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54	Method for preparing novel fenofibrate galenic formulations, galenic formulations obtained and applications

57	Abstract (not more than 150 words)

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The invention concerns a method of preparing novel galenic formulations for providing fenofibrate within enhanced bioavailability when it is orally absorbed, and consisting in: (a) micronizing fenofibrate; (b) granulating the fenofiberate in the presence of a liquid medium comprising a surfactant, water and water-miscible alcohol; and (c) drying the resulting granular material. The invention also concerns the galenic formulations obtained by said method. Said formulations are used for preparing a medicine for oral administration and comprising fenofibrate as active principle, in particular for treating hypercholesterolemia and hypertriglyceridemia

METHOD FOR PREPARING NOVEL FENOFIBRATE GALENIC FORMULATIONS, GALENIC FORMULATIONS OBTAINED AND APPLICATIONS

The present invention relates to a method which makes it possible to prepare galenic formulations comprising fenofibrate as active principle, and which makes it possible to confer on this active principle, when it is orally absorbed, a significantly enhanced bioavailability ("*suprabioavailability*") compared to that obtained with currently available fenofibrate-based pharmaceutical compositions, to the galenic formulations obtained by said method as well as to the applications of this method and of these galenic formulations, in particular for the preparation of medicines intended for oral administration.

Fenofibrate (INN) or isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropionate is one of the hypolipidemic agents most widely used worldwide in the treatment of isolated or associated endogenous hypercholesterolemia and hypertriglyceridemia in adults. Its efficacy in these therapeutic indications has been widely demonstrated. Thus, administered long term at therapeutically effective doses, fenofibrate makes it possible to lower the cholesterolemia by 20 to 25% and the triglyceridemia by 40 to 50%, this being from the first month of treatment.

Fenofibrate was marketed for the first time in France in 1975, in the form of gelatin capsules containing 100-mg doses of active principle (LIPANTHYL® 100) and with a dosage of 3 or 4 gelatin capsules per day to be divided between the various meals, therefore corresponding to a daily administration of 300 to 400 mg of active principle. This proprietary medicinal product is still marketed today in France, but under the name SECALIP® 100.

In 1986, a second dosage intended to offer patients requiring only 300 mg of fenofibrate per day a better therapeutic compliance, was marketed in the form

of gelatin capsules containing 300 mg of active principle (LIPANTHYL® 300), the dosage being in this case a single gelatin capsule per day. Such a dosage is made possible by the long period of action of the fenofibrate whose elimination half-life is indeed about 20 hours. This proprietary medicinal product is also still available in France, but under the name SECALIP® 300.

Since the work by DESAGER et al. (*J. Clin. pharmacol.*, 1978, 26, 570-574) and that by WEIL et al. (*Drug metabolism*, 1980, 18, 115-120), it is known that when fenofibrate is administered in a solid form (powder or granules), its intestinal absorption is very incomplete since the fenofibric acid which is its principal circulating active metabolite is only present in an amount of 20% of the dose of fenofibrate administered if the administration is made on an empty stomach, and in an amount of 60% if the administration is made with a meal. The latter data was subsequently confirmed by STROLIN BENEDETTI and coworkers (*Acta Pharmacol. Toxicol.*, 1986, 59, suppl. 5, 167) who showed that after administration of a gelatin capsule containing a 300-mg dose of fenofibrate with a meal, only 60% of the administered fenofibrate dose is effectively absorbed and reaches the blood circulation in the form of fenofibric acid.

It is found moreover that a long-term treatment with fenofibrate is not completely free of undesirable effects, cases of muscular conditions (diffuse myalgia, painful sensitivity, rhabdomyolysis and the like), digestive disorders, rise in transaminases and biliary lithiases preventing such a treatment from being maintained having indeed been reported.

Because of this, a number of studies have been carried out with the aim of developing galenic formulations capable of increasing the bioavailability of fenofibrate when the latter is orally absorbed, so as to reduce the dose of fenofibrate necessary for

obtaining a therapeutic benefit and for thereby reducing the risks of undesirable effects.

French Patent Application No. 80 24568, filed in 1980 in the joint names of Claude LARUELLE and DESHORS, represents a first technological advance in this direction. Indeed, this patent describes a galenic formulation provided in the form of granules which comprise a neutral core coated with a fenofibrate-based intermediate layer and with a protective external layer formed of a polymer compatible with oral administration and which, when combined into gelatin capsules with 250-mg doses, make it possible to obtain, through a single daily dose, therapeutically effective plasma levels of fenofibric acid.

