Title: **MULTIPLE DOSAGE FORMS COMPRISING FENOFRIBRATE OR FENOFRIBRIC ACID IN COMBINATION WITH HMG CO A REDUCTASE INHIBITORS SUCH AS STATINS**

Abstract: The present invention relates to pharmaceutical formulations comprising a HMG-CoA reductase enzyme inhibitor and a fibric acid derivative in order to be used in the treatment of hyperlipoproteinemia, hypertriglyceridemia, hypercholesterolemia, myocardial infarction and stroke and/or related diseases.
MULTIPLE DOSAGE FORMS

Background of the Invention

The present invention relates to pharmaceutical formulations comprising a HMG-CoA reductase enzyme inhibitor and a fibric acid derivative in order to be used in the treatment of hyperlipoproteinemia, hypertriglyceridemia, hypercholesterolemia, myocardial infarction and stroke and/or related diseases.

The Prior Art

Cardiovascular disease is one of the leading causes of death in the world. One of the most significant factors for these diseases is total/high density lipoprotein (HDL) cholesterol level. Thus, new developments are required in the treatment of dislipidemia. In line with this need, researchers have found that use of various cardiovascular active agents in combination provides a more effective treatment method. Fibrate and statin combinations can be given as an example of these combinations.

Use of fibrate and fibric acid derivatives with statins was firstly disclosed in the article titled "Potential use of fenofibrate and other fibric acid derivatives in the clinic" in 1987. In said publication, it is indicated that use of fenofibrate and other fibric acid derivatives with HMG-CoA enzyme reductase inhibitors in combination helps control triglyceride levels in blood and it is more effective than use of the active agents alone. In addition to this publication, use of the two active agent group together is explained in the literature as seen below:


Atorvastatin (Formula I), which has the chemical name (R, <5i?)-2-(4-fluoro-phenyl)- β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4- [(phenylamino)carbanoyl]- 1H-pyrrol- 1-heptanoic acid, is a HMG CoA reductase inhibitor firstly described in the patent numbered EP409281 Bl.
Another HMG CoA reductase inhibitor rosuvastatin, which has the chemical name
(3i?,5S,6E)-7-[4-(4-fluorophenyl)-6-(l-methylethyl)-2[methyl(methylsulphonyl)amino]-5-
pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, is a HMG CoA enzyme inhibitor displayed in
formula (II):

It is indicated in the patent numbered US5260440 that rosuvastatin that is displayed in
formula (I) inhibits the activation of the enzyme named HMG-CoA reductase which is
responsible for cholesterol synthesis in the body and prevents cholesterol formation and it is
effective in the treatment of cardiovascular diseases such as hypercholesterolemia,
hyperlipoproteinemia and atherosclerosis.

Fenofibrate, which has the chemical name 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl -
propanoic acid, 1- methylethyl ester, is a fibric acid derivative lipid regulating agent firstly
disclosed in the patent numbered US4058552 (A):
Fenofibrate starts its action by being hydrolyzed to fenofibric acid and when considered from this aspect, it is a prodrug. It is used in the treatment of lipid diseases such as type IV and type V hyperlipoproteinemia which are related with extremely high levels of serum triglyceride and very high density lipoprotein (VHDL). It has been seen in fenofibrate treatments that triglyceride levels decrease approximately at 30%. Its non-micronized form has been used in the treatment of type IIa, type lib and type IV dislipidemia in various countries for more than 10 years. It is produced in micronized form in order to increase absorption and provide use of a single dose per day. It is hardly dissolved in water or does not dissolve at all.

There exist various documents in the prior art on use of fibric acid derivatives with statins. However, when these documents are examined, it is seen that statin group active agents easily disintegrate affected by external factors such as humidity, light, and this poses serious obstacles in development of stable pharmaceutical formulations and combinations. Both rosvastatin and atorvastatin are transformed into lactone as a result of "intramolecular esterification" reaction which occurs between carboxylic acid in its structure and hydroxyl groups on β and δ carbons of this carboxylic acid. These reactions take place in acidic environment and basic agents cause the reaction to be reversed. Major degradation products (3R, 5S) produced as a result of disintegration of statins are lactones and oxidation products. This feature reduces the stability of atorvastatin and therefore shortens its shelf life.

Solutions developed aiming to disintegration of statins in acidic environment are about keeping pH of the environment neutral and even basic, if possible. For instance, use of calcium, magnesium or lithium ions in order to provide stability of pharmaceutical formulations comprising atorvastatin.
However, as indicated in the patent numbered WO0035425, use of much basic agents in the formulations causes regional irritation in the digestive tract.

