(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING FENOFOBRATE AND SIMVASTATIN

(57) Abstract: Pharmaceutical compositions in particulate form or in solid dosage forms comprising a combination of a reduced or low dose of fenofibrate and the HMG CoA reductase inhibitor simvastatin or a pharmaceutically active salt thereof. Simvastatin is optionally provided as a controlled release or a delayed release formulation, which may result in a maintained LDL-lowering effect at a reduced dosage. Fenofibrate is provided in a formulation being bioequivalent to commercially available Antara® capsules, or exhibiting increased bioavailability as compared thereto, and also reduced food effect.
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PHARMACEUTICAL COMPOSITIONS COMPRISING FENOFIBRATE AND SIMVASTATIN

Technical field

[0001] The present invention relates to compositions, particularly, pharmaceutical compositions in particulate form such as granulate or in solid dosage forms comprising a combination of a fibrate and a simvastatin (also known as a HMG CoA reductase inhibitor), the in optimized relative amounts providing effective AUC₀₋₂₄ when administered orally to mammals. More specifically, the invention relates to a solid pharmaceutical composition comprising simvastatin and a low dose, i.e. a reduced amount, of fenofibrate having improved bioavailability and/or improved pharmacological response, i.e. improved effect. The composition may be in the form of an immediate release formulation, a controlled release formulation or a combination thereof. The invention also relates to methods for making the compositions in particulate form, i.e. as particles, and in solid dosage forms.

Background art

[0002] Fibrates are drug substances that generally are poorly and variably absorbed after oral administration. Normally they are prescribed to be taken with food in order to increase the bioavailability. There has been a number of improvements in dosage form of the currently most used fibrate, fenofibrate, in an effort to increase the bioavailability of the drug and hence its efficacy. Furthermore, clinical guidelines indicate that not only fibrate therapy but also a combination therapy with e.g. fenofibrate and a statin should be the most effective means of cholesterol and lipid management. In fact, treatment with fenofibrate is often prescribed together with a statin as clinicians seem to prefer the use of e.g. fenofibrate due to its triglyceride-lowering and HDL-C increasing effects while a statin is used for its positive effects on lowering LDL-C and raising HDL-C.

However, at present, such a combination therapy can only be achieved by the use of two separate products, i.e. the patient needs to take e.g. one fenofibrate tablet together with another tablet or capsule containing a statin.

[0003] Fenofibrate is chemically named 2-[4-(4-chlorobenzoyl)-2-methyl-propanoic acid, 1-methylethyl ester and has the following structural formula:
[0004] 

[0005] Fenofibrate is a white solid. The compound is insoluble in water. The melting point is 79-82°C. Fenofibrate is metabolised to the active substance fenofibric acid. Fenofibric acid has an elimination half-life of about 20 hours.

Measurement of the detected amount of fenofibric acid in the blood of a patient can reflect the efficacy of fenofibrate uptake. Fenofibric acid produces reductions in total cholesterol (total-C), LDL-C, apo-lipoprotein B, total triglycerides, and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apo-lipoprotein apoAI and apo AII. Fenofibrate acts as a potent lipid regulating agent offering unique and clinical advantages over existing products in the fibrate family of drug substances. Fenofibrate produces substantial reduction in plasma triglyceride levels in hypertriglyceridemic patients and in plasma cholesterol and LDL-C in hypercholesterolemic and mixed dyslipidemic patients.

[0006] Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal subjects by increasing the urinary excretion of uric acid.

[0007] Clinical studies have demonstrated that elevated levels of total cholesterol, low density lipoprotein cholesterol (LDL-C), and apo-lipoprotein B (apo B) are associated with human atherosclerosis. Decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis.

[0008] Fenofibrate is also effective in the treatment of Diabetes Type II and metabolic syndrome.

[0009] Further, the lipid improvements seen with fenofibrate therapy are associated with reduced progression to microalbuminuria in patients with Diabetes Type II. A recent study shows that fenofibrate treatment for at least 3 years is effective in reducing the progression of renal disease in patients with Diabetes Type II without diabetic nephropathy (Am. J. Kidney Dis. 2005, vol. 45, p. 485-493).
[0010] Fenofibrate is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia and thereby obviating the need for pharmacologic intervention.

[0011] Fibrates are drug substances known to be are poorly and variably absorbed after oral administration. Normally they are prescribed to be taken with food in order to increase the bioavailability.

[0012] In general, it is known that the absorption and bioavailability of a therapeutically active substance can be affected by a variety of factors when administered orally. Such factors include the presence of food in the gastrointestinal tract and, in general, the gastric residence time of a drug substance is significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug substance is affected beyond a certain point due to the presence of food in the gastrointestinal tract, the drug substance is said to exhibit a food effect. Food effects are important because there is a risk associated with administering the drug substance to a patient who has eaten recently. The risk derives from the potential that absorption into the bloodstream may be adversely affected to the point that the patient risks insufficient absorption to remedy the condition for which the drug was administered. In the case of e.g. fenofibrate the situation is different in that food increases the uptake. Thus, lack of intake of food simultaneously with the drug substances may lead to insufficient absorption. The extent of absorption of a commercially available product Tricor® (Lipanthyl®) containing fenofibrate (from Abbott Laboratories, IL, U.S.A.) is increased by approximately 35% under fed as compared to fasting conditions.

[0013] Examples of commercially available fenofibrate drug products are: From Abbott Laboratories: TriCor® tablets 160 mg, 145 mg, 54 mg, 48 mg, Lipanthyl® capsules; from Reliant Pharmaceuticals Inc., NJ, U.S.A.: Antara® capsules 130 mg, 43 mg. The fenofibrate present in these commercial products is in micronized form, i.e. crystalline fenofibrate in the form of fenofibrate particles as such, prepared by subjecting crystalline fenofibrate to a mechanical milling in order to reduce the particle size.
[0014] WO 04/041250 relates to nanoparticulate compositions of fenofibrate, i.e. fenofibrate particles having an effective average particle size of less than about 2000 nm.

[0015] Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of Aspergillus terreus. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding (beta)-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

[0016] Simvastatin is butanoic, 2,2-dimethyl-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-{tetrahydro-4-hydroxy-6-oxo-2 H -pyran-2-yl}-ethyl]-1-naphthalenyl ester, [1 S -[1(alpha),3(alpha),7(beta),8(beta)(2 S *,4 S *),-8a(beta)]]]. The empirical formula of simvastatin is C_{28}H_{38}O_5 and its molecular weight is 418.57.

[0017] The structural formula of simvastatin is:

![Simvastatin Structural Formula]

[0018]

[0019] Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

[0020] Simvastatin is commercially available e.g. from Merck & Co., Inc. under the tradename ZOCOR®. Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of Simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a preservative.

[0021] Simvastatin is a synthetic lipid-lowering agent. Simvastatin is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these
complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

[0022] Elevated plasma levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of high-density lipoprotein cholesterol (HDL-C) and its transport complex, Apo A-I, are associated with decreased cardiovascular risk. High plasma triglycerides (TG) and cholesterol-enriched TG-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG is frequently found in a triad with low HDL-C and small LDL particles, as well as in association with non-lipid metabolic risk factors for CHD. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolized predominantly by the high-affinity LDL receptor.

[0023] Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be > 60% in man), the availability of drug to the general circulation is low.

[0024] US 4,444,784 discloses simvastatin and the production thereof.

[0025] WO 03/013608 describes semi-solid pharmaceutical compositions containing a fibrate and a statin prepared by melting the inactive substances,
adding the active substances and filling the melt into pharmaceutically acceptable capsules.

[0026] WO 03013608 describes semi-solid pharmaceutical compositions containing a fibrate and a statin prepared by melting the inactive substances, adding the active substances and filling the melt into pharmaceutically acceptable capsules.

[0027] WO 03103640 discloses nanoparticulate compositions comprising statin particles having an effective average particle size of less than about 2000 nm, optionally in combination with other cholesterol lowering agents.

[0028] There is a need for developing a pharmaceutical composition that in a single formulation, preferably in a single solid dosage form, contains a fibrate and simvastatin as active substances, which composition is stable and provides suitable and desirable biopharmaceutical properties of the active substances (e.g. for each of the active substances a suitable bioavailability, a suitable pharmacological response, less dependency on food intake etc), and which composition can be easily manufactured in large scale. Furthermore, there is a need for developing formulations containing a fibrate and a statin, which formulations can be further processed into pharmaceutical dosage forms with a high degree of flexibility of choosing the particular kind of dosage form. Within the pharmaceutical field such flexibility can be obtained when the formulation is in the form of a solid product such as powder or particles.

[0029] Also, there is still a need for a composition that has a suitable or even improved bioavailability, that can substantially reduce or overcome the differential between the bioavailability of the drug in patients who are fasted versus the bioavailability of the drug (in particular relevant for fenofibrate) in patients who are fed, and/or than can substantially reduce or overcome the intra- and/or inter-individual variations observed with the current treatment. Furthermore, there is also a need for a composition that enables reduction in observed side effects and minimized any possible drug-drug interactions.

Disclosure of the invention
Summary of the invention

[0030] The inventors have now successfully formulated a solid pharmaceutical composition in particulate form comprising a combination of two active
substances, namely fenofibrate and simvastatin or a pharmaceutically active salt thereof, where the fenofibrate is at least bioequivalent to the commercially available drug containing the lowest dose of fenofibrate (presently 130 mg).

[0031] The inventors have found that the bioavailability of the combination drug can be significantly enhanced by dissolving the active substance fenofibrate in a suitable vehicle and using the resulting composition for preparing a solid dosage form, i.e. a dosage form excluding material in liquid form. Fenofibrate is known to be insoluble in water and the present invention includes pharmaceutical compositions and formulations exhibiting release profiles which have significantly increased in vivo bioavailability in patients in need thereof, especially eliminating the food effect of fenofibrate known from commercially available fenofibrate tablets (Tricor/Lipanthyl tablets or other drug products containing micronized fenofibrate). Especially, the inventors have succeeded in preparing a solid dosage form, such as a tablet, which ensures suitable bioavailability of the active substances upon oral administration. The advantages of a solid and stable dosage form useful for oral administration are well-known.

[0032] Further, the inventors have found that it is possible to obtain the desired pharmacological response in vivo (a reduction of the LDL-cholesterol level) and at the same time maintain the maximum obtainable increase in HDL-cholesterol by administering a fenofibrate-simvastatin combination composition comprising a controlled release formulation of simvastatin, preferably a delayed release formulation, even a formulation with a reduced amount of simvastatin is contemplated, including a time-controlled coating or an enzyme controlled coating or a pressure controlled coating.

[0033] The compositions, i.e. the particulate composition and the solid dosage forms, are manufactured without any need of addition of water or an aqueous medium. As a result, the compositions of the invention have a very low content of moisture, i.e. less than about 2.5% w/w water, or less than about 2% w/w water, or less than about 1% w/w water are obtained, thereby ensuring suitable storage stability, since both fenofibrate is degradable by water.

[0034] The solid pharmaceutical compositions in the form of particles and solid dosage forms of the present invention are useful for treatment of conditions that
respond to fibrate and simvastatin treatment, including hypercholesterolemia and hyperlipidemia.

[0035] Accordingly, in a first aspect the present invention provides a solid pharmaceutical composition in particulate form, which composition comprises a vehicle, an effective amount of simvastatin or a pharmaceutically acceptable salt thereof, and an effective amount of fenofibrate exhibiting a bioavailability which is at least bioequivalent to a 130 mg Antara® capsule.

[0036] Thus, the composition of the invention provides a combination drug product with a low dose of fenofibrate, i.e. a reduced amount of this active substance, while at the same time providing a pharmaceutical composition being bioequivalent to commercially available fenofibrate-containing medicaments or, alternatively, being even more efficient by exhibiting an increased bioavailability such as an AUC₁₅₋₆₀ value for fenofibrate relative to the AUC₀₋₂₄ value for a 130 mg Antara® tablet of at least about 1.3.

[0037] In a preferred embodiment of the invention, the amount of fenofibrate is less than 130 mg. That is a low dosage, i.e. a reduced amount, as compared to the commercially available medicaments providing various dosage forms typically containing 160 mg, 145 mg or 130 mg of fenofibrate, usually micronized fenofibrate.

[0038] In another preferred embodiment, the composition of the invention comprises about 120 mg of fenofibrate. It is contemplated that the minimum effective amount of fenofibrate is about 30 mg. The amount of simvastatin in the composition may vary from about 5 mg to about 80 mg. Conventionally the amount of fenofibrate present in the combination composition is higher that the amount of simvastatin. However, effective co-formulations comprising a higher amount of simvastatin than of fenofibrate is contemplated. The relative amount of simvastatin to fenofibrate is at least 1:15.

[0039] Especially, essentially all of the fenofibrate present in the composition is dissolved in a suitable vehicle, which may be hydrophobic, hydrophilic or water-miscible.

[0040] In a second aspect, the invention relates to a solid oral dosage form comprising the pharmaceutical composition. Useful solid dosage forms are in the
form of tablets, beads, capsules, grains, pills, granulate, granules, powder, pellets, sachets or troches.

[0041] In a third aspect, the invention relates to a solid oral dosage form comprising an immediate release formulation of fibrate, preferably fenofibrate, and a controlled release formulation of simvastatin. In a preferred embodiment, the solid dosage form may be tablets prepared by compressing a mixture of fibrate granulate and entero-coated simvastatin granulate. In another preferred embodiment, the solid dosage form may be fibrate granulate, fibrate granules, fibrate grains, fibrate beads and/or fibrate pellets filled into capsules or sachets together with entero-coated simvastatin granules, simvastatin grains, simvastatin beads and/or simvastatin pellets.

[0042] In yet another aspect, the invention relates to a method of manufacturing the pharmaceutical compositions and the solid oral dosage forms of the invention.

[0043] In further aspects, the invention relates to a method of treating hyperlipidemia or hypercholesterolemia comprising administering to a human in need of such treatment the pharmaceutical composition of this invention, and to use of the pharmaceutical composition or a solid dosage form of this invention for manufacturing a medicament for treatment of hyperlipidemia or hypercholesterolemia in mammals.

[0044] The pharmaceutical composition of the invention is advantageous by being in the form of particles, for example granulate, which can easily be further processed into solid dosage forms, especially tablets or filled into capsules. That is, the pharmaceutical composition of the invention exhibits suitable properties such as for example being free-flowing, non-adherent and compressible.

[0045] Further aspects of the invention are evident from the following description.

[0046] Comparison in vivo tests in dogs have shown, cf. the examples herein, that solid dosage forms and compositions of the invention exhibit significantly enhanced bioavailability of fenofibrate compared to commercially available solid dosage forms containing the same active ingredient, i.e. to Tricor® (Lipanthyl ®) tablets and Lipanthyl® capsules (both from Abbott Laboratories, Illinois, U.S.A.).

[0047] Further, it is believed that the present invention provides solid dosage forms and compositions of fenofibrate and simvastatin capable of significantly reducing the intra- and/or inter-individual variation normally observed after oral
administration. Furthermore, the compositions and dosage forms according to the invention provide for a significant reduced food effect, i.e. the absorption is relatively independent on whether the patient takes the composition or dosage form together with or without any meal. It is contemplated that a modified release formulation may reduce the number of gastro-intestinal related side effects. Furthermore, it is contemplated that in comparison with commercially available drug products, a significantly larger amount of fenofibrate is absorbed from the present composition and, accordingly, an equally less amount is excreted unchanged via faeces. Finally, it is contemplated that the reduced amount of fenofibrate in the composition of the invention significantly reduces any negative effects of possible drug-drug interactions (i.e. fenofibrate-simvastatin).

[0048] As mentioned above, the present invention fulfils the need for pharmaceutical compositions containing a combination of fenofibrate and simvastatin or a pharmaceutically acceptable salt thereof for oral use that lead to an improved treatment of conditions requiring lipid management (e.g., atherosclerosis, coronary heart diseases, diabetes management, obesity, overweight, metabolic syndrome etc).

[0049] Furthermore, it is contemplated that the invention provides improved bioavailability, especially of the fenofibrate component, and an improved pharmacological response (LDL-cholesterol lowering and HDL-cholesterol increase) of simvastatin. Fenofibrate has a very poor solubility in water, which property is regarded as one of the major reasons for the poor bioavailability of fenofibrate. Accordingly, it is advantageous to provide a composition in which the fenofibrate is mainly in dissolved form. Improved bioavailability results in improved treatment. However, it may also be possible to obtain the same therapeutic response with a decreased dose and/or a less frequent administration and less variability in plasma levels and no food restrictions. Another way of obtaining an improved treatment of conditions where fenofibrate is indicated is by balancing the release of fenofibrate to the gastro-intestinal tract in such a manner that an enhanced plasma concentration of fenofibrate is obtained initially or delayed with respect to the time of administration, i.e. by administering modified or delayed release compositions containing fenofibrate.

