

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
25 March 2004 (25.03.2004)

PCT

(10) International Publication Number
WO 2004/024128 A2

(51) International Patent Classification⁷: **A61K 31/00**

(21) International Application Number:
PCT/SI2003/000033

(22) International Filing Date:
10 September 2003 (10.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P-200200220 11 September 2002 (11.09.2002) SI

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **LEK PHARMACEUTICALS D.D.** [SI/SI]; Verovskova 57, 1526 Ljubljana (SI).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **SIRCA, Judita** [SI/SI]; Gaspersiceva 7, 1000 Ljubljana (SI). **MOHAR, Milojka** [SI/SI]; Gosticeva 9, 1230 Ljubljana (SI).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODIFIED RELEASE PHARMACEUTICAL COMPOSITION

(57) Abstract: The present invention relates to a modified release pharmaceutical composition of ketoprofen which comprises uncoated pellets designed to an immediate release of ketoprofen, and coated pellets release designed to a delayed and prolonged release. This composition is suitable for twice daily administration.

WO 2004/024128 A2

Lek Pharmaceuticals d. d.

Modified release pharmaceutical composition

The present invention belongs to the field of pharmaceutical technology and relates to a modified release pharmaceutical composition of ketoprofen.

Ketoprofen, [2-(3-benzoylphenyl)propionic acid], is a non-steroidal, anti-inflammatory drug which exhibits analgesic and anti-rheumatic properties.

In the group of the active substances known as the non-steroidal anti-inflammatory agents there is a constant need for pharmaceutical compositions that would have an immediate analgesic effect and a prolonged anti-rheumatic effect. This is difficult to achieve with conventional pharmaceutical compositions which release the entire active substance quickly, have an immediate analgesic effect and an anti-rheumatic effect is lost. Contrary, with controlled release pharmaceutical compositions due to prolonged release of the active substance from a pharmaceutical composition an anti-rheumatic effect is obtained but the concentration of the active substance released initially is too low to provide an analgesic effect.

A number of compositions, containing pellets or granules of ketoprofen or other non-steroidal anti-inflammatory drugs, are known from prior art.

US 4980170 describes pharmaceutical compositions of the active substances from the group of non-steroid anti-inflammatory agents, which comprise two types of the pellets. The first pellets comprising a two-layer coating membrane are resistant to gastric juices. The second pellets have a retard permeable diffusion membrane.

US 5043167 relates to programmed release pharmaceutical compositions comprising non-steroidal anti-inflammatory drug substances, which contain two types of the granulates, the immediate release granulate and the controlled release granulate. The release rate of active substances is governed by the granulate composition.

WO 99/12542 describes modified release multiple-units pharmaceutical compositions of non-steroidal anti-inflammatory drug substances which comprise two fractions of the particles with the different release profile. The first fraction, which may be in the form of granules or coated pellets, provides a very quick onset of the therapeutic effect. At least 50% w/w of the active substance is released from the first fraction within the first 20 minutes. The second fraction is in a form of three-layer coated pellets adjusting release of the active substance for a relatively long period of time. The composition is also suitable for once-a-day administration.

Thus it is the object of the present invention to provide improved modified release composition of ketoprofen.

Description of the invention

The present invention thus relates to a modified release pharmaceutical composition of ketoprofen which comprises uncoated pellets (pellet cores) which are designed to an immediate release of ketoprofen, and coated pellets which are designed to a delayed and prolonged release of ketoprofen. This composition is able to maintain therapeutically effective blood levels of ketoprofen over 12 hours and is suitable for twice daily administration. It solves the problem of managing pain relief and inflammation in patients in need thereof.

The novel pharmaceutical composition is patient-friendly. In the stomach it disintegrates very quickly and the pellets are distributed inside the stomach. Local gastric irritation is thus greatly decreased in comparison with a conventional pharmaceutical composition, e.g., tablet comprising the entire dose of the active substance in a single unit and causes a strong local irritation that may also damage the mucous membrane. Coated pellets additionally protect the mucosa.

The release rate of ketoprofen from the composition of present invention is governed by the composition of the pellet cores, the ratio of the uncoated pellets to the coated pellets and the composition and thickness of the coating.

