Abstract: The present invention relates to an oral pharmaceutical composition comprising the fenofibrate and a preparation method thereof. More specifically, the present invention is directed to an orally-administered pharmaceutical composition with improved bioavailability for treating hyperlipidemia and the preparation method thereof, where the solid dispersion is prepared by spray-drying a mixture of 100 parts by weight of fenofibrate dispersed in 20-200 parts by weight of water-soluble polymer, and 5-50 parts by weight of surfactant. The oral pharmaceutical composition has high bioavailability because of the increased solubility of amorphous fenofibrate. In addition, the spraying and drying can be performed at a time and low temperature, and thus a loss of activity of drug can be minimized, unlike the mechanical milling method.
A PHARMACEUTICAL COMPOSITION FOR ORAL COMPRISING FENOFIBRATE AND PREPARATION METHOD THEREOF

CROSS REFERENCE TO RELATED APPLICATION

The present application claims priority to and the benefit of Korean Patent application No. 10-2006-0072550 filed in the Korea Intellectual Property Office on August 1, 2006, the entire content of which is incorporated hereinto by reference.

FIELD OF INVENTION

The present invention relates to an oral pharmaceutical composition comprising fenofibrate which is called isopropyl-2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropionate as a chemical name and a preparation method thereof. More specifically, the present invention provides an oral pharmaceutical composition comprising the fenofibrate with an increased bioavailability, because fenofibrate is amorphous form, and in a dosage form of solid dispersion.

BACKGROUND OF THE INVENTION

Fenofibrate is one of therapeutic agents which are mostly used in worldwide for endogenous hypercholesterolaemia and hypertriglyceridemia in adult. The fenofibrate has a molecular structure of C_{20}H_{31}ClO_{4}, and a molecular weight of 360.84 g/mol, and is white powder. The fenofibrate has a low solubility in water in general. However, the fenofibrate is dissolved in methanol and ethanol partly, and is well dissolved in acetone, ether and benzene.

WO 01/80828 discloses an improved water-insoluble drug particle process, and more particularly a process for preparation of small particles containing a poorly water-soluble drug. The process comprises the steps of mixing at high shear an admixture of a poorly water soluble drug and one or more than one surface active substance, heating the mixture to temperature at or above the melting point of the poorly water soluble drug, and homogenizing said heated suspension. However, as...
disclosed in the process, the heating of drug to temperature at or above the melting point is not desired, because the heating disrupts the crystalline structure of the drug. When cooling the heated mixture, the structure of drug is changed to non-crystalline form or is recrystallized to a different isoform, thereby forming a different composition in physical and structural aspects.

EP 0 904 781 discloses a process of making a solid dispersion of fenofibrate to granules, and more specifically the process comprises the steps of melting the fenofibrate, blending the disintegrant into the molten fenofibrate, and solidifying the mixture. The solid disintegrant is polymer such as starch, croscarmellose sodium, sodium starch glycolate and cross-linked crospovidone (PVP). PVP is dissolved poorly in the molten fenofibrate and has a problem of phase compatibility, which was supported by M. T. Sheu et al, Int. J. Pharm. 1994, 103 (2), 137-146. In addition, because the fenofibrate is not compatible with PVP, the preparation method of a pharmaceutical composition by using melting and solidifying processes makes dispersion and composition be undesirable in granule of fenofibrate, thereby affecting the bioavailability of active materials. In addition, "co-melting" process requires a special equipment (see WO 2004/000279).

WO1998/031361 discloses a method of preparing a pharmaceutical composition including fenofibrate comprising the steps of suspending fenofibrate in micronized form in a solution containing hydrophilic polymer, solvent, and optionally surfactant to make a suspension, and spraying the suspension on inert support. The hydrophilic polymer is polyvinylpyrrolidone, and the inert support is lactose, and surfactant is sodium laurylsulfate. The preparation method was used widely, and improves solubility and bioavailability compared to the conventional method. However, the fenofibrate as an active agent must be micronized according to the complex processes for a long time, thereby reducing productivity and heat-stability of heat-labile drug in the micronizing process. In addition, the sodium laurylsulfate stimulates mucous membrane of gastro intestine disadvantageously.
SUMMARY OF THE INVENTION

To resolve the problems of the prior art, the object of the present invention is to provide a dosage form of solid dispersion of amorphous fenofibrate as poorly water-soluble therapeutic agent for hyperlipidemia by using the spray-drying method. Another object of the present invention is to provide orally-administered pharmaceutical composition with improved bioavailability and the preparation method thereof.