European Patent Application No. 0 256 933, filed in 1987 in the name of ETHYPHARM, describes a galenic formulation capable of promoting in particular the intestinal absorption of fenofibrate and which also exists in the form of granules consisting of a neutral core, a fenofibrate-based intermediate layer and a protective external layer, but these granules have the characteristic that the fenofibrate is present therein in the form of crystalline particles having a size of less than or equal to 50 µm, and preferably of the order of 10 µm.

French Patent Application No. 88 02359, filed in 1988 in the name of FOURNIER INNOVATION ET SYNERGIE, provides, for its part, a therapeutic composition which exists in the form of gelatin capsules with 200-mg doses of fenofibrate and comprising fenofibrate and a solid surfactant which have been subjected to comicronization. This therapeutic composition, which was marketed in France in 1991 under the name of LIPANTHYL® 200 Micronisé, unquestionably represents an improvement since studies demonstrated that a kinetic bioequivalence exists between a gelatin capsule of this composition and a gelatin capsule of LIPANTHYL® 300 (GUICHARD and LEVY-PRADES SAURON, *J. Int. Med.*, 1991, 48-50), and between a gelatin capsule of LIPANTHYL® 200

Micronisé and 3 gelatin capsules of LIPANTHYL® 100 (Laboratoires FOURNIER, *LIPANTHYL, Documentation scientifique et technique destinée aux Pharmaciens des Hôpitaux et des Etablissements de soins* (*Scientific and technical documentation intended for pharmacists in hospitals and healthcare establishments*) 1992).

Moreover, BRODIE and coworkers (*Arzneimittel Forschung*, 1976, 26, 896-901) have shown that the administration of fenofibrate, which is a lipophilic molecule, in sunflower oil makes it possible to obtain an almost complete intestinal absorption of this active principle unlike its administration in solid form. However, it is found that the use of sunflower oil as solvent for fenofibrate cannot be envisaged for the production of medicines, because it requires a relatively large volume of oil, of the order of 5 ml, which is incompatible with a production in capsules of suitable volume acceptable by the patients.

Also, it has been proposed in International Patent Application WO 96/21439, filed in 1996 in the name of GALEPHAR P.R., to produce a medicine in the form of gelatin capsules filled with a mixture consisting of fenofibrate dissolved in polyglycosylated glycerides such as for example mixtures of esters of glycerol and fatty acids or esters of polyethylene glycols and fatty acids. According to this application, 3 gelatin capsules with 67-mg doses of fenofibrate of such a medicine would be bioequivalent to 3 gelatin capsules of LIPANTHYL® 100, whereas a gelatin capsule with a 200-mg dose of this same medicine would be bioequivalent to one gelatin capsule of LIPANTHYL® 200 Micronisé.

In parallel, in French Patent Application No. 95 09142, filed in 1995 in the name of CL PHARMA, it has been suggested to improve the dissolution of fenofibrate and thereby its bioavailability by administering it in the form of soft capsules in which it exists in solution in a nonionic and amphiphilic surfactant, namely diethylene glycol monoethyl ether.

This galenic formulation makes it possible to obtain, by a daily administration of 100 mg of fenofibrate, plasma concentrations of fenofibric acid considered to be therapeutically effective. However, the cost of manufacture of such capsules limits the benefit of their exploitation.

However, the inventors, in the context of their research studies on the improvement of the bioavailability of fenofibrate, observed, surprisingly, that it is possible to obtain galenic formulations which, while existing in a solid form, make it possible to confer on the fenofibrate, when it is administered orally, a significantly higher bioavailability than that obtained with the fenofibrate-based pharmaceutical compositions currently available and to thus offer an identical therapeutic benefit for notably lower doses of this active principle, by subjecting micronized fenofibrate to granulation in the presence of a liquid medium comprising both water, a water-miscible alcohol and a surfactant, and by drying the granular material thus prepared.

The subject of the present invention is therefore a method for preparing a galenic formulation comprising fenofibrate as active principle, characterized in that it consists in:

(a) micronizing fenofibrate,

(b) granulating the fenofibrate thus micronized in the presence of a liquid medium comprising a surfactant, water and a water-miscible alcohol, and

(c) drying the granular material thus obtained.

