IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

LUPIN ATLANTIS HOLDINGS S.A.,

Plaintiff,

v.

RANBAXY LABORATORIES LIMITED, RANBAXY PHARMACEUTICALS INC., RANBAXY, INC. and ETHYPHARM S.A.,

Defendants.

COMPLAINT

Plaintiff Lupin Atlantis Holdings S.A., by its attorneys, for its complaint against Ranbaxy Laboratories Limited, Ranbaxy Pharmaceuticals Inc., Ranbaxy, Inc. (collectively, "Ranbaxy") and Ethypharm S.A., allege as follows:

THE PARTIES

1. Plaintiff Lupin Atlantis Holdings S.A. ("Lupin Atlantis") is a corporation organized and existing under the laws of Switzerland, with a principal place of business at Bachstrasse 56, 8200 Schaffhausen SH, Switzerland.

2. Upon information and belief, Defendant Ranbaxy Laboratories Limited is a company organized and existing under the laws of India with a principal place of business at Plot 90, Sector 32, Gurgaon (Haryana) 122 001, India.

3. Upon information and belief, Ranbaxy Laboratories Limited is in the business of, among other activities, manufacturing and selling copies of branded

pharmaceutical products which are used and sold throughout the United States, including in the Commonwealth of Pennsylvania and in this judicial district, through various operating subsidiaries, including Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc.

4. Upon information and belief, Defendant Ranbaxy Pharmaceuticals Inc. is a corporation organized and existing under the laws of Delaware, and is a wholly-owned subsidiary and alter ego of Ranbaxy Laboratories Limited. Ranbaxy Pharmaceuticals Inc. has a principal place of business at 600 College Road East, Princeton, New Jersey 08540.

5. Upon information and belief, Defendant Ethypharm S.A. ("Ethypharm") is a corporation organized and existing under the laws of France, with its principal offices at 194 Bureaux de la Colline, 922 13 St. Cloud, France.

6. Upon information and belief, Ranbaxy Pharmaceuticals Inc. is in the business of, among other activities, offering for sale, selling and/or importing copies of branded pharmaceutical products manufactured by, among others, Ranbaxy Laboratories Limited, throughout the United States, including in the Commonwealth of Pennsylvania and in this judicial district.

7. Upon information and belief, Ranbaxy Pharmaceuticals Inc. is a United States agent for Ranbaxy Laboratories Limited for, among others, making regulatory submissions to the United States Food and Drug Administration ("FDA").

8. Upon information and belief, Defendant Ranbaxy Inc. is a corporation organized and existing under the laws of Delaware, and is a wholly-owned subsidiary and alter ego of Ranbaxy Laboratories Limited. Ranbaxy Inc. has a principal place of business at 600 College Road East, Princeton, New Jersey 08540.

9. Upon information and belief, Ranbaxy Inc. is in the business of, among other activities, offering for sale, selling and/or importing copies of branded pharmaceutical products manufactured by, among others, Ranbaxy Laboratories Limited, throughout the United States, including in the Commonwealth of Pennsylvania and in this judicial district.

10. Upon information and belief, consistent with their practice with respect to other generic products, Ranbaxy Laboratories Limited, Ranbaxy Pharmaceuticals Inc.

and Ranbaxy Inc. collaborated in the research and development of Ranbaxy's Abbreviated New Drug Application ("ANDA") No. 201748 for capsules that contain 43 mg and 130 mg of fenofibrate as the active ingredient ("the Ranbaxy ANDA Product"), continue to collaborate in seeking approval of that application by the FDA, and intend to collaborate in the commercial manufacture, marketing, offer for sale and sale of the Ranbaxy ANDA Product throughout the United States, including in the Commonwealth of Pennsylvania and in this judicial district, in the event the FDA approves the Ranbaxy ANDA.

JURISDICTION AND VENUE

11. This is a civil action arising under the patent laws of the United States, Title 35, United States Code, for infringement of U.S. Patent 7,101,574 ("the '574 patent"). This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

12. Upon information and belief, Ranbaxy Laboratories Limited is subject to personal jurisdiction in this judicial district because, *inter alia*, Ranbaxy Laboratories Limited alone, and through its wholly-owned subsidiaries and alter egos Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc., has purposely availed itself of the benefits and protections of this Commonwealth's laws such that it should reasonably anticipate being haled into court in this judicial district. On information and belief, Ranbaxy Laboratories Limited, itself and through its wholly-owned subsidiaries Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc., markets and sells branded and generic drugs throughout the United States, and in particular within this judicial district, and therefore Ranbaxy Laboratories Limited has engaged in systematic and continuous business within this judicial district. In addition, and upon information and belief, Ranbaxy Laboratories Limited controls and dominates Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc., and thus the activities of the latter two entities in this judicial district are attributable to Ranbaxy Laboratories Limited.

13. Upon information and belief, Ranbaxy Pharmaceuticals Inc. is subject to personal jurisdiction in this judicial district because, *inter alia*, Ranbaxy Pharmaceuticals

Inc., alone and through its parent Ranbaxy Laboratories Limited and related company Ranbaxy Inc., has purposely availed itself of the benefits and protections of this Commonwealth's laws such that it should reasonably anticipate being haled into court in this judicial district. On information and belief, Ranbaxy Pharmaceuticals Inc., alone and through its parent Ranbaxy Laboratories Limited and related company Ranbaxy Inc., markets and sells branded and generic drugs throughout the United States, and in particular within this judicial district, and therefore Ranbaxy Pharmaceuticals Inc. has engaged in systematic and continuous business within this judicial district.

14. Upon information and belief, Ranbaxy Inc. is subject to personal jurisdiction in this judicial district because, *inter alia*, Ranbaxy Inc., alone and through its parent Ranbaxy Laboratories Limited and related company Ranbaxy Pharmaceuticals Inc., has purposely availed itself of the benefits and protections of this Commonwealth's laws such that it should reasonably anticipate being haled into court in this judicial district. On information and belief, Ranbaxy Inc., alone and through its parent Ranbaxy Laboratories Limited and related company Ranbaxy Pharmaceuticals Inc., markets and sells branded and generic drugs throughout the United States, and in particular within this judicial district, and therefore Ranbaxy Inc. has engaged in systematic and continuous business within this judicial district.

15. Upon information and belief, Ranbaxy Laboratories Limited, Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc. market Ranbaxy's branded and generic drug products to persons residing within this judicial district, for example, via its website.

16. Upon information and belief, Ranbaxy Laboratories Limited, Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc. offer Ranbaxy's branded and generic drug products for sale to persons residing within this judicial district on third-party websites that these persons can use to purchase Ranbaxy products for shipment to and within this judicial district.

17. Upon information and belief, persons residing within this judicial district purchase branded and generic drug products, including Ranbaxy products, from Ranbaxy Laboratories Limited (itself or through its wholly-owned subsidiaries Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc.) in this judicial district.

18. Upon information and belief, persons residing within this judicial district purchase branded and generic drug products, including Ranbaxy products, from Ranbaxy Pharmaceuticals Inc. in this judicial district.

19. Upon information and belief, persons residing within this judicial district purchase branded and generic drug products, including Ranbaxy products, from Ranbaxy Inc. in this judicial district.