On the other hand, the fact that both active agents have distinctive problems brings about the necessity to solve these problems in the most effective way in the formulations to be developed. For instance, intake of fenofibrate, which has quite low solubility and thus bioavailability, with meals improves its bioavailability at 35%. In contrast, bioavailability decreases at 70% when statin group active agents are taken on a full stomach. To this respect, these two active agents has to be formulated such that they have different release characteristics in the formulations.

The application numbered WO 2006/084474 discloses a layered dosage form comprising fenofibrate and a HMG-CoA reductase enzyme inhibitor as the active agent. In scope of this application, two active agents are formulated separately and prepared in layered tablet form. However, in a formulation prepared this way, it is not possible to formulate the active agents such that they can provide different release characteristics.

The patent numbered WO 2005/034908 defines fenofibrate and statin formulations combined in a single dosage form. However, statins tend to be oxidized and disintegrate; therefore it is rather difficult to combine them with another active agent in a single dosage form. At the same time, combining them in a single dosage form does not enable to provide the required characteristics as the two active agents have different release characteristics.

Hence, neither the pharmaceutical formulations comprising statin alone nor the combinations composed of statin and one or more active agents can be produced effectively.

Therefore, there is need for formulations with reduced side effects and high bioavailability in which the both active agents can remain stable. The techniques related to formulation of the two active agents together in the prior art cannot be applied effectively due to stability and solubility problems they have.

In line with this need, the inventors have solved these problems by designing multiple dosage forms having different release characteristics which comprise at least one HMG CoA reductase enzyme inhibitor and fenofibrate and/or fenofric acid. By formulating the two active agents independently in separate dosage forms, drug-drug interaction is minimized; therefore the distinctive problems of the two active agents can be solved effectively. At the
same time, having at least one of the active agents in fast-release form causes the bioavailability of the combination product to be improved.

The term "HMG CoA reductase inhibitor" used throughout the text refers to rosuvastatin, atorvastatin, simvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin and/or their pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or combinations thereof. HMG CoA reductase inhibitor used in the formulations of the present invention are preferably rosuvastatin and/or atorvastatin.

The terms "atorvastatin", "fenofibrate and/or fenofibric acid" and "rosuvastatin" used throughout the text comprise pharmaceutically acceptable salts such as choline fenofibrate, atorvastatin calcium, rosuvastatin calcium; hydrates, enantiomers, racemates, esters, polymorphs of these active agents and/or combinations thereof.

**Detailed Description of the Invention**

The present invention relates to pharmaceutical formulations designed based on the synergistic effect that use of fenofibrate and/or fenofibric acid with statins would induce. Said formulations are presented as multiple dosage forms produced by formulating the two active agents separately. The excipients used in the formulations are selected such that the interaction between them and the active agents is minimized and the formulations are prepared accordingly.

Multiple dosage forms prepared this way can be produced such that the two active agents can have different and/or the same release characteristics.

As mentioned above, both fenofibrate and/or fenofibric acid, and statin group active agents hardly dissolve in water. It is known that it is very difficult to develop a pharmaceutical form having high dissolving speed of a hardly dissolving drug.

Yet, the inventors have succeeded to produce multiple dosage forms comprising fenofibrate and/or fenofibric acid with statin in which at least one of the active agents have fast dissolving characteristics in scope of the present invention.

The expression "multiple dosage forms" used here refers to oral dosage forms produced by combining at least two unit dosage forms having different and/or the same physical features.

The unit dosage forms of the present invention can be in the form of granule, powder, pellet,
tablet, mini tablet, micro tablet, capsule or combinations thereof. The unit dosage forms prepared are combined preferably in a gelatin capsule in order to prepare multiple dosage forms according to the present invention.

In general, multiple dosage forms are more advantageous compared to single dosage forms such as pellets, micro tablets, granules, coated tablets. Multiple dosage forms are dispersed in gastrointestinal tract homogeneously and transmitted from the stomach to the intestines. By this way, both effective dispersion of the active agents in the stomach is ensured and the drug-food interaction is minimized.

Unit dosage forms of the present invention are preferably in micro tablet, granule and/or pellet form and they have pharmaceutically similar contents as known tablet and capsule dosage forms. Tablets, granules and/or pellets can be coated with protective coating, enteric coating, film coating and/or coatings that can enable different release characteristics afterwards. At least one active agent comprised in the formulations is in fast-release form.