Drawings
[0050] Figure 1 shows the mean plasma concentration data of Lipanthyl 160 mg fed state and Lipanthyl 160 mg fasted state (0-96 hours).

[0051] Figure 2 shows the mean plasma concentration data of invention fenofibrate formulation (LCP-feno) 160 mg fed state and invention fenofibrate formulation (LCP-feno) 160 mg fasted state (0-96 hours).

[0052] Figure 3 shows mean (average) AUC₀-₂₄ and mean (average) AUC₀-inf for each of Lipanthyl fasted state, Lipanthyl fed state, invention fenofibrate formulation (LCP-Feno) fasted state and invention fenofibrate formulation (LCP-Feno) fed state.

Definitions

[0053] As used herein, the terms "active substance", "active pharmaceutical substance", "active ingredient" and "active pharmaceutical ingredient" (API) denote any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect.

[0054] In the present context, the term "hydrophilic" describes that something 'likes water', i.e. a hydrophilic molecule or portion of a molecule is one that typically is electrically polarized and capable of forming hydrogen bonds with water molecules, enabling it dissolve more readily in water than in oil or other "non-polar" solvents.

[0055] In the present context, the term "amphiphilic" describes a molecule (as a surfactant) having a polar water-soluble group attached to a water-insoluble hydrocarbon chain. Thus, one end of the molecule is hydrophilic (polar) and the other is hydrophobic (non-polar).

[0056] In the present context, the term "hydrophobic" denotes a compound tending to be electrically neutral and non-polar, and thus preferring other neutral and non-polar solvents or molecular environments.

[0057] As used herein, the term "water-miscible" denotes a compound being fully or partly miscible with water. For example, certain polar lipids are partly water-miscible.
[0058] As used herein, the term "vehicle" means any solvent or carrier in a pharmaceutical product that has no pharmacological role. For example, water is the vehicle for xylocacline and propylene glycol is the vehicle for many antibiotics.

[0059] In the present context, the term "solid dispersion" denotes a drug or active ingredient or substance dispersed on a particulate level in an inert vehicle, carrier, diluent or matrix in the solid state, i.e. usually a fine particulate dispersion.

[0060] In the present context, the term "solid solution" denotes a drug or active ingredient or substance dissolved on a molecular level in an inert vehicle, carrier, diluent or matrix in the solid state.

[0061] In the present context, the term "interstitial crystalline solid solution" denotes a drug or active ingredient or substance dissolved on a molecular level in an inert vehicle, carrier, diluent or matrix in the solid state, where the inert vehicle, carrier, diluent or matrix forms a crystal lattice and the dissolved fenofibrate molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice, cf. the review article: Leuner C. and Dressman, J., European Journal of Pharmaceutics and Biopharmaceutics 50 (2000) 47-60.

[0062] As used herein, the term “analog” means a chemical compound that is structurally similar to another.

[0063] The term “drug” means a compound intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.

[0064] In this context, the term "dosage form" means the form in which the drug is delivered to the patient. Examples of known dosage forms are parenteral, topical, oral (liquid or dissolved powder, tablet, capsule, sachet), suppository, inhalation, transdermal, etc.

[0065] As used herein, the term "bioavailability" denotes the degree to which a drug or other substance becomes available to the target tissue after administration. In the present context, the term “suitable bioavailability” is intended to mean that administration of a composition according to the invention will result in a bioavailability that is improved compared to the bioavailability obtained after administration of the active substance(s) in a plain tablet; or the bioavailability is at least the same or improved compared to the bioavailability obtained after administration of a commercially available product containing the same active substance(s) in the same amounts. In particular it is desired to obtain quicker and
larger and/or more complete uptake of the active compound, and thereby provide for a reduction of the administered dosages or for a reduction in the number of daily administrations. Further, pharmaceutical compositions of the invention may also reduce or negate the need for the dosage form to be taken simultaneously with intake of food (this is in particular relevant fenofibrate) thereby allowing patients more freedom to choose when to administer the drug.

[0066] As used herein, the term “bioequivalency” denotes a scientific basis on which generic and brand name drugs are compared with one another. For example, drugs are bioequivalent if they enter circulation at the same rate when given in similar doses under similar conditions. Parameters often used in bioequivalence studies are $t_{\text{max}}$, $c_{\text{max}}$, $\text{AUC}_{0-\text{infinity}}$, $\text{AUC}_{0-t}$. Other relevant parameters may be $W_{50}$, $W_{75}$ and/or MRT. Accordingly, at least one of these parameters may be applied when determining whether bioequivalence is present.

In the present context, bioequivalency of two compositions is established by a 90% confidence interval of between 0.80 and 1.25 for AUC (either $\text{AUC}_{0-\text{infinity}}$ or $\text{AUC}_{0-24}$). In addition, a 90% confidence interval of between 0.80 and about 1.40 for $c_{\text{max}}$ is also required for bioequivalency. The combination composition of the invention, i.e. regarding the establishment of bioequivalency of the fenofibrate active ingredient, may be compared with standard commercial fenofibrate formulations, for example 160 mg or 145 mg Tricor®/Lipanthyl® tablets or capsules or 130 mg Antara® capsules or similar, preferably 130 mg Antara® capsules.

[0067] In the present context "$t_{\text{max}}$" denotes the time to reach the maximal plasma concentration ($c_{\text{max}}$) after administration; $\text{AUC}_{0-\text{infinity}}$ or AUC denotes the area under the plasma concentration versus time curve from time 0 to infinity; $\text{AUC}_{0-t}$ denotes the area under the plasma concentration versus time curve from time 0 to time t, especially, $\text{AUC}_{0-24}$ is the area under the plasma concentration versus time curve from time 0 to time 24 hr at steady state conditions; $W_{50}$ denotes the time where the plasma concentration is 50% or more of $c_{\text{max}}$; $W_{75}$ denotes the time where the plasma concentration is 75% or more of $c_{\text{max}}$; and MRT denotes mean residence time for each of the active pharmaceutical ingredients of the compositions of the present invention.
[0068] In this context, the term "medicine" or "medicament" means a compound used to treat disease, injury or pain. Medicine is designated "prophylactic," i.e. the art of preserving health, and "therapeutic", i.e. the art of restoring health.

[0069] In the present context, the terms "controlled release" and "modified release" are intended to be equivalent terms covering any type of release of active ingredient, e.g. fenofibrate or simvastatin, from a composition of the invention that is appropriate to obtain a specific therapeutic or prophylactic response after administration to a subject. A person skilled in the art knows how controlled release/modified release differs from the release of plain tablets or capsules. The terms “release in a controlled manner” and “release in a modified manner” have the same meaning as stated above. The terms include slow release (that results in a lower $C_{\text{max}}$ and later $t_{\text{max}}$, but the half-life remains unchanged), extended release (that results in a lower $C_{\text{max}}$, later $t_{\text{max}}$, but apparent half-life is longer); delayed release (that result in an unchanged $C_{\text{max}}$, but lag time and, accordingly, $t_{\text{max}}$ is delayed, and the half-life remains unchanged) as well as pulsatile release, burst release, sustained release, prolonged release, chrono-optimized release, fast release (to obtain an enhanced onset of action) etc. Included in the terms is also e.g. utilization of specific conditions within the body e.g., different enzymes or pH changes in order to control the release of the drug substance.

[0070] In this context, the term "erosion" or "eroding" means a gradual breakdown of the surface of a material or structure, for example of a tablet or the coating of a tablet.

The active drug substances

[0071] A first drug or active substance of the dosage forms and pharmaceutical compositions of this invention is a fibrate, usually fenofibrate as described above or an analog thereof. It should be understood that this invention includes dosage forms and compositions comprising a mixture of two, three or even four different fibrates and/or fibrac acids. Examples of other useful fibrates are bezafibrate, ciprofibrate, clinofibrate, clofibrate, etofylline, clofibrate, gemfibrozil, pirifibrate, simfibrate and tocofibrate; particularly useful are gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate and active metabolites and analogues thereof including any relevant fibrac acid such as fenofibrac acid.
[0072] A second drug or active substance of the dosage forms and pharmaceutical compositions of this invention is simvastatin as described above or a pharmaceutically acceptable salt thereof. It is contemplated that any type and physical form of simvastatin is useful in the compositions and solid dosage forms of the present invention.

[0073] The first and second active substance, i.e. fenofibrate and simvastatin or a pharmaceutically acceptable salt thereof, is present in the composition or the solid dosage form of the invention in effective amounts together with a vehicle and optionally further excipients or additives. It is believed that fenofibrate in combination with simvastatin has an added effect; it has been shown that use of the combination results in TG and LDL levels being more decreased while HDL level is increased.

[0074] More specifically, the effective amount of fenofibrate is an amount which is at least bioequivalent to a 130 mg Antara® capsule.

[0075] Alternatively, the amount of fenofibrate present in the composition of the invention exhibits an increased bioavailability as compared to 130 mg Antara® capsule by exhibiting a relative AUC0-24 value of 1.3 (AUC of fenofibrate of the invention relative to AUC of the 130 mg Antara® capsule).

[0076] In one embodiment, fenofibrate is present in the composition of the invention in an amount below about 130 mg.

[0077] In another embodiment, fenofibrate is present in the composition of the invention in an amount of about 120 mg.

[0078] The fenofibrate of the solid composition or the solid dosage form of this invention provides, after oral administration, an AUC0-24 value of fibric acid (arithmetic mean) of at least 28,000 ng•h/mL, or at least of about 40,000 ng•h/mL, or at least of about 79,000 ng•h/mL, or at least of about 118,000 ng•h/mL.

[0079] In the solid composition or the solid dosage form of this invention at least about 50% w/w, preferably at least about 75% w/w, of the total amount of active substances or essentially all of the fenofibrate is dissolved in vehicle selected from the group consisting of a hydrophobic, a hydrophilic and a water-miscible vehicle.

[0080] Normally, at least about 85% w/w, at least about 90% w/w, at least about 95% w/w or at least about 98% w/w, or at least about 99% w/w, or at least about 99.5% w/w, or 100% w/w of the fenofibrate is dissolved in the vehicle.
[0081] If those embodiments where the total amount of fenofibrate present in the composition or the solid dosage form of the invention is completely (100%) dissolved in the vehicle, fenofibrate is present in the form of a solid solution in the particulate composition. The presence of a solid solution can be tested by a DSC test mentioned herein. It is contemplated that the fenofibrate forms an interstitial crystalline solid solution with the vehicle. The simvastatin component may be co-dissolved or, at least when crystalline simvastatin is used, dispersed homogeneously in the solid solution. However, it is contemplated that crystallization of a diminutive amount of any of the active substances from the solid solution may occur during storage of the solid dosage form of the invention, especially in tablets due to the possibility of formation of cavities in the tablet during manufacturing (tablet compression), which cavities may leave space for crystallization. Thus, the present invention includes particulate material wherein the active substances, or at least the fenofibrate, are present in the form of a solid solution, but it is within the scope of the present invention that a minor or diminutive amount of the active substance(s) in solid solution may precipitate or crystallize upon storage.

[0082] In another embodiment of the invention, at least about 80% w/w, preferably 100% w/w, of fenofibrate is dissolved in the vehicle, which is further processed into the particulate form as described herein. The solid particles, for examples granulate, comprising the dissolved fenofibrate is then mixed or blended with micronized simvastatin, and the resulting composition is optionally subjected to conventional methods for preparing solid dosage forms, especially tablets. Alternatively, the solid fenofibrate particles are mixed with entero-coated simvastatin particles, for example entero-coated granulate, and subjected to conventional methods for preparing tablets or simply filled into capsules or sachets.

[0083] As mentioned above, sufficient flowability is required of the particulate composition of the invention in order to obtain a suitable flexibility so that different dosage forms can be obtained. In a preferred embodiment, the solid composition of the invention is free-flowing, i.e. has a suitable flowability as determined according to the method described in the European Pharmacopoeia (Ph.Eur.)
measuring the flow rate of the composition out of a funnel with a nozzle diameter of 10.0 mm.

[0084] In a specific embodiment, the concentration of fenofibrate in the vehicle is at least about 10% w/w, based on the total weight of the fibrate, the statin and the vehicle. In particular, the concentration of fenofibrate in the vehicle is at least about 15% w/w, or at least about 16% w/w, or at least about 17% w/w, or at least about 20% w/w, preferably at least 25% w/w, more preferably at least about 30% w/w, especially at least about 35% w/w, based on the total weight of the fibrate, the statin and the vehicle.

[0085] The concentration of simvastatin in the vehicle of the solid composition or solid dosage form according to the invention is at least about 1% w/w, based on the total weight of the fibrate, the statin and the vehicle. More specifically, the concentration of statin in the vehicle is at least about 1.5% w/w, or at least about 2.5% w/w, or at least about 5% w/w, or at least about 7.5% w/w or at least about 10% w/w, based on the total weight of the fibrate, the statin and the vehicle.

[0086] The present invention provides solid compositions and solid dosage forms for improved treatment of conditions that respond to fenofibrate and simvastatin treatment, for example hyperlipidemia and hypercholesterolemia.

[0087] In a preferred embodiment of the invention, the fibrate is fenofibrate present in the solid dosage form or the pharmaceutical composition of this invention in an amount selected from the group consisting of 160 mg, 145 mg, 130 mg, 120 mg, 110 mg, 100 mg, 90 mg, 87 mg, 80 mg, 70 mg, 60 mg, 50 mg, 48 mg, 45 mg, 43 mg, 40 mg, 35 mg and 30 mg of fenofibrate. In a preferred embodiment, the solid dosage form comprises 145 mg of fenofibrate. In another preferred embodiment, the solid dosage form comprises 130 mg of fenofibrate. In yet another preferred embodiment, the solid dosage form comprises 120 mg of fenofibrate. In yet another preferred embodiment, the solid dosage form comprises 110 mg of fenofibrate. In yet another preferred embodiment, the solid dosage form comprises 50 mg of fenofibrate. In yet another preferred embodiment, the solid dosage form comprises 48 mg of fenofibrate. In yet another preferred embodiment, the solid dosage form comprises 43 mg of fenofibrate. In yet another preferred embodiment, the solid dosage form comprises 87 mg of fenofibrate.
Simvastatin may be present (either in amorphous form, in semi-amorphous form, in semi-crystalline form or in crystalline form) in an amount of from about 5 mg to about 80 mg, for example in an amount of about 5 mg or about 10 mg or about 15 mg or about 20 mg or about 25 mg or about 30 mg or about 35 mg or about 40 mg or about 45 mg or about 50 mg or about 55 mg or about 60 mg or about 65 mg or about 70 mg or about 75 mg or about 80 mg of simvastatin or a pharmaceutically acceptable salt thereof.

Examples of useful combinations are about 120 mg of fenofibrate and about 10 mg of simvastatin; about 120 mg of fenofibrate and about 20 mg of simvastatin; about 120 mg of fenofibrate and about 30 mg of simvastatin; about 120 mg of fenofibrate and about 40 mg of simvastatin; about 120 mg of fenofibrate and about 10 mg of simvastatin; about 110 mg of fenofibrate and about 10 mg of simvastatin; about 110 mg of fenofibrate and about 20 mg of simvastatin; about 110 mg of fenofibrate and about 30 mg of simvastatin; about 110 mg of fenofibrate and about 40 mg of simvastatin.

Bioavailability

As described above, there remains a need for novel pharmaceutical compositions comprising fenofibrate and simvastatin exhibiting suitable bioavailability and/or suitable pharmacological response of the active substances and/or reduced or eliminated food effect.

Clinical trial studies have shown, cf. the example herein, that the fenofibrate solid dosage forms and pharmaceutical compositions of the present invention eliminate the food effect, i.e. may be administered in the fed or the fasted state. Accordingly, the present invention provides the patient the choice of taking only one tablet daily at any time over the commercially available fenofibrate-containing medicament which should be taken with food in order to achieve the desired bioavailability of the active ingredient.