20. Upon information and belief, Ranbaxy Laboratories Limited (itself or through its wholly-owned subsidiaries Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc.) receives revenue from the sales and marketing of branded and generic drug products, including Ranbaxy products, within this judicial district.

21. Upon information and belief, Ranbaxy Pharmaceuticals Inc. receives revenue from the sales and marketing of branded and generic drug products, including Ranbaxy products, within this judicial district.

22. Upon information and belief, Ranbaxy Inc. receives revenue from the sales and marketing of branded and generic drug products, including Ranbaxy products, within this judicial district.

23. Upon information and belief, Ranbaxy Laboratories Limited itself, or through its wholly-owned subsidiaries Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc., intends to market and sell the Ranbaxy ANDA Product, if approved, to residents of this judicial district.

24. Upon information and belief, Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Inc. admitted in Civil Action No. 2:06-cv-2768-MSG (E.D. Pa.), in which an action against each of them was brought arising under, *inter alia*, the Patent Laws of the United States (35 U.S.C. § 1 et seq.), and the Hatch-Waxman Act (21 U.S.C. § 301 et seq., that venue in this judicial district was proper. Upon information and belief, Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Inc. did not contest personal jurisdiction in that action.

25. Upon information and belief, Ethypharm is in the business of, among other activities, manufacturing pharmaceutical products for importation into and sale

throughout the United States and promotes the importation and sale of such products, including in the Commonwealth of Pennsylvania and in this judicial district.

26. Ranbaxy Laboratories Limited, Ranbaxy Pharmaceuticals Inc., Ranbaxy, Inc. and Ethypharm are subject to personal jurisdiction in this judicial district.

27. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b) and (c) and § 1400(b).

BACKGROUND

28. Lupin Atlantis is the owner of the approved New Drug Application ("NDA") No. 21-695 for ANTARA® capsules.

29. On information and belief, Ranbaxy submitted ANDA No. 201748 to the FDA under the provisions of 21 U.S.C. § 355(j) seeking approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of generic copies of ANTARA® capsules.

30. The ANTARA® capsules contain 43 mg and 130 mg of micronized fenofibrate as the active ingredient, and are currently approved for the treatment of hypercholesterolemia and hypertriglyceridemia.

31. Upon information and belief, the Ranbaxy ANDA Product that is the subject of Ranbaxy ANDA No. 201748 are capsules containing 43 mg and 130 mg of micronized fenofibrate as the active ingredient, and the Ranbaxy ANDA seeks approval for the treatment of hypercholesterolemia and hypertriglyceridemia.

THE PATENT-IN-SUIT

32. On September 5, 2006, the U.S. Patent and Trademark Office duly and legally issued the '574 patent entitled "Pharmaceutical Composition Containing Fenofibrate and the Preparation Method." A true and correct copy of the '574 patent is attached hereto as Exhibit A.

33. Ethypharm is the owner of the '574 patent which discloses and claims, *inter alia*, a pharmaceutical composition containing fenofibrate and a method for preparing the composition.

34. Lupin Atlantis holds a license from Ethypharm under the '574 patent which contains provisions concerning the right to enforce the '574 patent in the case of an ANDA filing by a third party.

35. As owner of the '574 patent and licensor of the '574 patent to Lupin Atlantis, Defendant Ethypharm is jointly interested with, and contractually obligated to cooperate with, Lupin Atlantis in this cause of action, including without limitation joining this action if necessary. Although requested to file suit as Co-Plaintiff, Ethypharm has not, as of the date of the filing of this action, agreed to do so. For that reason, Ethypharm is named as a defendant.

COUNT FOR PATENT INFRINGEMENT

36. Lupin Atlantis incorporates paragraphs 1-35 of this Complaint as if fully set forth herein.

37. Upon information and belief, Ranbaxy sent a letter dated June 24, 2010, to Lupin Atlantis and Ethypharm which purported to comply with the provisions of 21 U.S.C. § 355(j)(2)(B). This letter purportedly advised Lupin Atlantis and Ethypharm that Ranbaxy's ANDA contains a Paragraph IV certification with respect to the '574 patent, and that no valid, enforceable claim of the '574 patent would be infringed by the manufacture, importation, use, sale or offer for sale of the Ranbaxy ANDA Product.

38. Upon information and belief, the '574 patent was properly listed in the FDA publication entitled Approved Drug Products and Therapeutic Equivalence Evaluations ("the Orange Book") relative to ANTARA® on the date Ranbaxy filed ANDA No. 201748.

39. Upon information and belief, Ranbaxy submitted Ranbaxy ANDA No. 201748 to the FDA for purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of a generic copy of the ANTARA® product prior to the expiration of the '574 patent.

40. Upon information and belief, the Ranbaxy ANDA contains a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certification") asserting that, in

its opinion, the '574 patent is invalid or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of the Ranbaxy ANDA Product.

41. 21 U.S.C. § 355(j)(2)(A)(vii)(IV) requires, *inter alia*, certification by the ANDA applicant that the subject patent, here the '574 patent, "is invalid or will not be infringed by the manufacture, use, offer for sale or sale of the new drug for which the application is submitted . . . ." The statute (21 U.S.C. § 355(j)(2)(B)(iv)) also requires a Paragraph IV notice to "include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed." The FDA Rules and Regulations (21 C.F.R. § 314.95(c)) specify, *inter alia*, that a Paragraph IV notification must include "[a] detailed statement of the factual and legal basis of applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement is to include "(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds of supporting the allegation.

42. Upon information and belief, at the time Ranbaxy's letter of June 24, 2010, was mailed (this letter purportedly serving as a notice of Paragraph IV certification relative to the '574 patent, *i.e.,* "Ranbaxy's Notice of Certification"), Ranbaxy was aware of the statutory provisions and regulations referred to in paragraph 41, *supra.*

43. Ranbaxy's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding all bases for noninfringement, does not do so and provides only conclusory statements.

44. Ranbaxy's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding alleged invalidity, does not allege invalidity of any claims of the '574 patent.

45. Ranbaxy's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding alleged unenforceability, does not allege unenforceability or allege inequitable conduct of the '574 patent.

46. Ranbaxy's Notice of Certification fails to comply with the law, as specified in 21 U.S.C. § 355(j), and FDA rules and regulations, as specified in 21 C.F.R. § 314.95.

47. By filing ANDA No. 201748 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of the Ranbaxy ANDA Product prior to the expiration of the '574 patent, Ranbaxy has committed an act of infringement under 35 U.S.C. § 271(e)(2). Further, on information and belief, Ranbaxy plans to commercially use, offer for sale, and/or sell the Ranbaxy ANDA Product, and/or to induce or contribute to such activity, and by such actions Ranbaxy would infringe one or more claims of the '574 patent under 35 U.S.C. § 271(a), (b) and/or (c).

48. Upon information and belief, Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc. participated in, contributed to, aided, and/or induced the submission of Ranbaxy ANDA No. 201748 and its Paragraph IV certification to the FDA. Additionally, upon information and belief, Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc. will market and/or distribute the Ranbaxy ANDA Product in the United States, and within this judicial district, if Ranbaxy ANDA No. 201748 is approved by the FDA. Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc. thus are jointly and severally liable with Ranbaxy Laboratories Limited for infringement of the '574 patent.