Furthermore, preparation of the unit dosage forms of fenofibrate and/or fenofibric acid and statins having different physical features and contents reduced the interaction of these two active agents both with each other and with other pharmaceutically acceptable excipients. Thus, the problems of the active agents are solved effectively and efficiency of the combined drug is improved.

The term "micro tablet" used throughout the text refers to tablets, round ones of which have a radius smaller than 10 mm or the longest one of which is smaller than 10 mm.

The present invention in the form of micro tablet, granule and/or pellet contained in gelatin capsules comprises an effective amount of fenofibrate and/or fenofibric acid, at least one statin group active agent, coating materials so as to provide different release characteristics, polymers and pharmaceutically acceptable excipients. Gelatin capsules used here can be hard or soft.

In an aspect, the present invention comprises statin and fenofibrate and/or fenofibric acid formulations which are prepared such that they have sufficient stability.

In another aspect, the present invention comprises statin and fenofibrate and/or fenofibric acid formulations which have different or similar release characteristics.
In another aspect, the present invention relates to multiple dosage forms comprising fenofibrate and/or fenofibric acid and a statin group active agent having fast release characteristics.

In another aspect, the present invention comprises a production method designed in order to minimize the interaction of fenofibrate and/or fenofibric acid and statin group active agents both with each other and with other pharmaceutically acceptable excipients.

In one aspect, the present invention comprises formulations which can be formulated without causing abdominal tenderness in patients.

The invention further comprises formulating the active agents separately in order to minimize drug-drug interaction and preparing the two different formulations by combining them in a capsule.

Atorvastatin used in the formulations according to the present invention is preferably atorvastatin calcium trihydrate and it is preferably in crystalline form polymorphically.

Rosuvastatin used in the formulations according to the present invention is preferably in the form of a pharmaceutically acceptable salt thereof and it is preferably in amorphous form polymorphically.

Fenofibrate and/or fenofibric acid used in the formulations of the present invention is preferably in the form of a pharmaceutically acceptable salt of fenofibric acid; more preferably used salt is cholin fenofibrate.

The particle size of fenofibrate and/or fenofibric acid used in the formulations of the present invention is preferably in the range of 1-500 μη, more preferably in the range of 1-300 μη, even more preferably in the range of 1-200 μη.

In another aspect, the present invention relates to multiple dosage forms comprising fenofibrate and/or fenofibric acid and statin, at least one of which has fast release characteristics.

The formulations of the present invention can comprise pharmaceutically acceptable components such as additives selected from binders, disintegrants, viscosity enhancing components, filling materials, drying agents, lubricants, diluents, binders, glidants,
surfactants, wetting agents, coating agents designed so as to provide various release characteristics, anti-adhesive agents, solvents, sweeteners and excipients.

In the formulations of the present invention; antioxidants, chelating agents, alkalinizing agents and photoprotective agents can be used as the stabilizer. The stabilizer/stabilizers used in the formulations of the present invention are preferably alkalinizing agents and they can be selected from a group comprising alkaline metal salts such as sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; alkaline earth metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, calcium acetate, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulfate, magnesium acetate, magnesium silicate, magnesium aluminate; and organic compounds such as primary, secondary and tertiary amines, cyclic amines, N,N'dibenzylethylendiamine, dietanolamine, ethylendiamine, meglumine, tromethamol, monosodium glutamate, polacrilline sodium, sodium alginate and/or pharmaceutically acceptable hydrates and/or derivatives thereof.

The filling materials used in the invention comprise one or more components selected from a group comprising lactose, sugar, starch, modified starch, mannitol, sorbitol, inorganic salts, microcrystalline cellulose, cellulose, calcium sulfate, xylitol and lactitol.

The disintegrant used in the present invention enables the dosage form to disperse in water easily and rapidly, and it is significant from this aspect. The disintegrants can be selected from a group comprising polymers having high dispersing characteristics for instance cross-linked hydroxypropyl cellulose, polyvinylpyrrolidone, high molecular weight polymers, microcrystalline cellulose, sodium starch glycolate, croscarmellose sodium, povidone; the products known under the trademarks Crospovidone®, Polyplasdone® or colloidal silicon dioxide, alginic acid, sodium alginate, corn starch.

