...STRUCTIONS
...Convention
...plication insert
..."Convention"

AMENDED

AUSTRALIAN Sec 104 PATENT OFFICE

(a) Convention

AUSTRALIA 614577

Patents Act

(b) Delete one

APPLICATION FOR A STANDARD/PETTY PATENT

(c) Insert FULL name(s) of applicant(s)

I/We (c) Fournier Industrie Et Sante

(d) Insert FULL address(es) of applicant(s)

of (d) 38 Avenue Hoche 75008, Paris, France

(e) Delete one

hereby apply for the grant of a (e) Standard/Petty Patent for an invention entitled

(f) Insert TITLE of invention

(f) NOVEL DOSAGE FORM OF FENOFIBRATE

(g) Insert "complete" or "provisional" or "petty patent"

which is described in the accompanying (g) complete specification.

(Note: The following applies only to Convention applications)

Details of basic application(s)

(h) Insert number, country and filing date for the/or each basic application

	Application No.	Country	Filing Date
(h)	88 02359	France	26 February 1988

Address for Service: PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia 3000

(i) Insert date of signing

Dated (i) 3 April 1991

(j) Signature of applicant(s) (For body corporate see headnote*)

(k) Corporate seal if any

(k)

(j) PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
FOURNIER INDUSTRIE ET SANTE

David B Fitzpatrick

Note: No legalization or other witness required

PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

P17/2/83

CONVENTION.
Company.

FORM 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(1) Here insert (in full) Name of Company.

In support of the Convention Application made by[1] FOURNIER INNOVATION ET SYNERGIE

(2) Here insert title of Invention

for a patent application for an invention entitled[2] Novel dosage form of fenofibrate

(3) Here insert Name and Address of Company Official authorised to make declaration.

I,[3] François PICART of FOURNIER INNOVATION ET SYNERGIE of 38, avenue Hoche 75008 PARIS, France

do solemnly and sincerely declare as follows:

1. I am authorised by[1] FOURNIER INNOVATION ET SYNERGIE the applicant for the patent application to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

made in[4] France on the 26th day of February 1988, by FOURNIER INNOVATION ET SYNERGIE

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors.

3.[5] Bernard CURTET, of 57 rue du Carré, 21160 MARSANNAY LA COTE, France ; Eric TEILLAUD, of 1, allée Roger Bernard, 21240 TALANT, France ; Philippe REGINAULT, of 13 rue de Provence, 21121 FONTAINE LES DIJON, France

the actual inventor of the invention, and the facts upon which [1] FOURNIER INNOVATION ET SYNERGIE is entitled to make the application, are as follows:

The said [1] FOURNIER INNOVATION ET SYNERGIE is the assignee of the said[6] Bernard CURTET, Eric TEILLAUD and Philippe REGINAULT

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Paris,

this 17th day of January 198 9

FOURNIER INNOVATION ET SYNERGIE

(7) Signature.

(7) François Picart

To:

THE COMMISSIONER OF PATENTS

Propriété Industrielle

Directeur du Service

(12) PATENT ABRIDGMENT (11) Document No. AU-B-29828/89
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NOVEL DOSAGE FORM OF FENOFIBRATE

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(57) Claim

1. A therapeutic composition, which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant, wherein the mean particle size of said co-micronized mixture is less than 15 µm.

10. A method for improving the bioavailability of fenofibrate in vivo, which comprises co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 µm.

12. A method for treatment of hyperlimidemia or hypercholesterolemia comprising orally administering the therapeutic composition of claim 6 to a patient in need of such.

AUSTRALIA

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614577

COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

APPLICANT'S REFERENCE: 9296/SC/SH

Name(s) of Applicant(s):
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PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Complete Specification for the invention entitled:

NOVEL DOSAGE FORM OF FENOFIBRATE

Our Ref : 121777
POF Code: 1172/96150

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

NOVEL DOSAGE FORM OF FENOFIBRATE

The present invention relates to a novel dosage form of fenofibrate. It relates more precisely to a therapeutic composition containing fenofibrate and ensuring an improved bioavailability, and to a method for the preparation of this composition.

Fenofibrate (international common name), which is recommended in the treatment of hyperlipidemia and hypercholesterolemia, corresponds to the nomenclature isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methyl-propionate. The customary adult dosage is three gelatin capsules per day, each containing 100 mg of fenofibrate.