49. To further investigate whether Ranbaxy's ANDA Product infringed any of the '574 patent claims, Lupin Atlantis, in a letter dated July 19, 2010, Lupin Atlantis requested access to certain documents and information, as well as access to Ranbaxy's ANDA No. 201748 and DMF. Lupin Atlantis requested the information to permit further evaluation and investigation relating to Ranbaxy's ANDA and its ANDA Product.

50. In response, on July 28, 2010, counsel for Ranbaxy advised Lupin Atlantis that Ranbaxy would agree only to provide certain selected Ranbaxy ANDA Product information. Ranbaxy refused to produce a full and complete copy of ANDA No. 201748 and any related DMF.

51. In addition, Ranbaxy did not agree with Lupin Atlantis' request that certain in-house personnel be permitted to have access to the Ranbaxy selected

information, under confidentiality restrictions, to investigate Ranbaxy's ANDA Product for infringement of the '574 patent, and Ranbaxy further required that any technical expert that may be selected by Lupin Atlantis would need to be identified to and vetted by Ranbaxy before the selected Ranbaxy information could be provided to such technical expert.

52. In response, Lupin Atlantis advised Ranbaxy's counsel on August 2, 2010, that because of Ranbaxy's refusal to provide the information requested by Lupin Atlantis on July 19, 2010, Lupin Atlantis would need physical samples of the Ranbaxy ANDA Product.

53. Ranbaxy did not provide access to any physical samples of the Ranbaxy ANDA Product as requested by Lupin Atlantis, nor did Ranbaxy withdraw its requirement regarding access by a Lupin Atlantis technical expert.

54. Ranbaxy's failure to agree to provide Lupin Atlantis with the requested information under terms that would have allowed Lupin Atlantis a reasonable opportunity to evaluate Ranbaxy's otherwise unsupported, conclusory statements as made by Ranbaxy in the Ranbaxy Notice of Certification, precluded Lupin Atlantis from fully evaluating the issues in this case.

55. Lupin Atlantis brings this action, in part, to employ the judicial process and the aid of discovery to obtain under appropriate judicial safeguards information to confirm that Ranbaxy's ANDA Product infringes one or more claims of the '574 patent.

56. This action is being filed within 45 days of receipt by Lupin Atlantis and Ethypharm of the Ranbaxy letter dated June 24, 2010, which purportedly advised Lupin Atlantis and Ethypharm of Ranbaxy's Paragraph IV certification with respect to the '574 patent

57. Upon information and belief, Ranbaxy had actual and constructive notice of the '574 patent prior to filing Ranbaxy ANDA No. 201748, and Ranbaxy's infringement of the '574 patent has been, and continues to be, willful.

58. Lupin Atlantis is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Ranbaxy ANDA

No. 201748 be a date that is not earlier than the expiration of the '574 patent, or any later expiration of exclusivity for the '574 patent to which it becomes entitled.

59. Lupin Atlantis will be irreparably harmed if Ranbaxy is not enjoined from infringing or actively inducing or contributing to infringement of the '574 patent, as Lupin Atlantis has no adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Lupin Atlantis respectfully requests the following relief:

A. A judgment that Ranbaxy has infringed one or more claims of the '574 patent under 35 U.S.C. § 271(e)(2);

B. An order pursuant to 35 U.S.C. § 271(e)(4) providing that the effective date of any FDA approval of Ranbaxy's ANDA No. 201748 be not earlier than the expiration date of the '574 patent or any later expiration of exclusivity for this patent to which it may become entitled;

C. A permanent injunction restraining and enjoining Ranbaxy Laboratories Limited, Ranbaxy Pharmaceuticals Inc. and Ranbaxy Inc. and each of their officers, agents, servants, employees and those persons acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale or sale within the United States or its territories, or importation into the United States or its territories, of the Ranbaxy ANDA Product, or any product that infringes the '574 patent;

D. Damages and treble damages from Ranbaxy from any commercial activity constituting infringement of the '574 patent;

E. That Defendant Ethypharm be realigned and named as a Plaintiff in this action;

F. Costs and expenses in this action; and

G. Such other and further relief as this Court determines to be just and proper.

Respectfully submitted,

Date: August 4, 2010

John J. Higson
DILWORTH PAXSON LLP
1500 Market Street, 3500E
Philadelphia, Pennsylvania 19102
Voice: (215) 575-7000
Fax: (215) 575-7200
jhigson@dilworthlaw.com

Of Counsel:

Robert F. Green
Christopher T. Griffith
Kate M. Lesciotto
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601
Voice: (312) 616-5600
Fax: (312) 616-5700
rgreen@leydig.com
cgriffith@leydig.com
klesciotto@leydig.com

Attorneys for Plaintiff
Lupin Atlantis Holdings S.A.

EXHIBIT A

US007101574B1

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

(10) **Patent No.: US 7,101,574 B1**
(45) **Date of Patent: Sep. 5, 2006**

(54) **PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND THE PREPARATION METHOD**

(75) Inventors: **Bruno Criere**, Gravigny (FR); **Pascal Suplie**, Montaure (FR); **Philippe Chenevier**, Montréal (CA)

(73) Assignee: **Laboratoires des Produits Ethiques Ethypharm**, Houdan (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 44 days.

(21) Appl. No.: **10/030,262**
(22) PCT Filed: **Jul. 7, 2000**
(86) PCT No.: **PCT/FR00/01971**

§ 371 (c)(1),
(2), (4) Date: **Apr. 17, 2002**

(87) PCT Pub. No.: **WO01/03693**

PCT Pub. Date: **Jan. 18, 2001**

(30) **Foreign Application Priority Data**

Jul. 9, 1999 (FR) 99 08923

(51) **Int. Cl.**

A61K 9/14	(2006.01)
A61K 9/64	(2006.01)
A61K 9/56	(2006.01)
A61K 9/58	(2006.01)

(52) **U.S. Cl.** **424/489**; 424/456; 424/459; 424/462

(58) **Field of Classification Search** 424/489, 424/462, 456, 459, 497, 490; 514/49

See application file for complete search history.

(56) **References Cited**

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Primary Examiner—Lakshmi Channavajjala
(74) *Attorney, Agent, or Firm*—Buchanan Ingersoll & Rooney PC

(57) **ABSTRACT**

The invention concerns a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, as solubilizing adjuvant, preferably hydroxypropylmethylcellulose. The cellulose derivative represents less than 20 wt. % of the composition. The association of micronized fenofibrate with a binding cellulose derivative, as solubilizing adjuvant and a surfactant enables enhanced bioavailability of the active principle. The invention also concerns a method for preparing said composition without using any organic solvent.