According to a first advantageous feature of this method, it further comprises, prior to and/or subsequent to the granulation operation, the addition of one or more excipients chosen from binding agents, diluents, disintegrating agents, lubricating agents, glidants, colorings and flavor modifiers conventionally used for the preparation of solid galenic formulations.

Thus, for example, micronized fenofibrate may be advantageously mixed, prior to the granulation, with

one or more binding agents such as starch, pregelatinized starch, sugars (lactose, glucose, dextrose and the like), polyvinylpyrrolidone, methyl cellulose, ethyl cellulose, carboxymethyl cellulose or microcrystalline cellulose, and/or with one or more diluents such as lactose, kaolin, mannitol, starch, sodium chloride or calcium phosphate, and/or with one or more disintegrating agents of the starch, sodium carboxymethyl starch, chalk, carboxymethyl cellulose or alginic acid type, while it may be advantageous to add to the granular material resulting from the granulation, once dry, one or more lubricating agents such as magnesium stearate, calcium stearate or talc, starches, cellulose and its derivatives and/or one or more glidants of the colloidal silica, magnesium stearate, sodium carboxymethyl starch, dicalcium phosphate, granulated mannitol or microcrystalline cellulose type, and/or one or more colorings and/or one or more flavor modifiers, depending on the constitution which it is desired to give the galenic formulation and its destination (putting into gelatin capsules, compressing for the production of tablets, and the like).

According to another advantageous feature of the method in accordance with the invention, it comprises, in addition, subsequent to the drying of the granular material and prior to its possible mixing with one or more excipients, the sizing of this granular material, which is advantageously performed under conditions which make it possible to remove all the grains having a size greater than or equal to 150 µm.

According to yet another advantageous feature of this method, the micronization of the fenofibrate is carried out so as to obtain a powder whose particles have a homogeneous size at most equal to 10 µm and preferably of between 5 and 10 µm.

According to a preferred feature of the method in accordance with the invention, the particles resulting from the micronization of the fenofibrate

have a specific surface area of between 0.7 and 1.6 m^2/g and preferably in the region of 1 m^2/g.

Indeed, the inventors have observed, without however being able to explain the reasons therefor, that by micronizing, under the same conditions, fenofibrates derived from different methods of manufacture, particles are obtained which do not have the same specific surface area from one fenofibrate to another, and this being for identical physical characteristics: density, porosity (measured on pores having a diameter of between 1 and 100 nm), melting point, absence of polymorphic variety, crystalline system. This difference in intrinsic specific surface area is in fact correlated with a specific transition energy which is different, nevertheless in a smaller proportion (difference of 10 to 20% between the transition energies expressed in J/g). Moreover, the inventors have found that while the wettability of the fenofibrate particles or of the fenofibrate particles/excipient(s) mixture by the liquid medium during the granulation operation - on which the success of this operation depends to a large extent and, consequently, the quality of the granular material obtained -, is improved by the presence of an alcohol in this medium, it is all the more so if the fenofibrate particles have a specific surface area of between 0.7 and 1.6 m^2/g, and more particularly of close to 1 m^2/g.

In accordance with the invention, the surfactant is present in the liquid medium used for the granulation at a molar concentration which is between 0.1 and 1, and preferably between 0.2 and 5, while the ratio between the volumes of water and alcohol present in this same medium is, for its part, between 0.25 and 4, and preferably between 0.5 and 2. This water/alcohol volume ratio will be advantageously chosen according to the specific surface area of the particles resulting from the micronization of the fenofibrate. Indeed, it has been found that, in order to obtain a granulation

of the same quality, it is generally necessary to use a water/alcohol volume ratio which is all the more high if the specific surface area of the fenofibrate particles is itself higher. By contrast, this ratio generally needs to be reduced when the specific surface area of said particles is smaller.

According to yet another advantageous feature of the method in accordance with the invention, the quantity of liquid medium used for the granulation is between 5 and 70% and, preferably, between 15 and 50% by weight relative to the weight of the fenofibrate particles or of the fenofibrate particles/excipient(s) mixture intended to be subjected to this granulation.

Preferably, the surfactant is sodium lauryl sulfate, while the water-miscible alcohol is ethanol. However, other surfactants such as sodium dioctylsulfosuccinate, sodium dodecylbenzenesulfonate, halides of quaternary ammonium-based compounds, polysorbates and ethers of aliphatic alcohols and polyethylene glycol, as well as other water-miscible alcohols such as isopropanol, are also capable of being used for carrying out the method in accordance with the invention.