Without being bound to this theory, it is contemplated that the best possible total in vivo efficacy of orally administered simvastatin may be obtained by providing the drug in a controlled release formulation or, alternatively, in a delayed release formulation, for example an in vivo delayed release of about 8 to about 10 hours of an IR (immediate release) formulation, thus allowing the active substances to be released in areas of the intestine having a reduced CYP3A4
activity and optionally over an extended period of time. Typically, administration of
simvastatin shows increasing HDL-levels with increasing statin doses.

[0093] In one embodiment, the invention relates to a pharmaceutical composition
in particulate form or solid dosage form comprising fenofibrate and simvastatin,
wherein the composition upon oral administration to a mammal in need thereof
exhibits an AUC/AUC\textsubscript{Control} value for fenofibrate of at least about 1.0, the AUC\textsubscript{Control}
being determined using a commercially available product containing fenofibrate,
and the AUC values being determined under similar conditions.

[0094] No absolute bioavailability data based on an injectable composition are
available e.g., for fenofibrate (most likely due to solubility problems in aqueous
media). The commercially available compositions containing fenofibrate include
surface-active agents and/or e.g., a lipophilic medium. The surface-active agents
may impart improved bioavailability and therefore, the bioavailability of such a
composition may be sufficient already. However, there is still a need for
developing a flexible formulation technique that enables preparation of a variety of
dosage forms. Accordingly, the requirement to such improved and/or more flexible
compositions may be to obtain the same or better bioavailability than already seen
from the commercially available products.

[0095] Accordingly, in further embodiments of the invention, the AUC/AUC\textsubscript{Control}
value for fenofibrate obtained by administering the solid dosage form or
pharmaceutical composition of the invention is at least about 1.1 such as, e.g., at
least about 1.2, at least about 1.3, at least about 1.4, at least about 1.5, about 1.75
or more, about 1.8 or more, about 1.9 or more, about 2.0 or more, about 2.5 or
more, about 2.75 or more, about 3.0 or more, about 3.25 or more, about 3.5 or
more, about 3.75 or more, about 4.0 or more, about 4.25 or more, about 4.5 or
more, about 4.75 or more or about 5.0 or more, the AUC values being determined
under similar conditions.

[0096] Likewise, the c\textsubscript{max} value for fenofibrate obtained by administering the solid
dosage form or pharmaceutical composition of the invention relative to the c\textsubscript{max}
value of commercially available Tricor\textsuperscript{®} (Lipanthyl \textsuperscript{®}) tablets, or alternatively to
commercially available Antara\textsuperscript{®} capsules, is at least about 1.1, or at least about
1.2, or at least about 1.3, or at least about 1.4, or at least about 1.5, or at least
about 1.6 or more, or at least about 2.0, or at least about 2.5, or at least about 3.0, the \( c_{\text{max}} \) values being determined under similar conditions.

[0097] Another object of the invention is to reduce or eliminate the food effect. Thus, in another aspect, the invention relates to a pharmaceutical composition in particulate form or solid dosage form comprising one or more fibrates, especially fenofibrate, wherein the composition or solid dosage form upon oral administration to a mammal in need thereof does not exhibit a significant adverse food effect as evidenced by a value of \( (\text{AUC}_{\text{fed}}/\text{AUC}_{\text{fasted}}) \) of at least about 0.85 with a lower 90% confidence limit of at least 0.75. In a specific embodiment, the pharmaceutical composition or solid dosage form of the invention has a value of \( (\text{AUC}_{\text{fed}}/\text{AUC}_{\text{fasted}}) \) that is about 0.9 or more such as, e.g., about 0.95 or more, about 0.97 or more or about 1 or more.

[0098] In other words, the difference between a bioequivalence parameter measured after oral administration to a mammal with and without food, respectively, is less than about 25% such as, e.g., less than about 20%, less than about 15%, less than about 10% or less than about 5%.

[0099] In another aspect, the invention relates to a pharmaceutical composition in particulate form or solid dosage form comprising fenofibrate, wherein the composition upon oral administration to a mammal in need thereof is essentially bioequivalent with a commercially available product containing fenofibrate when administered in the same or lower dose as the commercially available product containing fenofibrate.

[00100] In specific embodiments thereof, the dose is at the most about 98% w/w such as, e.g., at the most about 95% w/w, at the most about 90% w/w, at the most about 85% w/w, at the most about 80% w/w, at the most about 75% w/w, at the most about 70% w/w, at the most about 65% w/w, at the most about 60% w/w, at the most about 55% w/w or at the most about 50% w/w of the dose of fenofibrate administered in the form of a commercially available product containing fenofibrate.

[00101] A major problem with treatment with fenofibrate is the large intra- or inter-individual variation. Thus, in a further aspect the invention relates to a pharmaceutical composition in particulate form comprising fenofibrate, wherein the composition upon oral administration to a mammal in need thereof reduces inter-
and/or intra-individual variations compared to those of a commercially available product containing fenofibrate under the same conditions and in a dose that provides an equivalent therapeutic effect.

[00102] In the comparison tests mentioned above, the commercially available fenofibrate product is Tricor® (Lipanthyl ®) in the form of tablets or, alternatively, Tricor® in the form of capsules, or Antara® capsules.

[00103] A convenient method for determining whether a suitable amount of fenofibrate has been absorbed may be to determine the content of unchanged fibrate excreted via the faeces. Thus, in one embodiment the invention relates to a solid pharmaceutical composition or solid dosage form, wherein at most about 25% w/w such as, e.g., at the most about 20% w/w, at the most about 15% w/w, at the most about 10% w/w, at the most about 5% w/w of the fenofibrate contained in the composition is excreted in the faeces after oral administration.

The vehicle

[00104] Vehicles useful in the present context are vehicles, which are water-miscible, hydrophilic or hydrophobic. Useful vehicles are non-aqueous substances which may be hydrophilic, lipophilic, hydrophobic and/or amphiphilic materials. The hydrophobic or hydrophilic or water-miscible vehicles will normally be liquid at ambient or elevated temperature. In the present context the term "a hydrophobic or a hydrophilic or water-miscible vehicle" is used in a very broad sense including oils, waxes, semi-solid materials and materials that normally are used as solvents (such as organic solvents) or co-solvents within the pharmaceutical industry, and the term also includes therapeutically and/or prophylactically active substances that are in liquid form at ambient temperature; furthermore the term includes emulsions like e.g., micro-emulsions and nanoemulsions and suspensions.

[00105] The oils or oily materials that are suitable for use in the present context are substances or materials, which have a melting point of at least about 10°C and at the most about 250°C. In specific embodiments of the invention, the oily material has a melting point of about 5°C or more such as, e.g., about 10°C or more, about 15°C or more, about 20°C or more or about 25°C or more. In further embodiments of the invention, the oily material has a melting point of at least about 25°C such as, e.g., at least about 30°C at least about 35°C or at least about 40°C. For practical reasons, the melting point may normally not be too high, thus
the oily material normally has a melting point of at the most about 250°C, at the
most about 200°C, at the most about 150°C or at the most about 100°C. If the
melting point is higher a relatively high temperature may promote e.g. oxidation or
other kind of degradation of an active substance in those cases where e.g. a
therapeutically and/or prophylactically active substance is included.

[00106] Typically, a suitable hydrophiliic oil or oily material is selected from
the group consisting of: polyether glycols such as, e.g., polyethylene glycols,
polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers and
mixtures thereof, or it may be selected from the group consisting of: xylitol,
sorbitol, potassium sodium tartrate, sucrose tribenenate, glucose, rhamnose,
lactitol, behenic acid, hydroquinon monomethyl ether, sodium acetate, ethyl
fumarate, myristic acid, citric acid, Sucro-ester 7, Sucro-ester 11, Sucro-ester 15,
maltose, mannitol and mixtures thereof.

[00107] The pharmaceutical composition or a solid dosage form according to
the invention may have a concentration of oil or oily material in the composition or
the dosage form of about 5% w/w or more such as, e.g., about 10% w/w or more,
about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about
30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45%
w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or
more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more,
about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about
95% w/w or more.

[00108] In specific embodiments the concentration of the oily material in a
composition or solid dosage form of the invention is in a range from about 20% to
about 80% w/w such as, e.g., from about 25% to about 75% w/w.

[00109] In general, the hydrophobic or hydrophilic or water-miscible vehicles
that are suitable for use in the present context are substances or materials having
a melting point of at least about 0°C and at the most about 250°C.

[00110] Interesting hydrophobic or hydrophilic or water-miscible vehicles are
generally substances, which are used in the manufacture of pharmaceuticals as
so-called melt binders or solid solvents (in the form of solid dosage form), or as co-
solvents or ingredients in pharmaceuticals for topical use.
[00111] It may be hydrophilic, hydrophobic and/or have surface-active properties. In general hydrophilic and/or hydrophobic vehicles are suitable for use in the manufacture of a solid pharmaceutical composition in particulate form or a solid dosage form according to the invention. In a specific embodiment they may be used when the release of the active substance from the pharmaceutical composition is designed to be immediate or non-modified or modified. Hydrophobic vehicles are normally used in the manufacture of a modified release pharmaceutical composition. These considerations are simplified to illustrate general principles, but there are many cases where other combinations of vehicles and other purposes are relevant and, therefore, the examples above should not in any way limit the invention.

[00112] Examples of hydrophobic vehicles useful in the present invention are straight chain saturated hydrocarbons, paraffins; fats and oils such as cacao butter, beef tallow, lard; higher fatty acid such as stearic acid, myristic acid, palmitic acid; hydrogenated tallow, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, Japan wax, and mixtures thereof.

[01113] Examples of water-miscible vehicles useful in the present invention are:

[01114] water-miscible polar lipids such as sorbitan esters, polyether glycol esters; higher alcohols such as cetanol, stearyl alcohol; glyceryl monooleate, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, and mixtures thereof.

[01115] In a more preferred embodiment, the vehicle is hydrophilic or water-miscible. Preferably, the vehicle is selected from the group consisting of polyethylene glycols, polyoxyethylene oxides, poloxamers, polyoxyethylene stearates, poly-epsilon caprolactone and mixtures thereof.

[01116] Examples of useful hydrophilic or water-miscible vehicles are polyvinylpyrrolidones, polyvinyl-polyvinylacetate copolymers (PVP-PVA), polyvinyl alcohol (PVA), PVP polymers, acrylic polymers, polymethacrylic polymers (Eudragit RS; Eudragit RL, Eudragit NE; Eudragit E), myristyl alcohol, cellulose derivatives including hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl
cellulose, pectins, cyclodextrins, galactomannans, alginates, carragenates, xanthan gums and mixtures thereof.

[0117] The vehicle is preferably a mixture of two or more substances.

[0118] The vehicle may also be an oily material as defined and described below.

[0119] Preferably, the melting point of the vehicle is preferably in the range of 10°C to 250°C, preferably in the range of 30°C to 100°C, more preferably in the range of 40°C to 75°C, especially in the range of 40°C to 70°C. In specific embodiments of the invention, the hydrophobic or hydrophilic or water-miscible vehicles have a melting point of about 5°C or more such as, e.g., about 10°C or more, about 15°C or more, about 20°C or more or about 25°C or more. Normally, vehicles having such a low melting point require addition of an oil-sorption material. However, a person skilled in the art will know when it is necessary to add such an oil-sorption material.

[0120] In the present context, melting points are determined by DSC (Differential Scanning Calorimetry). The melting point is determined as the temperature at which the linear increase of the DSC curve intersects the temperature axis.

[0121] In a preferred embodiment of the invention, the vehicle is a polyethylene glycol having an average molecular weight in a range of from about 400 to about 35,000 such as, e.g., from about 800 to about 35,000, from about 1,000 to about 35,000 such as, e.g., polyethylene glycol 1,000, polyethylene glycol 2,000, polyethylene glycol 3,000, polyethylene glycol 4,000, polyethylene glycol 5,000, polyethylene glycol 6,000, polyethylene glycol 7,000, polyethylene glycol 8,000, polyethylene glycol 9,000 polyethylene glycol 10,000, polyethylene glycol 15,000, polyethylene glycol 20,000, or polyethylene glycol 35,000. In certain situations polyethylene glycol may be employed with a molecular weight from about 35,000 to about 100,000.

[0122] In another interesting embodiment, the vehicle is polyethylene oxide having a molecular weight of from about 2,000 to about 7,000,000 such as, e.g. from about 2,000 to about 100,000, from about 5,000 to about 75,000, from about 10,000 to about 60,000, from about 15,000 to about 50,000, from about 20,000 to about 40,000, from about 100,000 to about 7,000,000 such as, e.g., from about 100,000 to about 1,000,000, from about 100,000 to about 600,000, from about 100,000 to about 400,000 or from about 100,000 to about 300,000.
[0123] In another embodiment, the vehicle is a poloxamer (PEO-PPO-PEO, a polyethylene oxide-polypropylene oxide-polyethylene oxide tri-block polymer), for example Poloxamer 188, Poloxamer 237, Poloxamer 338 or Poloxamer 407 or other block copolymers of ethylene oxide and propylene oxide such as the Pluronic® and/or Tetronic® series from BASF. Suitable block copolymers of the Pluronic® series include polymers having a molecular weight of about 3,000 or more such as, e.g. from about 4,000 to about 20,000 and/or a viscosity (Brookfield) from about 200 to about 4,000 cps such as, e.g., from about 250 to about 3,000 cps. Suitable examples include Pluronic® F38, P65, P68LF, P75, F77, P84, P85, F87, F88, F98, P103, P104, P105, F108, P123, F123, F127, 10R8, 17R8, 25R5, 25R8 etc. Suitable block copolymers of the Tetronic® series include polymers having a molecular weight of about 8,000 or more such as, e.g., from about 9,000 to about 35,000 and/or a viscosity (Brookfield) of from about 500 to about 45,000 cps such as, e.g., from about 600 to about 40,000. The viscosities given above are determined at 60°C for substances that are pastes at room temperature and at 77°C for substances that are solids at room temperature.

[0124] In a specific embodiment a particulate material according to the invention comprises as vehicle a mixture of a polyethylene glycol and a poloxamer in a proportion (weight) of between about 1:3 and about 10:1, preferably between about 1:1 and about 5:1, more preferably between about 3:2 and about 4:1, especially between about 2:1 and about 3:1, in particular about 7:3.

[0125] In a preferred embodiment of the invention, the poloxamer is poloxamer 188.

[0126] In another preferred embodiment, polyethylene glycol is employed as a vehicle, the PEG having an average molecular weight of about 6000 (PEG 6000).

[0127] The vehicle may also be a sorbitan ester such as, e.g., sorbitan di-isostearate, sorbitan dioleate, sorbitan monolaurate, sorbitan monoisostearate, sorbitan monoooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesqui-isostearate, sorbitan sesquioleate, sorbitan sesquistearate, sorbitan tristearate, sorbitan trioleate, sorbitan tristearate or mixtures thereof.

[0128] The vehicle may also comprise a mixture of different vehicles, for example a mixture of hydrophilic and/or hydrophobic materials.
[0129] Other suitable vehicles may be solvents or semi-solid excipients, for example propylene glycol, complex fatty materials of plant origin including theobroma oil, carnauba wax, vegetable oils like e.g. almond oil, coconut oil, corn oil, cottonseed oil, sesame oil, soy bean oil, olive oil, castor oil, palm kernels oil, peanut oil, rape oil, grape seed oil etc., hydrogenated vegetable oils such as, e.g. hydrogenated peanut oil, hydrogenated palm kernels oil, hydrogenated cottonseed oil, hydrogenated soy bean oil, hydrogenated castor oil, hydrogenated coconut oil; natural fatty materials of animal origin including beeswax, lanolin, fatty alcohols including cetyl, stearyl, lauric, myristic, palmitic, stearic fatty alcohols; esters including glycerol stearate, glycol stearate, ethyl oleate, isopropyl myristate; liquid interesterified semi-synthetic glycerides including Miglycol 810/812; amide or fatty acid alcolamides including stearamide ethanol, diethanolamide of fatty coconut acids, acetic acid esters of mono and di-glycerides, citric acid esters of mono and di-glycerides, lactic acid esters of mono and diglycerides, mono and di-glycerides, poly-glycerol esters of fatty acids, poly-glycerol poly-ricinoleate, propylene glycol esters of fatty acids, sorbitan monostearates, sorbitan tristearates, sodium stearoyl lactylates, calcium stearoyl lactylates, diacetyl tartaric acid esters of mono and diglycerides etc.

