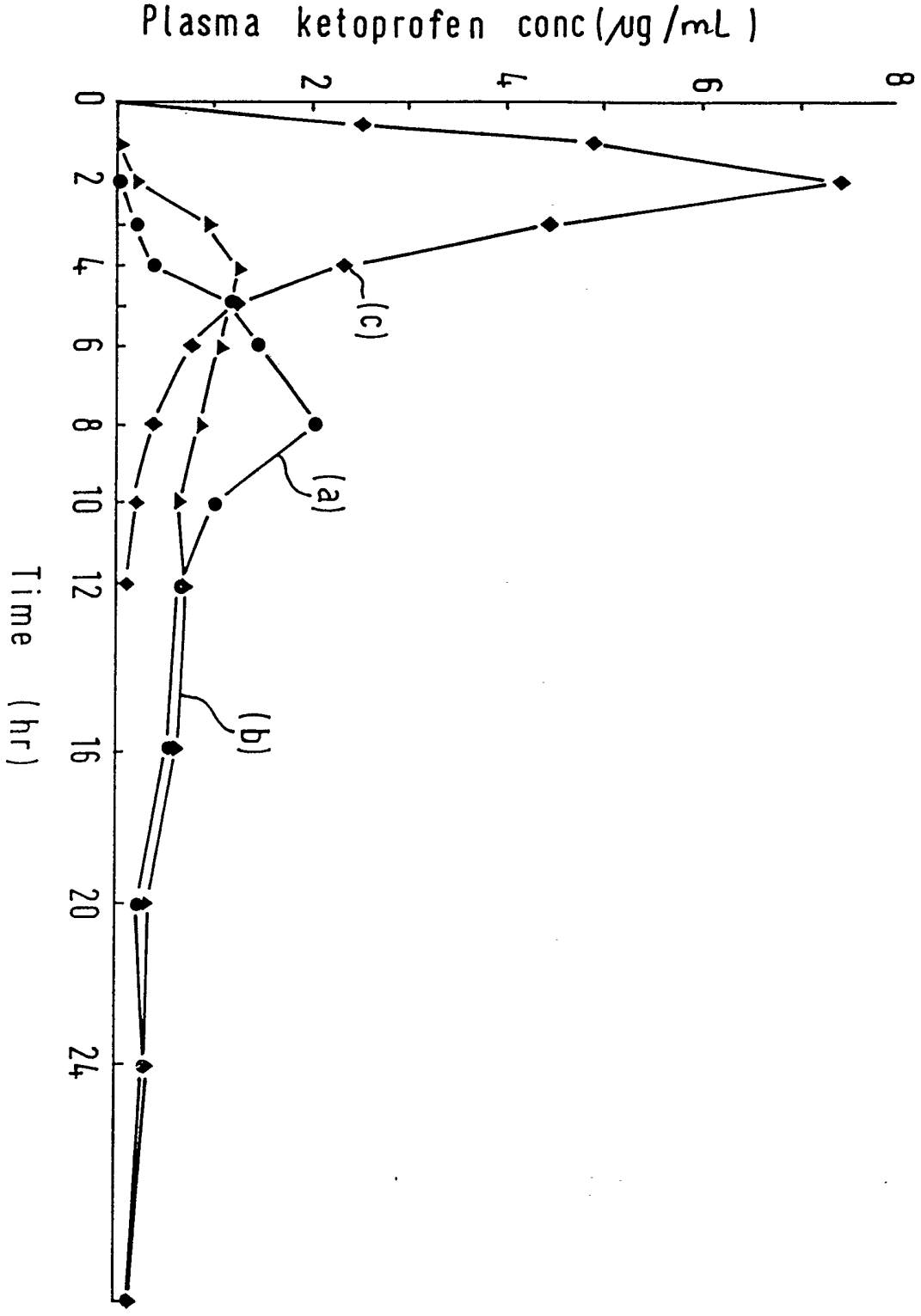
Plasma ketoprofen conc (μg/mL)
0
2
4
6
8
Time (hr)
0
2
4
6
8
10
12
16
20
24
(a)
(b)
(c)

SPECIFICATION

Controlled release ketoprofen pharmaceutical formulation

This invention relates to a controlled release ketoprofen pharmaceutical formulation. More particularly, the invention relates to a pharmaceutical formulation for oral administration of ketoprofen having a controlled rate of progress and drug release along the gastro-intestinal tract.