For the patient's comfort, it is advantageous to try and find a dosage form which has to be taken only once a day and whose physiological effect is identical to that obtained when multiple doses are taken. A gelatin capsule containing 300 mg of fenofibrate has therefore been proposed, the dosage recommended in this case being only one administration per day.

However, it is possible to try and improve the dosage form still further. It is known, in fact, that the bioavailability of fenofibrate is not equal to 100%. It is therefore desirable to develop a dosage form in which the bioavailability of the fenofibrate is improved and which can be administered only once a day.

It is known that the micronization of an active principle is capable of improving the dissolution of the said active principle in vivo, and hence its bioavailability. It is also known that the addition of a

surfactant excipient to a formulation of an active principle is capable of improving the absorption and consequently the bioavailability of the said active principle.

It has now been discovered that the co-micronization of fenofibrate and a solid surfactant (i.e. the micronization of an intimate mixture of fenofibrate and a solid surfactant) makes it possible to improve the bioavailability of the fenofibrate to a significantly greater extent than that which would be achieved either by adding a surfactant, or by micronizing the fenofibrate on its own, or by intimately mixing the separately micronized fenofibrate and surfactant.

Therefore it is an object of the present invention to provide a novel therapeutic composition, which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant, wherein the mean particle size of said co-micronized mixture is less than 15 µm.

It is a further object of the invention to provide a method for improving the bioavailability of fenofibrate in vivo, which comprises co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 µm.

~~surfactant excipient to a formulation of an active~~ principle is capable of improving the absorption and consequently the bioavailability of the said active principle.

It has now been discovered that the co-micronization of fenofibrate and a solid surfactant (i.e. the micronization of an intimate mixture of fenofibrate and a solid surfactant) makes it possible to improve the bioavailability of the fenofibrate to a significantly greater extent than that which would be achieved either by adding a surfactant, or by micronizing the fenofibrate on its own, or by intimately mixing the separately micronized fenofibrate and surfactant.

The present invention therefore proposes a novel therapeutic composition ~~presented in the form of gelatin capsules~~ which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, the said composition containing fenofibrate and a solid ~~surfactant which have been co-micronized.~~

The recommended amount of fenofibrate is about 200 mg per therapeutic unit.

The surfactant will be selected from solid surfactants so that it can be co-micronized with the fenofibrate. An alkali metal sulfate of lauryl alcohol, for example sodium lauryl-sulfate (alternative name: sodium dodecyl-sulfate), will be preferred. The recommended amount of sodium lauryl-sulfate will be between 0.5% and 7% by weight, relative to the total weight of the formulation. The weight ratio surfactant/fenofibrate will advantageously be between about 0.75/100 and 10.5/100.

The co-micronization of the fenofibrate and the solid surfactant will advantageously be carried out in an accelerated air-jet mill until the powder obtained is such that the mean particle size is less than 15 µm,

preferably less than 10 µm and particularly preferably less than 5 µm.

To obtain a powder which can be formulated into gelatin capsules, conventional filling, dispersing and flow-enhancing excipients, for example lactose, starch, polyvinylpyrrolidone and magnesium stearate, may be added to the co-micronizate of fenofibrate and solid surfactant.

According to the invention, a method for the preparation of a therapeutic composition containing fenofibrate and a solid surfactant is recommended which comprises:

(i) intimately mixing and then co-micronizing the fenofibrate and the solid surfactant,

(ii) adding lactose and starch to the mixture obtained,

(iii) converting the whole to granules in the presence of water,

(iv) drying the granules until they contain no more than 1% of water,

(v) grading the granules,

(vi) adding polyvinylpyrrolidone and magnesium stearate to the graded granules, and

(vii) filling gelatin capsules with the mixture obtained in stage (vi).

The invention will be understood more clearly from the description of the Preparative Examples which follow and from the description of the results obtained in comparative tests, which show that the invention is non-obvious.

EXAMPLE I

For 100,000 gelatin capsules, each weighing 350 mg and containing 200 mg of fenofibrate, the amounts of products used are as follows:

fenofibrate	:	20.0 kg
sodium lauryl-sulfate	:	0.7 kg
α-lactose monohydrate	:	10.1 kg
pregelatinized starch	:	3.0 kg
crosslinked polyvinyl-pyrrolidone	:	0.7 kg
magnesium stearate	:	0.5 kg

The fenofibrate/sodium lauryl-sulfate mixture is co-micronized in an air-jet micronizer to give a powder with a median particle size of 3 µm. The lactose and the starch are then added to this powder and the whole is converted to granules in the presence of 8.9% of distilled water, relative to the total weight of the mixture. The granules obtained in this way are dried for one day at 50°C and then graded so as to retain only the particles with sizes less than or equal to 1000 µm. The polyvinylpyrrolidone and the magnesium stearate are then added and the whole is mixed until homogeneous. The powder obtained is used to fill size 1 gelatin capsules on an automatic machine with the compression set to a maximum of 150 N.