According to a particularly preferred feature of the method in accordance with the invention, it consists in:

(a) micronizing fenofibrate,

(b) mixing the fenofibrate thus micronized with one or more binding agents and/or diluents and/or disintegrating agents,

(c) preparing the liquid medium intended for performing the granulation by dissolving sodium lauryl sulfate in a aqueous-alcoholic solution,

(d) granulating the mixture obtained in step b) in the presence of said liquid medium,

(e) drying the granular material thus obtained,

(f) sizing this granular material, and

(g) mixing said granular material with one or more lubricating agents and/or glidants and/or colorings and/or flavor modifiers.

The method for preparing a galenic formulation which is the subject of the present invention has many advantages. Indeed, in addition to leading to the production of galenic formulations conferring a suprabioavailability on the fenofibrate and allowing a reduction in the doses of fenofibrate which are to date recommended for obtaining a therapeutic efficacy as will be demonstrated below, it has the advantage, by virtue of the fact that it envisages incorporating the surfactant directly into the liquid medium intended for performing the granulation of the fenofibrate, of comprising one operation less than the methods used for the preparation of the currently available fenofibrate-based medicines, and of thus allowing better reproducibility of the manufacturing batches and substantial savings on the cost of production. In addition, it does not require specific equipment and can easily be carried out by means of apparatus with which laboratories of galenic pharmacology are conventionally equipped for the manufacture of medicines provided in solid form, and in particular for the granulation of active principles in a wet medium.

The subject of the present invention is also a galenic formulation comprising fenofibrate as active principle, characterized in that it is capable of being obtained using a method as defined above.

The subject of the present invention is also a medicine intended for oral administration, characterized in that it comprises an effective quantity of a galenic formulation obtained using a method as defined above.

According to a preferred embodiment of this medicine, it is provided in the form of gelatin capsules, preferably made of gelatin. It can, under these conditions, be prepared by an operation consisting in filling gelatin capsules of a suitably

chosen size with a predetermined quantity of a galenic formulation in accordance with the invention.

As a variant, it is however possible to produce such a medicine, in the form of uncoated or film-coated tablets, by compression of a galenic formulation in accordance with the invention and, where appropriate, film-coating the products resulting from said compression.

According to another preferred embodiment of this medicine, it comprises a fenofibrate dose of between 100 and 200 mg per therapeutic unit for the administration of one therapeutic unit per day.

The subject of the present invention is also the use of a liquid medium comprising a surfactant, water and a water-miscible alcohol for carrying out the granulation of fenofibrate or of a mixture comprising fenofibrate and one or more excipients.

The subject of the present invention is, in addition, the use of fenofibrate particles having a specific surface area of between 0.7 and 1.6 m^2/g and, preferably, in the region of 1 m^2/g for the preparation of a medicine intended for oral administration.

In addition to the preceding features, the invention also comprises other features which will emerge from the additional description which follows, which relates to examples of producing medicines in accordance with the invention and of demonstrating their pharmacokinetics, as well as to the appended Figure 1 which illustrates the mean plasma concentrations of fenofibric acid, expressed in µg per ml of plasma, which are obtained in healthy subjects respectively after administration of a medicine in accordance with the invention (20 minutes after having a standard breakfast) in the form of a gelatin capsule with a 200-mg dose of fenofibrate (♦), and administration of 3 gelatin capsules of SECALIP® 100 (▲) under the same conditions.

It should be understood, however, that these examples are given solely by way of illustration of the

subject of the invention and do not constitute in any manner a limitation thereto.

EXAMPLE 1: Preparation of a medicine provided in the form of gelatin capsules containing 150 mg of fenofibrate

Gelatin capsules are prepared each having the following qualitative and quantitative composition:

Fenofibrate (specific surface area after micronization: 0.80-0.85 m^2/g)	150 mg
Lactose monohydrate	25.9 mg
Microcrystalline cellulose	13.5 mg
Povidone	5.2 mg
Sodium carboxymethyl starch	16.8 mg
Sodium lauryl sulfate	4.5 mg
Magnesium stearate	2.2 mg

by carrying out the procedure in the following manner:

- the fenofibrate is micronized in an air-jet apparatus so as to obtain a powder whose particles have a homogeneous size of the order of 5 to 10 µm and whose specific surface area, measured by the conventional BET gas adsorption technique (*ADSORPTION SURFACE AREA AND POROSITY*, 1982, S.J. GREGG and K.S.W. SING, ACADEMIC PRESS), is between 0.80 and 0.85 m^2/g;
- this powder is mixed with lactose monohydrate, povidone, microcrystalline cellulose and 2/3 by weight of sodium carboxymethyl starch;
- the granulation of the resulting mixture is carried out in the presence of 23% (by weight relative to the weight of this mixture) of an aqueous-alcoholic solution (distilled water/ethanol, 40/60, v/v) containing 0.23 mol/liter of sodium lauryl sulfate;
- the granules thus obtained are subjected to drying for 10 hours at 55°C, and then to sizing so as to retain only those which have a size of less than or equal to 150 µm;
- magnesium stearate and the remainder of the sodium carboxymethyl starch are added to these granules and

the whole is mixed until a homogeneous powder is obtained; and

- No. 1 size gelatin capsules are filled so that they each contain 218.2 mg of this powder.

EXAMPLE 2: Preparation of a medicine provided in the form of gelatin capsules containing 200 mg of fenofibrate

Gelatin capsules are prepared each having the following qualitative and quantitative composition:

Fenofibrate (specific surface area after micronization: 1.38-1.50 m^2/g)	200 mg
Lactose monohydrate	50 mg
Povidone	7 mg
Pregelatinized starch	30 mg
Sodium lauryl sulfate	6 mg
Magnesium stearate	4.5 mg
Anhydrous colloidal silica	1.5 mg

by carrying out the procedure in the following manner:

- the fenofibrate is micronized in an air jet apparatus so as to obtain a powder whose particles have a homogeneous size of the order of 5 to 10 µm and whose specific surface area, measured by BET gas adsorption, is between 1.38 and 1.50 m^2/g;
- this powder is mixed with lactose monohydrate, povidone and pregelatinized starch;
- the granulation of the resulting mixture is carried out in the presence of 17% (by weight relative to the weight of this mixture) of an aqueous-alcoholic solution (distilled water/ethanol, 60/40, v/v) containing 0.38 mol/liter of sodium lauryl sulfate;
- the granules thus obtained are subjected to drying and to sizing as described in Example 1 above;
- magnesium stearate and anhydrous colloidal silica are added to these granules and the whole is mixed until a homogeneous powder is obtained; and then
- No. 1 size gelatin capsules are filled so that they each contain 299 mg of this powder.

EXAMPLE 3: Pharmacokinetic study of a medicine in accordance with the invention

The capacity of a galenic formulation obtained in accordance with the invention to confer a "*suprabioavailability*" on fenofibrate was established by a study intended to compare the pharmacokinetic profile of a medicine in accordance with the invention - that is to say comprising such a galenic formulation - with that of a reference fenofibrate-based medicine, in this case SECALIP® 100 which, as indicated above, has replaced LIPANTHYL® 100 on the French market since 1991.

To do this, in a cross-over trial, 18 healthy volunteers, aged between 21 and 31, successively received, orally, 1 gelatin capsule containing 200 mg of fenofibrate and prepared in accordance with Example 2 - hereinafter treatment A - and 3 gelatin capsules of SECALIP® 100 as a single dose - hereinafter treatment B -.

The order of treatments was randomized and an interval of 14 days was left between the two treatments so as to allow total elimination of the fenofibric acid resulting from the first treatment.

In all cases, the treatments were administered 20 minutes after having a standard breakfast. Blood samples intended to assess the plasma levels of fenofibric acid were taken before the administration of the treatments and then 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96 and 120 hours after this administration. After immediate centrifugation, the plasma was separated and stored at -20°C until the fenofibric acid assays were performed, which assays were carried out by high-performance liquid chromatography.

For all the subjects, the following pharmacokinetic parameters were determined for each of the treatments:

- the maximum plasma concentration of fenofibric acid observed at the concentration peak (C_{max}),

- the time of appearance of this concentration peak (T_{max}),

- the area under the curve for the plasma concentrations of fenofibric acid as a function of time (AUC_{0-t}), and

- the area under the curve for the plasma concentrations of fenofibric acid as a function of time extrapolated to infinity ($AUC_{0-\alpha}$).

Table 1 below presents the mean values ± standard deviation of the pharmacokinetic parameters thus obtained.

