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ABBOTT LABORATORIES, an Illinois corporation, FOURNIER INDUSTRIE ET SANTÉ, a French corporation, and LABORATOIRES FOURNIER S.A., a French corporation,

Plaintiffs,

v.

PAR PHARMACEUTICAL, INC., a New Jersey corporation,

Defendant.

Civil No. 03-809 (JAP)

FIRST AMENDED COMPLAINT

Plaintiffs Abbott Laboratories, Fournier Industrie et Santé, and Laboratoires Fournier S.A., for their first amended complaint, allege against Defendant Par Pharmaceutical, Inc., as follows:

THE PARTIES

1. Plaintiff Abbott Laboratories ("Abbott") is a corporation organized under the laws of the State of Illinois, having its headquarters and principal place of business at Abbott Park, Illinois 60064.

2. Plaintiffs Fournier Industrie et Santé, formerly known as Fournier Innovation et Synergie, and Laboratoires Fournier S.A. (collectively "Fournier") are French corporations having their principal place of business at 42 Rue de Longvic, 21300 Chenôve, France.

3. Defendant Par Pharmaceutical, Inc. ("Par") is a corporation organized and existing under the laws of the State of New Jersey having its principal place of business at One Ram Ridge Road, Spring Valley, NY 10977.

JURISDICTION AND VENUE

4. This Complaint is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, §§ 1 et seq. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. § 1338(a).

5. Venue properly exists in this judicial district pursuant to 28 U.S.C. § 1391 and § 1400(b) in that Par is a New Jersey corporation and therefore resides here.

6. This Court has personal jurisdiction over Par because it is a New Jersey corporation and transacts business in New Jersey.

FACTUAL BACKGROUND

7. Fournier is the owner by assignment of U.S. Patent No. 6,074,670, entitled "Fenofibrate Pharmaceutical Composition Having High Bioavailability and Method for Preparing It" (the '670 patent) (attached hereto as Exhibit 1) and U.S. Patent No. 6,277,405, entitled "Fenofibrate Pharmaceutical Composition Having High Bioavailability and Method for

Preparing It" (the '405 patent)(attached hereto as Exhibit 2) (collectively referred to as the "patents-in-suit").

8. Abbott is the exclusive licensee of the patents-in-suit.

9. The '670 patent, which issued on June 13, 2000, claims, *inter alia*, a novel immediate-release fenofibrate composition containing a hydrosoluble carrier, fenofibrate and a hydrophilic polymer. The '670 patent expires on January 9, 2018.

10. The '405 patent, which issued on August 21, 2001, claims a novel fenofibrate composition that exhibits a particular dissolution profile. The '405 patent expires on January 9, 2018.

11. Fenofibrate is useful as a lipid and cholesterol lowering agent for treatment of adults with increased triglyceride levels.

12. Abbott has approval from the United States Food and Drug Administration ("FDA") to market fenofibrate tablets under the name TRICOR®.

13. TRICOR® (fenofibrate) is included in the FDA's list of "Approved Drug Products With Therapeutic Equivalence Evaluations" also known as the "Orange Book." Approved drugs may be used as the basis of a later applicant's Abbreviated New Drug Application ("ANDA") to obtain approval of the ANDA applicant's drug product under provisions of 21 U.S.C. § 355(j).

14. The FDA's "Orange Book" also lists patents associated with approved drugs. The patents-in-suit are listed in the "Orange Book" in association with TRICOR® (fenofibrate).

15. Abbott and Fournier received a letter from Par dated January 10, 2002, stating that Par had filed an ANDA, designated as No. 76-520, requesting FDA approval to market a generic version of Abbott's TRICOR® (fenofibrate) tablets in 54mg, 107mg and 160mg dosages before the expiration of the patents-in-suit.

16. 35 U.S.C. § 271(e)(2) provides that the submission of an application under 21 U.S.C. § 355(j) for a drug claimed in a patent or for a drug use claimed in a patent is an act of infringement if the applicant seeks FDA marketing approval effective prior to the expiration of the patent. Par's submission of an ANDA for approval to sell fenofibrate tablets in 54mg, 107mg and 160mg dosages prior to the expiration of the patents-in-suit constitutes an act of infringement of one or more claims of the '670 and '405 patents under 35 U.S.C. § 271(e)(2). In addition, Par's generic version of TRICOR® (fenofibrate) infringes one or more claims of the '670 and '405 patents. On information and belief, Par's infringement is willful and deliberate.

17. Plaintiffs have no adequate remedy at law to redress Par's infringement.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for relief and judgment as follows:

(a) a judgment that the '670 and '405 patents remain valid and enforceable, and are infringed under 35 U.S.C. § 271(e)(2) by Par's filing of its ANDA No. 76-520;

(b) an order that the effective date of the approval of ANDA No. 76-520 be subsequent to the expiration dates of the '670 and '405 patents;

(c) an injunction prohibiting Par from commercially manufacturing, selling, using, or importing the fenofibrate compositions claimed in the '670 and '405 patents or otherwise infringing one or more claims of said patents;

(d) damages and/or other monetary relief pursuant to 35 U.S.C. § 284 for any commercial manufacture, use or sale of fenofibrate compositions falling within the scope of one or more claims of the '670 or '405 patents by Par;

(e) a judgment that Par willfully infringed the '670 and '405 patents;

(f) an award of Plaintiffs' interest, costs, reasonable attorneys' fees and such other relief as the Court deems just and proper pursuant to 35 U.S.C. § 271(e)(4) and 35 U.S.C. § 285; and,

(g) such other and further relief as this Court may deem just and proper.

Date: February 13, 2004

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CERTIFICATION PURSUANT TO L.Civ.R. 11.2

I hereby certify that, to the best of my knowledge, the within matter in controversy is not the subject of any other action pending in any court or of a pending arbitration proceeding, nor are any other actions or arbitration proceedings contemplated. Furthermore, I am not presently aware of any other party who should be joined in this action.

RIKER, DANZIG, SCHERER, HYLAND & PERRETTI LLP
Attorneys for Plaintiff
Abbott Laboratories

Date: February 13, 2004

By: Kelly S. Crawford
Kelly S. Crawford

CERTIFICATION OF NON-ARBITRABILITY AND NON-MEDIATION

Pursuant to Local Civil Rule 201.1(d)(1), I hereby certify that this action is not subject to compulsory arbitration or to mediation because this action seeks injunctive relief.

RIKER, DANZIG, SCHERER, HYLAND & PERRETTI LLP
Attorneys for Plaintiff
Abbott Laboratories

Date: February 13, 2004

By: Kelly S. Crawford
Kelly S. Crawford

Exhibit 1

US006074670A

United States Patent [19]

Stamm et al.

[11] **Patent Number: 6,074,670**

[45] **Date of Patent: Jun. 13, 2000**

[54] **FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT**

[75] Inventors: **André Stamm**, Griesheim, France; **Pawan Seth**, Irvine, Calif.

[73] Assignee: **Laboratoires Fournier, S.A.**, Dijon, France

[21] Appl. No.: **09/005,128**

[22] Filed: **Jan. 9, 1998**

[30] **Foreign Application Priority Data**

Jan. 17, 1997 [FR] France 97 00479

[51] **Int. Cl.**[7] **A61K 9/16**; A61K 9/20; A61K 9/50

[52] **U.S. Cl.** **424/462**; 424/456; 424/458; 424/459; 424/489; 424/490; 424/497; 424/464; 424/465; 424/469; 424/470

[58] **Field of Search** 424/465, 464, 424/470, 472, 479, 482, 489, 2.15, 451, 456, 458, 462, 490, 497

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,412,986	11/1983	Kawata et al. .	
4,800,079	1/1989	Hoyer .	
4,895,726	1/1990	Curtet et al. .	
4,992,277	2/1991	Sangekar et al. .	
5,545,628	8/1996	Deboeck et al. .	
5,776,495	7/1998	Duclos et al. .	

FOREIGN PATENT DOCUMENTS

256 933	2/1988	European Pat. Off. .
330 532	8/1989	European Pat. Off. .
519 144	12/1992	European Pat. Off. .
92/01649	5/1982	WIPO .
98/31361	7/1998	WIPO .

OTHER PUBLICATIONS

Temeljotov et al., Solubilization and Dissolution Enhancement for Sparingly Soluble Fenofibrate, Acta Pharm., 46 pp 131–136, 1996.

Primary Examiner—Thurman K. Page
Assistant Examiner—Brian K. Seidleck
Attorney, Agent, or Firm—Hale and Dorr LLP

[57] **ABSTRACT**

The invention provides an immediate-release fenofibrate composition comprising (a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 μm, a hydrophilic polymer and, optionally, a surfactant, the polymer making up at least 20% by weight of (a); and (b) optionally one or several outer phase(s) or layers(s). The invention also provides a method for preparing said composition.