BRIEF DESCRIPTION OF THE DRAWING

A more complete appreciation of the invention, and many of the attendant advantages thereof, will be readily apparent as the same becomes better understood by reference to the following detailed description when considered in conjunction with the accompanying drawing, wherein:

Fig. 1 shows graphs of fenofibrate, solid dispersions of Example 2 and particles prepared by mechanical milling in Comparative Example 1 obtained by using X-ray Diffractometer to determine crystal structures of the fenofibrate.

Fig 2 is a graph showing the result of Comparative Dissolution test of fenofibrate and solid dispersions of Example 2.

Fig. 3 is a graph showing the result of Comparative Dissolution test of commercial drug and the compositions of Examples 6 to 7.

Fig. 4 shows a graph of particle diameter distribution of solid dispersion obtained by Example 2.

DETAILED DESCRIPTION

A more complete appreciation of the invention, and many of the attendant advantages thereof, will be readily apparent as the same becomes better understood by reference to the following detailed description.

To achieve the objects, the present invention provides a solid dispersion comprising an amorphous fenofibrate dispersed in drug carrier, and a oral
pharmaceutical composition for treating hyperlipidemia comprising the solid dispersion.

In addition, the present invention provides a method of increasing bioavailability, solubility, and/or dissolution rate of fenofibrate by preparing solid dispersion comprising an amorphous fenofibrate dispersed in drug carrier.

The present invention provides a method of preparing a solid dispersion comprising an amorphous fenofibrate dispersed in drug carrier.

Preferably, the solid dispersion is prepared by spray-drying a mixture of 100 parts by weight of fenofibrate dispersed in 20-200 parts by weight of a water-soluble polymer, and 5-50 parts by weight of a surfactant.

The pharmaceutical composition further comprises at least an additive selected from the group consisting of an excipient, a binder, a disintegrant, a plasticizer, a lubricant and a mixture thereof.

The present invention provides a method of preparing a solid dispersion comprising the steps of:

dissolving fenofibrate in an organic solvent, and mixing with 20-200 parts by weight of a water-soluble polymer and 5-50 parts by weight of a surfactant on the basis of 00 parts by weight of fenofibrate to produce a mixed solution, and

spray-drying the mixed solution to obtain a solid dispersion comprising an amorphous fenofibrate dispersed in a drug carrier.

In the method, the solid dispersion further comprises at least one selected from the group consisting of excipient, binder, plasticizer, disintegant, and lubricant.

The present invention will be described in more detail.

To improve a bioavailability of a poorly water-soluble drug, fenofibrate, fenofibrate, water-soluble polymer and surfactant is dissolved and mixed in an organic solvent and spray-dried to make fenofibrate be amorphous, thereby increasing solubility of fenofibrate.

The present invention using the solid dispersion can make the particle still smaller and more uniform particle than a method of micronizing the drug by
mechanical pulverizing method prior art, and is an effective method for making a
drug be amorphous. In general, the term "solid dispersion" means at least an active
agent dispersed in solid state in an inert support or a matrix.

When the mechanical pulverizing method is used, the crystalline property of
drug remains after pulverizing. However, in a spray-drying method, the
amorphousness can be achieved sufficiently by appropriately controlling the
composition of drug and hydrophilic polymer, and the condition of spray-drying. In
the mechanical pulverizing method, a large amount of heat generated at pulverizing
process deteriorates the crystalline property of drug disadvantageously. The spray-
drying method does not change the crystalline property of drug without affecting the
drug by making a particle with evaporation of optimized temperature and operating
condition.

In particular, the fenofibrate which has a low melting point (79-82 °C) and is
poorly water soluble dissolved in an organic solvent, and dried under the condition
which is optimal for making a particulate without changing the melting point, to
produce a solid dispersion. Thus, compared to the conventional method, the present
invention provides an improved productivity, stability, solubility and bioavailability.

The reduced particle size of water-insoluble drug obtained by pulverizing
increases theoretically soluble surface area, but aggregates the particles together so as
to make the drug dissolve difficultly. Thus, there is suggested a process of preparing
dispersion with partly increased solubility in solid dispersion and a process of
maximizing the contact surface of solute and solubility of support. A poorly water
soluble drug is dispersed in a polymer at a molecular level to achieve optimization for
oral administration.