The surfactants used in the present invention are selected from a group comprising hydroxypropyl methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, vinyl acetate, sodium lauryl sulfate, dioctyl sulfosuccinate, gelatin, casein, lecithin, dextran, sorbitan esters, polyoxy ethylene alkyl ethers, polyethylene glycols, polyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethyl cellulose calcium, carboxy methyl cellulose sodium, triethanolamine, polyvinyl alcohol, hydroxy propyl methyl cellulose phthalate.
Anti-adhesive agents of the present invention are used in order to prevent the mixture comprising active agents to adhere onto device and machine surfaces and create rough surfaces. The substances used for this purpose comprise one or more components selected from a group comprising talc, colloidal silicone dioxide (Aerosil, Syloid, Cab-OSil), magnesium stearate and corn starch.

The binders used in the present invention comprise one or more components selected from a group comprising potato, wheat or corn starch; microcrystalline cellulose, for instance Avicel®, Filtrak®, Heweten® or Pharmacel®; hydroxypropyl cellulose, hydroxyethyl cellulose; hydroxypropylmethyl cellulose, for instance hydroxypropylmethyl cellulose-type 2910 USP; hypromellose and polyvinylpyrrolidone, for instance Povidone® K30(BASF), lactose, guar gum, pectin, gelatin, sodium alginate.

The lubricants used in the present invention comprise one or more components selected from a group comprising metallic stearates (such as magnesium stearate, calcium stearate, aluminum stearate), fatty acid esters (such as sodium stearyl fumarate), fatty acids (such as stearic acid), fatty alcohol, glycercyl behenate, mineral oil, paraffins, hydrogenated vegetable oil, leucine, polyethylene glycols (PEG), metallic lauryl sulfates (such as sodium lauryl sulfate, magnesium lauryl sulfate), sodium chloride, sodium benzoate, sodium acetate, talc and/or hydrates thereof.

The diluents used in the present invention comprise one or more components selected from a group comprising alkali metal carbonates, cellulose derivatives (microcrystalline cellulose, cellulose acetate, etc.), dextrin, fructose, dextrose, glycercyl palmitostearate, lactitol, lactose, direct compression lactose, maltose, mannitol, simethicone, sorbitol, starch, talc, xylitol and/or hydrates thereof and/or derivatives thereof.

The pharmaceutically acceptable emulsifying agents according to the present invention can be selected from the group comprising carbomer, cetostearyl alcohol, cetyl alcohol, cholesterol, dietanolamine, ethylene glycol, polmito stearate, glycercyl mono stearate, hydroxy propyl cellulose, lanoline, lecithine, methyl cellulose, monoethanol amine, oleic acid, polyoxy ethylene alkyl ester, propylene glycol alginate, sodium citrate dihydrate, sodium lauryl sulfate, sorbitan esters, polysorbate.

The pharmaceutically acceptable carriers of the present invention can be selected from a group comprising polyether glycols, polypropylenes, xylitol, sorbitol, potassium sodium
tartrate, sucrose tribehenate, glucose, lactitol, behenic acid, hydroquinone, monomethyl ether, sodium acetate, ethyl fumarate, myristic acid, citryl acid, saturated hydrocarbons, paraffins, sorbitan esters, fats, waxes, polyvinylpyrrolidone polymers, acrylic polymers and/or mixtures thereof.

The release rate determinant polymers that can be used in the formulations of the present invention can be pH-dependant polymers, non pH-dependant polymers, swellable polymers, non-swellable polymers, hydrophilic polymers, hydrophobic polymers and/or one or more hydrophobic substances; ionic polymers such as sodium alginate, carbomer, calcium carboxy methyl cellulose or carboxy methyl cellulose; non-ionic polymers such as hydroxy propyl methyl cellulose; natural or/synthetic polysaccharides such as alkyl celluloses, hydroxyl alkyl celluloses, cellulose ethers, nitrocellulose, dextrin, agar, carrageenan, pectin, starch and starch derivatives or mixtures thereof; cellulosic polymers; methacrylate polymers, methacrylate copolymers, polyvinylpyrrolidone, polyvinylpyrrolidone-polyvinyl acetate copolymer, ethyl cellulose, cellulose acetate, cellulose propionate (high, medium and low molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, polyvinyl acetate, polyvinyl chloride.

The release rate determinant polymers used in fast release dosage forms are generally carboxy alkyl cellulose derivatives (for instance carboxy methyl cellulose sodium) and they sufficiently comprise unbound hydroxyl group. These hydroxyl groups help provide water solubility by binding to microcrystalline structures in the formulations during drying.