38 Claims, 2 Drawing Sheets

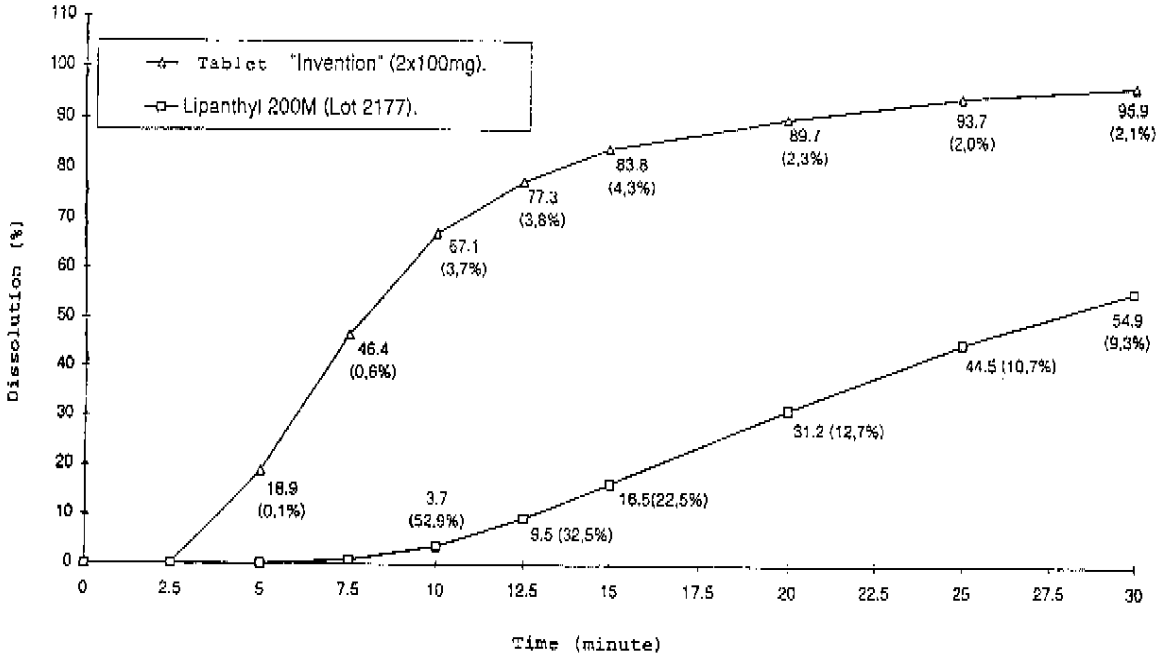
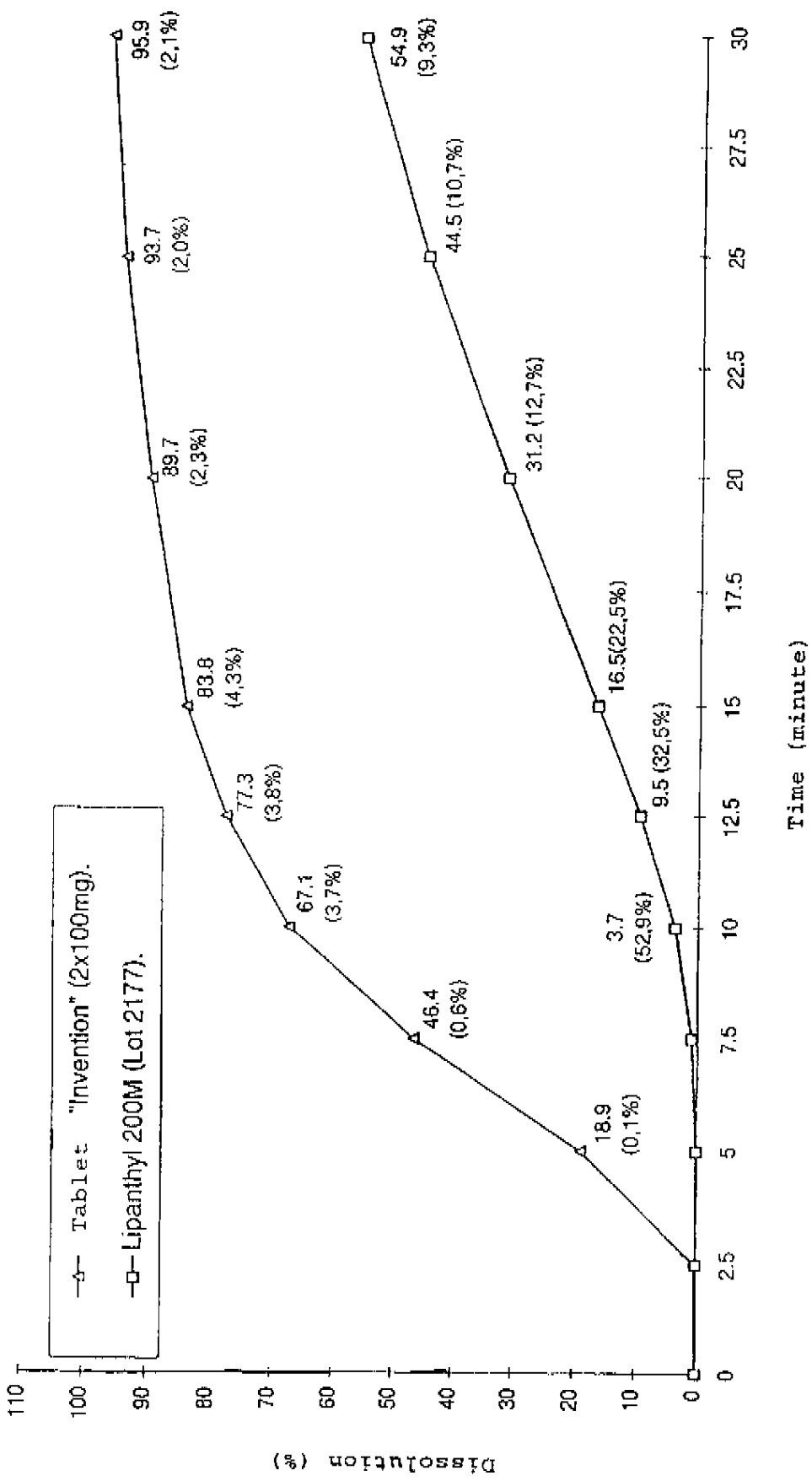


FIG 1


Tablet "Invention" (2x100mg).
Lipanthyl 200M (Lot 2177).
Dissolution (%)
Time (minute)
0
10
20
30
40
50
60
70
80
90
100
110
0
2.5
5
7.5
10
12.5
15
17.5
20
22.5
25
27.5
30
95.9 (2,1%)
93.7 (2,0%)
89.7 (2,3%)
83.8 (4,3%)
77.3 (3,8%)
67.1 (3,7%)
46.4 (0,6%)
18.9 (0,1%)
54.9 (9,3%)
44.5 (10,7%)
31.2 (12,7%)
16.5(22,5%)
9.5 (32,5%)
3.7 (52,9%)

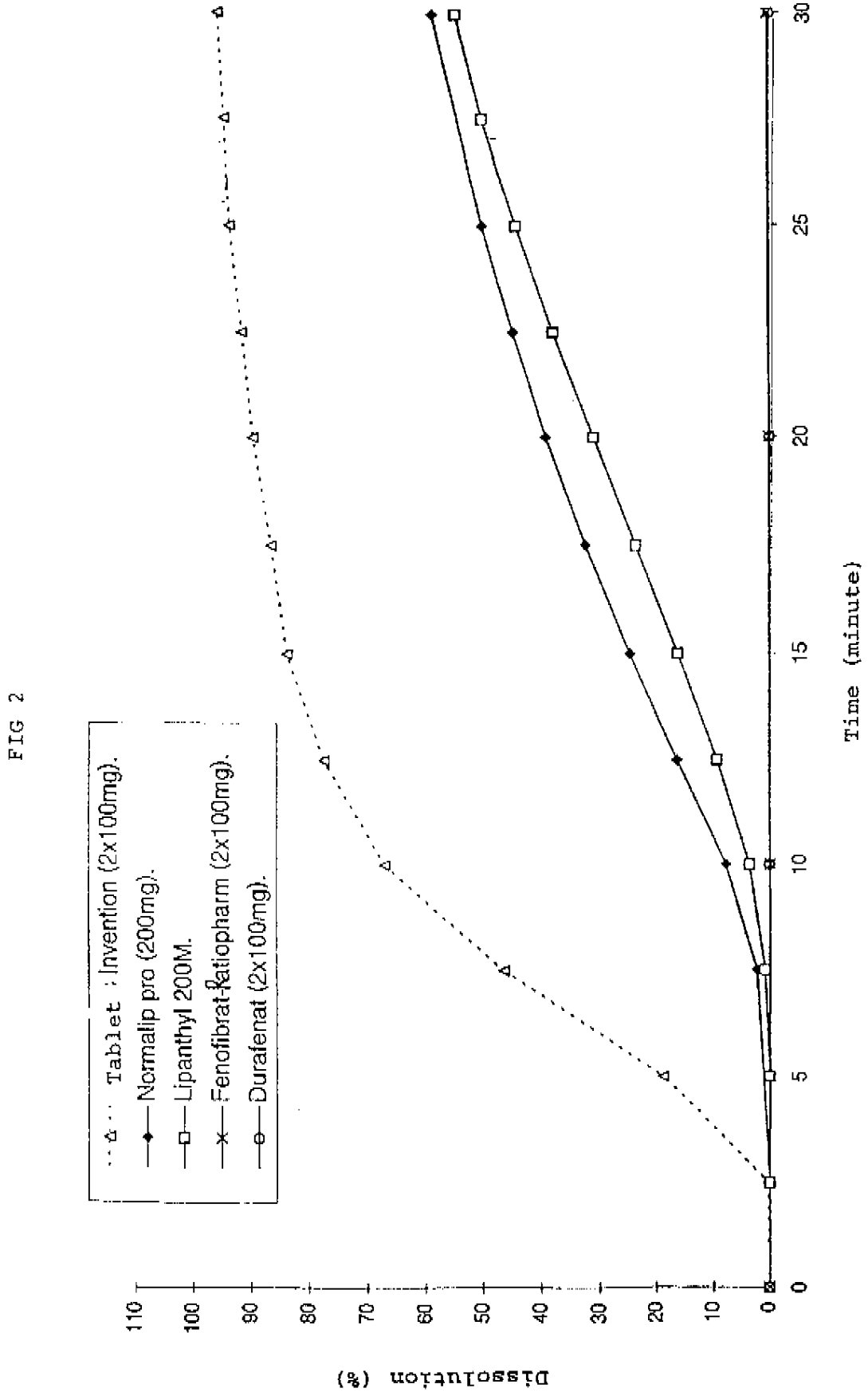

Tablet : Invention (2x100mg).
Normalip pro (200mg).
Lipanthyl 200M.
Fenofibrat-Ratiopharm (2x100mg).
Durafenat (2x100mg).
Dissolution (%)
Time (minute)
0
10
20
30
40
50
60
70
80
90
100
110
0
5
10
15
20
25
30

FIG 2

FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT

BACKGROUND OF THE INVENTION

The present invention relates to a novel pharmaceutical composition having high bioavailability through improved dissolution, and a method for preparing it. The invention more particularly relates to a pharmaceutical composition for administration by oral route, containing an active ingredient of poor aqueous solubility.

Numerous active ingredients suffer from the disadvantage of being poorly soluble in an aqueous medium, thus having an insufficient dissolution profile and, consequently, poor bioavailability within the organism, following oral administration. The therapeutic dose required to be administered must thus be increased in order to obviate this disadvantage. This particularly applies to numerous hypolipemiant active ingredients, such as those belonging to the fibrate family.

Fenofibrate is a well-known hypolipemiant from the family of fibrates, which is commercially available in various doses (100 and 300 mg for example Secalip®) but in a form leading to poor bioavailability of the active ingredient. Indeed, due to it poor hydrosolubility, fenofibrate is poorly absorbed in the digestive tract and consequently its bioavailability is incomplete, irregular and often varies from one person to another.