EXAMPLE II

The procedure indicated in Example ~~Preparation~~ I is followed using a fenofibrate/sodium lauryl-sulfate mixture with a median particle size of 6-7 µm.

EXAMPLE III

For 100,000 size 1 gelatin capsules, each weighing 297 mg and containing 200 mg of active principle, the amounts of products used are as follows:

fenofibrate	:	20.0 kg
sodium lauryl-sulfate	:	0.3 kg
α-lactose monohydrate	:	6.8 kg
pregelatinized starch	:	1.5 kg
crosslinked polyvinyl-pyrrolidone	:	0.6 kg
magnesium stearate	:	0.5 kg

The procedure is analogous to that used for Example ~~Preparation~~ I, the co-micronization of the fenofibrate/sodium lauryl-sulfate mixture being such that the median particle size is 6-7 µm and the granulation being carried out in the presence of 10% of distilled water, relative to the weight of the fenofibrate/sodium lauryl-sulfate/lactose/starch mixture.

EXAMPLE IV

Following a procedure analogous to that described in Example ~~Preparation~~ I, using a co-micronized mixture of fenofibrate and sodium lauryl-sulfate with a median particle size of 6-7 µm, the formulations collated in Table I below were prepared:

TABLE I

COMPOSITION (in mg) PER GELATIN CAPSULE

INGREDIENT	FORMULATION					
	A	B	C	D	E	F
Fenofibrate	200	200	200	200	200	200
Na lauryl-sulfate	0	3	7	12	17.5	26.5
Lactose	108	105	101	95	90.5	83.5
Starch	30	30	30	30	30	30
Polyvinylpyrrolidone	7	7	7	7	7	7
Mg stearate	5	5	5	5	5	5
Percentage of Na lauryl-sulfate	0	0.86	2	3.4	5	7.53

Taking these formulations, the dissolution curve shown in Figure 1 was plotted, the percentage of dissolved fenofibrate (Y) being given as a function of the percentage of sodium lauryl-sulfate contained in the formulation (X). The dissolution kinetics are determined, as specified in the European Pharmacopoeia, using a rotating-vane apparatus, the eluent consisting of water and 0.1 M sodium lauryl-sulfate. The fenofibrate is determined by UV spectrophotometry at 282 nm. The curve in Figure 1 is given by the values obtained after 20 minutes.

These results show that 82% of fenofibrate is dissolved at a sodium lauryl-sulfate concentration of 0%, 87% of fenofibrate is dissolved at a concentration

of 0.5%, 92% of fenofibrate is dissolved at a concentration of 1% and a maximum dissolution of 95 to 96% of fenofibrate is obtained as from a sodium lauryl-sulfate concentration of 4%.

The dissolution curves were also plotted, in a continuous-flow cell with a flow rate of 20 ml/min of 0.1 M sodium lauryl-sulfate, for formulations containing co-micronized fenofibrate and sodium lauryl-sulfate (NaLS), by comparison with micronized fenofibrate and with formulations obtained by intimately mixing separately micronized fenofibrate and lauryl-sulfate. The comparison is made by means of T 50%, i.e. the time required for 50% of the fenofibrate to dissolve. The results obtained are collated in Table II below:

TABLE II

VALUE OF THE T 50% TIMES (in minutes)

INGREDIENTS	A	B	C
Micronized pure fenofibrate	37.165	37.165	0
Fenofibrate + 1% of NaLS	18.01	8.62	-52.14
Fenofibrate + 3% of NaLS	23.75	12.68	-46.61
Fenofibrate + 5% of NaLS	20.35	11.425	-43.86
Fenofibrate + 7% of NaLS	14.5	10.76	-25.79

Notes

A: mixture of micronizates

B: co-micronization of the mixture of ingredients

C: variation $\frac{B - A}{A} \times 100$ (in %)

These results show that the T 50% of the fenofibrate is very significantly reduced (hence the dissolution rate of the fenofibrate is very significantly increased) when the fenofibrate and the sodium laurylsulfate are co-micronized, compared with the mixture of separately micronized fenofibrate and sodium laurylsulfate and compared with fenofibrate alone.