[0130] One of the advantages is that it is possible to incorporate a relatively large amount of vehicle and still have a material that is solid. Thus, it is possible to prepare solid compositions with a relatively high load of vehicle by use of an oil sorption material as mentioned above. Within the pharmaceutical field it is an advantage to be able to incorporate a relatively large amount of a vehicle (e.g., with oil or oily-like characteristics) in a solid composition especially in those situations where the active substance does not have suitable properties with respect to water solubility (e.g., poor water solubility), stability in aqueous medium (i.e. degradation occurs in aqueous medium), oral bioavailability (e.g. low bioavailability) etc., or in those situations where it is desired to modify the release of an active substance from a composition in order to obtain a controlled, modified, delayed, sustained and/or pulsed delivery of the active substance.

[0131] It is within the skills of the average practitioner to select a suitable vehicle being pharmaceutical acceptable, capable of dispersing, dissolving or at least partly dissolving the active substances and having a melting point in the desired
range using general knowledge and routine experimentation. Suitable vehicles are for example disclosed in WO 03/004001, which is incorporated herein by reference.

[0132] The solid composition of the invention has a suitable flowability. In order to avoid any adherence to the manufacturing and/or filling equipment it is important that the particulate material is free-flowing. This characteristic is also important in those cases where it is desired to process the particulate material further, for example into solid dosage forms. When the particulate composition of the invention is a free-flowing powder it can be immediately processed into e.g. solid dosage forms such as tablets, capsules or sachets. Normally, the particulate composition has properties so as to allow manufacturing of tablets by direct compression without addition of large amounts of further additives.

[0133] In some embodiments of the invention, the used vehicle is an oily material which may be present in a relatively high amount. In such cases it may be necessary to include in the material a substance that has adsorbing or absorbing properties so that the final particulate material appears as a non-oily powder and not during storage release some of the vehicle that could result in a oily surface. Accordingly, the particulate material may contain one or more oil-sorption materials, which - when tested as described herein - i) has an oil threshold value of 10% or more, when tested according to the Threshold Test herein, and at least one of ii) releases at least 30% of an oil, when tested according to the Release Test herein, and iii) in the form of a tablet, has a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more of the oil-sorption material. In certain situations, it has been found that it is an advantage to incorporate a sorption material in the composition in order e.g., to enable a high concentration of a vehicle has oil or oily-like character. In those cases where the vehicle has a melting point of at the most about 25°C, it may be especially suitable to incorporate a sorption material. Suitable examples of materials suitable as vehicles as well as sorption materials are given herein.

Pharmaceutically acceptable excipients and additives

[0134] In the present context the term "pharmaceutically acceptable excipient(s)" is intended to denote any material, which is inert in the sense that it substantially
does not have any therapeutic and/or prophylactic effect per se. Such an excipient may be added with the purpose of making it possible to obtain a pharmaceutical, cosmetic and/or foodstuff composition, which have acceptable technical properties. A pharmaceutical composition or a solid dosage form according to the invention may contain one or more pharmaceutically acceptable excipients.

[0135] Examples of suitable excipients for use in a composition or solid dosage form according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixtures thereof. As the composition or solid dosage form according to the invention may be used for different purposes, the choice of excipients is normally made taken such different uses into considerations. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalizing agents, preservatives, antioxidants, buffering agents, chelating agents, coloring agents, complexing agents, emulsifying and/or solubilizing agents, flavors and perfumes, humectants, sweetening agents, wetting agents etc.

[0136] Examples of suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, a-lactose, b-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivace®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g., Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g., basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

[0137] Specific examples of diluents are e.g., calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose,
powdered cellulose, dextans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pre-gelatinized starch, sucrose, sugar etc.

[0138] Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrilllin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

[0139] Specific examples of binders are e.g., acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

[0140] Glidants and lubricants may also be included in the second composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

[0141] Other excipients which may be included in a composition or solid dosage form of the invention are e.g., flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

[0142] Other additives in a composition or a solid dosage form according to the invention may be antioxidants like e.g. ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, potassium metabisulfite, propyl gallate, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sulfur dioxide, tocopherol, tocopherol acetate, tocopherol hemisuccinate, TPGS or other tocopherol derivatives, etc. The carrier composition may also contain e.g., stabilising agents. The concentration of an antioxidant and/or a stabilizing agent in the carrier composition is normally from about 0.1 % w/w to about 5% w/w.

[0143] A composition or solid dosage form according to the invention may also include one or more surfactants or substances having surface-active properties. It
is contemplated that such substances are involved in the wetting of the slightly soluble active substance and thus, contributes to improved solubility characteristics of the active substance. Suitable surfactants for use in a composition or a solid dosage form according to the invention are surfactants such as, e.g., hydrophobic and/or hydrophilic surfactants as those disclosed in WO 00/50007 in the name of Lipocine, Inc.

[0144] Specific examples of suitable surfactants are polyethoxylated fatty acids such as, e.g., fatty acid mono- or diesters of polyethylene glycol or mixtures thereof such as, e.g., mono- or diesters of polyethylene glycol with lauric acid, oleic acid, stearic acid, myristic acid, ricinoleic acid, and the polyethylene glycol may be selected from PEG 4, PEG 5, PEG 6, PEG 7, PEG 8, PEG 9, PEG 10, PEG 12, PEG 15, PEG 20, PEG 25, PEG 30, PEG 32, PEG 40, PEG 45, PEG 50, PEG 55, PEG 100, PEG 200, PEG 400, PEG 600, PEG 800, PEG 1000, PEG 2000, PEG 3000, PEG 4000, PEG 5000, PEG 6000, PEG 7000, PEG 8000, PEG 9000, PEG 1000, PEG 10,000, PEG 15,000, PEG 20,000, PEG 35,000, polyethylene glycol glycerol fatty acid esters, i.e. esters like the above-mentioned but in the form of glyceryl esters of the individual fatty acids; glycerol, propylene glycol, ethylene glycol, PEG or sorbitol esters with e.g., vegetable oils like e.g., hydrogenated castor oil, almond oil, palm kernel oil, castor oil, apricot kernel oil, olive oil, peanut oil, hydrogenated palm kernel oil and the like, polyglycerized fatty acids like e.g., polyglycerol stearate, polyglycerol oleate, polyglycerol ricinoleate, polyglycerol linoleate, propylene glycol fatty acid esters such as, e.g., propylene glycol monolaurate, propylene glycol ricinoleate and the like, mono- and diglycerides like e.g. glyceryl monooleate, glyceryl dioleate, glyceryl mono- and/or dioleate, glyceryl caprylate, glyceryl caprate etc.; sterol and sterol derivatives; polyethylene glycol sorbitan fatty acid esters (PEG-sorbitan fatty acid esters) such as esters of PEG with the various molecular weights indicated above, and the various Tween® series (from ICI America, Inc.); polyethylene glycol alkyl ethers such as, e.g., PEG oleyl ether and PEG lauryl ether; sugar esters like e.g. sucrose monopalmitate and sucrose monolaurate; polyethylene glycol alkyl phenols like e.g. the Triton® X or N series (Union Carbide Chemicals & Plastics Technology Corporation); polyoxyethylene-polyoxypropylene block copolymers such as, e.g., the Pluronic® series from BASF Aktiengesellschaft, the Synperonic® series from
ICI America, Inc., Emkalyx, Lutrol® from BASF Aktiengesellschaft, Supronic etc. The generic term for these polymers is "poloxamers" and relevant examples in the present context are Poloxamer 105, 108, 122, 123, 124, 181, 182, 183, 184, 185, 188, 212, 215, 217, 231, 234, 235, 237, 238, 282, 284, 288, 331, 333, 334, 335, 338, 401, 402, 403 and 407; sorbitan fatty acid esters like the Span® series (from ICI) or Arlacel® series (from ICI) such as, e.g., sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate etc.; lower alcohol fatty acid esters like e.g., oleate, isopropyl myristate, isopropyl palmitate etc.; ionic surfactants including cationic, anionic and zwitterionic surfactants such as, e.g., fatty acid salts, bile salts, phospholipids, phosphoric acid esters, carboxylates, sulfates and sulfonates etc.

[0145] When a surfactant or a mixture of surfactants is present in a composition or a solid dosage form of the invention, the concentration of the surfactant(s) is normally in a range of from about 0.1 – 80% w/w such as, e.g., from about 0.1 to about 20% w/w, from about 0.1 to about 15% w/w, from about 0.5 to about 10% w/w, or alternatively, from about 0.10 to about 80% w/w such as, e.g. from about 10 to about 70% w/w, from about 20 to about 60% w/w or from about 30 to about 50% w/w.

[0146] In a specific aspect of the invention, the at least one of the one or more pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

Sorption materials

[0147] Materials such as those mentioned immediately above are especially useful as a sorption material for oily materials in pharmaceuticals, cosmetics and/or foodstuff. In a specific embodiment, the material is used as a sorption material for oily materials in pharmaceuticals. The material that has the ability to function as a sorption material for oily materials is also denoted "oil sorption material".

[0148] Furthermore, in the present context the term "sorption" is used to denote "absorption" as well as "adsorption". It should be understood that whenever one of the terms is used it is intended to cover the phenomenon absorption as well as
adsorption. The terms "sorption material" and "oil sorption material" is intended to have the same meaning.

[0149] A sorption material suitable for use according to the present invention is a solid pharmaceutically acceptable material, which - when tested as described herein - i) has an oil threshold value of 10% or more, when tested according to the Threshold Test disclosed herein, and which material is used in a composition of the invention further fulfilling one or both of i) and ii): i) the composition releases at least 30% of the hydrophobic or a hydrophilic or water-miscible vehicle, when tested according to the Release Test; ii) the composition contains, in the form of a tablet, at least about 90% w/w of the oil-sorption material, and exhibits a disintegration time of at the most 60 minutes when tested according to the Ph. Eur. Disintegration Test.

[0150] The material is especially useful as a sorption material for oily materials in pharmaceuticals, cosmetics and/or foodstuff, especially in pharmaceuticals.

[0151] It is important that the oil sorption material fulfils at least two tests. One of the tests is mandatory, i.e. the Threshold Test must be met. This test gives a measure for how much oily material the oil sorption material is able to absorb while retaining suitable flowability properties. It is important that an oil sorption material for use according to the invention (with or without oil absorbed) has a suitable flowability so that it easily can be admixed with other excipients and/or further processed into compositions without significant problems relating to e.g. adherence to the apparatus involved. The test is described below in Materials and Methods and guidance is given for how the test is carried out. The Threshold Test involves the determination of the flowability of the solid material loaded with different amounts of oil.

[0152] From above it is seen that the oil threshold value normally must exceed 10% and often the oil sorption material has an oil threshold value of at least about 15%, such as, e.g., at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, or at least about 45%.

[0153] An especially suitable material for use according to the invention, Aeroperl® 300, has a very high oil threshold value of about 60%. Accordingly, materials that have an oil threshold value of at least about 50%, such as, e.g., at least about
55% or at least about 60% are used in specific embodiments of the present invention.

[0154] Furthermore, an oil sorption material for use according to the invention must fulfil at least one further test, namely a release test and/or a disintegration test.

[0155] The release test gives a measure of the ability of an oil sorption material to release the oil that is absorbed to the material when contacted with water. This ability is very important especially in those situations where an active substance is contained in the oily material. If the oil sorption material is not capable of releasing the oil from the material then there is a major risk that the active substance will only to a minor degree be released from the material. Accordingly, it is envisaged that bioavailability problems relating to e.g., poor absorption etc. will occur in such situations.

[0156] The requirements for the release test are that the solid pharmaceutical acceptable material, when tested as described herein, releases at least about 30% such as, e.g., at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 60% of an oil. As it appears from the examples herein a suitable oil sorption material like Aeroperl® 300 has a much higher release. Therefore, in a specific embodiment of the invention, the solid pharmaceutical acceptable material, when tested as described herein, releases at least about 65% such as, e.g., at least about 70%, at least about 75% or at least about 80% of an oil.

[0157] The disintegration test is not performed on the solid composition in particulate form but on a tablet made of the solid material. A requirement with respect to disintegration is important in order to ensure that the solid composition, when included in solid dosage forms, does not impart unwanted properties to the dosage form e.g., leading to unwanted properties with respect to dissolution and bioavailability of the active substance contained in the dosage form. For some of the materials suitable for use according to the invention it is possible to press tablets containing 100% w/w of the solid material itself. If this is the case, the test is carried out on such tablets. However, it is envisaged that there may be situations where it is rather difficult to prepare tablets from the solid material alone. In such cases it is possible to add pharmaceutically acceptable excipients normally used in the preparation of compressed tablets up to a concentration of 10% w/w or
less. Examples of suitable pharmaceutically acceptable excipients include fillers, diluents, binders and lubricants. However, excipients, normally classified as disintegrants, should be avoided.

[0158] Accordingly, the solid pharmaceutical acceptable material for use according to invention, when tested as described herein, in the form of a tablet should have a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the pharmaceutically acceptable material.

[0159] In a further embodiment, the solid pharmaceutical acceptable material, when tested as described herein, in the form of a tablet has a disintegration time of at the most about 50 min, such as, e.g., at the most about 40 min, at the most about 30 min, at the most about 20 min, at the most about 10 min or at the most about 5 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the pharmaceutically acceptable material.

[0160] In a specific embodiment, the solid material used as a sorption material fulfils all three tests. Thus, the solid pharmaceutical acceptable material, when tested as described herein, i) has an oil threshold value of at least about 10%, such as, e.g., at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 60%, ii) releases at least about 30% such as, e.g., at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75% or at least about 80% of an oil, and iii) in the form of a tablet has a disintegration time of at the most 1 hour such as at the most about 50 min, at the most about 40 min, at the most about 30 min, at the most about 20 min, at the most about 10 min or at the most about 5 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the pharmaceutically acceptable material.
[0161] Other specific embodiments of the invention are those, wherein the solid pharmaceutical material used as a sorption material in a composition of the invention, when tested as described herein, i) has an oil threshold value of at least about 55%; the solid pharmaceutical material, when tested as described herein, ii) releases at least about 75% of an oil; and/or the solid pharmaceutical material, when tested as described herein, iii) in the form of a tablet has disintegration time of at the most about 10 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 97.5% w/w of the pharmaceutically acceptable material.

[0162] The solid pharmaceutically acceptable material used as a sorption material in a composition according to the invention is normally a particulate material in the form of e.g. powders, particles, granules, granulates etc.

[0163] Such particulate material suitable for use as an oil sorption material has normally a bulk density of about 0.15 g/cm³ or more such as, e.g., at least about 0.20 g/cm³ or at least about 0.25 g/cm³.

[0164] Furthermore, the oil sorption material normally has an oil absorption value of at least about 100 g oil/100 g such as, e.g., at least about 150 g oil/100 g, at least about 200 g oil/100g, at least about 250 g oil/100 g, at least about 300 g oil/100 g or at least about 400 g oil/100 g pharmaceutically acceptable material. The oil absorption value is determined as described in the experimental section herein.

[0165] The present inventors have found that a common feature of some of the materials suitable for use as oil sorption material is that they have a relatively large surface area. Accordingly, pharmaceutically acceptable material for use as an oil sorption material according to the invention may have a BET surface area of at least 5 m²/g such as, e.g., at least about 25 m²/g, at least about 50 m²/g, at least about 100 m²/g, at least about 150 m²/g, at least about 200 m²/g, at least about 250 m²/g or at least about 275 m²/g.

[0166] As mentioned above one of the characteristic features of a pharmaceutically acceptable material for use as an oil sorption material according to the invention is that it retains a good flowability even if it has been loaded with oily material. Thus, the flowability of the pharmaceutically acceptable material loaded with about 25% w/w or more such as, e.g. about 30% w/w or more, about
40% w/w or more, about 45% w/w or more, about 50% w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more or about 70% w/w viscoleo will normally meet the Ph. Eur. requirements.

[0167] Notably, the oil sorption material may comprise a silica acid or a derivative or salt thereof such as, e.g., silicon dioxide or a polymer thereof as a pharmaceutically acceptable excipient. However, dependent on the quality employed a silicon dioxide may be a lubricant or it may be an oil sorption material. Qualities fulfilling the latter function seem to be most important.

[0168] In a specific embodiment, a composition or solid dosage form according to invention comprises a pharmaceutically acceptable excipient that is a silicon dioxide product that has properties corresponding to Aeroperl® 300.