To improve the dissolution profile of fenofibrate and its bioavailability, thereby reducing the dose requiring to be administered, it would be useful to increase its dissolution so that it could attain a level close to 100%.

Moreover, for patient comfort, it is advantageous to seek a dosage form that only requires the medicament to be taken once daily while giving the same effect as one administered several times daily.

EP-A-0330532 discloses a method for improving bioavailability of fenofibrate. This patent describes the effect of co-micronizing fenofibrate with a surfactant, for example sodium laurylsulfate in order to improve fenofibrate solubility and thereby increase its bioavailability. This patent teaches that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than the improvement that would be obtained either by adding a surfactant, or through solely micronizing the fenofibrate, or, yet again, through intimately mixing the fenofibrate and surfactant, micronized separately. The dissolution method employed is the conventional rotating blade technique (European Pharmacopoeia): product dissolution kinetics are measured in a fixed volume of the dissolution medium, agitated by means of a standardized device; a test was also carried out with an alternative technique to the European Pharmacopoeia, using the continuous-flow cell method.

The process of EP-A-0330532 leads to a new dosage form in which the active ingredient, co-micronized with a solid surfactant, has improved fenofibrate dissolution, and thus increased bioavailability, which makes it possible, for a given level of effectiveness, to decrease the daily dose of the medicament: respective 67 mg and 200 mg instead of 100 mg and 300 mg.

However, the preparation method in that patent is not completely satisfactory inasmuch as it does not lead to complete bioavailability of the active ingredient, and suffers from several disadvantages. The technique of co-micronizing fenofibrate with a solid surfactant does, it is true, improve dissolution of the active ingredient, but this dissolution remains, however, incomplete.

There is thus a need to improve fenofibrate bioavailability in order to attain, over very short periods of time, a level close to 100% (or, in any case, better than the following limits: 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes in a medium consisting of 1200 ml water to which 2% Polysorbate 80 is added, or of 1000 ml of water to which 0.025M sodium lauryl sulfate sodium is added, with a blade rotation speed of 75 rpm), and this even when dissolution media having a low surfactant content are used.

Applicant has found that, surprisingly, it is possible to resolve this problem by a new method for preparing a pharmaceutical composition by spraying a suspension of the active ingredient onto an inert hydrosoluble carrier. The present invention also relates to pharmaceutical compositions thus prepared.

The use is already known of a polymer, such as polyvinylpyrrolidone for producing tablets, in concentrations of the order of 0.5 to 5% by weight, at a maximum 10% by weight. In this case, the polyvinylpyrrolidone is used as a binder. Similarly, the use of a polymer such as hydroxymethylpropylmethyl cellulose as a granulation binder is known. Thus, European patent application 0,519,144 discloses pellets of a poorly soluble substance, omeprazole, obtained by spraying a dispersion or suspension of the active ingredient in a solution containing said polymer onto inert pellets in a fluidized-bed granulator. However, here again, the polymer (HPMC and HPC) is only used as a granulation binder, in an amount of about 50% by weight, based on the weight of the active ingredient, which, bearing in mind the presence of the inert pellets of a large size (about 700 μm) and the overall final weight leads to final active ingredient and polymer contents which are very low, of the order of barely a few percent based on the weight of the final covered pellet. Finally, it will be noted that the size of the inert pellets in this documents is fairly large, which, in the case of fenofibrate, would lead to a final formulation having a volume which is much too large for ready oral administration.

The use of polymer, such as polyvinylpyrrolidone for manufacturing "solid dispersions" is also known, obtained in general by co-precipitation, co-fusion or liquid-phase mixing followed by drying. What we have here is fixation of the active ingredient in isolated microparticles on the polyvinylpyrrolidone, which avoids problems of poor wetting of the solid and re-agglomeration of the particles. The article "Stable Solid Dispersion System Against Humidity" by Kuchiki et al., Yakuzaigaku, 44 No. 1, 31-37 (1984) describes such a technique for preparing solid dispersions using polyvinylpyrrolidone. The amounts of PVP here are very high, and the ratio between the active ingredient and PVP are comprised between 1/1 and 1/20. In the case however there is no inert carrier.

WO-A-96 01621 further discloses a sustained release composition, comprising an inert core (silica in all examples) coated with a layer which contains the active ingredient in admixture with a hydrophilic polymer, the weight ratio active ingredient/polymer being comprised between 10/1 and 1/2 and the weight ratio active ingredient/inert core being comprised between 5/1 and 1/2, with an outer layer to impart the sustained release property. These compositions can be compressed. The hydrophilic polymer can be polyvinylpyrrolidone. This document also discloses a

process for preparing said composition; for example in a fluidized-bed granulator one will spray a dispersion of active ingredient in a polymer solution onto the inert cores. This document solely relates to sustained release compositions, the technical problem to be solved being the compression, without damages, of the outer layer imparting the sustained release property.

Nevertheless, nothing in the state of the art teaches nor suggest the present invention.

SUMMARY OF THE INVENTION

Thus, the present invention provides an immediate-release fenofibrate composition comprising:

(a) an inert hydrosoluble carrier covered with at least one layer containing a fenofibrate active ingredient in a micronized form having a size less than 20 μm, a hydrophilic polymer and, optionally, a surfactant; said hydrophilic polymer making up at least 20% by weight of (a); and

(b) optionally one or several outer phase(s) or layer(s).

In one embodiment, a surfactant is present with the active ingredient and the hydrophilic polymer.

The invention also provides a composition comprising fenofibrate having a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or in a dissolution medium constituted by water with 0.025M sodium lauryl sulfate.

A method for preparing a pharmaceutical composition is also provided, comprising the steps of:

(a) preparing a fenofibrate suspension in micronized form with a particle size below 20 μm, in a solution of hydrophilic polymer and, optionally surfactant;

(b) applying the suspension from step (a) to an inert hydrosoluble carrier;

(c) optionally, coating granules thus obtained with one or several phase(s) or layer(s).

Step (b) is preferably carried out in a fluidized-bed granulator.

The method can comprise a step in which products obtained from step (b) or (c) are compressed, with or without additional excipients.

The invention also provides a suspension of fenofibrate in micronized form having a size less than 10 μm, in a solution of hydrophilic polymer and, optionally, surfactant.

The invention will be described in more detail in the description which follows, with reference to the attached drawings.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** is a graph of a comparative study of the dissolution profile of a composition according to the invention, compared to that of Lipanthyl® 200M;

FIG. **2** is a graph illustrating a comparative study of the dissolution profile of a composition according to the invention and that of pharmaceutical products commercially available on the German market.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The expression "in micronized form" in this invention means a substance in a particulate form, the dimensions of the particles being less than or equal to about 20 μm.

Advantageously, this dimension is less than or equal to 10 μm.

In the framework of this invention, the expression "inert hydrosoluble carrier" means any excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed, and which is soluble in an aqueous medium, notably in a gastric acid medium. Examples of such excipients are derivatives of sugars, such as lactose, saccharose, hydrolyzed starch (malto-dextrine), etc. Mixture are also suitable. The individual particle size of the inert hydrosoluble carrier can be, for example, between 50 and 500 micron.

The expression "hydrophilic polymer" in the invention should be taken to mean any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel. Examples of such polymers are polyvinylpyrrolidone, poly(vinyl alcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, etc. Polymer blends are also suitable.

The preferred hydrophylic polymer is polyvinylpyrrolidone (PVP). The PVP used in this invention has, for example, a molecular weight comprised between 10,000 and 100,000, preferably for example between 20,000 and 55,000.

The term "surfactant" is used in its conventional sense in this invention. Any surfactant is suitable, whether it be amphoteric, non-ionic, cationic or anionic. Examples of such surfactants are: sodium lauryl sulfate, monooleate, monolaurate, monopalmitate, monostearate or another ester of polyoxyethylene sorbitane, sodium dioctylsulfosuccinate (DOSS), lecithin, stearylic alcohol, cetostearylic alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty acid glycerides, poloxamer®, etc. Mixtures of surfactants are also suitable.

The preferred surfactant is sodium laurylsulfate, which can be co-micronized with fenofibrate.

The compositions according to the invention can additionally contain any excipient conventionally used in the pharmaceutical and chemical fields which is compatible with the active ingredient, such as binders, fillers, pigments, disintegrating agents, lubricants, wetting agents, buffers, etc. As examples, excipients able to be used in this invention we can cite: microcrystalline cellulose, lactose, starch, colloidal silica, talc, glycerol esters, sodium stearyl fumarate, titanium dioxide, magnesium stearate, stearic acid, cross-linked polyvinyl pyrrolidone (AC DI SOL®), carboxymethyl starch (Explotab®, Primojel®), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, etc.

Here, the expression "outer phase or layer" should be taken to mean any coating on the element (a) with the active ingredient (forming a "core"). Indeed, it can be useful to have available one or several phase(s) or layer(s) on top of the coated core. The invention thus covers a single core with one layer, but also several cores in a phase, as is the case of tablets which are formed from "cores" mixed with a phase.

This outer layer comprises conventional excipients.

It is also possible to provide a layer comprising additives, for the manufacture of tablets. In this embodiment, the outer layer comprises a disintegration agent and, for example, a lubricant; the thus covered and mixed granules can then be readily compressed and easily disintegrate in water.

The compositions according to the invention comprise, in general, based on the total composition weight excluding the

outer phase or layer, an inert hydrosoluble carrier making up from 10 to 80% by weight, preferably 20 to 50% by weight, the fenofibrate representing from 5 to 50% by weight, preferably from 20 to 45% by weight, the hydrophilic polymer representing from 20 to 60% by weight, preferably 25 to 45% by weight, the surfactant making up from 0 to 10% by weight, preferably 0.1 to 3% by weight.

The outer layer or phase if present, can make up to 80% by weight of the total weight, preferably up to 50% by weight.

The hydrophilic polymer represents preferably more than 25% by weight, based on the weigt of (a).

The weight ration fenofibrate/hydrophilic polymer can for example be comprised between 1/10 and 4/1, preferably, for example, between 1/2 and 2/1.

When a surfactant is employed, the weight ratio surfactant/hydrophilic polymer can be comprised for example between 1/500 and 1/10, preferably, for example, between 1/100 and 5/100.