The dissolution rate of fenofibrate is correlated with the bioavailability of fenofibrate, which increases with the dissolution rate. The above results show that it was not within the understanding of those skilled in the art to prepare a therapeutic composition characterized by the co-micronization of fenofibrate and a solid surfactant.

These results have been confirmed in clinical trials. Fenofibrate was administered to groups of healthy subjects, (a) in the form of a single administration (1 gelatin capsule) of 300 mg of non-micronized fenofibrate (marketed under the tradename "LIPANTHYL 300") and (b) in the form of a single administration of 200 mg of co-micronized fenofibrate obtained according to ~~Preparation~~ Example III described above. Blood samples are taken from the subjects at regular intervals and one of the active metabolites - 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionic acid - is determined. The curve showing the concentration of this metabolite as a function of time is plotted and the area under the curve [AUC(0-∞)], expressed in mg/l.h, is calculated.

The results obtained are shown in Table III below:

TABLE III

BIOAVAILABILITY PARAMETER	FENOFIBRATE 200 mg (1)	FENOFIBRATE 300 mg (2)
AUC(0-∞)(mg/l.h)	174.15 ± 48.67	168.85 ± 57.68
C max (mg/l)	10.86 ± 2.13	10.39 ± 2.89
t max (h)	5.97 ± 2.50	5.52 ± 1.70
t 1/2 (h)	15.13 ± 4.27	17.79 ± 8.77

Notes
(1) co-micronized fenofibrate (200 mg)
(2) non-micronized fenofibrate (300 mg)

The results in Table III show that there is not a statistically significant difference between the in vivo bioavailability of 200 mg of co-micronized fenofibrate according to the invention and 300 mg of non-micronized fenofibrate (which is currently the preferred dosage form for a single daily administration). In other words, co-micronized fenofibrate at a 200 mg dose is bioequivalent to non-micronized fenofibrate at a 300 mg dose.

According to another aspect of the invention, a method for improving the bioavailability of fenofibrate in vivo is recommended, the said method comprising co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 µm and preferably less than or equal to 5 µm.

The claims defining the invention are as follows:-

1. A therapeutic composition, which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant, wherein the mean particle size of said co-micronized mixture is less than 15 µm.

2. A therapeutic composition according to claim 1 wherein the weight ratio surfactant/fenofibrate is between about 0.75/100 and 10.5/100.

3. A therapeutic composition according to claim 1 or claim 2 wherein the amount of fenofibrate is equal to 200 mg per therapeutic unit.

4. A therapeutic composition according to any one of claims 1 to 3 wherein the solid surfactant is sodium lauryl-sulfate.

5. A therapeutic composition according to claim 4, wherein the amount of sodium lauryl-sulfate is between 0.5 and 7% by weight, relative to the total weight of the formulation.

6. A therapeutic composition according to any one of claims 1 to 5 wherein said mean particle size is less than or equal to 10 µm and said solid surfactant is sodium lauryl-sulfate.

7. A therapeutic composition according to any one of claims 1 to 6 which also contains excipients such as dispersants, fillers and flow enhancers.

8. A method for the manufacture of a therapeutic composition according to any one of claims 1 to 7 which comprises:

(i) intimately mixing and then co-micronizing the fenofibrate and a solid surfactant,

(ii) adding lactose and starch to the mixture obtained,

(iii) converting the whole to granules in the presence of water,

(iv) drying the granules until they contain no more than 1% of water,

(v) grading the granules,

(vi) adding polyvinylpyrrolidone and magnesium stearate, and

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(vii) filling gelatin capsules.

9. A method according to claim 8, wherein the mean particle size of the co-micronized fenofibrate and sodium lauryl-sulfate is less than 15 µm.

10. A method for improving the bioavailability of fenofibrate in vivo, which comprises co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 µm.

11. A therapeutic composition according to any one of claims 1 to 7 which is presented in the form of gelatin capsules.

12. A method for treatment of hyperlimidemia or hypercholesterolemia comprising orally administering the therapeutic composition of claim 6 to a patient in need of such.

13. A method of treatment of claim 12, wherein said particle size is less than or equal to 5 µm.

14. A therapeutic composition according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.

15. A method for improving the bioavailability according to claim 10 substantially as hereinbefore described with reference to any one of the examples.

DATED: 18 June, 1991

FOURNIER INDUSTRIE ET SANTE
By their Patent Attorneys:
PHILLIPS ORMONDE & FITZPATRICK

David B Fitzpatrick

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