[0169] Use of an oil sorption material in compositions or dosage forms according to the invention is very advantageous for the preparation of pharmaceutical, cosmetic, nutritional and/or food compositions, wherein the composition comprises oily material. One of the advantages is that it is possible to incorporate a relatively large amount of and oily material and still have a material that is solid. Thus, it is possible to prepare solid compositions with a relatively high load of oily materials by use of an oil sorption material according to the invention. Within the pharmaceutical field it is an advantage to be able to incorporate a relatively large amount of an oily material in a solid composition especially in those situation where the active substance does not have suitable properties with respect to water solubility (e.g. poor water solubility), stability in aqueous medium (i.e. degradation occurs in aqueous medium), oral bioavailability (e.g. low bioavailability) etc., or in those situations where it is desired to modify the release of an active substance from a composition in order to obtain a controlled, delayed, sustained and/or pulsed delivery of the active substance. Thus, in a specific embodiment it is used in the preparation of pharmaceutical compositions.

[0170] The oil sorption material for use in the processing into solid compositions normally absorbs about 5% w/w or more, such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more,
about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of an oil or an oily material and is still a solid material.

[0171] The oils and oily-like materials that can be absorbed are normally liquid at ambient or elevated temperature (for practical reasons the max. temperature is about 250°C). They may be hydrophilic, lipophilic, hydrophobic and/or amphiphilic materials.

Method of manufacture

[0172] The particulate composition of the invention may be prepared by any method which is suitable for incorporation of poorly water-soluble active substances. The pharmaceutical compositions may be prepared by any convenient method such as, e.g. granulation, mixing, spray drying etc. A particularly useful method is the method disclosed in Applicants’ co-pending international application published as WO 03/004001, which describes a process for preparation of particulate material by a controlled agglomeration method, i.e. a method, which enables a controlled growth in particle size. The method involves spraying a first composition comprising the active substance and a vehicle in liquid form onto a solid carrier. Normally, the vehicle has a melting point of at least 5°C, but the melting point must indeed be below the melting point of the active substance. In the present invention, the melting point of the vehicle and should not exceed 250°C.

[0173] It is within the skills of the average practitioner to select a suitable vehicle being pharmaceutical acceptable, capable of dispersing or fully or at least partly dissolving the active substance and having a melting point in the desired range using general knowledge and routine experimentation. Suitable candidate for carriers are described in WO 03/004001, which is herein incorporated by reference.

[0174] In the present context, suitable vehicles are e.g., those mentioned as vehicles or as oily materials as well as those disclosed in WO 03/004001. An advantage of using the controlled agglomeration method described in WO 03/004001 is that it is possible to apply a relatively large amount of a liquid system to a particulate material without having an undesirable growth in particle size. Accordingly, in one embodiment of the invention, the particulate material of a pharmaceutical composition has a geometric weight mean diameter $d_{gw}$ of ≥ 10
mm such as, e.g. ≥ 20 mm, from about 20 to about 2000, from about 30 to about 2000, from about 50 to about 2000, from about 60 to about 2000, from about 75 to about 2000 such as, e.g. from about 100 to about 1500 mm, from about 100 to about 1000 mm or from about 100 to about 700 mm, or at the most about 400 mm or at the most 300 mm such as, e.g., from about 50 to about 400 mm such as, e.g., from about 50 to about 350 mm, from about 50 to about 300 mm, from about 50 to about 250 mm or from about 100 to about 300 mm.

[0175] The compositions and dosage forms of the invention are preferably formed by spray drying techniques, controlled agglomeration, freeze-drying or coating on carrier particles or any other solvent removal process. The dried product contains the active substances present preferably in dissolved form either fully dissolved as a solid solution, for example forming an interstitial crystalline solid solution, or partly dissolved as a solid dispersion including a molecular dispersion and a solid solution.

[0176] However, the composition and dosage forms of the invention are preferably manufactured by a method comprising the steps of: i) bringing the vehicle in liquid form, i.e. melting the vehicle if solid at room temperature, ii) maintaining the liquid vehicle at a temperature below the melting point of the fibrate, iii) dissolving the desired amount of fibrate in the vehicle, iv) spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle, v) mechanically working the resulting composition to obtain particles, i.e. a particulate material, and vi) optionally subjecting the particulate material to conventional methods for preparing solid dosage forms.

[0177] Alternatively, the solid oral dosage form of the invention may be prepared by a method comprising the steps of i) Bringing the vehicle in liquid form, if applicable, ii) Maintaining the liquid vehicle at a temperature below the melting point of fenofibrate or a pharmaceutically acceptable salt thereof, iii) Dissolving the desired amount of fibrate in the vehicle, iv) Spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle, v) Mechanically working the resulting composition to obtain particles, i.e. a particulate material containing fenofibrate, and, prior to or simultaneous with or after applying steps i) to v), vi) Bringing the vehicle in liquid form, if applicable, vii) Maintaining the liquid vehicle at a temperature below the melting point of simvastatin or a
pharmaceutically acceptable salt thereof, viii) Dissolving the desired amount of simvastatin in the vehicle, ix) Spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle, x) Mechanically working the resulting composition to obtain particles, i.e. a particulate material containing simvastatin, followed by the steps of xi) Mixing the particulate material containing fenofibrate and the particulate material containing simvastatin, and xii) Optionally subjecting the particulate material to conventional methods for preparing solid dosage forms.

[0178] In yet another embodiment, the solid oral dosage form of the invention is prepared by a method comprising the steps of: i) bringing the vehicle in liquid form, if applicable, ii) maintaining the liquid vehicle at a temperature below the melting point of fenofibrate or a pharmaceutically acceptable salt thereof, iii) dissolving the desired amount of fenofibrate in the vehicle, iv) spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle, v) Mechanically working the resulting composition to obtain particles, i.e. a particulate material containing fenofibrate, and, prior to or simultaneous with or after applying steps i) to v), vi) micronizing simvastatin or a pharmaceutically acceptable salt thereof, if applicable, followed by the steps of vii) mixing the particulate material containing fenofibrate and micronized simvastatin, and viii) optionally subjecting the particulate material to conventional methods for preparing solid dosage forms.

[0179] In yet another embodiment, the solid oral dosage form of the invention is prepared by a method comprising the steps of: i) Bringing the vehicle for fibrate in liquid form, if applicable, ii) Maintaining the liquid vehicle at a temperature below the melting point of the fibrate or a pharmaceutically acceptable salt thereof, iii) Dissolving the desired amount of fibrate in the vehicle, iv) Spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle, v) Mechanically working the resulting composition to obtain particles, i.e. a particulate material containing fibrate, and, prior to or simultaneous with or after applying steps i) to v), vi) Bringing the vehicle for simvastatin in liquid form, if applicable, vii) dissolving or dispersing the desired amount of simvastatin in the vehicle, viii) Spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle, ix) Mechanically working the resulting composition to obtain particles, i.e. a particulate material containing
simvastatin, x) subjecting the particles to enteric coating, followed by the steps of
xi) Mixing the particulate material containing fibrate and the entero-coated
particulate material containing simvastatin, and xii) Optionally subjecting the
particulate material to conventional methods for preparing solid dosage forms, for
example compression into tablets of filling into capsules or sachets.

[0180] In an important embodiment of the invention, at least part of the active
substances is present in the composition in the form of a solid dispersion including
a molecular dispersion and a solid solution and an interstitial crystalline solid
solution. Normally, about 10% or more such as, e.g., about 20% or more, about
30% or more, about 40% or more, about 50% or more, about 60% or more, about
70% or more, about 80% or more, about 90% or more such as, e.g., about 95% or
more or about 100% w/w of either the fenofibrate or the simvastatin is present in
the vehicle in the form of a solid dispersion, provided that at least about 80% w/w
of the total amount of active substances is dissolved in the vehicle.

[0181] The pharmaceutical compositions comprising the active substance at least
partly in form of a solid dispersion or solution may in principle be prepared using
any suitable procedure for preparing pharmaceutical compositions known within
the art.

[0182] A solid dispersion may be obtained in different ways e.g., by employing
organic solvents or by dispersing or dissolving the active substance in another
suitable medium (e.g. an oily material that is in liquid form at room temperature or
at elevated temperatures). Solid dispersions (solvent method) are prepared by
dissolving a physical mixture of the active substance (e.g. a drug substance) and
the carrier in a common organic solvent, followed by evaporation of the solvent.
The carrier is often a hydrophilic polymer. Suitable organic solvents include
pharmaceutical acceptable solvent in which the active substance is soluble such
as methanol, ethanol, methylene chloride, chloroform, ethylacetate, acetone or
mixtures thereof.

[0183] Suitable water-soluble carriers include polymers such as polyethylene
glycol, poloxamers, polyoxyethylene stearates, poly-epsilon-caprolactone,
polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-
PVA (Kollidon VA64), poly-methacrylic polymers (Eudragit RS, Eudragit RL,
Eudragit NE, Eudragit E) and polyvinyl alcohol (PVA), hydroxypropyl cellulose
(HPC), hydroxypropyl methyl cellulose (HPMC), methyl cellulose, and poly(ethylene oxide) (PEO).

[0184] Polymers containing acidic functional groups may be suitable for solid dispersions, which release the active substance in a preferred pH range providing acceptable absorption in the intestines. Such polymers may be one or more selected from the group comprising hydroxypropyl methylcellulose phtalate (HMPCP), polyvinyl acetate phtalate (PVAP), hydroxypropylethylcellulose acetate succinate (HPMCAS), alginate, carborner, carboxymethylcellulose, methacrylic acid copolymer (Eudragit L, Eudragit S), shellac, cellulose acetate phthalate (CAP), starch glycolate, polacrylin, methyl cellulose acetate phtalate, hydroxypropylethylcellulose acetate phthalate, cellulose acetate terephtahalate, cellulose acetate isophthalate and cellulose acetate trimellitate.

[0185] The weight ratio of active substance to polymer may be in a range of from about 3:1 to about 1:20. However, narrower ranges of from about 3:1 to about 1:5, such as, e.g., from about 1:1 to about 1:3 or about may also be used.

[0186] Apart from using the organic solvent based method, solid dispersion or solid solutions of one or more fibrates may be also obtained by dispersing and/or dissolving the active compound in the carrier composition used in the controlled agglomeration method. Stabilizing agents etc. may be added in order to ensure the stability of the solid dispersion/solution.

[0187] There are a number of methods for combining fenofibrate and simvastatin in the composition or solid dosage form of the invention:

1. In a first embodiment, a fenofibrate granulate is prepared as disclosed in International Application PCT/DK2004/000667 and example 9 herein. The fenofibrate granulate may be in the form of an immediate release formulation or in the form of a delayed release or even a controlled release formulation. A simvastatin granulate is prepared in the same manner as the fenofibrate granulate, i.e. by dissolving or dispersing simvastatin in a suitable vehicle such as the vehicle used for dissolving/dispersing fenofibrate and spraying the dispersion onto a suitable carrier to obtain a granulate. The two granulates are mixed and either compressed into tablets or filled into hard gelatine capsules. The simvastatin granulate is optionally subjected to enterico-coating prior to mixing, thus providing a
controlled release simvastatin formulation. The simvastatin granulate may also be in the form of a delayed release formulation.

2. In a second embodiment, a single granulate of fenofibrate and simvastatin is prepared by dissolving fenofibrate together with simvastatin in a suitable vehicle as described herein, followed by spraying the solution (or dispersion) on a a suitable carrier (as described herein), thereby obtaining a particulate material, i.e. a single granulate, which may be compressed into tablets in a conventional manner or filled into hard gelatine capsules.

3. In a third embodiment, a single granulate of fenofibrate and simvastatin is prepared by dissolving fenofibrate in a suitable vehicle as described herein, followed by spraying the solution (or dispersion) on a mixture of a suitable carrier (as described herein) and the desired amount of simvastatin, thereby obtaining a particulate material, i.e. a single granulate, which may be compressed into tablets in a conventional manner or filled into hard gelatine capsules.

4. In a fourth embodiment, a fenofibrate granulate is prepared as disclosed in International Application PCT/DK2004/000667 and example 9 herein.

5. An simvastatin granulate corresponding to the granulate composition of Zocor® tablets is prepared. The two granulates are mixed and either comprosseinto tablets or filled into hard gelatine capsules.

6. In a fifth embodiment, a fenofibrate granulate is prepared as disclosed in International Application PCT/DK2004/000667 and example 9 herein. Simvastatin is micronized and mixed with fenofibrate granulate and optionally conventional excipients and/or additives such as glidants, fillers, binders or disintegrators. The mixture may be compressed into tablets or filled into hard gelatine capsules.

7. In a sixth embodiment, a fenofibrate granulate is prepared as disclosed in International Application PCT/DK2004/000667 and example 9 herein. Granulate is compressed into a tablet, and the tablet is coated with an aqueous suspension comprising a sufficient amount of simvastatin including a film-forming polymer and stabilizers (antioxidants). The tablets might be sub-coated with a film-forming polymer before coating with the statin suspension below.

[0188] Examples of film polymers include water soluble agents such as hydroxypropylmethylcellulose, Metolose® (HPMC), hydroxypropylmethylcellulose, Klucel® (HPC), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP) or
combinations of PVA and PVP (Kollicoat® IR) and acid soluble acrylic polymer (Eudragit E, soluble in gastric juice).

[0189] Examples of antioxidants includes butylhydroxyanisol (BHA), ascorbyl palmitate, ascorbic acid or combinations of BHA, ascorbyl palmitate and citric acid.

[0190] Wetting and pH adjusting agent might be included in the coating suspension.

[0191] The amount of simvastatin in the coating suspension is between about 2% w/w and about 40% w/w, such as for example between about 5% w/w and about 30% w/w. The skilled person will know how to determine the exact amount of simvastatin in the coating composition, when the desired amount of simvastatin in the final composition and/or dosage form is known, for example 20 mg simvastatin and 120 mg fenofibrate.

[0192] Coating of fenofibrate tablets is performed in conventional coating equipment such as drum coater, perforated vessel or fluidized bed (Wurster insert).

[0193] The simvastatin coated fenofibrate tablets might be further coated with a suitable polymer to protect the simvastatin from degradation.

Solid dosage forms

[0194] The pharmaceutical composition according to the invention is in solid, particulate form and may be employed as such. However, in many cases it is more convenient to present the composition in the form of granules, pellets, microspheres, nanoparticles and the like or in the form of solid dosage forms including tablets, tablets, beads, capsules, grains, pills, granulates, granules, powder, pellets, sachets, lozenges, troches and the like.

[0195] A solid dosage form according to the invention may be a single unit dosage form or it may in the form of a poly-depot dosage form contain a multiplicity of individual units such as, e.g., pellets, beads and/or granules.

[0196] Usually, a pharmaceutical composition or a solid dosage form of the invention is intended for administration via the oral, buccal or sublingual administration route.

[0197] The dosage form of the invention is truly a solid, i.e. the dosage form does not comprise any liquid, semi-liquid or semi-solid material. Neither does the solid
dosage form of the invention comprise a suspension, an emulsion or a micro-emulsion.

[0198] The invention also relates to the above-mentioned presentation form. Within the scope of the invention are compositions/solid dosage forms that are intended to release the active substance in a fast release, a delayed release or modified release manner.

[0199] A solid dosage form according to the present invention comprises a pharmaceutical composition in particulate form as described above. The details and particulars disclosed under this main aspect of the invention apply mutatis mutandis to the other aspects of the invention. Accordingly, the properties with respect to increase in bioavailability, changes in bioavailability parameters, reduction in adverse food effect as well as release of one or more fibrates etc. described and/or claimed herein for pharmaceutical compositions in particulate form are analogues for a solid dosage form according to the present invention.

[0200] The solid dosage form of the invention, i.e. in unit dosage form, comprises comprises from about 30 to about 170 mg of fenofibrate and from about 5 to about 80 mg of simvastatin or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the unit dosage form comprises about 160 mg of fenofibrate, or about 145 mg of fenofibrate, or about 130 mg, or about 120 mg of fenofibrate, or about 110 mg of fenofibrate, and about 10 mg of simvastatin, or about 15 mg of simvastatin, or about 20 mg of simvastatin, or about 25 mg of simvastatin, or about 30 mg of simvastatin, or about 40 mg of simvastatin, or of a pharmaceutically acceptable salt of simvastatin. Preferably, the unit dosage form comprises fenofibrate and simvastatin or pharmaceutically acceptable salt thereof in the (relative) weight ratio between fenofibrate and simvastatin or a pharmaceutically acceptable salt thereof from about 1:1 to about 40:1.