34 Claims, 4 Drawing Sheets

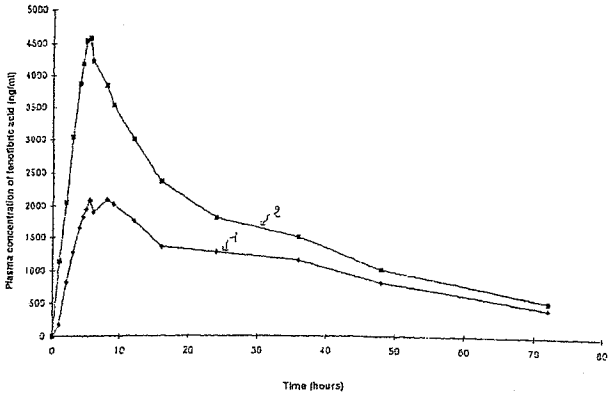

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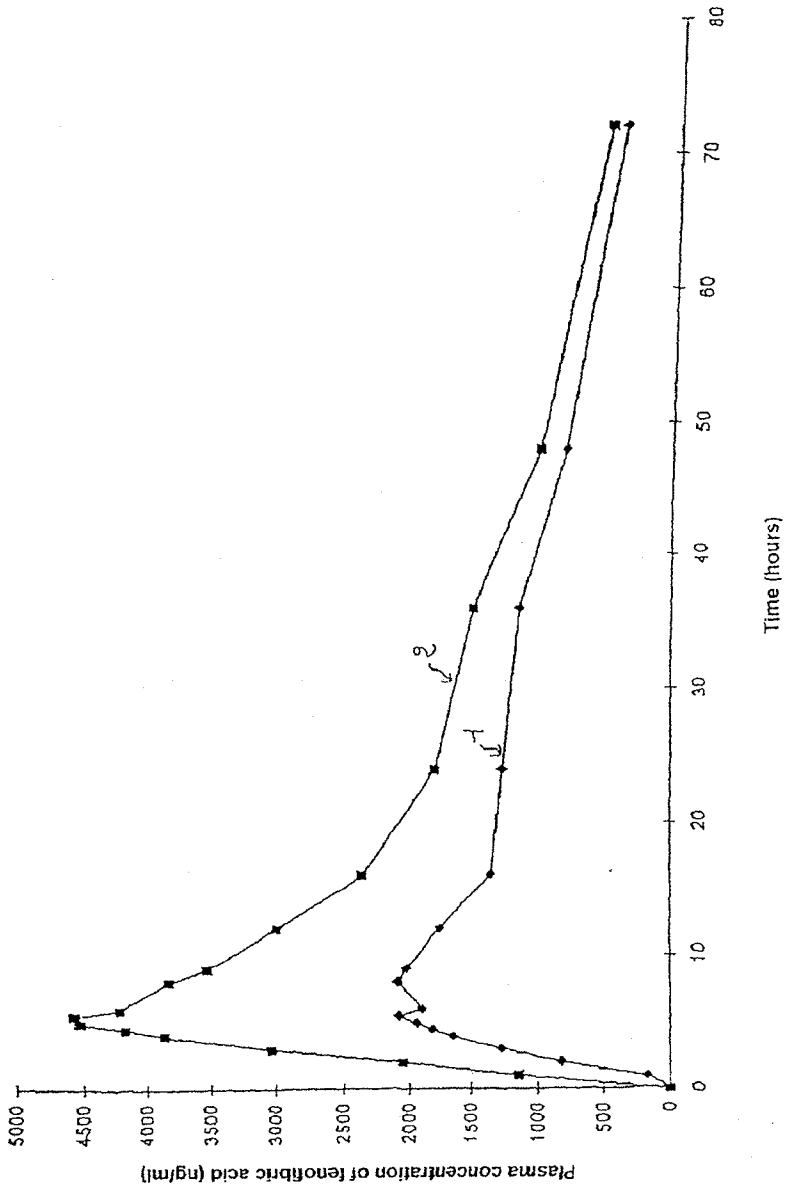
Figure 1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4000
3500
3000
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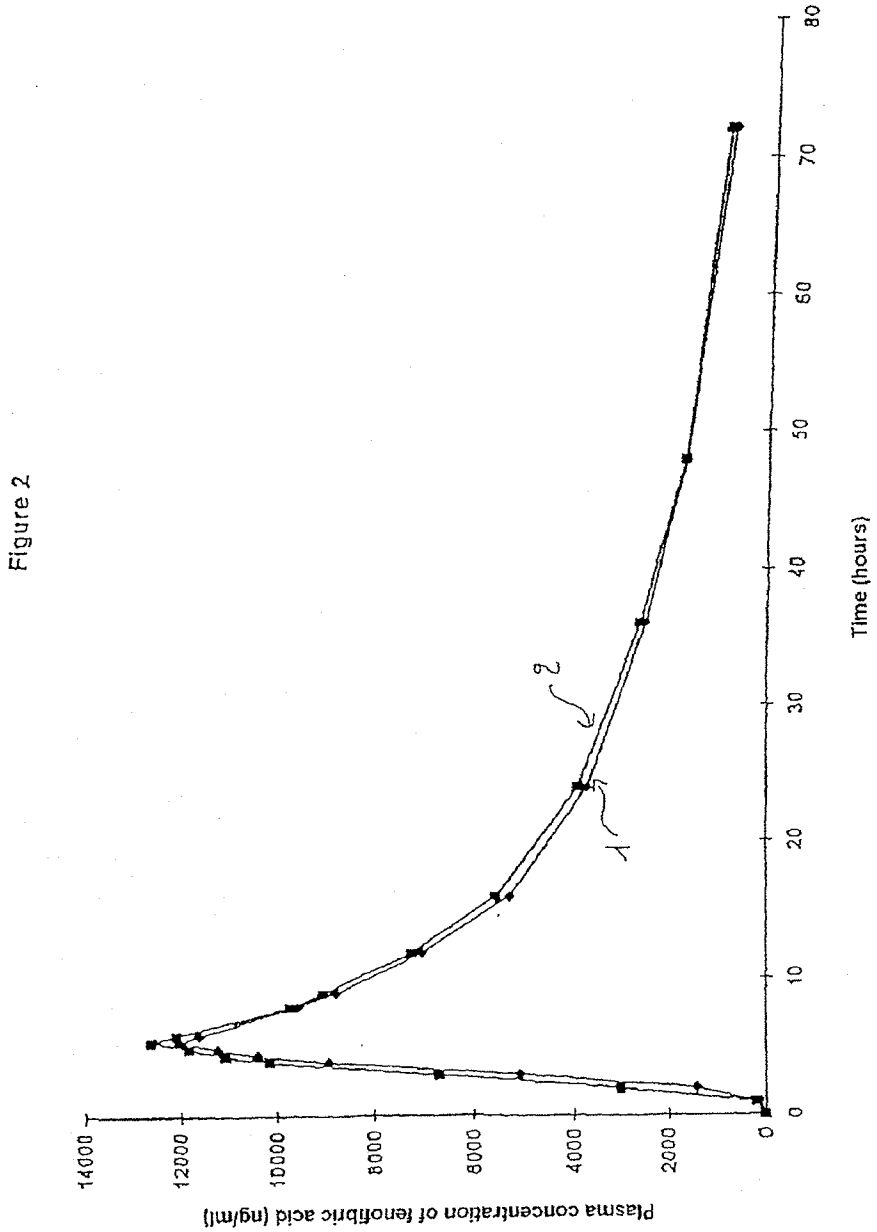
30
40
50
60
70
80
Time (hours)
2
1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12000
10000
8000
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0
Time (hours)
0
10
20
30
40
50
60
70
80
1
2