In one embodiment, the composition according to the invention takes the form of tablets.

This tablet preferably results from the compression of elements (a) (under the form of granules) together with an outer phase.

In another embodiment, the composition of the invention takes the form of granules enclosed inside a capsule, for example in gelatin, or inside a bag.

The compositions of the invention are particularly suitable for administering active ingredients by oral route.

The composition according to the invention is prepared by a novel process comprising spraying a suspension of the active ingredient in a micronized form in a solution of a hydrophilic polymer and, optionally, a surfactant, onto the inert core.

When a surfactant is present, the active ingredient can be co-micronized with the surfactant. One will then use with advantage the teachings of EP-A-0330532.

The method according to the invention consists in using the fluidized bed granulation principle, but with specific starting materials, in order to arrive at an improved dissolution profile and thus, at elevated bioavailability. In particular, the invention employs a suspension of the micronized active ingredient in a solution of a hydrophylic polymer and, optionally, a surfactant.

The fluidized-bed granulation technique is widely used in the pharmaceutical industry for preparing capsules or tablets. Conventionally, according to the prior art, a powder or a mixture of powders (active ingredient+excipients) is put into suspension in the fluidized bed in a granulator, and a solution containing a binder and, optionally, a surfactant, is sprayed onto this bed to form granules. The fluidized-bed granulation technique is well known to those skilled in the art and reference should be made to standard works such as for example "Die Tablette", by Ritschel, Ed. Cantor Aulendorf, pages 211–212.

The invention, as has been indicated, comprises spraying a suspension of an active ingredient micronized with a hydrophilic polymer onto an inert carrier. Following granulation, the granulate formed consists of crystals of, for example, lactose, which are isolated (or possibly agglomerated together by the spray solution) and particles of active ingredient and PVP adhering to the crystal surface. The granule could similarly be constituted of coated crystals which are agglomerated, or even of such an agglomerate having received a coating.

The compositions according to the invention can also be prepared by other methods, for example by spraying a solution of the micronized active ingredient onto the hydrosoluble inert carrier.

The granulates thus obtained can, if desired, be provided with an outer coating or compressed into tablets, or form agglomerates.

The outer layer or layer is/are applied using conventional coating techniques such as coating in a pan or fluidized bed coater.

When the granulate obtained (whether subsequently coated or not) is compressed to form tablets, this step can be implemented using any conventional technique which is suitable, for example using an alternating or rotating compressing equipment.

The significant starting product is the suspension of the active ingredient. This suspension is prepared by putting the micronized active ingredient into suspension in a solution comprising the hydrophylic polymer and, optionally, a surfactant, in solution in a solvent. If a surfactant is employed, it is put into solution in the solvent (beaker+magnetic or vane stirrer). Next, the hydrophylic polymer (PVP) is dispersed, while stirring, in the solution previously obtained. Depending on polymer solubility, this either dissolves in the solution or forms a gel or a suspension having varying degrees of thickness. While still stirring, the micronized active ingredient is dispersed in the form of a fine shower into the above solution or suspension, to form a homogeneous suspension. The order of these steps can be reversed. The solvent employed can be aqueous or organic (for example ethanol). For example demineralized water can be used.

The active ingredient concentration in the suspension is from 1 to 40% by weight, preferably from 10 to 25%.

The hydrophylic polymer concentration in the suspension is from 5 to 40% by weight, preferably 10 to 25%.

The surfactant concentration in the suspension is from 0 to 10% by weight, preferably below 5%.

The invention also covers this novel suspension.

Without wishing to be tied down to a specific theory, applicant believes that this novel method, through the use of a micronized active ingredient suspension in a hydrophilic polymer solution, enabled a novel composition to be obtained in which the active ingredient is in a non-re-agglomerated form.

The following examples illustrate the invention without limiting it.

EXAMPLE 1

Preparation of a pharmaceutical composition of fenofibrate according to the invention.

A composition containing, as the element a), micronized fenofibrate, Plasdone®, Capsulac® and sodium lauryl sulfate was prepared.

The micronized fenofibrate had a particle size of about 5 μm, as measured using a Coulter counter.

The Plasdone K25® corresponds to a polyvinylpyrrolidone PVP ISP and the Capsulac 60® corresponds to a coarse crystal lactose monohydrate (Meggle) (particle size between 100 and 400 μm).

The sodium laurylsulfate (7 g) is dissolved in water (demineralized water, 1750 g) and the micronized fenofibrate (350 g) is put into suspension in the mixture obtained (for example using a helix stirrer at 300 rpm for 10 minutes, then using an Ultra Turrax agitator at 10,000 rpm, for 10 minutes). Following this, the PVP (350 g) is added while

still agitating, stirring (helix stirrer) being continued until the latter had dissolved (30 minutes). It is all passed through a sieve (350 μm) to eliminate possible agglomerates.

Separately, the lactose (400 g) is put into suspension in a fluidized air bed granulator (of the Glatt® GPCG1—Top Spray type or equivalent) and heated to a temperature of 40° C.

The fenofibrate suspension is sprayed onto the lactose. This step is carried out under the following conditions: spraying pressure: 2.1 bar, air throughput 70 m^3/h, air inlet temperature: 45° C.; air outlet temperature: 33° C.; product temperature 34° C.; duration of spraying: 3 h.

The granulate thus obtained can be put inside capsules or transformed into tablets. Any suitable conventional technique for preparing such dosage forms can be used.

For transformation to tablet form, one will mix 191 g of the granulate obtained (using for example a mixer-grinder type mixing apparatus, a planetary mixer or turn-over mixer), with the outer phase having the following composition:

- 56 g Polyplasdone XL® (cross-linked polyvinylpyrrolidone ISP, as described in the USA Pharmacopoeia "USP - NF" under the name of crospovidone, mean molecular weight>1,000,000);
- 88 g Avicel® PH200 (microcrystalline cellulose);
- 3.5 g sodium stearyl fumarate (Mendell, U. S. A.); and
- 2 g Aerosil® 200 (colloidal silica).

The cross-linked polyvinylpyrrolidone, the microcrystalline cellulose, the sodium stearyl fumarate and the colloidal silica are respectively, disintegration agents, binders, lubricating and flow enhancing agents.

The tablet can be obtained on an alternating compression machine (for example Korsch EKO) or a rotary machine (for example Fette Perfecta 2).

One thus obtains tablets having the following composition, expressed in mg:

element (a):	
micronized fenofibrate	100.0
PVP	100.0
Lactose	114.3
sodium laurylsulfate	2.0
outer phase (or layer):	
cross-linked PVP	92.7
microcrystalline cellulose	145.7
sodium stearyl fumarate	5.8
colloidal silica	3.3

EXAMPLE 2

Dissolution of a composition according to the invention and a composition according to the prior art.

a) dissolution medium and procedure for measuring dissolution.

A dissolution medium which is discriminating, in other words one in which two products having very different dissolution profiles in gastric juices will have very different dissolution curves is looked for.

For this, an aqueous medium containing a surfactant, this being Polysorbate 80 (polyoxyethylene sorbitane monooleate) is used. This surfactant is readily available from various suppliers, is the object of a monograph in the Pharmacopoeias, and is thus easy to implement (being also a water-soluble liquid product). Other surfactants can also be used.

The rotating blade method (European Pharmacopoeia) is used under the following conditions: volume of medium: 1200 ml; medium temperature: 37° C.; blade rotation speed: 75 rpm; samples taken: every 2.5 minutes. Determination of the amount dissolved is carried out by spectrophotometry. Test are repeated 6 times over.

b) Results

The composition according to the invention consisted of two tablets containing about 100 mg fenofibrate prepared according to example 1.

The prior art composition was Lipanthyl® 200M from Laboratoires Fournier, containing 200 mg fenofibrate (corresponding to capsules of 200 mg fenofibrate, co-micronized with sodium laurylsulfate, and containing lactose, pre-gelatinized starch, cross-linked polyvinylpyrrolidone and magnesium stearate, in line with the teachings of EP-A-0330532.

The results obtained are shown graphically in FIG. 1, on which the percentage of dissolution is shown, the observed standard deviation being indicated between brackets.

These results clearly show that the compositions according to the invention have a dissolution profile which is distinctly better than that of the prior art compositions.

These results also clearly show that with the compositions of the invention, the standard deviation observed is distinctly lower than is the case with prior art compositions.

EXAMPLE 3

Study of bioavailability of compositions according to the invention and prior art compositions.

A test of bioavailability on healthy volunteers was carried out.

The following compositions were tested:

- composition according to the invention: capsules containing granules prepared according to example 1, containing 200 mg fenofibrate.
- first composition according to the prior art: Lipanthyl® 200M from Laboratoires Fournier, containing 200 mg fenofibrate, identical to that in the previous example.
- second prior art composition: Secalip® in capsule form (300 mg fenofibrate in the form of three 100 mg capsules).

The study was carried out on 6 healthy volunteers receiving a single dose of fenofibrate, with a minimum 6-day rest period between administrations. The samples for pharmacokinetic analysis were collected after each administration at the following times: 0.5 h; 1 h; 2 h; 3 h; 4 h; 5 h; 6 h; 8 h; 10 h; 12 h; 24 h; 36 h; 48 h; 72 h; and 96 hours following administration of the medicament. Fenofibric acid content in plasma was measured for each sample.

The results obtained are given in table 1 below.

TABLE 1

Product	dose (mg)	Cmax (μg/ml)	tmax (h)	t½ (h)	AUC 0-t (μg · h/ml)	AUC 0-∞ (μg · h/ml)
Invention	200	5.4	6	23	148	162
Secalip ® 100	3 × 100	1.1	25	39	53	56
Lipanthyl ® 200M	200	1.6	8.3	41	71	92

Cmax: maximum plasma concentration
tmax: time to reach Cmax
t½: plasma half-life
AUC 0 - t: area under the curve from 0 to t
AUC 0 - ∞: area under the curve from 0 to ∞.

The results clearly show that the compositions of the present invention have a dissolution profile that is an

improvement over compositions of the prior art, leading to a considerably enhanced bioavailability of the active ingredient compared to that obtained with compositions of the prior art.

EXAMPLE 4

Comparison of the dissolution profile of compositions according to the invention and that of products currently on the German market.