TABLE 1

	Treatment A	Treatment B
C_{max} (µg/ml)	9.36 ± 3.41	3.80 ± 1.52
T_{max} (h)	4.4 ± 1.3	5.3 ± 2
AUC_{0-t} (µg/ml.h)	143 ± 73	84.2 ± 45.9
$AUC_{0-\alpha}$ (µg/ml.h)	148 ± 74	92.5 ± 46.2

Figure 1 illustrates, moreover, the mean values of the plasma concentrations of fenofibric acid, expressed in µg per ml of plasma, which are obtained during the 120 hours following the administration of treatment A (♦) and the administration of treatment B (▲).

The results presented in Table 1 as in Figure 1 show that, in the case of treatment A:

-on the one hand, the quantity of fenofibrate absorbed is much higher since not only is the maximum plasma concentration of fenofibric acid at the concentration peak (C_{max}) on average more than twice as high (2.4 times in the light of Table 1 and 2.16 times in the light of Figure 1) as that obtained with treatment B, but furthermore, the mean values of the areas under the curve for the plasma concentrations of fenofibric acid as a function of time (AUC_{0-t} and $AUC_{0-\alpha}$)

are significantly higher than those recorded with treatment B, and

- on the other hand, the fenofibrate is absorbed as rapidly since, according to Table 1, the concentration peak is situated on average one hour before the appearance of the concentration peak generated by treatment B, whereas in Figure 1, these two peaks coincide over time,

this being the case although the fenofibrate dose administered is lower than that ingested in the case of treatment B (200 mg instead of 3 × 100 mg).

Moreover, since it has been shown in the literature that a kinetic bioequivalence exists between 3 gelatin capsules of SECALIP® 100 - since this proprietary medicinal product has replaced, identically, LIPANTHYL® 100 - and 1 gelatin capsule of LIPANTHYL® 200 Micronisé, the results presented in Table 1 and Figure 1 mean that a galenic formulation prepared in accordance with the invention and comprising 200 mg of fenofibrate is capable of ensuring an intestinal absorption of this active principle which is more complete and more rapid than a gelatin capsule of LIPANTHYL® 200 Micronisé - which is the fenofibrate-based medicine exhibiting up until now the best effect/dose ratio - and that it allows the administration of daily doses of fenofibrate of less than 200 mg for obtaining the same therapeutic benefit.

Such a galenic formulation thus allows the preparation of medicines capable of reducing the risks of side effects and of improving the comfort of patients and compliance with a long-term treatment with fenofibrate.

As is evident from the above, the invention is not at all limited to its embodiments, implementations and applications which have just been described explicitly; it embraces on the contrary all the variants thereof which may occur to a specialist in this field, without departing from the framework or the scope of the present invention.

CLAIMS

1. A method for preparing a galenic formulation comprising fenofibrate as active principle, characterized in that it consists in:

(a) micronizing fenofibrate,

(b) granulating the fenofibrate in the presence of a liquid medium comprising a surfactant, water and a water-miscible alcohol, and

(c) drying the granular material thus obtained.

2. The method as claimed in claim 1, characterized in that it comprises, prior to and/or subsequent to the granulation, the addition of one or more excipients chosen from binding agents, diluents, disintegrating agents, lubricating agents, glidants, colorings and flavor modifiers.

3. The method as claimed in claim 1 or claim 2, characterized in that it comprises, subsequent to the drying of the granular material and prior to its possible mixing with one or more excipients, the sizing of this granular material.

4. The method as claimed in any one of claims 1 to 3, characterized in that the micronization of the fenofibrate is carried out so as to obtain a powder whose particles have a homogeneous size at most equal to 10 μm and preferably of between 5 and 10 μm.

5. The method as claimed in any one of claims 1 to 4, characterized in that the particles resulting from the micronization of the fenofibrate have a specific surface area of between 0.7 and 1.6 m^2/g and preferably in the region of 1 m^2/g.

6. The method as claimed in any one of claims 1 to 5, characterized in that the surfactant is present in the liquid medium used for the granulation at a molar concentration which is between 0.1 and 1, and preferably between 0.2 and 5.

7. The method as claimed in any one of claims 1 to 6, characterized in that the ratio between the volumes

of water and alcohol present in the liquid medium used for the granulation is between 0.25 and 4, and preferably between 0.5 and 2.

8. The method as claimed in any one of claims 1 to 7, characterized in that the quantity of liquid medium used for the granulation is between 5 and 70% and, preferably, between 15 and 50% by weight relative to the weight of the fenofibrate particles or of the fenofibrate particles/excipient(s) mixture intended to be subjected to this granulation.