Figure 2

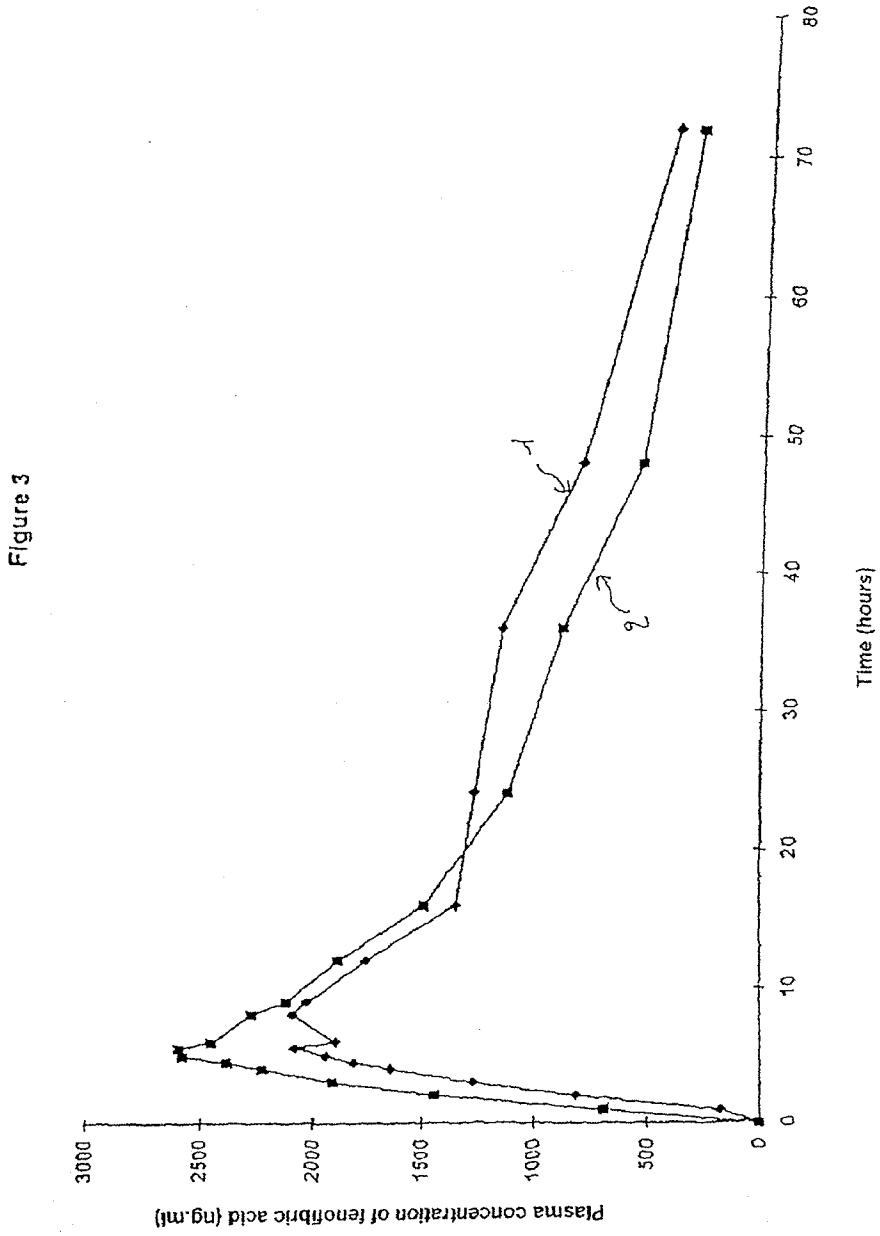
Plasma concentration of fenofibric acid (ng.ml)
3000
2500
2000
1500
1000
500
0
Time (hours)
0
10
20
30
40
50
60
70
80
1
2

Figure 3

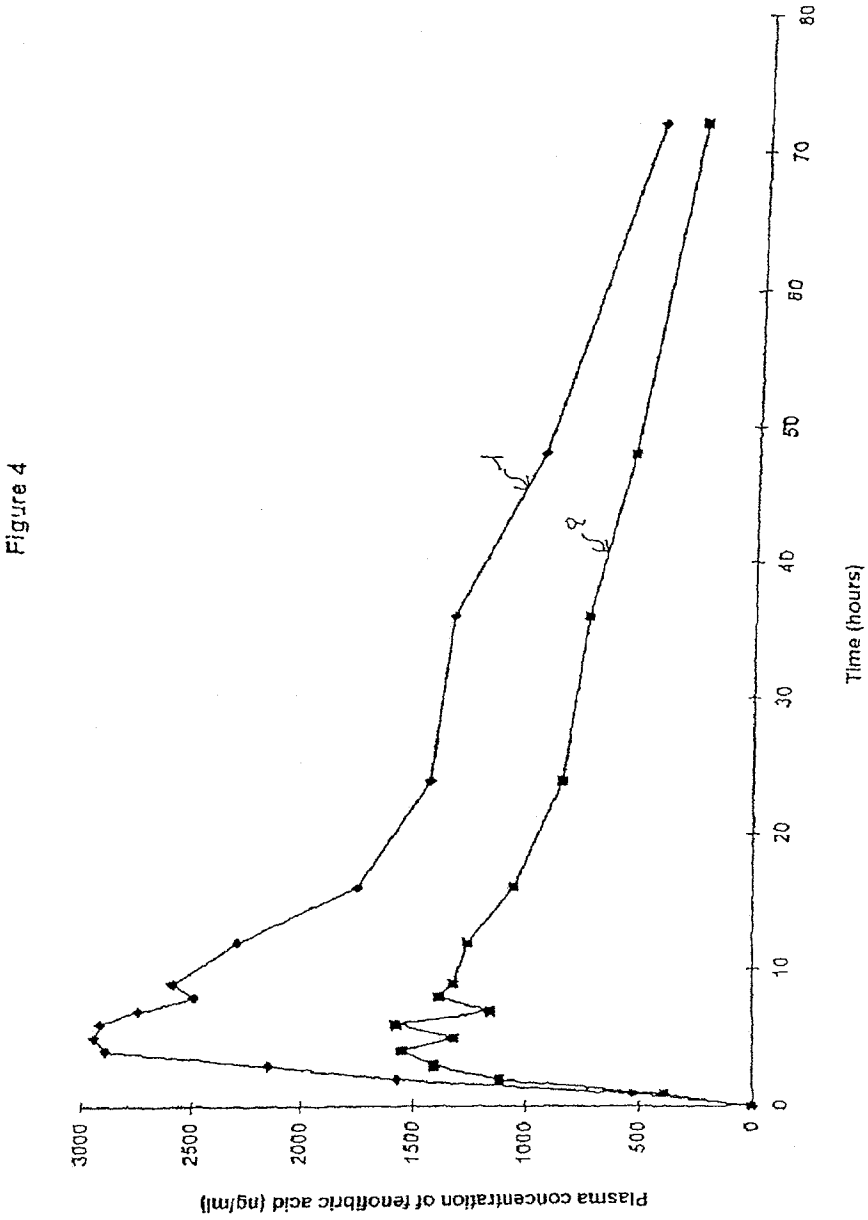
Plasma concentration of fenofibric acid (ng/ml)
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
Time (hours)
1
2

Figure 4

PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND THE PREPARATION METHOD

This application is a 371 of PCT/FR00/01971 filed on Jul. 7, 2000.