On the German market, immediate or sustained-release fenofibrate formulations exist. Like in France, the 100 mg and 300 mg (conventional) forms coexist with 67 and 200 mg forms (having enhanced bioavailability, according to the teaching of EP-A-0330532). These products are as follows:

Fenofibrate—ratiopharm; Ratiopharm—Ulm;
Capsules;
Composition: 100 mg fenofibrate;
Excipients: lactose, corn starch, magnesium stearate, E 171 colorant, gelatine.

Durafenat; Durachemie—Wolfratshausen Capsules;
Composition: 100 mg fenofibrate;
Excipients: lactose, corn starch, magnesium stearate, E 171 colorant, gelatine.

Normalip pro; Knoll—Ludwigshafen;
Capsules;
Composition: 200 mg Fenofibrate;
Excipients: Crospovidone, gelatine, monohydrate lactose, magnesium stearate, corn starch, sodium laurylsulfate, E 132 and E 171 colorants.

A comparison was made between:

the tablet of the invention as prepared using example 1 (2×100 mg)

Normalip pro® (200 mg);

Lipanthyl® 200M (200 mg) (according to the preceding example);

Fenofibrate by Ratiopharm® (2×100 mg);

Durafenat® (2×100 mg)

The tests were implemented under the same conditions as in the previous examples. FIG. 2 summarizes the results.

These results clearly show that the compositions of the invention have a distinctly improved dissolution compared to prior art compositions.

Obviously, the present invention is not limited to the embodiments described but may be subject to numerous variations readily accessible to those skilled in the art.

What is claimed is:

1. An immediate-release fenofibrate composition comprising:

(a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 μm, a hydrophilic polymer and a surfactant; and

(b) optionally one or several outer phase(s) or layer(s),

wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45% by weight, said hydrophilic polymer makes up from 20 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight.

2. The composition according to claim **1**, wherein the composition has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or with 0.025M sodium lauryl sulfate.

3. The composition according to claim **1**, in which the hydrophilic polymer is polyvinylpyrrolidone.

4. The composition according to claim **1**, in which fenofibrate and the surfactant are co-micronized.

5. The composition according to claim **1**, in which said surfactant is sodium lauryl sulfate.

6. The composition according to claim **5**, in which fenofibrate and sodium lauryl sulfate are co-micronized.

7. The composition according to claim **1**, in which the weight ratio fenofibrate/hydrophilic polymer is comprised between 1/10 and 4/1.

8. The composition according to claim **6**, in which the weight ratio fenofibrate/hydrophilic polymer is comprised between 1/10 and 4/1.

9. The composition according to claim **1**, in which the weight ratio fenofibrate/hydrophilic polymer is comprised between 1/2 and 2/1.

10. The composition according to claim **6**, in which the weight ratio fenofibrate/hydrophilic polymer is comprised between 1/2 and 2/1.

11. The composition according to claim **1**, in which the individual particle size of said inert hydrosoluble carrier is comprised between 50 and 500 microns.

12. An immediate-release fenofibrate composition comprising:

(a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 μm, polyvinylpyrrolidone, and a surfactant; and

(b) optionally one or several outer phase(s) or layer(s),

wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45% by weight, said polyvinylpyrrolidone makes up from 25 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight, and

wherein fenofibrate and the surfactant are co-micronized.

13. The composition according to claim **12**, in which said surfactant is sodium laurylsulfate.

14. The composition according to claim **12**, wherein said fenofibrate has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or with 0.025M sodium lauryl sulfate.

15. The composition according to claim **1**, under the form of a tablet.

16. The composition according to claim **6**, under the form of a tablet.

17. The composition according to claim **12**, under the form of a tablet.

18. The composition according to claim **14**, under the form of a tablet.

19. The composition according to claim **15** under the form of a tablet resulting from the compression of elements (a) together with an outer phase.

20. The composition according to claim **16** under the form of a tablet resulting from the compression of elements (a) together with an outer phase.

21. The composition according to claim **17** under the form of a tablet resulting from the compression of elements (a) together with an outer phase.

22. A method for preparing a composition according to claim **1**, comprising the steps of:

(a) preparing a fenofibrate suspension in micronized form with a particle size below 20 μm, in a solution of hydrophilic polymer and a surfactant;

(b) applying the suspension from step (a) to an inert hydrosoluble carrier;

(c) optionally, coating granules thus obtained with one or several phase(s) or layer(s).

23. The method according to claim **22**, in which step (b) is carried out in a fluidized-bed granulator.

24. The method according to claim **22**, comprising a step in which products obtained from step (b) or (c) are compressed.

25. The composition according to claim **1**, under the form of granules inside a capsule.

26. The composition according to claim **6**, under the form of granules inside a capsule.

27. The composition according to claim **12**, under the form of granules inside a capsule.

28. The composition according to claim **14**, under the form of granules inside a capsule.

29. The composition according to claim **4**, wherein the fenofibrate has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or with 0.025M sodium lauryl sulfate.

30. The composition according to claim **6**, wherein the fenofibrate has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or with 0.025M sodium lauryl sulfate.

31. The composition according to claim **2**, under the form of granules inside a capsule.

32. The composition according to claim **4**, under the form of granules inside a capsule.

33. The composition according to claim **29** under the form of granules inside a capsule.

34. The composition according to claim **30**, under the form of granules inside a capsule.

35. The composition according to claim **2**, under the form of a tablet.

36. The composition according to claim **4**, under the form of a tablet.

37. The composition according to claim **20**, under the form of a tablet.

38. The composition according to claim **30**, under the form of a tablet.

* * * * *

Exhibit 2

US006277405B1

(12) **United States Patent**
Stamm et al.

(10) **Patent No.: US 6,277,405 B1**
(45) **Date of Patent: *Aug. 21, 2001**

(54) **FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT**

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(73) Assignee: **Laboratoires Fournier, S.A.**, Dijon (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/572,330**

(22) Filed: **May 18, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/005,128, filed on Jan. 9, 1998, now Pat. No. 6,074,670.

(30) **Foreign Application Priority Data**

Jan. 17, 1997 (FR) 97 00479

(51) **Int. Cl.**[7] **A61K 9/16**; A61K 9/20; A61K 9/50

(52) **U.S. Cl.** **424/462**; 424/456; 424/458; 424/459; 424/489; 424/490; 424/497; 424/464; 424/465; 424/469; 424/470; 514/543

(58) **Field of Search** 424/462, 456, 424/458, 459, 489, 490, 497, 464, 465, 469, 470; 514/543

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Assistant Examiner—Brian K. Seidleck
(74) *Attorney, Agent, or Firm*—Hale and Dorr LLP

(57) **ABSTRACT**

The invention provides a micronized fenofibrate composition. The micronized fenofibrate composition has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or with 0.025M sodium lauryl sulfate. The composition can further comprise hydrophilic polymers, surfactants, hydrosoluble carriers, outer phases or layers, or other pharmaceutically acceptable excipients. The immediate-release fenofibrate composition is preferably in the form of a tablet or in the form of granules inside a capsule.

13 Claims, 2 Drawing Sheets

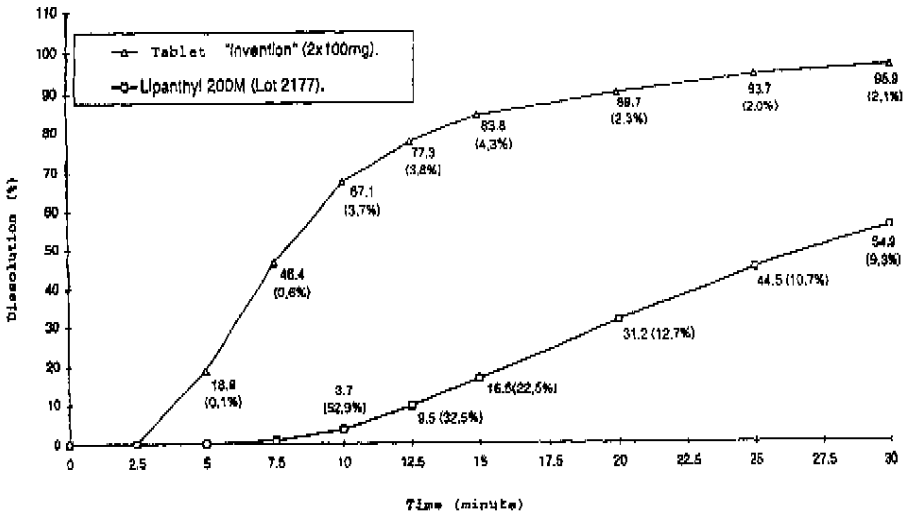
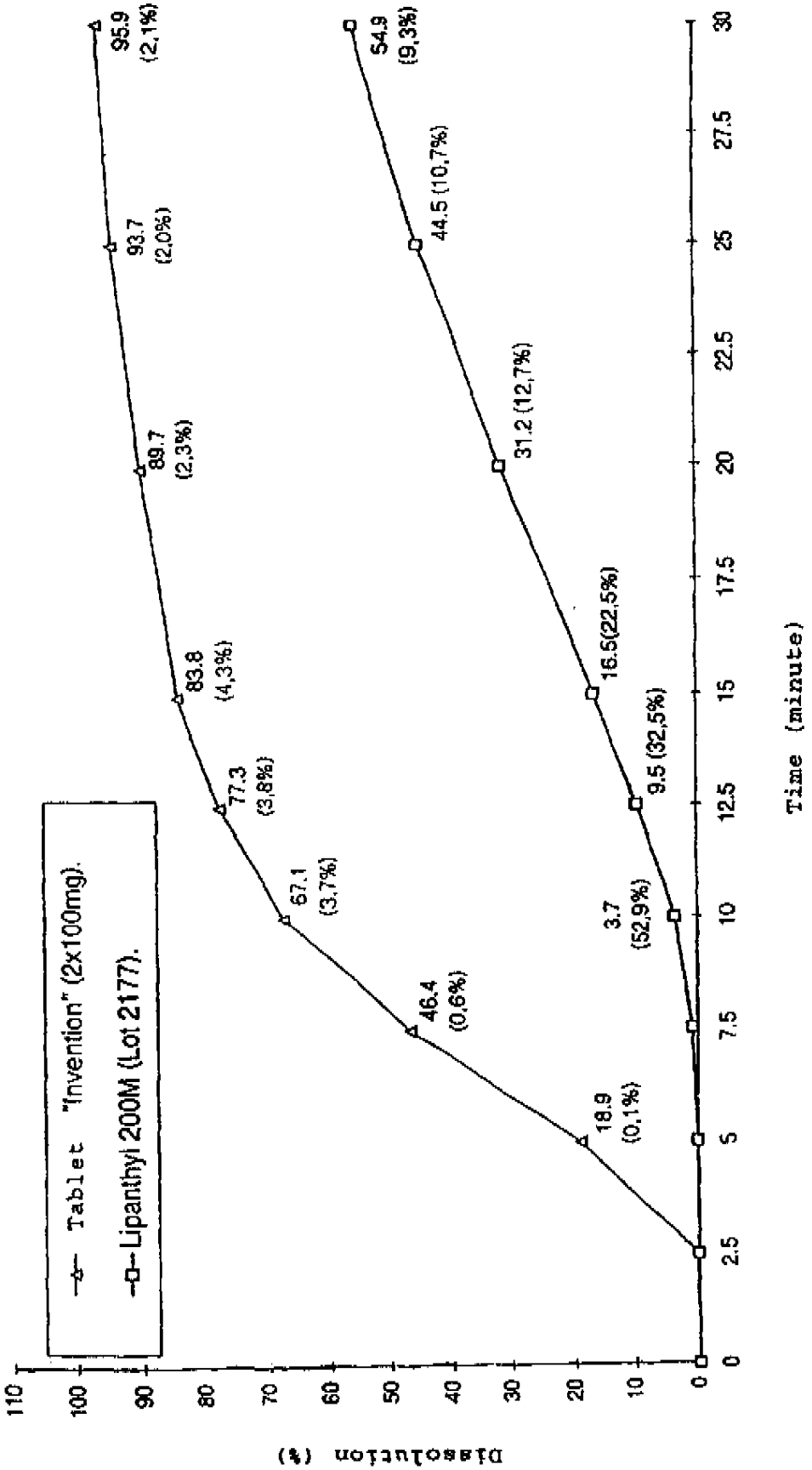