The uncoated pellets (pellet cores) comprise ketoprofen and excipients which are conventionally used for the production of pellets. Pellet cores may comprise one or more diluents, such as lactose, saccharose, glucose, starch, microcrystalline cellulose, mannitol, sorbitol, calcium hydrogen phosphate and others, one or more binding agents, such as starch, gelatin, polyvinylpyrrolidone, sodium alginate, microcrystalline cellulose, carboxymethylcellulose, low-substituted hydroxypropyl cellulose and others, one or more disintegrants, such as starch, croscarmellose sodium, cross-linked polyvinylpyrrolidone, sodium starch glycollate and others. The pellet cores may further comprise one or more surfactants, such as ionic surfactants, e.g., sodium lauryl sulfate, nonionic surfactants, such as natural or synthesized lecithins and esters of sorbitan and fatty acids (such as Span[®]), esters of polyoxyethylenesorbitan and fatty acids (such as, Polysorbates or Tween[®]), polyoxyethylated hydrogenated castor oil (such as Cremophor[®]) or any combination of the herein above mentioned surfactants

Pellet cores may optionally be composed of inert seed to which ketoprofen is applied on together with a binding agent, selected from the group consisting of starch, gelatin, polyvinylpyrrolidone, sodium alginate, microcrystalline cellulose, carboxymethylcellulose, low-substituted hydroxypropyl cellulose and others.

The proportion of ketoprofen in the pellet cores is from 5 to 95% w/w, preferably 60 to 90 % w/w.

Delayed release coated pellets are the pellet cores coated with a pH independent semi-permeable polymer. The coating preferably comprises copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. A preferred coating comprises the combination of ammonio methacrylate copolymer type A and ammonio methacrylate copolymer type B (according to USP 25-NF 20) in the ratio of 7:3 to 3:7, preferably 1:1. The polymers are commercially available in the form of 30% aqueous dispersion as Eudragit RS 30 D and Eudragit RL 30 D from Röhm Pharma.

The coating may further comprise one or more plasticizers, such as polyethylene glycol with different molecular weights, triethyl citrate, dibutyl sebacate, tributyl sebacate, cetyl alcohol, olive or castor oil, monoglycerides and other conventional

pharmaceutically acceptable ingredients which are used for the production of coatings, such as talc, Polysorbate 80, pigments and magnesium stearate.

The coated pellets may comprise from 3 to 50% w/w of the coating, preferably 5 to 15% w/w.

The composition of the uncoated pellets may be the same as the composition of the pellet cores of coated pellets. The composition of the uncoated pellets may be different from the composition of the pellet cores of coated pellets.

Pellet cores may be produced in the manner conventional in the pharmaceutical industry. A wet mixture of ketoprofen and excipients is extruded in a screw extruder and the resulting extrudate is spheronized into pellets in a spheronizer. The pellets thus produced are dried in a fluidized bed. The pellet cores are coated with a polymer coating by the methods conventional in the pharmaceutical technology.

Pellet cores may optionally be prepared by coating the inert core seeds with ketoprofen and binding agent.

Uncoated pellets and coated pellets in the desired ratio may be encapsulated into gelatin capsules. They may be also compressed into tablets together with the excipients such as, for example, lactose, saccharose, glucose, starch microcrystalline cellulose, mannitol, sorbitol, calcium hydrogen phosphate, neutral pellet cores and others.

The ratio of uncoated pellets to the coated pellets in the formulation of the present invention may be from 80:20 to 20:80, preferably about 60:40 to the dose of ketoprofen in the pharmaceutical composition. It means that 60% w/w of the ketoprofen dose is in a form of the pellet cores and 40% w/w of the ketoprofen dose in a form of the coated pellets.

The pharmaceutical composition of the present invention may contain from 50 to 250 mg of ketoprofen, preferably 150 mg.

The object of the present invention is a modified release composition of ketoprofen wherefrom 15 to 35% w/w of ketoprofen is released within the first two hours, 50 to 80% w/w of ketoprofen after 6 hours and at least 80% w/w after 8 hours, measured 2 hours in 1000 ml of simulated gastric juice having a pH of 1.2, 4 hours in 1000 ml of phosphate buffer having a pH of 4.5 and 2 hours in 1000 ml of phosphate buffer having a pH of 6.8, in the rotating basket (USP 25) at 50 rpm.