Various controlled or sustained release pharmaceutical formulations are known. In general, the sustained release of active ingredient may be achieved by the use of special polymer coatings or membranes which allow a progressive release of active ingredient and may be influenced by particular environmental conditions, such as pH.

Most drugs have a unique profile of activity *in vivo* and pharmaceutical formulations have to be specifically formulated to achieve the desired profile of activity, in particular, plasma concentration levels must in general be accurately controlled. Patient compliance is also important and a major factor in ensuring that the desired effect of a drug is achieved. Accordingly, a pharmaceutical formulation for once or twice daily administration is favoured. Many drugs are required to act at a particular time of the day, for example, in the case of drugs for use in the treatment of rheumatoid arthritis maximum therapeutic effect of the drug is required on rising in the morning when pain and stiffness are usually at their greatest.

Ketoprofen (m-Benzoylhydratropic acid) is a drug commonly used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gout and has analgestic, anti-inflammatory and anti-pyretic properties. The usual dose is 50 mg thrice daily with food, increased to four times daily if required. Ketoprofen is readily absorbed from the gastro-intestinal tract, with peak plasma concentrations occurring 0.5 to 2 hours after a dose. The plasma half-life is about 1.6 to 1.9 hours. Ketoprofen is available as capsules containing 50 mg of the drug sold under the Trade Mark ORUDIS. A controlled release form of Ketoprofen in the form of coated pellets again in capsular form is also available and is sold under the Trade Mark ORUVAIL (100 or 200 mg capsules). ORUVAIL is stated to be suitable for once daily administration and to give a very gradual and slow release over 12–18 hours. The ORUVAIL pellets are not enteric coated and accordingly gastric irritation is a problem. Also at the lower dose of 100 mg daily therapeutic levels of the drug may not be achieved.

It is an object of the present invention to provide a controlled release ketoprofen pharmaceutical formulation suitable for oral administration and which allows maximum therapeutic levels of a drug to be achieved at a pre-determined time after administration. More particularly, it is an object of the invention to provide a controlled release form of ketoprofen following single dosage per day which allows for peak plasma levels of the drug *circa* 8 hours after administration and effective therapeutic levels extending over 24 hours.

Accordingly, the invention provides a controlled release ketoprofen pharmaceutical formulation for oral administration in the form of microcapsules comprising

(a) a core containing:
20–60% by weight of ketoprofen as active ingredient;
10–40% by weight of a sphere-forming binder; and
20–70% of a non-toxic, inert inorganic material having a specific gravity in the range 1.5–3.5 and less than 5% moisture; and

(b) an enteric coating.

Preferably, the core contains:
30–50% by weight of active ingredient;
15–25% of sphere-forming binder; and
35–45% of the non-toxic, inert inorganic material and less than 5% moisture.

The core is formed by the conventional technique of spheronisation which comprises mixing the three components of the core with sufficient water to form a wet mass, extruding the mass, cutting the extrudate into lengths of about 1 mm diameter and 1–4 mm in length and then spheronising the cut lengths to form spheres about 1 mm in diameter which are dried and them coated with the enteric coating material. The enteric coating material consists of a suitable polymer or mixture of polymers. The coating step is carried out by conventional pan coating techniques using a solution of the polymer or polymer mixture in a suitable solvent system which is evaporated off, during appli-cation of the polymeric coating in conventional manner.

The sphere-forming binder is preferably microcrystalling cellulose as sold under the Trade Mark AVICEL, such as Avicel-RC 591 or Avicel-PH 101.

The non-toxic, inert inorganic material which is of a relatively high density is preferably heavy kaolin (specific gravity 1.8–2.6), calcium carbonate (specific gravity 1.7–2.8) or talc (specific gravity 2.7–2.8).

Kaolin being a pseudo-plastic material moulds well to give spheres with a smooth surface which reduces the amount of coating material necessary to form the enteric coating. Kaolin not only acts as an aid to spheronisation and as a densifying agent but also has binding sites which

attach drugs such as ketoprofen and hinder their absorption. Likewise calcium carbonate promotes the formation of uniform, high-density, spherical cores. It can form complexes with drugs like ketoprofen to reduce their rate of absorption and produce a product with a very long duration of action.