9. The method as claimed in any one of claims 1 to 8, characterized in that the surfactant is sodium lauryl sulfate.

10. The method as claimed in any one of claims 1 to 9, characterized in that the water-miscible alcohol is ethanol.

11. The method according to any one of claims 1 to 10, characterized in that it consists in:

(a) micronizing fenofibrate,

(b) mixing the fenofibrate thus micronized with one or more binding agents and/or diluents and/or disintegrating agents,

(c) preparing the liquid medium intended for performing the granulation by dissolving sodium lauryl sulfate in a aqueous-alcoholic solution,

(d) granulating the mixture obtained in step b) in the presence of said liquid medium,

(e) drying the granular material thus obtained,

(f) sizing this granular material, and

(g) mixing said granular material with one or more lubricating agents and/or glidants and/or colorings and/or flavor modifiers.

12. A galenic formulation comprising fenofibrate as active principle, characterized in that it is capable of being obtained using a method according to any one of claims 1 to 11.

13. A medicine intended for oral administration, characterized in that it comprises an effective

quantity of a galenic formulation obtained using a method according to any one of claims 1 to 11.

14. The medicine as claimed in claim 13, characterized in that it is provided in the form of gelatin capsules, preferably made of gelatin.

15. The medicine as claimed in claim 13 or claim 14, characterized in that it comprises a fenofibrate dose of between 100 and 200 mg per therapeutic unit for the administration of one therapeutic unit per day.

16. The use of a liquid medium comprising a surfactant, water and a water-miscible alcohol for carrying out the granulation of fenofibrate or of a mixture comprising fenofibrate and one or more excipients.

17. The use of fenofibrate particles having a specific surface area of between 0.7 and 1.6 m^2/g and, preferably, in the region of 1 m^2/g for the preparation of a medicine intended for oral administration.

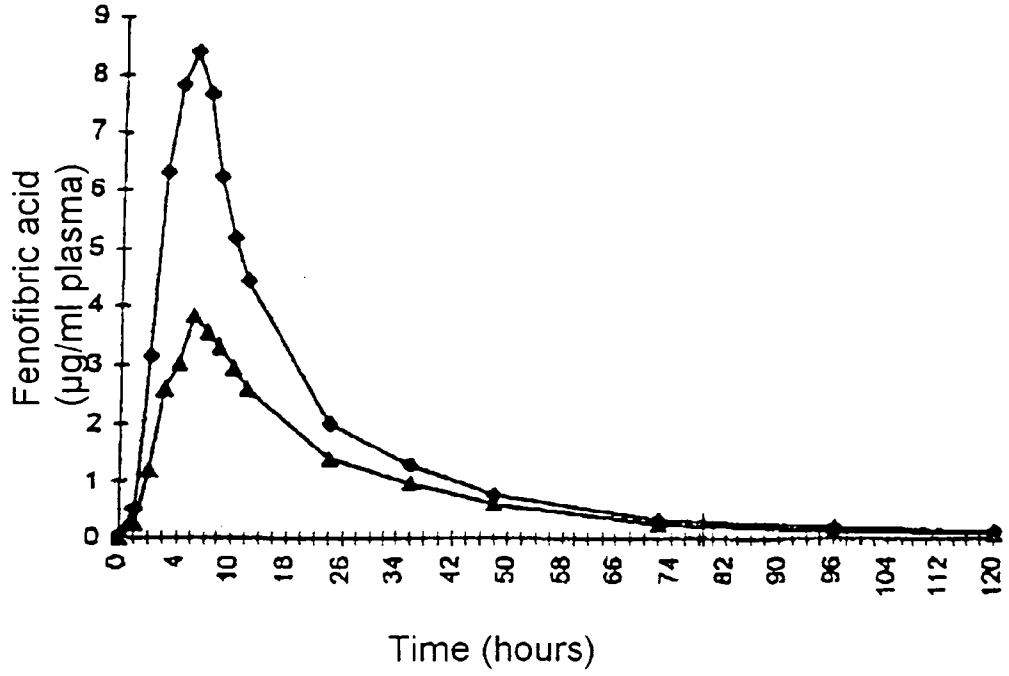
Fenofibric acid
(µg/ml plasma)
0
1
2
3
4
5
6
7
8
9
0
4
10
18
26
34
42
50
58
66
74
82
90
96
104
112
120
Time (hours)

FIG. 1