The object of the present invention is a hard gelatine capsule containing 150 mg of ketoprofen. 60% w/w of the ketoprofen dose is in the form of uncoated pellets and 40% w/w of the ketoprofen dose is in the form of coated pellets.

The present invention is illustrated but in no way limited by the following examples:

Example 1

CORES			
<i>ketoprofen</i>	<i>mg</i>	<i>150.00</i>	<i>Active substance</i>
<i>Avicel PH101</i>	<i>mg</i>	<i>34.00</i>	<i>Diluent</i>
<i>Lactose 200</i>	<i>mg</i>	<i>20.00</i>	<i>Diluent</i>
<i>PVP K 25</i>	<i>mg</i>	<i>10.00</i>	<i>Binding agent</i>
<i>Ac-Di-Sol</i>	<i>mg</i>	<i>5.00</i>	<i>Disintegrant</i>
<i>Polysorbate 80</i>	<i>mg</i>	<i>1.00</i>	<i>Surfactant</i>

COATING			
<i>Eudragit RS 30 D</i>	<i>mg</i>	<i>34.84</i>	<i>Film former</i>
<i>Eudragit RL 30 D</i>	<i>mg</i>	<i>34.84</i>	<i>Film former</i>
<i>Triethyl citrate</i>	<i>mg</i>	<i>5.00</i>	<i>Plasticizer</i>
<i>Polysorbate 80</i>	<i>mg</i>	<i>0.04</i>	<i>Surfactant</i>
<i>Talc</i>	<i>mg</i>	<i>6.00</i>	<i>Anti-adherent</i>

Ketoprofen, microcrystalline cellulose, lactose and polyvinylpyrrolidone were mixed and 140 g of demineralized water was added. The wet mixture was extruded in a screw extruder and the resulting extrudate was spheronized into pellets in a spheronizer. The wet pellets thus obtained were dried in a fluidized bed. 60% w/w of the dry pellets (pellet cores) was set aside to be capsulated, and the remainder 40% w/w was coated. The pellet cores were placed in a fluidized bed apparatus and sprayed with an aqueous dispersion Eudragit RS 30 D and Eudragit RL 30 D by further added triethyl citrate, Polysorbate and talc.

The pellet cores and the coated pellets were dosed into capsules using a capsule filling machine. Each capsule contained 60% w/w pellet cores and 40% w/w coated pellets.

Dissolution test

Medium:

<i>Acid phase</i>	1000 ml simulated gastric juice pH 1.2	2 hours
<i>Buffer phase</i>	1000 ml phosphate buffer pH 4.5	4 hours
	1000 ml phosphate buffer pH 6.8	2 hours

Apparatus: Rotating basket (USP 25)

Rotations per minute: 50

capsule	Percentage dissolved in hours			
	2	4	6	8
1	24.8	56.0	72.2	95.7
2	22.7	54.9	71.8	98.3
3	25.0	54.7	69.9	96.6
4	21.8	53.6	70.8	99.1
5	22.4	55.8	70.6	98.7
6	21.9	46.8	61.9	99.6
mean	23.1	53.6	69.5	98.0
SD	1.4	3.5	3.8	1.5
RSD (%)	6.2	6.4	5.5	1.6
minimum	21.8	46.8	61.9	95.7
maximum	25.0	56.0	72.2	99.6

Example 2

CORES			
ketoprofen	mg	150.00	Active substance
Avicel PH101	mg	24.00	Diluent
Lactose 200	mg	30.00	Diluent
PVP K 25	mg	7.00	Binding agent
Ac-Di-Sol	mg	8.00	Disintegrant
Polysorbate 80	mg	1.00	Surfactant

COAT			
Eudragit RS 30 D	mg	27.84	Film former
Eudragit RL 30 D	mg	27.84	Film former
Triethyl citrate	mg	2.00	Plasticizer
Polysorbate 80	mg	0.04	Surfactant
Talc	mg	6.00	Anti-adherent

Ketoprofen, microcrystalline cellulose, lactose and polyvinylpyrrolidone were mixed and 140 g of demineralized water was added. The wet mixture was extruded on a screw extruder and resulting extrudate was spheronized into pellets in a spheronizer. The wet pellets thus obtained were dried in a fluidized bed. 60% w/w of the dry pellets (pellet cores) was set aside to be capsulated, and the remainder 40% w/w was coated.