The film coating material of the present invention can be the following components and/or combinations thereof: lactose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, triacetine, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate phthalate, polyvinyl acetate phthalate, diethyl phthalate, sugar derivatives, polyvinyl derivatives, waxes, fats and gelatins, triethyl citrate, glyceride, titanium oxide, talc, sodium alginate, stearic acid, lecithin.

The solvents used in the present invention comprise one or more components selected from a group comprising toluene, benzene, acetone, methyl acetate, tetrahydrofurane, heptane, hexane, acetonitrile, alcohol and/or alcohol mixtures.

The production method proposed for the formulations of the present invention basically comprises the following steps:
1. Preparation of the first phase comprising statin
2. Preparation of the second phase comprising fast release fenofibrate and/or fenofibric acid
3. Preparation of the two mixtures obtained in the first two steps as micro tablet, granule and/or pellets
4. Filling the micro tablet, granule and/or pellets obtained into capsules made of gelatin

The phases comprising active agents can be produced by any methods in the prior art.

According to the present invention, fast release fenofibrate micro tablets are preferably prepared by the method below:

1. Effective amounts of fenofibrate and/or fenofibric acid, deionized water, surfactant are mixed
2. The release rate determinant polymer is added into the mixture and mixed
3. The mixture obtained is granulated by being sprayed on an inert carrier
4. The granules obtained are dried
5. The dry granules are compressed in tablet form, the diameter of which is in the range of 3-10 mm, and the micro tablets prepared this way are preferably coated with film.

The formulation comprising an effective amount of statin according to the present invention is preferably prepared by the following method:

1. An effective amount of statin, at least one pharmaceutically acceptable binder, diluent and filling material are mixed
2. At least one pharmaceutically acceptable binder and emulsifying agent are dissolved with deionized water and the granulation solution is prepared
3. The active agent mixture prepared in the first step is granulated wet and the granules are then dried
4. The granules obtained are compressed in pellet form and the pellets are optionally coated

Formulations comprising statin are preferably formulated according to the method described above. The pellets obtained can optionally be coated with film coating material or a coating material such that it can have certain release characteristics.
The active agent formulations prepared (pellet and micro tablet) are filled into gelatin capsules. Gelatin capsules are dissolved in the stomach in a few minutes and release the micro tablets and pellets into the stomach. Multiple dosage forms are completely mixed with chyme; therefore distribution and efficiency of the active agents are improved.

The formulations produced according to the present invention are used in the treatment of hyperlipoproteinemia, hypertriglyceridemia, hypercholesterolemia, myocardial infarction and stroke and/or related diseases.
EXAMPLES

Example 1. Formulation comprising fenofibrate and atorvastatin calcium

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<tr>
<th>Micro tablet formulation comprising fenofibrate</th>
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<tbody>
<tr>
<td>Content</td>
<td>Percentage (% of Weight)</td>
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<tr>
<td>Fenofibrate</td>
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<tr>
<td>Surfactant</td>
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<td>Rate determinant polymer / polymers</td>
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<table>
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<th>Pellet formulation comprising atorvastatin calcium</th>
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<tbody>
<tr>
<td>Content</td>
<td>Percentage (% of Weight)</td>
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<td>Diluent</td>
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<tr>
<td>Disintegrant</td>
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<tr>
<td>Emulsifying agent</td>
<td>0.50</td>
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<tr>
<td>Filling agent</td>
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<tr>
<td><strong>Total weight</strong></td>
<td><strong>100</strong></td>
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</table>

The formulations given above are prepared by the production method proposed in the description part. The obtained micro tablets comprising fenofibrate and pellets comprising atorvastatin are preferably filled into a capsule made of soft gelatin in the last step.
CLAIMS

1. A pharmaceutical formulation comprising at least one HMG Co A reductase enzyme inhibitor and fenofibrate and/or fenofibric acid as the active agents characterized in that said formulation is formulated in multiple dosage form.

2. The pharmaceutical formulation according to claim 1 characterized in that the multiple dosage form is composed of unit dosage form or forms having identical and/or different physical characteristics.

3. The unit dosage form according to claim 2 characterized in that said unit dosage form is selected from a group comprising granules, powder, pellets, tablet, mini tablet, micro tablet, capsule or combinations thereof.

4. The pharmaceutical formulation according to claim 1 characterized in that the multiple dosage form is prepared by combining the pellets comprising HMG Co A reductase enzyme inhibitor and micro tablets comprising fenofibrate and/or fenofibric acid in gelatin capsules.