[0201] Usually, the concentration of the pharmaceutical composition in particulate form is in a range of from about 5 to 100% w/w such as, e.g., from about 10% to about 90% w/w, from about 15% to about 85% w/w, from about 20% to about 80% w/w, from about 25% to about 80% w/w, from about 30% to about 80% w/w, from about 35% to about 80% w/w, from about 40% to about 75% w/w, from about 45% to about 75% w/w or from about 50% to about 70% w/w of the dosage form. In an
embodiment of the invention, the concentration of the pharmaceutical composition in particulate form is 50% w/w or more of the dosage form.

[0202] The solid dosage forms of the invention are stable. For example, the fenofibrate is present in an amount of at least about 90%, or at least about 95%, or at least about 99.3%, or at least about 100%, relative to the amount prior to storage, when assayed after 3 months of storage at a temperature of about 40°C and a relative humidity of about 75%. Also, the physical stability is high as can be seen from the Examples below.

[0203] The solid dosage form according to the invention is obtained by processing the particulate material according to the invention by means of techniques well-known to a person skilled in the art. Usually, this involves further addition of one or more of the pharmaceutically acceptable excipients mentioned herein.

[0204] The composition or solid dosage form according to the invention may be designed to release fenofibrate and/or simvastatin in any suitable manner provided that the increase in bioavailability is maintained. Thus, the active substance(s) may be released relatively fast in order to obtain an enhanced on-set of action, it may be released so as to follow zero or first order kinetics or it may be released in a controlled or modified manner in order to obtain a predetermined pattern of release. Plain formulations are also within the scope of the present invention.

[0205] The composition or solid dosage form according to the invention may also be coated with a film coating, an enteric coating, a modified release coating, a protective coating, an anti-adhesive coating etc. In one embodiment of the invention, a controlled release profile of simvastatin is obtained by means of applying a time-controlled coating or enzyme controlled coating or a pressure controlled coating.

[0206] A solid dosage form according to the invention may also be coated in order to obtain suitable properties e.g. with respect to release of the active substance. The coating may be applied on single unit dosage forms (e.g. tablets, capsules) or it may be applied on a poly-depot dosage form or on its individual units.

[0207] Suitable coating materials are e.g. methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate,
cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, zein.

[0208] Plasticizers and other ingredients may be added in the coating material. The same or different active substance may also be added in the coating material. [0209] The pharmaceutical composition or a solid dosage form according to the invention is designed to release the fenofibrate in a suitable manner. Specific release patterns are disclosed in the appended claims to which reference is made. Herein is also given specific relevant absorption patterns. In specific embodiments, the compositions (i.e. particulate material or the solid dosage form) may increase the bioavailability of the fibrate and/or the simvastatin after oral administration. The active substances may be released relatively fast in order to obtain an enhanced on-set of action, it may be released so as to follow zero or first order kinetics or it may be released in a controlled or modified manner in order to obtain a predetermined pattern of release. Plain formulations are also within the scope of the present invention.

[0210] In a specific embodiment a solid dosage form of the invention results in an increased bioavailability of fenofibrate and/or simvastatin relative to existing commercial fenofibrate and/or simvastatin dosage forms when administered to a mammal in need thereof.

[0211] With respect to fenofibrate a solid dosage form according to the invention may provide an \( AUC_{0-24} \) value of fibrin acid relative to that of commercially available Tricor\textsuperscript{®} (Lipanthyl \textsuperscript{®}) tablets, or alternatively of commercially available Antara\textsuperscript{®} capsules, of at least about 1.1, or at least about 1.2, or at least about 1.3, or at least about 1.4, or at least about 1.5, or at least about 1.75 or more, or at least about 2.0, or at least about 2.5, or at least about 3.0, the \( AUC_{0-24} \) values being determined under similar conditions. Moreover, a solid dosage form may provide a \( c_{\text{max}} \) value relative to that of commercially available Tricor\textsuperscript{®} (Lipanthyl \textsuperscript{®}) tablets, or alternatively of commercially available Antara\textsuperscript{®} capsules, of at least about 1.1, or at least about 1.2, or at least about 1.3, or at least about 1.4, or at least about 1.5, or at least about 1.6 or more, or at least about 2.0, or at least about 2.5, or at least about 3.0, the \( c_{\text{max}} \) values being determined under similar conditions.
[0212] With respect to simvastatin, a solid dosage form according to the invention may provide an AUC$_{0-24}$ value relative to that of commercially available Zocor® tablets of at least about 1.0, or at least about 1.1, or at least about 1.23, or at least about 1.3, or at least about 1.4, or at least about 1.75 or more, or at least about 2.0, or at least about 2.5, or at least about 3.0, the AUC$_{0-24}$ values being determined under similar conditions. Moreover, a solid dosage form may provide a $c_{\text{max}}$ value relative to that of commercially available Zocor® tablets of at least about 1.0, or at least about 1.1, or at least about 1.3, or at least about 1.4, or at least about 1.5 or more, or at least about 2.0, or at least about 2.5, or at least about 3.0, the $c_{\text{max}}$ values being determined under similar conditions.

[0213] In a typical average blood plasma sample, the AUC$_{0-24}$ of fenofibrate resulting from the administration of 160 mg fenofibrate tablets are about 118,300 ng h/mL. However, wide individual variations in bioavailability are usually observed.

Other aspects of the invention

[0214] A pharmaceutical composition or a solid dosage form according to the invention is designed to release the fenofibrate in a suitable manner. Specific release patterns as well as specific absorption patterns are mentioned below.

[0215] In specific embodiments, the fenofibrate and/or the simvastatin is released from the composition within about 2 hours such as, e.g., within about 1.5 hours or within about 1 hour after oral administration, and/or about 50% w/w or more of the fibrate and/or the statin is released from the composition within about 30 min after oral administration, and/or about 50% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min after oral administration, and/or about 60% w/w or more of the fibrate is released from the composition within about 1.5 hours after oral administration, and/or about 60% w/w or more of the fibrate and/or the statin is released from the composition within about 1 hour after oral administration, and/or about 70% w/w or more of the fibrate and/or the statin is released from the composition within about 1.5 hours after oral administration, and/or about 70% w/w or more of the fibrate and/or the statin is released from the composition within about 1 hour after oral administration, and/or about 85% w/w or more of the fibrate and/or the statin is released from the composition within about 45 min when tested in an in vitro dissolution test.
according to USP dissolution test (paddle) employing water as dissolution medium, 100 rpm and a temperature of about 37°C.

[0216] In another embodiment about 50% w/w or more of the fenofibrate and/or the simvastatin is released from the composition within about 20 min, 15 min or 10 min, and/or about 60% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min or 15 min, and/or about 70% w/w or more of the fibrate and/or the statin is released from the composition within about 20 min or 15 min, when tested in an in vitro dissolution test according to USP dissolution test (paddle) employing water as dissolution medium, 100 rpm and a temperature of about 37°C.

[0217] In a still further embodiment about 50% w/w or more of the fenofibrate and/or the simvastatin contained in the composition is absorbed within about 8 hours, 7 hours, 6 hours or 5 hours, and/or about 60% w/w or more of the fibrate and/or statin contained in the composition is absorbed within about 8 hours or 7 hours after oral administration, and/or about 60% w/w or more of the fibrate contained in the composition is absorbed within about 7 hours after oral administration, and/or about 70% w/w or more of the fibrate contained in the composition is absorbed within about 8 hours or 7 hours after oral administration.

[0218] The details and particulars disclosed under this main aspect of the invention apply mutatis mutandis to the other aspects of the invention. Accordingly, the properties with respect to increase in bioavailability, changes in bioavailability parameters, reduction in adverse food effect as well as release of one or more fibrates etc. described and/or claimed herein for pharmaceutical compositions in particulate form are analogues for a solid dosage form according to the present invention.

Materials and methods

Materials

[00219] Fenofibrate (supplied by Sigma)
[00220] Lactose monohydrate 200 mesh (from DMV)
[00221] Granulated silicium oxide, Aeroperl® 300, (Degussa)
[00222] Polyethylene glycol 6000, Pluracol® E6000 (from BASF)
[00223] Poloxamer 188, Pluronic® F-68 (from BASF)
Avicel PH200 (microcrystalline cellulose) (from FMC)
Magnesium stearate
Tablets, capsules or granules might be enteric coated with different types of polymers such as hydroxypropylmethylcellulose acetate succinate (Aqoat), cellulose acetate phthalate CAP, hydroxypropylmethylcellulose phtalate HPMCP or methacrylic acid copolymers such as Eudragit L30D, Eudragit 100/S, Eudragit 100/L.
TriCo®/Lipanthyl® tablet formulation
TRICOR® (Lipanthyl®) tablets from Abbott Laboratories are fenofibrate-containing tablets available for oral administration, either containing 48 mg or 54 mg or 145 mg or 160 mg of fenofibrate per tablet.
The tablets contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide, xanthan gum, colorant.
Equipment
Laboratory scale fluid bed equipment: Strea-1.
The melt feed unit is a prototype composed of separate units for heating of air supplies for the atomizer, pressure tank and feeding tube. Granulate was sieved manually and mixed with extragranular excipients in a Turbula mixer.
Tablet compression was performed on a single punch press, Diaf TM20.
Methods
According to the method of the invention, the fenofibrate drug was dissolved into the liquefied vehicle(s) and applied on the particulate carrier(s) as follows:
The vehicle(s) was melted in a beaker placed in a microwave oven. The beaker was transferred to a temperature controlled heating plate supplied with magnetic stirring. Fenofibrate was dissolved slowly in the liquefied vehicle at a temperature of 75°C under magnetic stirring. The hot solution was transferred to the pressure tank for melt spray application onto the carrier in the fluid bed. The granulate product was discharged from the fluid bed and sieved through sieve 0.7 mm or 1.0 mm manually. The sieved product was blended with magnesium
stearate for 0.5 min in a Turbula mixer. If an extragranular phase has to be incorporated, the extragranular phase was premixed with granulate in 3 minutes in a Turbula mixer.

[0235] The tablet compression was performed on a single punch machine Diaf TM20.

Threshold test
[0236] The test involves determination of flowability according to the method described in Ph.Eur. by measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

[0237] Viscoleo (medium chain triglycerides MCT; Miglyol 812 N from Condea) was added to 100 g of the solid pharmaceutically acceptable material to be tested for use according to the invention and mixed manually. The mixture obtained was sieved through sieve 0.3 mm to assure a homogenous mixture. The oil was added successively until a flow of 100 g of the mixture could not flow through the nozzle. If the material to be tested has a high bulk volume (e.g. like that of Aeroperl 300) only 50 g of the mixture is used when testing these blends. The maximal concentration of oil where flow of material could be obtained is called the Threshold Value (given as % w/w).

Release test
[0238] A fat-soluble colorant Sudan II (BDH Gur®) obtained from BDH VWR International 14.3 mg was dissolved in 50.0 g viscoleo (fractionated medium chain triglycerides).

[0239] 10 g of the oil was added to 10.0 g of the solid pharmaceutically acceptable material to be tested for use according to the present invention and mixed until the oil was fully absorbed in the solid material. The mixture was subsequently sieved through sieve 0.3 mm to achieve a homogeneous mixture.

[0240] 1.00 g of the mixture was transferred to a centrifugal tube and 3.00 ml of water was added. The suspension was mixed in a blood sample turner for 1 hour and subsequently centrifuged for 10 minutes at 5000 rpm. The upper phase of oil and water was transferred carefully to a beaker and the water was evaporated in an oven at 80 °C until constant weight. The amount of oil released from the solid material was calculated on basis of the weight of the remaining after evaporation of the water phase.
Disintegration test

0241] The disintegration time was determined according to the method described in to Ph. Eur.

Dissolution test

0242] The test was performed in accordance with Ph. Eur 2.9.3 using the paddle apparatus. The quantification was performed using HPLC with UV-detection.

0243] Medium: 900 ml water with 0.75 % sodium lauryl sulfate (SLS)

0244] Rotation speed: 50 rpm

0245] Temperature: 37°C

0246] Sampling time: 10, 20, 30, 45 and 60 minutes

0247] Acceptance criteria: > 75 % at 45 minutes (for the stability study)

Determination of Bulk Density

0248] The bulk density was measured by pouring 100 g of the powder in question in a 250 ml graduated cylinder. The bulk density is given as the tapped bulk density in g/ml. The determination was performed according to Ph. Eur. (apparent volume).

Determination of Oil Absorption Value

0249] The oil absorption value is determined by adding well-defined amounts (a 10 g) of viscoleo to a well-defined amount of the pharmaceutically acceptable material (100 g) to be tested. The oil absorption value (expressed as g viscoleo/100 g material) is reached when a further addition of 10 g oil results in a material that does not have suitable properties with respect to flowability, i.e. the material does not meet the requirements when tested according to Ph.Eur. (flowability test; see above under Threshold Test herein).

Determination of BET Surface Area

0250] The apparatus applied was a Micromeritics Gemini 2375. The method applied was according to USP volumetric methods based on multiple point determination.

Determination of Flowability

0251] The flowability was determined according to the method described in Ph.Eur. measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

Determination of weight variation
The tablets prepared in the Examples herein were subject to a test for weight variation performed in accordance with Ph. Eur.

Determination of average tablet hardness

The tablets prepared in the Examples herein were subject to a test for tablet hardness employing Schleuniger Model 6D apparatus and performed in accordance with the general instructions for the apparatus.

Determination of solid solution

According to the present invention, the fenofibrate is dissolved in a vehicle. In order to substantiate this, a test involving differential scanning calorimetry is performed. The test is performed on the particulate composition, solid dosage form or mixture of vehicle and fibrate (after the solid solution is supposed to form).

Standard DSC equipment connected to a PC is used.

Sample size: 10 mg in alu pans

Heating rate: 5°C/min from 27°C to 110°C

Evaluation: The fibrate and statin are considered to be in dissolved state or non-crystalline if neither fibrate nor statin endotherm peaks are observed and if the melting intervals do not significantly shift compared with the vehicle alone.

Determination of geometric weight mean diameter $d_{gw}$

The geometric weight mean diameter was determined by employment of a method of laser diffraction dispersing the particulate material obtained (or the starting material) in air. The measurements were performed at 1 bar dispersive pressure in Sympatec Helos equipment, which records the distribution of the equivalent spherical diameter. This distribution is fitted to a log normal volume-size distribution.

When used herein, “geometric weight mean diameter” means the mean diameter of the log normal volume-size distribution.

In vivo studies in Beagle dogs

In vivo studies with the purpose of determining the bioavailability of the compositions of the present invention relative to the bioavailability of the commercially available fenofibrate tablet formulation, i.e. Tricor®, was performed using Beagle dogs.
[0261] The experimental work was performed in Denmark using four male Beagle dogs each having a body weight of 12-18 kg (starting weight). The studies were conducted as open, non-randomised, cross-over studies. Each animal was its own control. Oral doses of fenofibrate were administered according to the data below.
[0262] The dogs were fasted overnight prior to dosing (water ad libitum) and were fed 5 hours after dosing (water ad libitum). Each dog was dosed with the specified dose of fenofibrate without taking the weight of the dog into consideration.
[0263] Blood samples were collected at vena jugularis externa at the following points of time:
[0264] Pre-dose, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after dosing. 4 ml of blood were collected, mixed with EDTA, and the samples were frozen (-80°C). The blood samples were analyzed using on-line extraction LC/MS and results were given in mg/mL.
[0265] The determined full blood concentration profiles of fenofibrate were treated using the Pharmacokinetic software WinNonlin®, (Pharsight, California; USA) to calculate the pharmacokinetic parameters. All data are dose adjusted, when necessary.
[0266] The following examples serve the purpose of illustration of the invention and are not intended to limiting the scope of the present invention.

Example 1

Immediate release tablet containing a fenofibrate and simvastatin

[0267]  

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>130.00</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>10.00</td>
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<tr>
<td>Carrier</td>
<td>Lactose</td>
<td>247.64</td>
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<td>Vehicle</td>
<td>PEG 6000</td>
<td>170.88</td>
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<tr>
<td>Vehicle</td>
<td>Poloxamer 188</td>
<td>73.24</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>2.69</td>
</tr>
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<td></td>
<td>Total</td>
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</table>
[0268] Fenofibrate and simvastatin are mainly dissolved/dispersed in polyethylene glycol 6000 and poloxamer 188 (70:30 w/w ratio) at 70°C. The dispersion is sprayed on 250 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particular material obtained is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

[0269] The powder mixture is compressed into 13 mm tablets with strength of 130 mg fenofibrate and 10 mg simvastatin in to a 637 mg tablet with compound cup shaped.