Talc, a silicate, does not exhibit the same degree of drug binding nor, indeed, the same ease of spheronisation as kaolin, but does, however, provide a relatively faster release of the drug ketoprofen, where peak plasma levels are required approximately 8 hours after administration.

The enteric coating material can be selected from a wide range of polymers or polymeric mixtures. Suitable enteric coating materials include Shellac, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylacetate phthalate, or a polymer selected from the Eudragit Series (Eudragit is a Trade Mark). Eudragit polymers are acrylic resins comprising copolymers of acrylic and methacrylic acid esters which are manufactured by Rohm Pharma GmbH. A particularly preferred enteric coating when applied by pan coating technology is dewaxed Shellac, which is insoluble below pH 7.0. The enteric coating material may include an anti-tack agent such as stearic acid. Stearic acid also has the property of prolonging stomach emptying time and thereby helps to further reduce gastric clearance of the formulation according to the invention.

The formulation according to the invention is normally administered in the form of hard gelating capsules, in particular CAPSUGEL gelatin capsules (CAPSUGEL is a Trade Mark). Each capsule may contain up to several hundred of the microcapsules according to the invention.

A pharmaceutical formulation in the form of an enteric coated tablet is irregularly cleared from the stomach through the pyloric sphincter following oral administration. It is found with the pharmaceutical formulation of the invention, which contains many sub-units, that the more uniform clearance of liberated microcapsules from the stomach is delayed relative to conventional microcapsules and this delay in clearance is attributed to their higher density. With the extended average clearance observed with the formulation according to the invention it is found that there is very little release of ketoprofen in the first few hours following administration as measured by plasma concentration levels as hereinafter demonstrated. Furthermore, it is also believed that due to their high density, the microcapsules according to the invention travel more slowly along the intestinal tract, because they are more effectively obstructed by the microvilli of the intestine.

The invention will be further illustrated by the following Example.

EXAMPLE

Controlled Release Ketoprofen Microcapsules

Katoprofen microcapsules were prepared in the following manner. Ketoprofen (50% by weight), talc (30% by weight) and Avicel-PH 101 (20% by weight) were mixed to a wet mass with water. The wet mass was extruded through an Alexanderwerk extruder (ALEXANDERWERK is a Trade Mark) and the extrudate cut into lengths 1 mm in diameter and 1–4 mm in length which were then subjected to spheronisation in a Caleva spheronizer (CALEVA is a Trade Mark). The spheres thereby obtained were dried and coated with a 10% solution of dewaxed Shellac in ethanol in a conventional coating pan. The coated cores were dried and loaded into CAPSUGEL hard gelatin capsule shells so as to give a product containing 100 mg of ketoprofen.

CLINCAL DATA

Clinical data was obtained by carrying out single dose studies in eight healthy volunteers. Mean plasma data was obtained for the eight subjects after receiving a single dose (100 mg) of ketoprofen capsules according to the invention and prepared in the Example, ORUVAIL (Trade Mark) or ORUDIS (Trade Mark). The results are shown in Table 1 and are demonstrated graphically in the accompanying Figure. In the Figure curve *a* corresponds to the product according to the invention, curve *b* corresponds to ORUVAIL and curve *c* corresponds to ORUDIS.

A lower incidence of gastric irritation was observed with the ketoprofen product according to the invention relative to either ORUDIS or ORUVAIL.

TABLE 1

Time	Plasma Ketoprofen conc ($\mu g\ ml^{-1}$)		
(hr)	Product according to the invention	Oruvail	Orudis
0.0	--	--	--
0.5	--	--	2.490
1.0	--	--	4.840
2.0	--	0.238	7.430
3.0	0.247	0.970	4.473
4.0	0.419	1.270	2.380
5.0	1.210	1.170	1.250
6.0	1.470	1.070	0.758
8.0	2.070	0.888	0.385
10.0	1.009	0.666	0.208
12.0	0.672	0.729	0.121
16.0	0.507	0.615	--
20.0	0.247	0.303	--
24.0	0.320	0.339	--
30.0	0.159	0.174	--

Mean pharmacokinetic data was obtained from the eight subjects after a single dose (100 mg) of ketoprofen capsules according to the invention and as prepared in the Example, ORUVAIL or ORUDIS. The results are shown in Table 2.