The present invention relates to a solid dispersion comprising an amorphous
fenofibrate (hereinafter, solid dispersion), which is prepared by mixing a fenofibrate,
a water-soluble polymer, a surfactant and an organic solvent, and then spray-drying.

The particle diameter of fenofibrate in the solid dispersion of the present
invention is 1 to 220 μm. The solid dispersion shows 5 -15 μg/mL of solubility of
fenofibrate at pH 6.5 to 7.5 and at 25°C, which is 25 times as high as fenofibrate untreated according to the present invention. When the dissolution rate of pharmaceutical composition comprising the solid dispersion is measured by the dissolution test at pH 6.5 to 7.5 and at 25°C according to the Paddle dissolution method, the initial dissolution rate for 30 minutes is about 72 w/w% (percentage of dissolved drug amount to initial drug amount).

The water-soluble polymer includes cellulose polymers, polyalkenylpyrrolidon, polyalkylene glycol, and metaacrylate copolymer. The examples of water-soluble polymer being capable of mixing with fenofibrate are at least one selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxybutylcellulose, hydroxypentylcellulose, hydroxypropylalkylcellulose, polyvinylpyrrolidone, polyvinylalcohol and a mixture thereof. The amount of water-soluble polymer is 20 to 200 parts by weight on the basis of 100 parts by weight of fenofibrate. In the present invention, the water-soluble polymer is used in a small amount relatively, thereby reducing the weight of composition and causing inconvenient administration.

If the amount of water-soluble polymer is less than 20 parts by weight, the structure of fenofibrate cannot be changed to amorphous form, and thus has low solubility. If the amount of water-soluble polymer exceeds 200 parts by weight, increased size and volume of preparation causes inconvenience for administration.

The surfactant can be amphoteric, non-ionic, cationic, and anionic, but not limited thereto. The surfactant includes pH-dependent hydrophilic polymer. The examples of surfactant are at least one selected from the group consisting of monooleic ester, monolauryl ester, monopalmitic ester, monostearic ester, polyoxyethylene, sorbitan ester, sodium dioctylsuccinate, lecitin, stearylalcohol, cetostearylalcohol, cholesterol, polyoxyethylen ricin oil, polyoxyethylene glyceride fatty acid, polyoxyethylene-polyoxypropylene block copolymer (example, poloxamer) and polyethyleneglycol derivatives (for example, cremophor). The
amount of surfactant is 5 to 50 parts by weight, and preferably 10 to 50 parts by weight on the basis of 100 parts by weight of fenofibrate in consideration of drug solubility improvement and weight of solid dispersion. If the surfactant is contained less than 5 parts by weight, it does not provide desirable solubility. If the amount of surfactant exceeds 50 parts by weight, the amorphous property of produced solid dispersion is reduced and weight of solid dispersion must increase.

The organic solvent used for preparation of the solid dispersion can be various solvent being capable of dissolving the fenofibrate, and the amount is not limited because it is used for dissolve an active agent, surfactant and water-soluble polymer. Moreover, the preferred examples of the solvent are at least one selected from the group consisting of ethanol, dichloromethane, acetone, and methanol. More preferably, the solvent is a mixture of ethanol and dichloromethane in the ratio of 1:1(v/v).

The solid dispersion is prepared by spray-drying method, and more specifically can be performed as below.

In a preferred embodiment, fenofibrate, hydroxypropylmethylcellulose, and surfactant such as Poloxamer or Cremophor are dissolved in an organic solvent to obtain a mixed solution (8%(w/v)), and then dried with a spray-drier to produce solid dispersion. That is, in a spray-drying process, after setting an optimal temperature for making particle without affecting a melting point of fenofibrate, the mixed solution is sprayed and immediately dried under the optimal condition the present invention. In the combined spraying and drying process of the present invention, spraying and drying is carried out simultaneously, and thus quick drying deprives the crystal of an sufficient time of rearranging. Thus, the amorphous fenofibrate is obtained is solid dispersion.

More preferably, the spray-drying is carried out with a spray-drier under the condition of a feeding temperature of 75 - 77 °C, chamber temperature of 55 - 58 °C, disc rotating number of 7,000 - 10,000 rpm/min and a fluid rate of 16 - 20 kg/h.

The produced solid dispersion can be granulated to dry granules before being
prepared for a pharmaceutical composition.

In addition, the present invention provides an oral pharmaceutical composition comprising the solid dispersion.