[0270] Mean disintegration time: 20 min, Hardness: 45 N

Example 2

Immediate release tablet containing fenofibrate and simvastatin

[0271]

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>120.00</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>20.00</td>
</tr>
<tr>
<td>Carrier</td>
<td>Lactose</td>
<td>261.00</td>
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<td>Vehicle</td>
<td>PEG 6000</td>
<td>171.00</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Poloxamer 188</td>
<td>73.00</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>3.00</td>
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<tr>
<td>Total</td>
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<td>648.00</td>
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</tbody>
</table>

[0272] Fenofibrate and simvastatin are mainly dissolved/dispersed in polyethylene glycol 6000 and poloxamer 188 (70:30 w/w ratio) at 70°C. The dispersion is sprayed on 250 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particular material obtained is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

[0273] The powder mixture is compressed into 13 mm tablets with strength of 120 mg fenofibrate and 20 mg simvastatin into a 648 mg tablet with compound cup shaped.

[0274] Mean disintegration time: 25 min, Hardness: 47 N
Example 3

Immediate release tablet containing fenofibrate and simvastatin

Table 3

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>120.00</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>10.00</td>
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<tr>
<td>Carrier</td>
<td>Lactose</td>
<td>241.00</td>
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<tr>
<td>Vehicle</td>
<td>PEG 6000</td>
<td>171.00</td>
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<tr>
<td>Vehicle</td>
<td>Poloxamer 188</td>
<td>73.00</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>3.00</td>
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<tr>
<td>Total</td>
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<td>618.00</td>
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[0276] Fenofibrate and Simvastatin are mainly dissolved/dispersed in polyethylene glycol 6000 and poloxamer 188 (70:30 w/w ratio) at 70°C. The dispersion is sprayed on 250 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material obtained is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

[0277] The powder mixture is compressed into 12 mm tablets with strength of 120 mg fenofibrate and 10 mg simvastatin into a 618 mg tablet with compound cup shaped.

[0278] Mean disintegration time: 22 min, Hardness: 41 N

Example 4

Immediate release tablet containing fenofibrate and simvastatin

Table 4

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>120.00</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>30.00</td>
</tr>
<tr>
<td>Carrier</td>
<td>Lactose</td>
<td>266.00</td>
</tr>
<tr>
<td>Vehicle</td>
<td>PEG 6000</td>
<td>171.00</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Poloxamer 188</td>
<td>73.00</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>3.00</td>
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<tr>
<td>Total</td>
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<td>673.00</td>
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</table>

[0280] Fenofibrate and simvastatin are mainly dissolved/dispersed in polyethylene glycol 6000 and poloxamer 188 (70:30 w/w ratio) at 70°C. The dispersion is sprayed on 250 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

[0281] The powder mixture is compressed into 13 mm tablets with strength of 120 mg fenofibrate and 30 mg simvastatin into a 673 mg tablet with compound cup shaped.

[0282] Mean disintegration time: 25 min, Hardness: 39 N

Example 5

Table based on lipophilic matrix of glyceryl monostearate

[0283]

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>120.00</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
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<tr>
<td>Carrier</td>
<td>Lactose 200 mesh</td>
<td>100.00</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Glycerylmonostearate</td>
<td>300.00</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>532.00</td>
</tr>
</tbody>
</table>

[0284] Fenofibrate and simvastatin are mainly dissolved/dispersed in glyceryl monostearate at 70 °C. The solution is sprayed on 200 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

[0285] The powder mixture is compressed into 11 mm tablets with 532 mg tablet with compound cup shape.

[0286] Mean disintegration time: 45 min, Hardness: 48 N
Example 6

Modified release poly-depot capsule based on swelling hydrocolloid matrix of hydroxypropylcellulose

[0287]

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>120.00</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>20.00</td>
</tr>
<tr>
<td>Carrier</td>
<td>HPMC 2910 3 cp</td>
<td>150.00</td>
</tr>
<tr>
<td>Carrier</td>
<td>Lactose 200 mesh</td>
<td>50.00</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Glycerol monostearate</td>
<td>300.00</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>640.00</td>
</tr>
</tbody>
</table>

[0288] Fenofibrate and simvastatin are mainly dissolved/dispersed in glycercylmonostearate at 70°C. The solution is sprayed on a mixture of 50 g lactose and 150 g HPMC in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material is sieved through sieve 0.7 mm and filled into hard gelatine capsules (640 mg)

Example 7

Immediate release tablet

[0289]

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>120.00</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>40.00</td>
</tr>
<tr>
<td>Oil-sorption material</td>
<td>Aeroperl 300</td>
<td>95.00</td>
</tr>
<tr>
<td>Vehicle</td>
<td>PEG 3000</td>
<td>195.00</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>3.00</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>463.00</td>
</tr>
</tbody>
</table>
[0290] Fenofibrate and simvastatin are mainly dissolved/dispersed in polyethylene glycol 3000 at 70°C. The dispersion is sprayed on 95 g Aeroperl in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

[0291] The powder mixture is compressed into 11 mm tablets with strength of 120 mg fenofibrate and 40 mg simvastatin into a 463 mg tablet with compound cup shaped.

Example 8

Solid dosage forms according to the invention

[0292] The following compositions were prepared according to the method described in Example 1 above.

[0293]

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>B mg</th>
<th>C mg</th>
<th>D mg</th>
<th>E mg</th>
<th>F mg</th>
<th>G mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>50</td>
<td>50</td>
<td>50.1</td>
<td>160</td>
<td>130</td>
<td>43</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>10</td>
<td>10</td>
<td>10.0</td>
<td>40</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Vehicle 1</td>
<td>PEG6000</td>
<td>171.1</td>
<td>124.3</td>
<td>-</td>
<td>-</td>
<td>169</td>
<td>56</td>
</tr>
<tr>
<td>Vehicle 1</td>
<td>PEG4000</td>
<td>-</td>
<td>-</td>
<td>244.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vehicle 1</td>
<td>GMS (Rylo)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>86.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vehicle 2</td>
<td>Poloxamer188</td>
<td>73.3</td>
<td>53.3</td>
<td>-</td>
<td>-</td>
<td>72</td>
<td>24</td>
</tr>
<tr>
<td>Carrier</td>
<td>Lactose</td>
<td>231.9</td>
<td>-</td>
<td>232.0</td>
<td>163.0</td>
<td>304</td>
<td>101</td>
</tr>
<tr>
<td>Carrier</td>
<td>Aeroperl 300</td>
<td>-</td>
<td>63.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Excipients</td>
<td>Mg stearate</td>
<td>2.7</td>
<td>1.5</td>
<td>5.3</td>
<td>8.3</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Excipients</td>
<td>Avicel</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>417.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>53</td>
<td>30</td>
<td>54</td>
<td>87</td>
<td>69</td>
<td>234</td>
</tr>
<tr>
<td>Hardness</td>
<td>N</td>
<td>44</td>
<td>44</td>
<td>47</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disintegra</td>
<td>minutes</td>
<td>14</td>
<td>30</td>
<td>48</td>
<td>&gt;55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 9  (A-E)

Methods of manufacturing fenofibrate –simvastatin combinations

[0294] There are several useful methods for preparing combination products according to this invention. The method is primarily selected from the desired characteristics and performance of the composition or solid dosage form. In examples 9A-9E is given a number of compositions and methods of production. The methods shown are by no means intended to limit the scope of this invention. [0295] All granulates listed herein can either be filled into hard gelatin capsules or compressed into tablets.

[0296] The following fenofibrate granulate A is disclosed in international application PCT/DK2004/000667, granulate B is prepared in a similar manner:

[0297] Composition/table 9:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>A mg</th>
<th>B mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>160.0</td>
<td>120.0</td>
</tr>
<tr>
<td>Carrier</td>
<td>Lactose</td>
<td>356.5</td>
<td>292.0</td>
</tr>
<tr>
<td>Vehicle</td>
<td>PEG 6000</td>
<td>208.2</td>
<td>162.5</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Poloxamer 188</td>
<td>89.2</td>
<td>69.5</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>4.1</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>818.0</td>
<td>650.0</td>
</tr>
</tbody>
</table>

[0299]

Example 9A


[0301] The fenofibrate granulate A (table 9) was used.

[0302] The fenofibrate granulate is mixed with another granulate containing simvastatin. This statin granulate is as follows:

[0303]
Table 10

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>10.0</td>
</tr>
<tr>
<td>Carrier</td>
<td>Lactose 200 mesh</td>
<td>50.0</td>
</tr>
<tr>
<td>Vehicle</td>
<td>PEG 6000</td>
<td>66.0</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Poloxamer 188</td>
<td>22.0</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150.0</td>
</tr>
</tbody>
</table>

[0304] The granulate obtained is sieved through sieve 0.7 mm and blended with the fenofibrate granulate and magnesium stearate for 0.5 min in a Turbula mixer.

[0305] The final granulate is compressed into 13.5 mm tablets with strength of 160 mg fenofibrate and 10 mg simvastatin into a 970 mg tablet with compound cup shaped.

[0306] Mean disintegration time: 24 min, Hardness: 49 N


[0308] The fenofibrate granulate B (table 9) was used, and tablets having the following composition were prepared:

[0309] Tablet composition:

[0310]

Table 11

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug I</td>
<td>Fenofibrate</td>
<td>120.0</td>
</tr>
<tr>
<td>Drug II</td>
<td>Simvastatin</td>
<td>10.0</td>
</tr>
<tr>
<td>Carrier</td>
<td>Lactose monohydrate</td>
<td>332.0</td>
</tr>
<tr>
<td>Vehicle</td>
<td>PEG 6000 (Macrogol)</td>
<td>163.0</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Poloxamer 188</td>
<td>70.0</td>
</tr>
<tr>
<td>Excipients</td>
<td>Magnesium stearate</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>Avicel PH200 (microcryst. cellulose)</td>
<td>103.0</td>
</tr>
<tr>
<td></td>
<td>Calcium carbonate</td>
<td>33.0</td>
</tr>
<tr>
<td></td>
<td>Ac-di-sol (crocarmellose Na)</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Klucel (hydroxypropyl-</td>
<td>3.0</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>120.0</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>30.0</td>
</tr>
<tr>
<td>Carrier</td>
<td>Lactose</td>
<td>329.0</td>
</tr>
<tr>
<td>Vehicle</td>
<td>PEG 6000</td>
<td>188.0</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Poloxamer 188</td>
<td>81.0</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>4.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>752.0</td>
</tr>
</tbody>
</table>

[0315] Fenofibrate and simvastatin are mainly dissolved/dispersed in polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratios) at 70 °C. The dispersion is sprayed on 329 g lactose in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material obtained is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

[0316] The granulate is compressed into 13.5 mm tablets with strength of 120 mg fenofibrate and 30 mg simvastatin into a 752 mg tablet with compound cup shaped.
Example 9C

[0317] A single granulate comprising fenofibrate and simvastatin is made as follows:

[0318]

<table>
<thead>
<tr>
<th>Substance</th>
<th>Ingredient</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Fenofibrate</td>
<td>120.00</td>
</tr>
<tr>
<td>Drug</td>
<td>Simvastatin</td>
<td>10.00</td>
</tr>
<tr>
<td>Carrier</td>
<td>Lactose</td>
<td>349.00</td>
</tr>
<tr>
<td>Vehicle</td>
<td>PEG 6000</td>
<td>208.00</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Poloxamer 188</td>
<td>89.00</td>
</tr>
<tr>
<td>Excipient</td>
<td>Magnesium stearate</td>
<td>4.00</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>780.00</td>
</tr>
</tbody>
</table>

[0319] Fenofibrate is dissolved in polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratios) at 70°C. The dispersion is sprayed on a mixture of 349 g lactose and 10 g of simvastatin in a fluid bed Phast FB-100 with a Phast FS-1.7 melt-spray unit. The particulate material obtained is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

[0320] The granulate is compressed into 13.5 mm tablets with strength of 120 mg fenofibrate and 10 mg simvastatin into a 780 mg tablet with compound cup shaped.

Example 9D

[0321] A fenofibrate granulate A of table 9 was used.

[00322] The fenofibrate granulate is mixed with a granulate similar to the granulate composition of Zocor® tablets of either 10, 20 or 40 mg of simvastatin in order to obtain the same plasma profiles as those of Zocor®.

[00323] Zocor® based granulates may have the following composition(s):

[00324] 10 mg simvastatin per 100 mg granulate:

[00325] Simvastatin 10.0 mg

[00326] Microcrystalline cellulose 5.0 mg

[00327] Ascorbic acid 60.0 microgram

[00328] Lactose monohydrate 67.9 mg
[00329] Starch, pregelatinized 10.0 mg
[00330] Maize starch 5.0 mg
[00331] Propylene glycol 140.0 microgram
[00332] Citric acid, anhydrous 1.5 mg
[00333] BHA 20.0 microgram
[00334] Magnesium stearate 0.5 mg
[00335] 20 mg simvastatin per 200 mg granulate:
[00336] Simvastatin 20.0 mg
[00337] Microcrystalline cellulose 5.0 mg
[00338] Ascorbic acid 120.0 microgram
[00339] Lactose monohydrate 135.8 mg
[00340] Starch, pregelatinized 20.0 mg
[00341] Maize starch 10.0 mg
[00342] Propylene glycol 280.0 microgram
[00343] Citric acid, anhydrous 3.0 mg
[00344] BHA 40.0 microgram
[00345] Magnesium stearate 1.0 mg
[00346] 40 mg simvastatin per 400 mg granulate:
[00347] Simvastatin 40.0 mg
[00348] Microcrystalline cellulose 5.0 mg
[00349] Ascorbic acid 240.0 microgram
[00350] Lactose monohydrate 271.7 mg
[00351] Starch, pregelatinized 40.0 mg
[00352] Maize starch 20.0 mg
[00353] Propylene glycol 560.0 microgram
[00354] Citric acid, anhydrous 6.0 mg
[00355] BHA 80.0 microgram
[00356] Magnesium stearate 2.0 mg
[00357] The fenofibrate granulate and the “Zocor” granulate are mixed in a turbula mixer and the final granulate is then either filled into hard gelatin capsules or compressed into tablet with a suitable crushing strengths around 40-50 N.
Example 9E

[0358] A fenofibrate granulate B of table 9 was manufactured.
[0359] The fenofibrate granulate is mixed with micronized simvastatin, optionally added conventional excipients or additives for tablet production like a glidant, filler, binder, or disintegrator.
[0360] The granulate is either filled into hard gelatin capsules or compressed into tablet with a suitable crushing strength.

Example 9F

[0361] A fenofibrate granulate B of table 9 was manufactured. The fenofibrate granulate were compressed into oblong tablets 19.9 x 8 mm with a mean tablet hardness of 80 N.
[0362] The combination product of fenofibrate and simvastatin is prepared by coating the fenofibrate tablets with a coating comprising simvastatin, i.e. an aqueous suspension of simvastatin including a film-forming polymer and stabilizers (antioxidants).
[0363] The fenofibrate tablets may optionally be sub-coated with a film-forming polymer prior to coating with the simvastatin suspension.
[0364] The aqueous suspension of simvastatin has the following composition:

<table>
<thead>
<tr>
<th>Substance</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollicoat ®</td>
<td>10</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>0.03</td>
</tr>
<tr>
<td>BHA</td>
<td>0.01</td>
</tr>
<tr>
<td>Citric acid</td>
<td>0.75</td>
</tr>
<tr>
<td>Water</td>
<td>84.21</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

[0366] The fenofibrate tablets are coated with the coating suspension in a fluid bed Phast FB 100 equipped with a coating insert (top-spray) using an inlet air
temperature of 50°C, a product temperature of about 40-45°C, a feed rate of 9 g/min and a tablet load of 700 g.

[0367] Each tablet is coated with approx 171 g coating suspension corresponding to 10 mg simvastatin per tablet.

[0368] The simvastatin-coated fenofibrate tablets may additionally be coated with a suitable polymer to protect simvastatin from degradation.

Example 10

Formulations for in vivo studies in dogs

[0369] Compositions of the invention were investigated in in vivo studies in dog. As fenofibrate is a drug substance that has major bioavailability problems, the study was primarily to investigate whether an improved bioavailability could be obtained. Accordingly, no data with respect to the statin component is available.