The present invention relates to a novel pharmaceutical composition containing fenofibrate.

Fenofibrate is recommended in the treatment of adult endogenous hyperlipidemias, of hypercholesterolemias and of hypertriglyceridemias. A treatment of 300 to 400 mg of fenofibrate per day enables a 20 to 25% reduction of cholesterolemia and a 40 to 50% reduction of triglyceridemia to be obtained.

The major fenofibrate metabolite in the plasma is fenofibric acid. The half-life for elimination of fenofibric acid from the plasma is of the order of 20 hours. Its maximum concentration in the plasma is attained, on average, five hours after ingestion of the medicinal product. The mean concentration in the plasma is of the order of 15 micrograms/ml for a dose of 300 mg of fenofibrate per day. This level is stable throughout treatment.

Fenofibrate is an active principle which is very poorly soluble in water, and the absorption of which in the digestive tract is limited. An increase in its solubility or in its rate of solubilization leads to better digestive absorption.

Various approaches have been explored in order to increase the rate of solubilization of fenofibrate: micronization of the active principle, addition of a surfactant, and comicronization of fenofibrate with a surfactant.

Patent EP 256 933 describes fenofibrate granules in which the fenofibrate is micronized in order to increase its bioavailability. The crystalline fenofibrate microparticles are less than 50 μm in size. the binder used is polyvinylpyrrolidone. The document suggests other types of binder, such as methacrylic polymers, cellulose derivatives and polyethylene glycols. The granules described in the examples of EP 256 933 are obtained by a method using organic solvents.

Patent EP 330 532 proposes improving the bioavailability of fenofibrate by comicronizing it with a surfactant, such as sodium lauryl sulfate. The comicronizate is then granulated by wet granulation in order to improve the flow capacities of the powder and to facilitate the transformation into gelatin capsules. This comicronization allows a significant increase in the bioavailability compared to the use of fenofibrate described in EP 256 933. The granules described in EP 330 532 contain polyvinylpyrrolidone as a binder.

This patent teaches that the comicronization of fenofibrate with a solid surfactant significantly improves the bioavailability of the fenofibrate compared to the use of a surfactant, of micronization or of the combination of a surfactant and of micronized fenofibrate.

Patent WO 98/31361 proposes improving the bioavailability of the fenofibrate by attaching to a hydrodispersible inert support micronized fenofibrate, a hydrophilic polymer and, optionally, a surfactant. The hydrophilic polymer, identified as polyvinyl-pyrrolidone, represents at least 20% by weight of the composition described above.

This method makes it possible to increase the rate of dissolution of the fenofibrate, and also its bioavailability. However, the preparation method according to that patent is not entirely satisfactory since it requires the use of a considerable amount of PVP and of the other excipients. The example presented in that patent application refers to a composition containing only 17.7% of fenofibrate expressed as a mass ratio. This low mass ratio for fenofibrate leads to a final form which is very large in size, hence a difficulty in administering the desired dose of fenofibrate, or the administration of two tablets.

In the context of the present invention, it has been discovered that the incorporation of a cellulose derivative, used as a binder and solubilization adjuvant, into a composition containing micronized fenofibrate and a surfactant makes it possible to obtain a bioavailability which is greater than for a composition containing a comicronizate of fenofibrate and of a surfactant.

A subject of the present invention is therefore a pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative, which is a solubilization adjuvant, preferably hydroxypropylmethylcellulose (HPMC).

The composition of the invention is advantageously provided as gelatin capsules containing powder or granules, preferably in the form of granules. These granules may in particular be prepared by assembly on neutral microgranules, by spraying an aqueous solution containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension, or by wet granulation of powder, according to which the constituents, including in particular the micronized fenofibrate, the surfactant and the cellulose derivative, are granulated by wet granulation using an aqueous wetting solution, dried and calibrated.

The pharmaceutical composition according to the present invention has a high proportion of fenofibrate; it may therefore be provided in a formulation which is smaller in size than the formulations of the prior art, which makes this composition according to the invention easy to administer.

The amount of fenofibrate is greater than or equal to 60% by weight, preferably greater than or equal to 70% by weight, even more preferably greater than or equal to 75% by weight, relative to the weight of the composition.

In the context of the present invention, the fenofibrate is not comicronized with a surfactant. On the contrary, it is micronized alone and then combined with a surfactant and with the binding cellulose derivative, which is a solubilization adjuvant.

The surfactant is chosen from surfactants which are solid or liquid at room temperature, for example sodium lauryl sulfate, Polysorbate® 80 or Montane® 20, preferably sodium lauryl sulfate.

The fenofibrate/HPMC ratio is preferably between 5/1 and 15/1.

The surfactant represents between 1 and 10%, preferably between 3 and 5%, by weight relative to the weight of fenofibrate.

The binding cellulose derivative represents between 2 and 15%, preferably between 5 and 12%, by weight of the composition.

Hydroxypropylmethylcellulose is preferably chosen, the apparent viscosity of which is between 2.4 and 18 cP, and even more preferably between 2.4 and 3.6 cP, such as for example Pharmacoat 603®.

The mean size of the fenofibrate particles is less than 15 μm, preferably 10 μm, even more preferably less than 8 μm.

The composition of the invention may also contain at least one excipient such as diluents, for instance lactose, antifoaming agents, for instance DIMETHICONE and SIMETHICONE, or lubricants, for instance talc.

The pharmaceutical composition of the invention advantageously consists of granules in an amount equivalent to a dose of fenofibrate of between 50 and 300 mg, preferably equal to 200 mg.

The present invention also relates to a method for preparing the powder or the granules, the composition of which is described above. This method uses no organic solvent.

According to a first variant, the granules are prepared by assembly on neutral microgranules.

The neutral microgranules have a particle size of between 200 and 1 000 microns, preferably between 400 and 600 microns.

The assembly is carried out in a sugar-coating pan, in a perforated coating pan or in a fluidized airbed, preferably in a fluidized airbed.

The assembly of neutral microgranules is carried out by spraying an aqueous suspension containing the surfactant, the solubilized binding cellulose derivative, and the micronized fenofibrate in suspension.

According to a second variant, the granules are obtained by wet granulation of powder. The granulation enables the powders to be made dense and makes it possible to improve their flow properties. It also allows better preservation of the homogeneity, by avoiding the various constituents becoming unmixed.

The micronized fenofibrate, the surfactant, the cellulose derivative and, optionally, the other excipients are mixed, granulated, dried and then calibrated. The wetting solution may be water or an aqueous solution containing the binding cellulose derivative and/or the surfactant.

According to a particular embodiment, the fenofibrate and the other excipients are mixed in a planetary mixer. The wetting solution is added directly to the mixture. The wet mass obtained is granulated with an oscillating granulator, and then dried in an oven. The granules are obtained after passage over an oscillating calibrator.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in fasting individuals.

FIG. **2** represents the in vivo release profile of the formulation of example 1C and of a formulation of the prior art in individuals who have just eaten.

FIG. **3** represents the in vivo release profile of the formulation of example 2B and of a formulation of the prior art in fasting individuals.

FIG. **4** represents the in vivo release profile of the formulation of comparative example 3 and of a formulation of the prior art in individuals who have just eaten.