The term, "pharmaceutical composition" is referred to a pharmaceutical composition comprising solid dispersions of fenofibrate as an active agent. The oral pharmaceutical composition further includes pharmaceutically-acceptable additives such as liquid or solid carrier, and excipient in general. Preferably, the composition includes 30.0 to 70.0 wt% of the solid dispersion; and 30.0 to 70.0 wt% of at least an additive selected from the group consisting of excipient, disintegrant, plasticizer, binder, and lubricant. If the amount of solid dispersion is less than 30 wt%, the weight of composition increases excessively, thereby causing inconvenience for administration. If the amount exceeds 70 wt%, the sufficient dissolution rate cannot be achieved.

The is at least one selected from the group consisting of lactose, white sugar, glucose, fructose, mannitol, corn starch, potato starch, wheat starch, pregelatinized starch, microcrystalline cellulose or cellulose derivatives, dextrin, monobasic calcium phosphate, dibasic calcium phosphate, calcium carbonate, polacrilin potassium, acetic acid, ammonium carbonate, ammonium phosphate, boric acid, lactic acid, citric acid, potassium phosphate, sodium phosphate, sodium acetate, sodium citrate, sodium lactate, ascorbic acid, and ascorbyl palmitate. The amount of excipient is 20.0 to 60.0 wt% in reference to total content of additives contained in the pharmaceutical composition.

The disintegrant is at least one selected from the group consisting of microcrystalline cellulose, low-substituted hydroxypropyl cellulose, sodium croscarmellose, sodium starch glycolate, sodium carboxymethylcellulose, calcium carboxymethylcellulose, crospovidon and a mixture thereof. The amount of disintegrant is 0.1-20.0 wt% in reference to total content of additives contained in the pharmaceutical composition.

The plasticizer is at least one selected from the group consisting of colloidal
anhydrous silica, silicon dioxide precipitate, magnesium stearate, stearic acid, polyethylene glycol (PEG), and a mixture thereof. The amount of plasticizer is 0.1-3.0 wt% in reference to total content of additives contained in the pharmaceutical composition.

The dosage form of oral pharmaceutical composition can be solid dosage forms, liquid dosage form, and etc. The oral pharmaceutical composition is formulated to the oral dosage forms such as tablet, granule, powder, pill, and dry syrup, and more preferably to table or capsule for oral administration.

The preferred formulation is a unit form of administration. The composition is divided into unit administration form containing an active agent in a suitable amount. The unit administration form is a wrapped formulation containing a divided amount of active agent, for examples tablet, capsule or powder wrapped in vial or ampoule. More preferably, the formation is in a capsule form. The effective dosage is 160mg per day.

The present invention is further explained in more detail with reference to the following examples. These examples, however, should not be interpreted as limiting the scope of the present invention in any manner.

**EXAMPLES 1-5**

**Preparation of solid dispersion according to spray-drying method**

The solid dispersions containing fenofibrate according to the present invention were prepared in a composition of Table 1.
Fenofibrate was dissolved in a mixture of ethanol and dichloromethane in a ratio 1:1(v/v), and added with hydroxypropylmethylcellulose as a water-soluble polymer to obtain 8%(w/v) of mixed solution. The mixed solution was added with Poloxamer188, Poloxamer 407, CremophorRH-40, and Soybean Lecithin as a surfactant, respectively to produce each solution. Each solution was spray-dried with disc-typed spray-drier to obtain a solid suspension where fenofibrate was dispersed in hydroxypropylmethylcellulose. The spray-drying was performed under the condition of feed temperature of 75 - 77 °C, a chamber temperature of 55 - 58 °C, disc rotating number of 7,000 - 10,000 rpm/min, and fluid rate of 16 - 20 kg/h.

**COMPARATIVE EXAMPLES 1 - 4**

Preparation of mixture particle by performing mechanically pulverizing with Freezer-mill

The mixture particles were made by mechanical pulverization in a composition of Table 2.