FIG 1


Tablet "Invention" (2x100mg).
Lipanthyl 200M (Lot 2177).
Dissolution (%)
Time (minute)
110
100
90
80
70
60
50
40
30
20
10
0
0
2.5
5
7.5
10
12.5
15
17.5
20
22.5
25
27.5
30
95.9 (2,1%)
93.7 (2,0%)
89.7 (2,3%)
83.8 (4,3%)
77.3 (3,8%)
67.1 (3,7%)
46.4 (0,6%)
18.9 (0,1%)
54.9 (9,3%)
44.5 (10,7%)
31.2 (12,7%)
16.5(22,5%)
9.5 (32,5%)
3.7 (52,9%)

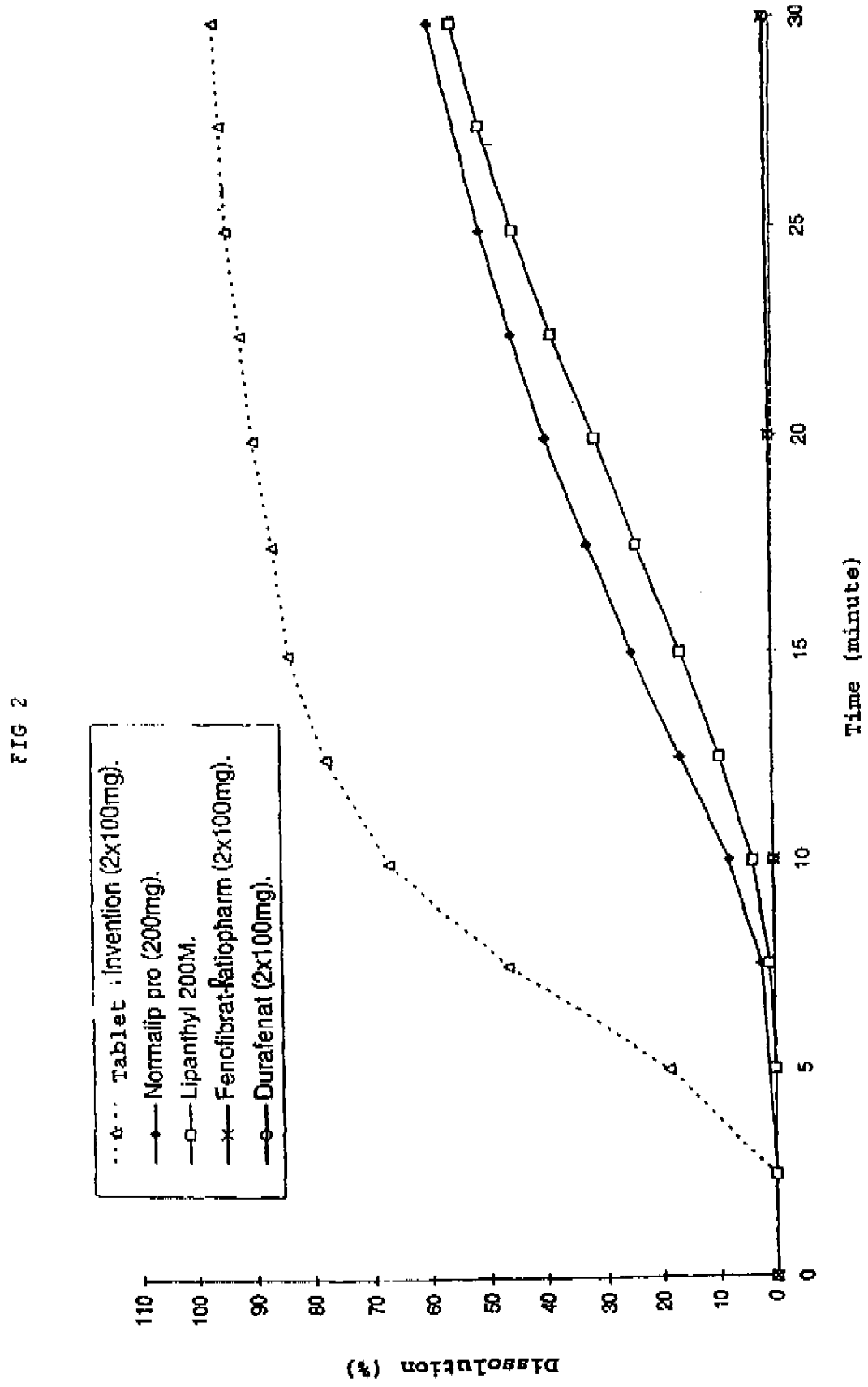

Tablet : Invention (2x100mg).
Normalip pro (200mg).
Lipanthyl 200M.
Fenofibrat-Ratiopharm (2x100mg).
Durafenat (2x100mg).
Dissolution (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (minute)

FIG 2

FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT

This is a continuation of U.S. application Ser. No. 09/005,128, filed Jan. 9, 1998, now U.S. Pat. No. 6,074,670, which claims priority to French Application No. 97 00 479, filed Jan. 17, 1997.

BACKGROUND OF THE INVENTION

The present invention relates to a novel pharmaceutical composition having high bioavailability through improved dissolution, and a method for preparing it. The invention more particularly relates to a pharmaceutical composition for administration by oral route, containing an active ingredient of poor aqueous solubility.

Numerous active ingredients suffer from the disadvantage of being poorly soluble in an aqueous medium, thus having an insufficient dissolution profile and, consequently, poor bioavailability within the organism, following oral administration. The therapeutic dose required to be administered must thus be increased in order to obviate this disadvantage. This particularly applies to numerous hypolipemiant active ingredients, such as those belonging to the fibrate family.

Fenofibrate is a well-known hypolipemiant from the family of fibrates, which is commercially available in various doses (100 and 300 mg for example Secalip®) but in a form leading to poor bioavailability of the active ingredient. Indeed, due to it poor hydrosolubility, fenofibrate is poorly absorbed in the digestive tract and consequently its bioavailability is incomplete, irregular and often varies from one person to another.

To improve the dissolution profile of fenofibrate and its bioavailability, thereby reducing the dose requiring to be administered, it would be useful to increase its dissolution so that it could attain a level close to 100%.

Moreover, for patient comfort, it is advantageous to seek a dosage form that only requires the medicament to be taken once daily while giving the same effect as one administered several times daily.

EP-A-0330532 discloses a method for improving bioavailability of fenofibrate. This patent describes the effect of co-micronizing fenofibrate with a surfactant, for example sodium laurylsulfate in order to improve fenofibrate solubility and thereby increase its bioavailability. This patent teaches that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than the improvement that would be obtained either by adding a surfactant, or through solely micronizing the fenofibrate, or, yet again, through intimately mixing the fenofibrate and surfactant, micronized separately. The dissolution method employed is the conventional rotating blade technique (European Pharmacopoeia): product dissolution kinetics are measured in a fixed volume of the dissolution medium, agitated by means of a standardized device; a test was also carried out with an alternative technique to the European Pharmacopoeia, using the continuous-flow cell method.

The process of EP-A-0330532 leads to a new dosage form in which the active ingredient, co-micronized with a solid surfactant, has improved fenofibrate dissolution, and thus increased bioavailability, which makes it possible, for a given level of effectiveness, to decrease the daily dose of the medicament: respective 67 mg and 200 mg instead of 100 mg and 300 mg.

However, the preparation method in that patent is not completely satisfactory inasmuch as it does not lead to complete bioavailability of the active ingredient, and suffers from several disadvantages. The technique of co-micronizing fenofibrate with a solid surfactant does, it is true, improve dissolution of the active ingredient, but this dissolution remains, however, incomplete.

There is thus a need to improve fenofibrate bioavailability in order to attain, over very short periods of time, a level close to 100% (or, in any case, better than the following limits : 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes in a medium consisting of 1200 ml water to which 2% Polysorbate 80 is added, or of 1000 ml of water to which 0.025M sodium lauryl sulfate sodium is added, with a blade rotation speed of 75 rpm), and this even when dissolution media having a low surfactant content are used.

Applicant has found that, surprisingly, it is possible to resolve this problem by a new method for preparing a pharmaceutical composition by spraying a suspension of the active ingredient onto an inert hydrosoluble carrier. The present invention also relates to pharmaceutical compositions thus prepared.