The invention is illustrated in a nonlimiting way by the following examples.

EXAMPLE 1

Granules

1A) Microgranules (XFEN 1735)

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The composition is given in the following table:

Formula	Amount (percentage by mass)
Micronized fenofibrate	64.5
Neutral microgranules	21
HPMC (Pharmacoat 603 ®)	11.2
Polysorbate ® 80	3.3
Fenofibrate content	645 mg/g

The in vitro dissolution was determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The percentages of dissolved product as a function of time, in comparison with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 1A (% dissolved)	73	95
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 1A dissolves more rapidly than Lipanthyl 200 M.

1B) Microgranules (X FEN 1935)

The mean size of the fenofibrate particles is equal to 6.9±0.7 microns.

The microgranules are obtained by spraying an aqueous suspension onto neutral cores. The suspension contains micronized fenofibrate, sodium lauryl sulfate and HPMC.

The assembly is carried out in a Huttlin fluidized airbed (rotoprocess).

The formula obtained is given below.

FORMULA	AMOUNT (percentage by mass)
Micronized fenofibrate	65.2
Neutral microgranules	20.1
HPMC (Pharmacoat 603 ®)	11.4
Sodium lauryl sulfate	3.3
Fenofibrate content	652 mg/g

The size of the neutral microgranules is between 400 and 600 μm.

1C) Gelatin Capsules of Microgranules (Y FEN 001)

Microgranules having the following composition are prepared:

RAW MATERIALS	AMOUNT (percentage by mass)
Micronized fenofibrate	67.1
Neutral microgranules	17.2
Pharmacoat 603 ® (HPMC)	11.7
Sodium lauryl sulfate	3.3
35% dimethicone emulsion	0.2
Talc	0.5
Fenofibrate content	671 mg/g

according to the method described in paragraph 1A).

The microgranules obtained are distributed into size 1 gelatin capsules, each containing 200 mg of fenofibrate.

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 1C (% dissolved)	76	100
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formula 1C dissolves more rapidly than Lipanthyl 200 M.

The gelatin capsules are conserved for 6 months at 40° C./75% relative humidity. The granules are stable under these accelerated storage conditions. In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

	Conservation time		
Dissolution time (min)	1 month (% dissolved product)	3 months (% dissolved product)	6 months (% dissolved product)
5	25.1	23.0	20.1
15	71.8	65.6	66.5
25	95.7	88.7	91.0
35	104.7	98.7	98.2
45	106.4	100.2	99.1
55	106.7	100.5	99.5
65	106.8	100.6	99.7

The evolution of the content of active principle during storage is given in the following table.

Content (mg/gelatin Capsule) Conservation time			
0	1 month	3 months	6 months
208.6	192.6	190.8	211.7

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the YFEN 01 granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **1**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (µg · h/ml)	76	119
AUC_{inf} (µg · h/ml)	96	137
C_{max} (µg/ml)	2.35	4.71
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.028
Elim ½ (hours)	26.7	24.9

The following abbreviations are used in the present application:

C_{max}: maximum concentration in the plasma,

T_{max}: time required to attain the Cmax,

$Elim_{1/2}$: plasmatic half-life,

AUC_{0-t}: area under the curve from 0 to t,

$AUC_{0-\infty}$: area under the curve from 0 to ∞,

Ke: Elimination constant.

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. **1** by curves **1** and **2**, respectively.

These results show that the composition according to the present invention has a bioavailability which is greater than that of Lipanthyl 200 M in fasting individuals.

Pharmacokinetic Study Carried Out in Individuals Who Have Just Eaten

The in vivo release profile of the gelatin capsules containing the YFEN 01 granules at a dose of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 18 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **2**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (µg · h/ml)	244	257
AUC_{inf} (µg · h/ml)	255	270
C_{max} (µg/ml)	12	13
T_{max} (hours)	5.5	5.5
Ke (1/hour)	0.04	0.04
Elim ½ (hours)	19.6	19.3

The results obtained for Lipanthyl 200 M and for the product of example 1C are represented on FIG. **2** by curves **1** and **2**, respectively.

These results show that the composition according to the present invention is bioequivalent to that of Lipanthyl 200 M in individuals who have just eaten.

EXAMPLE 2

Powder

2A) Granules (X FEN 1992)

Granules having the following composition are prepared

FORMULA	PERCENTAGE BY MASS
Micronized fenofibrate	71
Lactose	21.5
HPMC (Pharmacoat 603 ®)	5
Sodium lauryl sulfate	2.5

The micronized fenofibrate, the HPMC and the lactose are mixed using a planetary mixer. This mixture is granulated in the presence of a solution of sodium lauryl sulfate.

The flow time of the granules is 7 s. The compacting capacity and the particle size distribution are given in the following tables. These measurements were carried out in accordance with the standards of the European Pharmacopocia.

Compacting capacity (X FEN 1992)	
V0	204 ml
V10	186 ml
V500	168 ml
V1250	164 ml
V10–V500	22 ml

Particle size distribution (X FEN 1992)	
Sieve mesh size (mm)	% of oversize mass
0.6	8
0.5	9
0.355	12
0.2	30
0.1	23
0	18

2B) Gelatin Capsules of Granules (Y FEN 002)

Preparation

The micronized fenofibrate is mixed in a PMA mixer (Niro Fielder) with lactose and HPMC, and then wetted with an aqueous solution of sodium lauryl sulfate. The mass obtained is granulated by passage over an oscillating granulator, dried and then calibrated on a sieve with a mesh size of 1.25 mm.

The granules are then packaged in size 1 gelatin capsules at doses of 200 mg of fenofibrate.

Granules of the following composition are obtained.

FORMULA	PERCENTAGE BY MASS
Micronized fenofibrate	70
Lactose	21.5
Pharmacoat 603 ® (HPMC)	5
Sodium lauryl sulfate	3.5
Content	700 mg/g

Properties of the Granules

The flow time of the granules is 6 s. The compacting capacity and the particle size distribution are given in the following tables. These measurements were carried out in accordance with the standards of the European Pharmacopoeia.

Compacting capacity (Y FEN 002)	
V0	216 ml
V10	200 ml
V500	172 ml
V1250	170 ml
V10–V500	28 ml

Particle size distribution (Y FEN 002)	
Sieve mesh size (mm)	% of oversize mass
0.6	5
0.5	7

-continued

Particle size distribution (Y FEN 002)	
Sieve mesh size (mm)	% of oversize mass
0.355	11
0.2	30
0.1	25
0	22

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results for a formulation of the prior art, Lipanthyl 200 M, are given in the following table.

Time (min)	15	30
Example 2B (% dissolved)	82.2	88.5
Lipanthyl 200 M (% dissolved)	47.3	64.7

Formulation 2B dissolves more rapidly than Lipanthyl 200 M.

Stability Tests

The gelatin capsules conserved at 40° C./75% relative humidity are stable for 6 months.

In vitro dissolution tests (in continuous flow cells with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N) were carried out. The percentages of dissolved product as a function of time for gelatin capsules conserved for 1, 3 and 6 months are given in the following table.