**TABLE 1**

<table>
<thead>
<tr>
<th>Raw material</th>
<th>Weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example 1</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>160</td>
</tr>
<tr>
<td>HPMC2910</td>
<td>160</td>
</tr>
<tr>
<td>Poloxamer188</td>
<td>-</td>
</tr>
<tr>
<td>Poloxamer407</td>
<td>-</td>
</tr>
<tr>
<td>CremophorRH-40</td>
<td>-</td>
</tr>
<tr>
<td>Soybean Lecithin</td>
<td>-</td>
</tr>
<tr>
<td>Sum</td>
<td>320</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Raw material</th>
<th>Comparative Example 1</th>
<th>Comparative Example 2</th>
<th>Comparative Example 3</th>
<th>Comparative Example 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>HPMC2910</td>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>Poloxamer188</td>
<td>160</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Poloxamer407</td>
<td>160</td>
<td>160</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CremophorRH-40</td>
<td>160</td>
<td>-</td>
<td>160</td>
<td>-</td>
</tr>
<tr>
<td>Soybean Lecithin</td>
<td>160</td>
<td>-</td>
<td>-</td>
<td>160</td>
</tr>
<tr>
<td>Sum</td>
<td>336</td>
<td>336</td>
<td>336</td>
<td>336</td>
</tr>
</tbody>
</table>

Fenofibrate, hydroxypropylmethylcellulose as a water-soluble polymer and
each additive were mixed, and frozen for 5 minutes and pulverized for 5 minutes with a Freezer-mill. The prepared sample was dehydrated with a vacuum pump for a day in consideration of the hygroscopic property of water-soluble polymer contained in the sample. These comparative examples are performed by a simple mixing and pulverizing process without using an organic solvent.

EXAMPLES 6 to 7

Preparation of table containing fenofibrate solid dispersion

The fenofibrate solid dispersion of Example 2 was granulated according to dry granulating method, well mixed with microcrystalline cellulose, lactose and Crospovidone in a same amount, mixed colloidal anhydrous silica as a plasticizer, Magnesium stearate as a lubricant, and then produced to tablet.

The fenofibrate solid dispersion was granulated with Crospovidone as a disintegrant for Example 6, but without adding Crospovidone for Example 7.

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMPLE 6</td>
</tr>
<tr>
<td>solid dispersion</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
</tr>
<tr>
<td>Lactose</td>
</tr>
<tr>
<td>Crospovidone</td>
</tr>
<tr>
<td>Colloidal anhydrous silica</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td>sum</td>
</tr>
</tbody>
</table>

| EXAMPLE 7 | Component | Content (mg) |
| solid dispersion | | 336.0 |
| Microcrystalline cellulose | | 75.0 |
| Lactose | | 60.0 |
| Crospovidone | | 85.0 |
| Colloidal anhydrous silica | | 6.0 |
| Magnesium stearate | | 5.0 |
| sum | | 567.0 |

TEST EXAMPLE 1

Comparison of Solubility

The solid dispersion containing fenofibrate obtained in Examples 1 to 5, and untreated fenofibrate were tested for solubility. To measure the solubility, a solution (pH 6.8) was made by 250 mL of 0.2 mol/L monobasic potassium solution as a pH adjusting agent, 118 mL of 0.2 mol/L sodium hydroxide solution, and water to be volume of 1000 mL. The obtained solution is transparent and colorless. The solubility was measured by adding an excessive amount of solid dispersion to the solution (pH 6.8), agitating at 25°C for 2 hours, sonicating for 2 hours, filtering with 0.45 µm
PVDF syringe filter, and then analyzing the filtrate with HPLC. The analyzed result is shown in Table 4.

Column: Xterra™ RP 18 5µm, 4.6 x 150mm Column

Mobile phase: acetonitrile: refined water = 7 : 3 (v/v, adjusted to pH 2.5)

Feed amount: \( \mu \text{g} \)

Fluid rate: 1.0mL/min

Detection: 286nm

<table>
<thead>
<tr>
<th>classification</th>
<th>Dissolution rate(µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw material</td>
<td>0.2</td>
</tr>
<tr>
<td>Example 1</td>
<td>5.2</td>
</tr>
<tr>
<td>Example 2</td>
<td>9.9</td>
</tr>
<tr>
<td>Example 3</td>
<td>8.3</td>
</tr>
<tr>
<td>Example 4</td>
<td>10.6</td>
</tr>
<tr>
<td>Example 5</td>
<td>5.9</td>
</tr>
</tbody>
</table>

As described in Table 4, the solubility of solid dispersion of the present invention was 25 times or 50 times or higher than raw material. Thus, the present invention provides an active agent with increased solubility, resulting in improved bioavailability.