The use is already known of a polymer, such as polyvinylpyrrolidone for producing tablets, in concentrations of the order of 0.5 to 5% by weight, at a maximum 10% by weight. In this case, the polyvinylpyrrolidone is used as a binder. Similarly, the use of a polymer such as hydroxymethylpropylmethyl cellulose as a granulation binder is known. Thus, European patent application 0,519,144 discloses pellets of a poorly soluble substance, omeprazole, obtained by spraying a dispersion or suspension of the active ingredient in a solution containing said polymer onto inert pellets in a fluidized-bed granulator. However, here again, the polymer (HPMC and HPC) is only used as a granulation binder, in an amount of about 50% by weight, based on the weight of the active ingredient, which, bearing in mind the presence of the inert pellets of a large size (about 700 μm) and the overall final weight leads to final active ingredient and polymer contents which are very low, of the order of barely a few percent based on the weight of the final covered pellet. Finally, it will be noted that the size of the inert pellets in this documents is fairly large, which, in the case of fenofibrate, would lead to a final formulation having a volume which is much too large for ready oral administration.

The use of polymer, such as polyvinylpyrrolidone for manufacturing "solid dispersions" is also known, obtained in general by co-precipitation, co-fusion or liquid-phase mixing followed by drying. What we have here is fixation of the active ingredient in isolated microparticles on the polyvinylpyrrolidone, which avoids problems of poor wetting of the solid and re-agglomeration of the particles. The article "Stable Solid Dispersion System Against Humidity" by Kuchiki et al., Yakuzaigaku, 44 No. 1, 31–37 (1984) describes such a technique for preparing solid dispersions

using polyvinylpyrrolidone. The amounts of PVP here are very high, and the ratio between the active ingredient and PVP are comprised between 1/1 and 1/20. In the case however there is no inert carrier.

WO-A-96 01621 further discloses a sustained release composition, comprising an inert core (silica in all examples) coated with a layer which contains the active ingredient in admixture with a hydrophilic polymer, the weight ratio active ingredient/polymer being comprised between 10/1 and 1/2 and the weight ratio active ingredient/inert core being comprised between 5/1 and 1/2, with an outer layer to impart the sustained release property. These compositions can be compressed. The hydrophilic polymer can be polyvinylpyrrolidone. This document also discloses a process for preparing said composition; for example in a fluidized-bed granulator one will spray a dispersion of active ingredient in a polymer solution onto the inert cores. This document solely relates to sustained release compositions, the technical problem to be solved being the compression, without damages, of the outer layer imparting the sustained release property.

Nevertheless, nothing in the state of the art teaches nor suggest the present invention.

SUMMARY OF THE INVENTION

Thus, the present invention provides an immediate-release fenofibrate composition comprising:

(a) an inert hydrosoluble carrier covered with at least one layer containing a fenofibrate active ingredient in a micronized form having a size less than 20 μm, a hydrophilic polymer and, optionally, a surfactant; said hydrophilic polymer making up at least 20% by weight of (a); and

(b) optionally one or several outer phase(s) or layer(s).

In one embodiment, a surfactant is present with the active ingredient and the hydrophilic polymer.

The invention also provides a composition comprising fenofibrate having a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or in a dissolution medium constituted by water with 0.025M sodium lauryl sulfate.

A method for preparing a pharmaceutical composition is also provided, comprising the steps of:

(a) preparing a fenofibrate suspension in micronized form with a particle size below 20 μm, in a solution of hydrophilic polymer and, optionally surfactant;

(b) applying the suspension from step (a) to an inert hydrosoluble carrier;

(c) optionally, coating granules thus obtained with one or several phase(s) or layer(s).

Step (b) is preferably carried out in a fluidized-bed granulator.

The method can comprise a step in which products obtained from step (b) or (c) are compressed, with or without additional excipients.

The invention also provides a suspension of fenofibrate in micronized form having a size less than 10 μm, in a solution of hydrophilic polymer and, optionally, surfactant.

The invention will be described in more detail in the description which follows, with reference to the attached drawings.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a graph of a comparative study of the dissolution profile of a composition according to the invention, compared to that of Lipanthyl® 200M;

FIG. 2 is a graph illustrating a comparative study of the dissolution profile of a composition according to the invention and that of pharmaceutical products commercially available on the German market.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The expression "in micronized form" in this invention means a substance in a particulate form, the dimensions of the particles being less than or equal to about 20 μm.

Advantageously, this dimension is less than or equal to 10 μm.

In the framework of this invention, the expression "inert hydrosoluble carrier" means any excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed, and which is soluble in an aqueous medium, notably in a gastric acid medium. Examples of such excipients are derivatives of sugars, such as lactose, saccharose, hydrolyzed starch (malto-dextrine) etc. Mixture are also suitable. The individual particle size of the inert hydrosoluble carrier can be, for example, between 50 and 500 micron.

The expression "hydrophilic polymer" in the invention should be taken to mean any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel. Examples of such polymers are polyvinylpyrrolidone, poly(vinyl alcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, etc. Polymer blends are also suitable.

The preferred hydrophylic polymer is polyvinylpyrrolidone (PVP). The PVP used in this invention has, for example, a molecular weight comprised between 10,000 and 100,000, preferably for example between 20,000 and 55,000.

The term "surfactant" is used in its conventional sense in this invention. Any surfactant is suitable, whether it be amphoteric, non-ionic, cationic or anionic. Examples of such surfactants are: sodium lauryl sulfate, monooleate, monolaurate, monopalmitate, monostearate or another ester of polyoxyethylene sorbitane, sodium dioctylsulfosuccinate (DOSS), lecithin, stearylic alcohol, cetostearylic alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty acid glycerides, poloxamer®, etc. Mixtures of surfactants are also suitable.

The preferred surfactant is sodium laurylsulfate, which can be co-micronized with fenofibrate.

The compositions according to the invention can additionally contain any excipient conventionally used in the pharmaceutical and chemical fields which is compatible with the active ingredient, such as binders, fillers, pigments,

disintegrating agents, lubricants, wetting agents, buffers, etc. As examples, excipients able to be used in this invention we can cite: microcrystalline cellulose, lactose, starch, colloidal silica, talc, glycerol esters, sodium stearyl fumarate, titanium dioxide, magnesium stearate, stearic acid, cross-linked polyvinyl pyrrolidone (AC DI SOL®), carboxymethyl starch (Explotab®, Primojel®), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, etc.

Here, the expression "outer phase or layer" should be taken to mean any coating on the element (a) with the active ingredient (forming a "core"). Indeed, it can be useful to have available one or several phase(s) or layer(s) on top of the coated core. The invention thus covers a single core with one layer, but also several cores in a phase, as is the case of tablets which are formed from "cores" mixed with a phase.

This outer layer comprises conventional excipients.

It is also possible to provide a layer comprising additives, for the manufacture of tablets. In this embodiment, the outer layer comprises a disintegration agent and, for example, a lubricant; the thus covered and mixed granules can then be readily compressed and easily disintegrate in water.

The compositions according to the invention comprise, in general, based on the total composition weight excluding the outer phase or layer, an inert hydrosoluble carrier making up from 10 to 80% by weight, preferably 20 to 50% by weight, the fenofibrate representing from 5 to 50% by weight, preferably from 20 to 45% by weight, the hydrophilic polymer representing from 20 to 60% by weight, preferably 25 to 45% by weight, the surfactant making up from 0 to 10% by weight, preferably 0.1 to 3% by weight.

The outer layer or phase if present, can make up to 80% by weight of the total weight, preferably up to 50% by weight.

The hydrophilic polymer represents preferably more than 25% by weight, based on the weigt of (a).

The weight ratio fenofibrate/hydrophilic polymer can for example be comprised between 1/10 and 4/1, preferably, for example, between 1/2 and 2/1.

When a surfactant is employed, the weight ratio surfactant/hydrophilic polymer can be comprised for example between 1/500 and 1/10, preferably, for example, between 1/100 and 5/100.

In one embodiment, the composition according to the invention takes the form of tablets.

This tablet preferably results from the compression of elements (a) (under the form of granules) together with an outer phase.

In another embodiment, the composition of the invention takes the form of granules enclosed inside a capsule, for example in gelatin, or inside a bag.

The compositions of the invention are particularly suitable for administering active ingredients by oral route.

The composition according to the invention is prepared by a novel process comprising spraying a suspension of the active ingredient in a micronized form in a solution of a hydrophilic polymer and, optionally, a surfactant, onto the inert cores.

When a surfactant is present, the active ingredient can be co-micronized with the surfactant. One will then use with advantage the teachings of EP-A-0330532.

The method according to the invention consists in using the fluidized bed granulation principle, but with specific starting materials, in order to arrive at an improved dissolution profile and thus, at elevated bioavailability. In particular, the invention employs a suspension of the micronized active ingredient in a solution of a hydrophylic polymer and, optionally, a surfactant.

The fluidized-bed granulation technique is widely used in the pharmaceutical industry for preparing capsules or tablets. Conventionally, according to the prior art, a powder or a mixture of powders (active ingredient+excipients) is put into suspension in the fluidized bed in a granulator, and a solution containing a binder and, optionally, a surfactant, is sprayed onto this bed to form granules. The fluidized-bed granulation technique is well known to those skilled in the art and reference should be made to standard works such as for example "Die Tablette", by Ritschel, Ed. Cantor Aulendorf, pages 211–212.

The invention, as has been indicated, comprises spraying a suspension of an active ingredient micronized with a hydrophilic polymer onto an inert carrier. Following granulation, the granulate formed consists of crystals of, for example, lactose, which are isolated (or possibly agglomerated together by the spray solution) and particles of active ingredient and PVP adhering to the crystal surface. The granulate could similarly be constituted of coated crystals which are agglomerated, or even of such an agglomerate having received a coating.

The compositions according to the invention can also be prepared by other methods, for example by spraying a solution of the micronized active ingredient onto the hydrosoluble inert carrier.

The granulates thus obtained can, if desired, be provided with an outer coating or compressed into tablets, or form agglomerates.

The outer layer or layer is/are applied using conventional coating techniques such as coating in a pan or fluidized bed coater.

When the granulate obtained (whether subsequently coated or not) is compressed to form tablets, this step can be implemented using any conventional technique which is suitable, for example using an alternating or rotating compressing equipment.

The significant starting product is the suspension of the active ingredient. This suspension is prepared by putting the micronized active ingredient into suspension in a solution comprising the hydrophylic polymer and, optionally, a surfactant, in solution in a solvent. If a surfactant is employed, it is put into solution in the solvent (beaker+magnetic or vane stirrer). Next, the hydrophylic polymer (PVP) is dispersed, while stirring, in the solution previously obtained. Depending on polymer solubility, this either dissolves in the solution or forms a gel or a suspension having varying degrees of thickness. While still stirring, the micronized active ingredient is dispersed in the form of a fine shower into the above solution or suspension, to form a homogeneous suspension. The order of these steps can be reversed. The solvent employed can be aqueous or organic (for example ethanol). For example demineralized water can be used.