5. The pharmaceutical formulation according to claim 4 characterized in that at least one of the active agents is in fast release form.

6. The pharmaceutical formulation according to claim 5 characterized in that the micro tablets comprising fenofibrate and/or fenofibric acid are in fast release form.

7. The pharmaceutical formulation according to claim 1 characterized in that HMG Co A reductase enzyme inhibitor is a statin group active agent.

8. The HMG Co A reductase enzyme inhibitor according to claim 7, wherein said HMG Co A reductase enzyme inhibitor is selected from a group comprising rosuvastatin, atorvastatin, simvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin and/or their pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystal forms and amorphous forms and/or combinations thereof.

9. The HMG Co A reductase enzyme inhibitor according to claim 7, wherein HMG Co A reductase enzyme inhibitor is preferably rosuvastatin, atorvastatin and/or their pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and/or combinations thereof.

10. The pharmaceutical formulation according to claim 1 characterized in that the active agent fenofibrate and/or fenofibric acid is selected from the group comprising their
pharmaceutically acceptable salts, hydrates, enantiomers, racemates, organic salts, inorganic salts, esters, polymorphs and/or combinations thereof.

11. The pharmaceutical formulation according to claim 10 characterized in that fenofibrate and/or fenofibric acid used in the formulations is a pharmaceutically acceptable fenofibric acid salt.

12. The pharmaceutical formulation according to claim 11 characterized in that fenofibric acid salt is cholin fenofibrate.

13. The pharmaceutical formulation according to claim 1 characterized in that the particle size of fenofibrate and/or fenofibric acid used in the formulations is preferably in the range of 1-500 \( \mu m \), more preferably in the range of 1-300 \( \mu m \), even more preferably in the range of 1-200 \( \mu m \).

14. The pharmaceutical formulation according to claim 1 characterized in that the production method basically comprise the following steps:
   - Preparation of the first phase comprising statin
   - Preparation of the second phase comprising fast release fenofibrate and/or fenofibric acid
   - Preparation of the two mixtures obtained in the first two steps as micro tablet, granule and/or pellets
   - Filling the micro tablet, granule and/or pellets obtained into capsules made of gelatin

15. The production method according to claim 14 characterized in that fast release micro tablets of fenofibrate are preferably prepared by the method below:
   - Effective amounts of fenofibrate and/or fenofibric acid, deionized water, surfactant are mixed
   - Rate determinant polymer is added into the mixture and mixed
   - The mixture obtained is granulated by being sprayed on an inert carrier
   - The granules obtained are dried
   - The dry granules are compressed in tablet form, the diameter of which is in the range of 3-10 mm, and the micro tablets prepared this way are preferably coated with film.

16. The production method according to claim 14 characterized in that the formulation comprising statin is preferably prepared by the method below:
- An effective amount of statin, at least one pharmaceutically acceptable binder, diluent and filling material are mixed
- At least one pharmaceutically acceptable binder and emulsifying agent are dissolved with deionized water and the granulation solution is prepared
- The active agent mixture prepared in the first step is granulated wet and the granules are then dried
- The granules obtained are compressed in pellet form and the pellets are optionally coated

17. The formulation according to claim 1 characterized in that said formulation is used in the treatment of hyperlipoproteinemia, hypertriglyceridemia, hypercholesterolemia, myocardial infarction and stroke and/or related diseases.
**INTERNATIONAL SEARCH REPORT**

**International application No.**
PCT/TR2011/000164

**A. CLASSIFICATION OF SUBJECT MATTER**

- INV. A61K31/00
- A61K31/192
- A61K31/216
- A61K31/22
- A61K31/366
- A61K31/40
- A61K31/405
- A61K31/47
- A61K31/505
- A61K9/54

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)
  - A61K
  - A61P

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 practical, search terms used)

- EPO-Internal
- WPI Data
- BIOSIS
- EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>wo 2005/013940 AI (GALEPHAR M F [BE]) ; VANDERBIST FRANCIS [BE] ; BAUDIER PHI LI PPE [BE] ; DEB 17 February 2005 (2005-02-17) example 10 claims</td>
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☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

- Special categories of cited documents:
  - "X" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  - "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  - "X" document member of the same patent family

Date of the actual completion of the international search

7 November 2011

Date of mailing of the international search report

17/11/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer

Herrera, Suzanne
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