The pellet cores were placed in a fluidized bed apparatus and sprayed with an aqueous dispersion Eudragit RS 30 D and Eudragit RL 30 D by further added triethyl citrate, Polysorbate and talc.

The pellet cores and the coated pellets were dosed into capsules using a capsule filling machine. Each capsule contained 60% w/w pellet cores and 40% w/w coated pellets.

Dissolution test

Medium:

Acid phase	1000 ml simulated gastric juice pH 1.2	2 hours
Buffer phase	1000 ml phosphate buffer pH 4.5	4 hours
	1000 ml phosphate buffer pH 6.8	2 hours

Apparatus: Rotating basket (USP 25)

Rotations per minute: 50

capsule	Percentage dissolved in hours			
	2	4	6	8
1	21.4	50.0	66.2	98.4
2	23.9	51.5	65.5	92.7
3	25.0	53.7	69.7	97.1
4	26.4	55.6	70.6	96.6
5	27.4	56.8	70.0	96.6
6	25.9	55.5	69.2	96.9
7	26.1	59.3	72.2	97.0
8	24.2	54.7	70.1	95.7
9	25.4	55.5	70.6	98.8
10	25.4	56.8	71.4	96.5
11	24.5	56.1	72.1	97.7
12	24.5	56.0	70.8	95.5
Mean	25.0	55.1	69.9	96.6
SD	1.5	2.5	2.1	1.6
RSD (%)	6.1	4.5	3.0	1.6
minimum	21.4	50.0	65.5	92.7
maximum	27.4	59.3	72.2	98.8

CLAIMS

1. A modified release pharmaceutical composition of ketoprofen comprising uncoated pellets designed to an immediate release of ketoprofen and coated pellets designed to a controlled release of ketoprofen, wherein from said composition 15 to 35% w/w of ketoprofen is released within the first two hours, 50 to 80% w/w of ketoprofen after 6 hours, and at least 80% w/w after 8 hours, measured by the method of a rotating basket at 50 rpm, 2 hours in 1000 ml of simulated gastric juice ml having a pH of 1.2, 4 hours in 1000 ml of phosphate buffer having a pH of 4.5 and 2 hours in 1000 ml of phosphate buffer having a pH of 6.8.
2. The composition according to claim 1, which comprises from 50 to 250 mg of ketoprofen.
3. The composition according to claims 1, which comprises 150 mg of ketoprofen.
4. The composition according to claim 1, wherein the coated pellets comprise a pellet core and a pH independent semi-permeable polymer coating.
5. The composition according to claim 1 and 4, wherein the composition of uncoated pellets is the same as composition of pellet cores of coated pellets
6. The composition according to claim 4, wherein the pellet cores contain from 5 to 90% w/w of ketoprofen.
7. The composition according to claims 4, wherein the pellet cores contain from 60 to 90% w/w of ketoprofen.
8. The composition according to claim 4, wherein the coating comprises copolymers of acrylic and methacrylic acid esters

9. The composition according to claim 4, wherein the coating comprises the combination of ammonio methacrylate copolymer type A and ammonio methacrylate copolymer type B in the ratio of 7:3 to 3:7.
10. The composition according to claims 8, wherein the ratio of ammonio methacrylate copolymer type A and ammonio methacrylate copolymer type B in the coating is 1:1.
11. The composition according to claims 1 and 4, wherein the coated pellets contain from 3 to 50% w/w of the coating.
12. The composition according to claims 1 and 4, wherein the coated pellets contain from 5 to 15% w/w of the coating.
13. The pharmaceutical composition according to claim 1, wherein the ratio of the uncoated pellets to the coated pellets is from 80:20 to 20:80.
14. The pharmaceutical composition according to claims 1 and 13, wherein the ratio of the uncoated pellets to the coated pellets is 60:40.
15. The composition according to claim 1, which is a hard gelatine capsule.