The active ingredient concentration in the suspension is from 1 to 40% by weight, preferably from 10 to 25%.

The hydrophylic polymer concentration in the suspension is from 5 to 40% by weight, preferably 10 to 25%.

The surfactant concentration in the suspension is from 0 to 10% by weight, preferably below 5%.

The invention also covers this novel suspension.

Without wishing to be tied down to a specific theory, applicant believes that this novel method, through the use of a micronized active ingredient suspension in a hydrophilic polymer solution, enabled a novel composition to be obtained in which the active ingredient is in a non-re-agglomerated form.

The following examples illustrate the invention without limiting it.

EXAMPLE 1

Preparation of a Pharmaceutical Composition of Fenofibrate According to the Invention

A composition containing, as the element a), micronized fenofibrate, Plasdone®, Capsulac® and sodium lauryl sulfate was prepared.

The micronized fenofibrate had a particle size of about 5μm, as measured using a Coulter counter.

The Plasdone K25® corresponds to a polyvinylpyrrolidone PVP ISP and the Capsulac 60® corresponds to a coarse crystal lactose monohydrate (Meggle) (particle size between 100 and 400 μm).

The sodium laurylsulfate (7 g) is dissolved in water (demineralized water, 1750 g) and the micronized fenofibrate (350 g) is put into suspension in the mixture obtained (for example using a helix stirrer at 300 rpm for 10 minutes, then using an Ultra Turrax agitator at 10,000 rpm, for 10 minutes). Following this, the PVP (350 g) is added while still agitating, stirring (helix stirrer) being continued until the latter had dissolved (30 minutes). It is all passed through a sieve (350 μm) to eliminate possible agglomerates.

Separately, the lactose (400 g) is put into suspension in a fluidized air bed granulator (of the Glatt® GPCG1—Top Spray type or equivalent) and heated to a temperature of 40° C.

The fenofibrate suspension is sprayed onto the lactose. This step is carried out under the following conditions: spraying pressure : 2.1 bar, air throughput 70 m^3/h, air inlet temperature: 45° C.; air outlet temperature: 33° C.; product temperature 34° C.; duration of spraying: 3 h.

The granulate thus obtained can be put inside capsules or transformed into tablets. Any suitable conventional technique for preparing such dosage forms can be used.

For transformation to tablet form, one will mix 191 g of the granulate obtained (using for example a mixer-grinder type mixing apparatus, a planetary mixer or turn-over mixer), with the outer phase having the following composition:

56 g Polyplasdone XL® (cross-linked polyvinylpyrrolidone ISP, as described in the USA Pharmacopoeia "USP-NF" under the name of crospovidone, mean molecular weight<1,000,000);

88 g Avicel® PH200 (microcrystalline cellulose);

3.5 g sodium stearyl fumarate (Mendell, U.S.A.); and

2 g Aerosil® 200 (colloidal silica).

The cross-linked polyvinylpyrrolidone, the microcrystalline cellulose, the sodium stearyl fumarate and the colloidal silica are respectively, disintegration agents, binders, lubricating and flow enhancing agents.

The tablet can be obtained on an alternating compression machine (for example Korsch EKO) or a rotary machine (for example Fette Perfecta 2).

One thus obtains tablets having the following composition, expressed in mg:

element (a)	
micronized fenofibrate	100.0
PVP	100.0
Lactose	114.3
sodium laurylsulfate	2.0
outer phase (or layer)	
cross-linked PVP	92.7
microcrystalline cellulose	145.7
sodium stearyl fumarate	5.8
colloidal silica	3.3

EXAMPLE 2

Dissolution of a composition according to the invention and a composition according to the prior art. a) dissolution medium and procedure for measuring dissolution.

A dissolution medium which is discriminating, in other words one in which two products having very different dissolution profiles in gastric juices will have very different dissolution curves is looked for.

For this, an aqueous medium containing a surfactant, this being Polysorbate 80 (polyoxyethylene sorbitane monooleate) is used. This surfactant is readily available from various suppliers, is the object of a monograph in the Pharmacopoeias, and is thus easy to implement (being also a water-soluble liquid product) Other surfactants can also be used.

The rotating blade method (European Pharmacopoeia) is used under the following conditions: volume of medium: 1200 ml; medium temperature: 37° C.; blade rotation speed: 75 rpm; samples taken: every 2.5 minutes. Determination of the amount dissolved is carried out by spectrophotometry. Test are repeated 6 times over. b) Results

The composition according to the invention consisted of two tablets containing about 100 mg fenofibrate prepared according to example 1.

The prior art composition was Lipanthyl® 200M from Laboratoires Fournier, containing 200 mg fenofibrate (corresponding to capsules of 200 mg fenofibrate, co-micronized with sodium laurylsulfate, and containing lactose, pre-gelatinized starch, cross-linked polyvinylpyrrolidone and magnesium stearate, in line with the teachings of EP-A-0330532).

The results obtained are shown graphically in FIG. 1, on which the percentage of dissolution is shown, the observed standard deviation being indicated between brackets.

These results clearly show that the compositions according to the invention have a dissolution profile which is distinctly better than that of the prior art compositions.

These results also clearly show that with the compositions of the invention, the standard deviation observed is distinctly lower than is the case with prior art compositions.

EXAMPLE 3

Study of bioavailability of compositions according to the invention and prior art compositions.

A test of bioavailability on healthy volunteers was carried out.

The following compositions were tested:

composition according to the invention: capsules containing granules prepared according to example 1, containing 200 mg fenofibrate.

first composition according to the prior art: Lipanthyl® 200M from Laboratoires Fournier, containing 200 mg fenofibrate, identical to that in the previous example.

second prior art composition: Secalip® in capsule form (300 mg fenofibrate in the form of three 100 mg capsules).

The study was carried out on 6 healthy volunteers receiving a single dose of fenofibrate, with a minimum 6-day rest period between administrations. The samples for pharmacokinetic analysis were collected after each administration at the following times: 0.5 h; 1 h; 2 h; 3 h; 4 h; 5 h; 6 h; 8 h; 10 h; 12 h; 24 h; 36 h; 48 h; 72 h; and 96 hours following administration of the medicament. Fenofibric acid content in plasma was measured for each sample.

The results obtained are given in table 1 below.

TABLE 1

Product	dose (mg)	Cmax (μg/ml)	tmax (h)	t½ (h)	AUC 0-t (μg.h/ml)	AUC 0-∞ (μg.h/ml)
Invention	200	5.4	6	23	148	162
Secalip ® 100	3 × 100	1.1	25	39	53	56
Lipanthyl ® 200M	200	1.6	8.3	41	71	92

Cmax: maximum plasma concentration
tmax: time to reach Cmax
t½: plasma half-life
AUC 0 - t: area under the curve from 0 to t
AUC 0 - ∞: area under the curve from 0 to ∞

The results clearly show that the compositions of the present invention have a dissolution profile that is an improvement over compositions of the prior art, leading to a considerably enhanced bioavailability of the active ingredient compared to that obtained with compositions of the prior art.

EXAMPLE 4

Comparison of the dissolution profile of compositions according to the invention and that of products currently on the German market.

On the German market, immediate or sustained-release fenofibrate formulations exist. Like in France, the 100 mg and 300 mg (conventional) forms coexist with 67 and 200 mg forms (having enhanced bioavailability, according to the teaching of EP-A-0330532). These products are as follows:

Fenofibrate—ratiopharm; Ratiopharm—Ulm; Capsules; Composition: 100 mg fenofibrate; Excipients: lactose, corn starch, magnesium stearate, E 171 colorant, gelatine.

Durafenat; Durachemie—Wolfratshausen Capsules; Composition: 100 mg fenofibrate; Excipients: lactose, corn starch, magnesium stearate, E 171 colorant, gelatine.

Normalip pro; Knoll—Ludwigshafen; Capsules; Composition: 200 mg Fenofibrate; Excipients: Crospovidone, gelatine, monohydrate lactose, magnesium stearate, corn starch, sodium laurylsulfate, E 132 and E 171 colorants.

A comparison was made between:

the tablet of the invention as prepared using example 1 (2×100 mg)

Normalip pro® (200 mg);

Lipanthyl® 200M (200 mg) (according to the preceding example);

Fenofibrate by Ratiopharm® (2×100 mg);

Durafenat® (2×100 mg)

The tests were implemented under the same conditions as in the previous examples. FIG. 2 summarizes the results.

These results clearly show that the compositions of the invention have a distinctly improved dissolution compared to prior art compositions.

Obviously, the present invention is not limited to the embodiments described but may be subject to numerous variations readily accessible to those skilled in the art.

What is claimed is:

1. A composition comprising a hydrosoluble carrier and micronized fenofibrate having a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or with 0.025M sodium lauryl sulfate.

2. The composition according to claim 1, under the form of a tablet.

3. The composition according to claim 1, under the form of granules inside a capsule.

4. The composition according to claim 1, wherein the micronized fenofibrate have a size less than or equal to 20 μm.

5. The composition according to claim 4, wherein the micronized fenofibrate have a size less than or equal to 10 μm.

6. The composition according to claim 1, wherein the micronized fenofibrate is present in an amount of 20 to 45% by weight.

7. The composition according to claim 1, further comprising a hydrophilic polymer.

8. The composition according to claim 7, wherein the hydrophilic polymer is polyvinylpyrrolidone, poly(vinyl alcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, or a mixture thereof.

9. The composition according to claim 7, wherein the hydrophilic polymer is present in an amount of 20 to 45% by weight.

10. The composition according to claim 1, further comprising a surfactant.

11. The composition according to claim 10, wherein the surfactant is sodium lauryl sulfate, monooleate, monolaurate, monopalmitate, monostearate, polyoxyethylene sorbitane, sodium dioctylsulfosuccinate, lecithin,

stearylic alcohol, cetostearylic alcohol, cholesterol, polyoxytheylene ricin oil, polyoxyethylene fatty acid glyceride, poloxamer, or a mixture thereof.

12. The composition according to claim **10**, wherein the surfactant is present in an amount of 0.1 to 3% by weight.

13. The composition according to claim **1**, wherein the hydrosoluble carrier is present in an amount of 20 to 50% by weight.

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