TABLE 2

	Product according to the invention	ORUVAIL	ORUDIS
C_{max} ($\mu g\ ml^{-1}$)	2.13	1.39	7.83
$AUC_{O\rightarrow\infty}$ ($\mu g\ ml^{-1}\ hr^{-1}$)	--	--	23.60
$AUC_{O\rightarrow t^*}$ ($\mu g\ ml^{-1}\ hr^{-1}$)	16.80	16.90	--
T_{max} (hr)	5.80	4.10	1.70
T* (hr)	10.50	13.00	6.75
T_d (hr)	20.60	24.50	9.00

C_{max} : maximum plasma ketoprofen concentration

$AUC_{O\rightarrow\infty}$: area under the plasma ketoprofen concentration time curve from time zero to infinity

$AUC_{O\rightarrow t^*}$: area under the plasma ketoprofen concentration time curve from time zero to t*, the last detectable data point

T_{max} : time of maximum plasma ketoprofen concentration

T* (hr) : length of time the plasma ketoprofen levels exceed the minimum therapeutic concentration ($0.5\ \mu g\ ml^{-1}$

T_d : length of time detectable plasma ketoprofen levels were observed.

As will be observed from the data given in Tables 1 and 2 and the accompanying Figure, the ketoprofen formulation according to the invention is ideally suited for the treatment of rheumatoid arthritis and other conditions characterised by morning stiffness and pain, since one can take the drug before retiring at night and will obtain maximum benefit when required i.e. in the morning. In contrast, lower peak plasma levels are observed with ORUVAIL approximately 3 to 6 hours following administration.

CLAIMS

1. A controlled release ketoprofen pharmaceutical formulation for oral administration in the form of microcapsules comprising

(a) a core containing:

20–60% by weight of ketoprofen as active ingredient;

10–40% by weight of a sphere-forming binder; and
20–70% of a non-toxic, inert inorganic material having a specific gravity in the range 1.5–3.5 and less than 5% moisture; and
(b) an enteric coating.

2. A pharmaceutical formulation according to claim 1, wherein the core contains 30–50% by weight of active ingredient, 15–25% of sphere-forming binder and 35–45% of the non-toxic, inert inorganic material and less than 5% moisture.

3. A pharmaceutical formulation according to claim 1 or 2, wherein the sphere-forming binder is microcrystalline cellulose.

4. A pharmaceutical formulation according to any one of claims 1–3, wherein the non-toxic, inert inorganic material is kaolin, calcium carbonate or talc.

5. A pharmaceutical formulation according to claim 4, wherein the non-toxic, inert inorganic material is kaolin having a specific gravity of 1.8–2.6.

6. A pharmaceutical formulation according to claim 4, wherein the non-toxic, inert inorganic material is calcium carbonate having a specific gravity of 1.7–2.8.

7. A pharmaceutical formulation according to claim 4, wherein the non-toxic, inert inorganic material is talc having a specific gravity of 2.7–2.8.

8. A pharmaceutical formulation according to any preceding claim, wherein the enteric coating material is a polymer or polymer mixture selected from shellac, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylacetate phthalate or a copolymer of acrylic and methacrylic acid esters.

9. A pharmaceutical formulation according to claim 8, wherein the enteric coating material is dewaxed shellac.

10. A pharmaceutical formulation according to any preceding claim, when the enteric coating material includes an anti-tack agent.

11. A pharmaceutical formulation according to claim 10, wherein the anti-tack agent is stearic acid.

12. A pharmaceutical formulation according to claim 1, substantially as hereinbefore described with particular reference to the accompanying Examples.

13. A pharmaceutical composition according to any preceding claim, which is in the form of capsules.

14. A process for preparing a pharmaceutical formulation according to any one of claims 1–12, which comprises mixing the three components of the core with sufficient water to form a wet mass, extruding the mass, cutting the extrudate into lengths of about 1 mm diameter and 1–4 mm in length, spheronising the cut lengths to form spheres about 1 mm in diameter, drying the spheres and then coating said spheres with the enteric coating material.

15. A process according to claim 14, substantially as hereinbefore described with particular reference to the accompanying Example.

16. A pharmaceutical formulation whenever prepared by a process according to claim 14 or 15.

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