**TEST EXAMPLE 2**

XRD pattern analysis of raw material and solid dispersion

The crystal structures of fenofibrate, and the solid dispersions obtained by Example 2 and Comparative Example 1 were determined by using X-ray Diffractometer (Rigaku), and the results were shown in Fig. 1. X-ray diffraction type was measured by sufficiently laminating an amount of sample on transparent glass slide with 0.3mm of width so as to prevent the orientation from generating, and was detected at interval 0.5°C of in the range of 5-40°C. The X-ray diffraction type was measured under the condition of voltage 40kv, current 70mA, and wavelength 1.542Å. As an analyzing result, a crystalline peak of untreated fenofibrate was very high and sharp, which meant a high crystalline property. For the mixture particle by performing mechanically pulverizing with Freezer-mill in the Comparative Example
1, a crystalline peak was lower than that of the untreated fenofibrate, but shown good crystalline property. On the other hand, for the solid dispersion of Example 2, as the crystalline peak is low significantly and very low crystalline property, the solid dispersion shown increased solubility and bioavailability.

**TEXT EXAMPLE 3**

Comparative dissolution test

The untreated fenofibrate and the solid dispersion of Example 2 were tested for the comparative dissolution according to second dissolution method (paddle dissolution method) described in Korea Pharmacopeia. In the dissolution test, the content of fenofibrate was performed by quantitative analysis using a dissolving solution (pH 6.8, added by 1% Tween 80) at a paddle speed of 50 rpm with HPLC. The result was shown in Fig. 2. As shown in Fig. 2, the dissolution rate of solid dispersion obtained by EXAMPLE 2 increased notably.

**TEXT EXAMPLE 4**

Comparative Dissolution Test

Tablets obtained by Examples 6 to 7, and a commercial drug (Lipidil supra\textsuperscript{TM}, Green cross. Co. Ltd, Republic of Korean) were tested for the comparative dissolution according to second dissolution method (paddle dissolution method) described in Korea Pharmacopeia. In the dissolution test, the content of fenofibrate was performed by quantitative analysis using a dissolving solution (pH 6.8, added by 15% Tween 80) at a paddle speed of 50 rpm with HPLC. The result was shown in Fig. 3 and Table 5.

**TABLE 5 (unit: wt%)**

<table>
<thead>
<tr>
<th></th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>30 min</th>
<th>1 hour</th>
<th>2 hour</th>
<th>4 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 6</td>
<td>34.4</td>
<td>50.6</td>
<td>59.1</td>
<td>71.9</td>
<td>79.7</td>
<td>84.0</td>
<td>85.5</td>
</tr>
<tr>
<td>Example 7</td>
<td>27.1</td>
<td>41.2</td>
<td>49.2</td>
<td>61.5</td>
<td>71.3</td>
<td>78.6</td>
<td>83.2</td>
</tr>
<tr>
<td>Commercial drug</td>
<td>12.8</td>
<td>34.1</td>
<td>45.9</td>
<td>62.3</td>
<td>70.1</td>
<td>80.5</td>
<td>84.0</td>
</tr>
</tbody>
</table>

As shown in Fig. 3 and Table 5, the compositions of Examples 6 to 7
suggested the dissolution rate of the present invention equivalent to the commercial
drug.

The present invention provides an orally-administered pharmaceutical
composition prepared by dissolving a poorly water-soluble fenofibrate,
hydroxypropylmethylcellulose, surfactant such as Poloxamer or Cremophor in an
organic solvent, and spray-drying the drug, water-soluble polymer and surfactant in a
short time. Thus, the composition can be prepared in a short time, and have an
amorphous form with improved bioavailability advantageously. In addition, because
amorphous solid suspension of the present invention is mixed with appropriated
carrier and granulated, the conventional granulating process can be applied for the
present invention. Thus, the present invention can be a simple and convenient process,
be commercialized easily and economically.
WHAT IS CLAIMED IS:

1. A solid dispersion comprising an amorphous fenofibrate dispersed in a water-soluble polymer.

2. The solid dispersion of Claim 1, wherein 100 parts by weight of fenofibrate is dispersed in 20-200 parts by weight of the water-soluble polymer, and 5-50 parts by weight of a surfactant.

3. The solid dispersion of Claim 1, wherein the solid dispersion is prepared by spray-drying a mixture of 100 parts by weight of fenofibrate dispersed in 20-200 parts by weight of water-soluble polymer, and 5-50 parts by weight of surfactant in an organic solvent.

4. The solid dispersion of Claim 1, wherein the solubility of fenofibrate in the solid dispersion is 5 - 15 μg/ml at pH 6.5 to 7.5, and at 25°C.