	Conservation time		
Dissolution time (min)	1 month (% dissolved product)	3 months (% dissolved product)	6 months (% dissolved product)
5	54.2	52.9	49.0
15	81.1	75.8	82.2
25	86.4	79.6	87.2
35	88.8	81.6	89.8
45	90.7	82.9	91.5
55	92.1	83.9	92.7
65	93.2	84.7	93.6

The evolution of the content of active principle during storage is given in the following table.

Content (mg/gelatin capsule)			
Conservation time			
0	1 month	3 months	6 months
196.6	190.0	199.8	203.3

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the YFEN 002 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 9 individuals. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **3**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 1C
AUC_{0-t} (µg · h/ml)	76	70
AUC_{inf} (µg · h/ml)	96	62
C_{max} (µg/ml)	2.35	2.8
T_{max} (hours)	8.0	5.5
Ke (1/hour)	0.032	0.033
Elim ½ (hours)	26.7	23.1

The results obtained for Lipanthyl 200 M and for the product of example 2B are represented on FIG. **3** by curves **1** and **2**, respectively.

These results show that the composition of example 2B is bioequivalent to that of Lipanthyl 200 M in fasting individuals.

COMPARATIVE EXAMPLE 3

Batch ZEF 001

This example illustrates the prior art.

It combines micronization of fenofibrate and the use of a surfactant. It differs from the present invention by the use of the mixture of binding excipients consisting of a cellulose derivative other than HPMC: Avicel PH 101 and polyvinylpyrrolidone (PVP K30).

It is prepared by extrusion-spheronization.

Theoretical Formula

Products	Theoretical amount (%)
Micronized fenofibrate	75.08
Montanox 80 ®	4.72
Avicel PH 101 ®	5.02
PVP K 30 ®	4.12
Explotab ®	11.06

In Vitro Dissolution Profile

The in vitro dissolution is determined according to a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N. The comparative results with Lipanthyl 200 M are given in the following table.

Time (min)	15	30
Example 3 (% dissolved)	24	40
Lipanthyl 200 N (% dissolved)	47.3	647

The dissolution is slower than that observed for Lipanthyl 200 M.

Pharmacokinetic Study Carried Out in Fasting Individuals

The in vivo release profile of the gelatin capsules containing the ZEF 001 granules at doses of 200 mg of fenofibrate is compared with that of the gelatin capsules marketed under the trademark Lipanthyl 200 M.

This study is carried out in 5 fasting individuals receiving a single dose. Blood samples are taken at regular time intervals and fenofibric acid is assayed.

The results are given in the following table and FIG. **4**.

Pharmacokinetic parameters	Lipanthyl 200 M	Example 3
AUC_{0-t} (µg · h/ml)	92	47
AUC_{inf} (µg · h/ml)	104	53
C_{max} (µg/ml)	3.5	1.7
T_{max} (hours)	5.6	4.6
Ke (1/hour)	0.04	0.038
Elim ½ (hours)	18.9	20.3

The results obtained for Lipanthyl 200 M and for the product of example 3 are represented on FIG. **4** by curves **1** and **2**, respectively.

These results show the greater bioavailability of Lipanthyl 200 M compared with this formulation based on the prior art.

Example 3 shows that combining the knowledge of the prior art (namely micronization or use of surfactants) does not make it possible to obtain rapid dissolution of fenofibrate. This results in low bioavailability compared with Lipanthyl 200 M.

The compositions prepared according to the present invention show more rapid dissolution than the formula of the prior art and improved bioavailability.

The invention claimed is:

1. A pharmaceutical composition in the form of granules, wherein each granule comprises a neutral microgranule on which is a composition comprising: micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization adjuvant, and

wherein said fenofibrate is present in an amount greater than or equal to 60% by weight, relative to the weight of said pharmaceutical composition, and further wherein said binding cellulose derivative represents between 2 to 15% by weight, relative to the weight of said pharmaceutical composition.

2. The pharmaceutical composition of claim **1**, wherein said binding cellulose derivative is hydroxypropylmethylcellulose (HPMC).

3. The pharmaceutical composition of claim **2**, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 18 cP.

4. The pharmaceutical composition of claim **1**, wherein said fenofibrate is present in an amount greater than or equal to 70% by weight, relative to the weight of said pharmaceutical composition.

5. The pharmaceutical composition of claim **1**, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

6. The pharmaceutical composition of claim **1**, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of said fenofibrate.

7. The pharmaceutical composition of claim **2**, wherein said fenofibrate/HPMC mass ratio is between 5/1 and 15/1.

8. The pharmaceutical composition of claim **1**, wherein said pharmaceutical composition further comprises at least one excipient.

9. The pharmaceutical composition of claim **1**, wherein said micronized fenofibrate has a mean particle size less than 15 µm.

10. The pharmaceutical composition of claim **1**, wherein said composition is contained in gelatin capsules.

11. A method for preparing the pharmaceutical composition of claim **1**, wherein said granules are prepared by

spraying onto neutral microgranules an aqueous suspension of micronized fenofibrate containing surfactant and solubilized binding cellulose derivative.

12. The pharmaceutical composition of claim **3**, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 3.6 cP.

13. The pharmaceutical composition of claim **1**, wherein said fenofibrate is present in an amount greater than or equal to 75% by weight, relative to the weight of said pharmaceutical composition.

14. The pharmaceutical composition of claim **1**, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of said fenofibrate.

15. The pharmaceutical composition of claim **1**, wherein said binding cellulose derivative represents between 5 and 12% by weight, relative to the weight of said pharmaceutical composition.

16. The pharmaceutical composition of claim **8**, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

17. The pharmaceutical composition of claim **8**, wherein said excipient is selected from the group consisting of lactose, α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)], a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide, and talc.

18. The pharmaceutical composition of claim **1**, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

19. A pharmaceutical composition in the form of granules, wherein each granule comprises a neutral microgranule on which is a composition comprising: micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization agent, wherein the mass ratio of said fenofibrate to said binding cellulose derivative is between 5/1 and 15/1.

20. The pharmaceutical composition according to claim **19**, wherein said binding cellulose derivative is hydroxypropylmethylcellulose.

21. The pharmaceutical composition of claim **19**, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 18 cP.

22. The pharmaceutical composition of claim **19**, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 3.6 cP.

23. The pharmaceutical composition of claim **19**, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

24. The pharmaceutical composition of claim **19**, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of said fenofibrate.

25. The pharmaceutical composition of claim **19**, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of said fenofibrate.

26. The pharmaceutical composition of claim **19**, wherein said pharmaceutical composition further comprises at least one excipient.

27. The pharmaceutical composition of claim **26**, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

28. The pharmaceutical composition of claim **27**, wherein said diluent is lactose.

29. The pharmaceutical composition of claim **27**, wherein said antifoaming agent is α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] or a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide.

30. The pharmaceutical composition of claim **27**, wherein said lubricant is talc.

31. The pharmaceutical composition of claim **19**, wherein said micronized fenofibrate has a mean particle size less than 15 μm.

32. The pharmaceutical composition of claim **19**, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

33. The pharmaceutical composition of claim **19**, wherein said composition is contained in gelatin capsules.

34. The pharmaceutical composition of claim **2**, wherein at least 95% of said fenofibrate is dissolved at 30 minutes, as measured using a continuous flow cell method with a flow rate of 8 ml/min of sodium lauryl sulfate at 0.1 N.

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