5. The solid dispersion of Claim 1, wherein the particle diameter of solid dispersion is 1 to 220 μm.

6. The solid dispersion of Claim 1, wherein the water-soluble polymer is cellulose polymer, polyalkenylpyrrolidone, polyalkylene glycol or methacrylate copolymer.

7. The solid dispersion of Claim 6, wherein the water-soluble polymer is at least one selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxybutylcellulose, hydroxypentylcellulose, hydroxypropylbutylcellulose, hydroxypropylalkylcellulose, polyvinylpyrrolidone, polyvinylalcohol and a mixture
8. The solid dispersion of Claim 2, wherein the surfactant is at least one selected from the group consisting of monooleic ester, monolauryl ester, monopalmitic ester, monostearic ester, polyoxyethylene, sorbitan ester, sodium dioctylsuccinate, lecitin, stearylalcohol, cetostearylalcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene glyceride fatty acid, polyoxyelthylene-polyoxypropylene block copolymer, polyethyleneglycol derivatives and a mixture thereof.

9. An oral pharmaceutical composition comprising a solid dispersion containing an amorphous fenofibrate dispersed in a water-soluble polymer according to any one of claim 1 to claim 8.

10. The oral pharmaceutical composition of Claim 9, wherein the composition further comprises at least an additive selected from the group consisting of excipient, disintergrant, plasticizer, binder, and lubricant, and the solid dispersion and the additives are contained in an amount of 30 to 70 weight %, and 70 to 30 weight % respectively.

11. The oral pharmaceutical composition of Claim 10, wherein the excipient is at least one selected from the group consisting of lactose, white sugar, glucose, fructose, mannitol, corn starch, potato starch, wheat starch, pregelatinized starch, microcrystalline cellulose or cellulose derivatives, dextrin, monobasic calcium phosphate, dibasic calcium phosphate, calcium carbonate, polacrilin potassium, acetic acid, ammonium carbonate, ammonium phosphate, boric acid, lactic acid, citric acid, potassium phosphate, sodium phosphate, sodium acetate, sodium citrate, sodium lactate, ascorbic acid, ascorbyl palmitate, and a mixture thereof.

12. The oral pharmaceutical composition of Claim 10, wherein the disintegrant is...
at least one selected from the group consisting of microcrystalline cellulose, low-substituted hydroxypropyl cellulose, sodium croscarmellose, sodium starch glycolate, sodium carboxymethylcellulose, calcium carboxymethylcellulose, crospovidon and a mixture thereof.

13. The oral pharmaceutical composition of Claim 10, wherein the plasticizer is at least one selected from the group consisting of colloidal anhydrous silica, silicon dioxide precipitate, magnesium stearate, stearic acid, polyethyleneglycol (PEG), and a mixture thereof.

14. The oral pharmaceutical composition of Claim 10, wherein the lubricant is at least one selected from the group consisting of magnesium stearate, stearic acid, zinc stearate, calcium stearate, talc, sodium stearyl fumarate, silicone dioxide, colloidal silicon dioxide and a mixture thereof.

15. The oral pharmaceutical composition of Claim 9, wherein the dosage form of pharmaceutical composition is tablet, capsule, granule, powder, pill, or dry syrup.

16. A method of preparing a solid dispersion comprising the steps of:

dissolving fenofibrate in an organic solvent, and mixing with 20-200 parts by weight of a water-soluble polymer and 5-50 parts by weight of a surfactant on the basis of 100 parts by weight of fenofibrate to produce a mixed solution, and

    spray-drying the mixed solution to obtain a solid dispersion comprising an amorphous fenofibrate.

17. The method of preparing a solid dispersion of Claim 16, wherein the spray-drying is performed with a disc-typed spray-dryer which is set to a feed temperature of 75 to 77 °C and a chamber temperature of 55 to 58 °C.
FIG. 2

- Example 2
- Untreated fenofibrate
### A. CLASSIFICATION OF SUBJECT MATTER

*A61K 9/14(2006.01)i, A61K31/216(2006.01)i*

According to International Patent Classification (IPC) or to both national classification and IPC.

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS (Key words  fenofibrate, solid dispersion, hydrophilic polymer, surfactant)

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<td>X</td>
<td>WO 2006-060817 A1 (ABBOTT LABORATORIES) 8 Jun 2006</td>
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  *&* document member of the same patent family

Date of the actual completion of the international search

14 NOVEMBER 2007 (14 11 2007)

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