[0370] Tablets of 50 mg and 160 mg strength with respect to fenofibrate, respectively and having the following compositions were prepared as described in Example 1:

[0371]

| Table 15 |
|----------|----------|----------|----------|----------|----------|
| Substance | Ingredient | A (mg) | B (mg) | C (mg) | D (mg) | E (mg) |
| Drug      | Fenofibrate | 160.09 | 50.05   | 50.08   | 50.09   | 159.99 |
| Vehicle 1 | PEG6000    | 208.12 | -       | 171.09  | -       | -       |
|           | PEG4000    | -      | -       | 124.29  | -       | 244.57  |
|           | GMS (Rylo) | -      | -       | -       | -       | 86.15   |
| Vehicle 2 | Poloxamer188 | 89.19 | 73.33   | 53.27   | -       | -       |
| Carrier   | Lactose    | 356.51 | 231.87  | -       | 232.02  | 163.01  |
|           | Aeroperl 300 | -     | -       | 63.89   | -       | -       |
| Excipients| Mg stearate| 4.09   | 2.65    | 1.47    | 5.32    | 8.35    |
|           | Avicel     | -      | -       | -       | -       | 417.50  |
| Total     |            | 818.00 | 529.00  | 293.00  | 532.00  | 835.00  |
| Hardness  | N          | 60     | 44      | 44      | 47      | 102     |
Disintegration time

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Minutes</th>
<th>25</th>
<th>14</th>
<th>30</th>
<th>48</th>
<th>&gt;55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mm</td>
<td>Oblong</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example 11

Dissolution tests

[0372] The tablet formulation A from Example 10 was subjected to a dissolution test as described in Methods with the following results:

[0373]

Table 16

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>% dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td>45</td>
<td>88</td>
</tr>
<tr>
<td>60</td>
<td>97</td>
</tr>
</tbody>
</table>

Example 12

Stability tests

[0374] Samples of the tablet formulation A from Example 10 was stored in PP bottles under the following conditions, respectively, and subjected to a dissolution (stability) test as described in Methods after 1 month and 3 months of storage; % dissolved is the percentage of fenofibrate dissolved after 45 minutes:

[0375]

Table 17

<table>
<thead>
<tr>
<th>Months</th>
<th>% dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25°C and 60% RH</td>
</tr>
<tr>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
</tr>
</tbody>
</table>
[0376] Samples of the tablet formulation A was stored under the following conditions, respectively, and subjected to a fibrate assay with the following results:

<table>
<thead>
<tr>
<th>Table 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

[0378] Samples of the inventive tablet formulation A was stored under the following conditions, respectively, and subjected to a degradation product test according to Ph. Eur. (Degradation products A, B, G and Unknown accumulated into Total Degradation Product; HPLC method) with the following results:

<table>
<thead>
<tr>
<th>Table 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

Example 13

In vivo study in dogs

[0380] An in vivo study of formulation A from Example 10 160 mg in Beagle dogs, performed as described above under Methods, relative to Tricor ®, 160 mg (Batch no.: 098212E21), gave the following results:

[0381] Blood concentrations (mg/mL) (average of 4 dogs) after administration of formulation:

<table>
<thead>
<tr>
<th>Table 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (hr)</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
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<tr>
<td>1.5</td>
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<tr>
<td>2.0</td>
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<td>3.0</td>
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<td>4.0</td>
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<tr>
<td>12.0</td>
</tr>
<tr>
<td>24.0</td>
</tr>
<tr>
<td>48.0</td>
</tr>
</tbody>
</table>

[0383] Relative bioavailability based on AUC (invention, A/Tricor®): 306%.

[0384] Relative $c_{\text{max}}$(invention, A/Tricor®): 356%.

Example 14

In vivo study in dogs

[0385] A second in vivo study of formulation A (Example 10), 160 mg in Beagle dogs, performed as described above under Methods, relative to Tricor®, 160 mg (Batch no.: 098212E21), gave the following results:

[0386] Blood concentrations (mg/mL) (average of 4 dogs) after administration of formulation:

<table>
<thead>
<tr>
<th>Time (hr)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tricor® (160mg)</td>
</tr>
<tr>
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<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>339.3</td>
</tr>
<tr>
<td>Time (hr)</td>
<td>Lipanthyl®67M (2x67mg)</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------</td>
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<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>0.5</td>
<td>187.3</td>
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<tr>
<td>1.0</td>
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<td>960.3</td>
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<td>895.3</td>
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<tr>
<td>3.0</td>
<td>433.0</td>
</tr>
<tr>
<td>4.0</td>
<td>240.0</td>
</tr>
</tbody>
</table>

[0388] Relative bioavailability based on AUC (invention, A/Tricor®): 198%.

[0389] Relative $c_{\text{max}}$(invention, A/Tricor®): 238%.

Example 15

In vivo study in dogs

[0390] An in vivo study of the formulations B, C and D (Example 10), 2x50 mg in Beagle dogs, performed as described above under Methods, relative to Lipanthyl®67M, 2x67 mg (Batch no.: 75641), gave the following results:

[0391] Blood concentrations (mg/mL) (average of 4 dogs) after administration of formulation:

[0392]
<table>
<thead>
<tr>
<th>6.0</th>
<th>77.8</th>
<th>809.5</th>
<th>655.8</th>
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<td>8.0</td>
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<td>1056.0</td>
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<tr>
<td>12.0</td>
<td>291.3</td>
<td>848.0</td>
<td>269.8</td>
<td>597.3</td>
</tr>
<tr>
<td>24.0</td>
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<td>163.8</td>
<td>282.8</td>
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<td>19.3</td>
<td>18.8</td>
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<td>72.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

[0393] Relative bioavailability based on AUC (invention, B/ Lipanthyl®67M): 532%.
[0394] Relative c_max(invention, BA/Lipanthyl®67M): 548%.
[0395] Relative bioavailability based on AUC (invention, C/ Lipanthyl®67M): 228%.
[0396] Relative c_max(invention, C/Lipanthyl®67M): 161%.
[0397] Relative bioavailability based on AUC (invention, D/ Lipanthyl®67M): 424%.
[0398] Relative c_max(invention, D/Lipanthyl®67M): 329%.

Example 16

Clinical trial of fenofibrate formulation used in the fenofibrate and simvastatin composition of the invention

[0399] A clinical trial study was carried out in order to determine the pharmacokinetic profile of the fenofibrate formulation used in the combination composition of this invention, 160 mg tablets taken with food and without food in comparison with Lipanthyl® (Tricor ®) 160 mg tablets taken with and without food.

[0400] The study was conducted in Switzerland as a randomized, four-way cross-over study including 24 healthy volunteers (aged 27-55 years; 21 males and 3 females; body weight > 65 kg); 23 subjects concluded the study, 1 subject dropped out after period 3 for personal reasons (missing period: Lipanthyl fasted).

[0401] The study was carried out as a combined PK and food-effect study according to FDA guidelines.

[0402] The objective was to demonstrate that the fenofibrate formulation used in the combination composition of the present invention (administered in fed state) and Lipanthyl (administered in fed state) are bioequivalent and, further that the present fenofibrate formulation, when administered in fed state, is bioequivalent to the identical formulation administered in fasted state.

[0403] Conditions (fed state) were according to Guidance for Industry: Food-effect Bioavailability and Fed Bioequivalence Studies; CDER December 2002: An
overnight fast of the subjects of at least 10 hours; high-fat, high-calorie breakfast within 30 minutes or less; 800-1000 calories in total (150 from protein; 250 from carbohydrate; 500-600 from fat); 240 ml plain water at study drug administration.

[0404] Conditions (fasted state) were according to Guidance for Industry: Food-effect Bioavailability and Fed Bioequivalence Studies; CDER December 2002: An overnight fast of the subjects of at least 10 hours; no breakfast and no food intake 4 hours after drug administration; 240 ml plain water at study drug administration.

[0405] The following results were found:

[0406] AUC_{0-24}(invention fenofibrate formulation fed)/ AUC_{0-24} (invention fenofibrate formulation fasted): 106.9% (CI 101-114%).

[0407] AUC_{0-24}(invention fenofibrate formulation fed)/ AUC_{0-24}(Lipanthyl fed): 98.0% (CI 93-103%).

[0408] AUC_{0-inf}(invention fenofibrate formulation fed)/ AUC_{0-inf} (invention fenofibrate formulation fasted): 104.9% (CI 98-111%).

[0409] AUC_{0-inf}(invention fenofibrate formulation fed)/ AUC_{0-inf}(Lipanthyl fed): 97.1% (CI 92-102%).

[0410] AUC_{0-inf}(Lipanthyl fed)/ AUC_{0-inf}(Lipanthyl fed): 136%.

[0411] A product is considered bioequivalent with a reference product, when AUC_{0-t}, AUC_{0-inf}, C_{max} is within 80-125% of the reference product, including the 90% Confidence Intervals (CI).

[0412] The results shows a markedly increased bioavailability of LCP-Feno fasted compared to Lipanthyl fasted.

[0413] The results demonstrate bioequivalence of the present fenofibrate formulation under fed conditions compared to Lipanthyl (AUC_{0-t}, AUC_{0-inf}, C_{max}) and of the present fenofibrate formulation fasted compared to the present fenofibrate formulation fed (AUC_{0-t}, AUC_{0-inf}). It can thus be concluded that the fenofibrate formulation used in the combination product of the invention has no food effect.

[0414] This invention may be embodied in other forms or carried out in other ways without departing from the spirit or essential characteristics thereof. The present disclosure is therefore to be considered as in all aspects illustrate and not restrictive, and all changes which come within the meaning and range of equivalency are intended to be embraced therein.
[0415] Various references are cited throughout this Specification, each of which is incorporated herein by reference in its entirety.
Claims
1. A solid pharmaceutical composition in particulate form comprising a vehicle, an effective amount of simvastatin or a pharmaceutically acceptable salt thereof, and an effective amount of fenofibrate exhibiting a bioavailability which is at least bioequivalent to a 130 mg Antara® capsule.
2. A pharmaceutical composition according to claim 1, which exhibits an AUC$_{0-24}$ for fenofibrate relative to AUC$_{0-24}$ for a 130 mg Antara® tablet of at least about 1.3.
3. A pharmaceutical composition according to claim 1, wherein the amount of fenofibrate is less than 130 mg.
4. A pharmaceutical composition according to claim 1, wherein the amount of fenofibrate is 120 mg.
5. A pharmaceutical composition according to claim 1, wherein the amount of fenofibrate is at least 30 mg.
6. A pharmaceutical composition according to claim 1, wherein the amount of simvastatin or a pharmaceutically acceptable salt thereof is between 5 mg and 80 mg.
7. A pharmaceutical composition according to claim 1, wherein the relative amount of simvastatin to fenofibrate is at least 1:15.
8. A pharmaceutical composition according to claim 1, wherein the amount of fenofibrate is 120 mg and the amount of simvastatin or a pharmaceutically acceptable salt thereof is 10 mg.
9. A pharmaceutical composition according to claim 1, wherein the amount of fenofibrate is 120 mg and the amount of simvastatin or a pharmaceutically acceptable salt thereof is 20 mg.
10. A pharmaceutical composition according to claim 1, wherein the amount of fenofibrate is 120 mg and the amount of simvastatin or a pharmaceutically acceptable salt thereof is 30 mg.
11. A pharmaceutical composition according to claim 1, wherein the amount of fenofibrate is 120 mg and the amount of simvastatin is or a pharmaceutically acceptable salt thereof 40 mg.
12. A pharmaceutical composition according to claim 1, wherein the fenofibrate is forming a solid solution in the vehicle.
13. A pharmaceutical composition according to claim 1, which is free-flowing.
14. A pharmaceutical composition according to claim 1, wherein the vehicle is a hydrophobic vehicle selected from the group consisting of straight chain saturated hydrocarbons, paraffins, cacao butter, beef tallow, lard, yellow beeswax, white beeswax, carnauba wax, castor wax, Japan wax, substituted and/or unsubstituted triglycerides, acrylic polymers, and mixtures thereof.
15. A pharmaceutical composition according to claim 1, wherein the vehicle is a hydrophilic or water-miscible vehicle selected from the group consisting of polyethylene glycols, polyoxyethylene oxides, poloxamers, polyoxyethylene stearates, poly-epsilon caprolactone, fatty acids, monoglycerides, diglycerides, fatty alcohols, fractionated phospholipids, polyvinylpyrrolidones, polyvinyl-polyvinylacetate copolymers (PVP-PVA), polyvinyl alcohol (PVA), polymethacrylic polymers, cellulose derivatives including hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, pectins, cyclodextrins, galactomannans, alginates, carragenates, xanthan gums, NVP polymers, PVP polymers and mixtures thereof.
16. A pharmaceutical composition according to claim 1, wherein the vehicle is a polyethylene glycol (PEG) having an average molecular weight of at least 1500.
17. A pharmaceutical composition according to claim 1, wherein the vehicle comprises a mixture of a polyethylene glycol and a poloxamer (a polyethylene oxide-polypropylene oxide-polyethylene oxide tri-block polymer) in a proportion of between about 1:3 and about 10:1, preferably between about 1:1 and about 5:1, more preferably between about 3:2 and about 4:1, especially between about 2:1 and about 3:1, in particular about 7:3.
18. A pharmaceutical composition according to claim 1 comprising polyethylene glycol having an average molecular weight of about 6000 (PEG6000) and poloxamer 188.
19. A pharmaceutical composition according to claim 11, wherein the fenofibrate and the polyethylene glycol forms an interstitial crystalline solid solution.
20. A pharmaceutical composition according to claim 1, wherein the vehicle is non-aqueous.
21. A pharmaceutical composition according to claim 1, wherein the concentration, in the vehicle, of fenofibrate or an analog thereof is at least about 10% w/w.

22. A pharmaceutical composition according to claim 1, wherein the concentration, in the vehicle, of fenofibrate is about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more or about 40% w/w or more.

23. A pharmaceutical composition according to claim 1, wherein the active substance simvastatin or a pharmaceutically acceptable salt thereof is selected from the group consisting of crystalline phase substance, a semi-crystalline phase substance, amorphous phase substance, a semi-amorphous phase substance, and mixtures thereof.

24. A pharmaceutical composition according to claim 1, wherein the concentration of simvastatin in the composition is at least about 0.5% w/w.

25. A pharmaceutical composition according to claim 1 having a moisture content of at the most about 2.5% w/w water.

26. A pharmaceutical composition according to claim 1 having a storage stability of about 2 months or more when tested at about 40°C and about 75% RH.

27. A pharmaceutical composition according to claim 1, wherein the particulate form (the particle) has a geometric weight mean diameter $d_{gw}$ of $\geq$10 mm such as, e.g. $\geq$ 20 mm, from about 20 to about 2000, from about 30 to about 2000, from about 50 to about 2000, from about 60 to about 2000, from about 75 to about 2000 such as, e.g., from about 100 to about 1500 mm, from about 100 to about 1000 mm or from about 100 to about 700 mm, or at the most about 400 mm or at the most 300 mm such as, e.g., from about 50 to about 400 mm such as, e.g., from about 50 to about 350 mm, from about 50 to about 300 mm, from about 50 to about 250 mm or from about 100 to about 300 mm.

28. A pharmaceutical composition according to claim 1, comprising one or more pharmaceutically acceptable excipients selected from the group consisting of fillers, disintegrants, binders, diluents, lubricants and glidants.

29. A pharmaceutical composition according to claim 21, wherein at least one excipient is selected from the group consisting of silica acid and a derivative or salt thereof including silicates, silicon dioxide and polymers thereof;
magnesium aluminosilicate, magnesium aluminometasilicate, bentonite, kaolin, magnesium tri-silicate, montmorillonite and saponite.

30. A pharmaceutical composition according to claim 1 further comprising a silica acid or a derivative or salt thereof.

31. A pharmaceutical composition according to claim 1 further comprising silicon dioxide or a polymer thereof.

32. A pharmaceutical composition according to claim 1 further comprising Aeroperl® 300.

33. A pharmaceutical composition according to claim 1 for oral administration once daily.

34. A solid dosage form comprising a solid pharmaceutical composition in particulate form comprising a vehicle, an effective amount of simvastatin or a pharmaceutically acceptable salt thereof, and an effective amount of fenofibrate exhibiting a bioavailability which is at least bioequivalent to a 130 mg Antara® tablet.

35. A solid dosage form according to claim 34, wherein the dosage form does not comprise any liquid, semi-liquid or semi-solid material.

36. A solid dosage form according to claim 34, wherein the dosage form does not comprise a suspension, an emulsion or a micro-emulsion.

37. A solid dosage form according to claim 34 having a storage stability of about 2 months or more when tested at about 40°C and about 75% RH.

38. A dosage form according to claim 34, wherein at least about 75% of the fenofibrate or the simvastatin is released from the composition within about 45 min when tested in an in vitro dissolution test according to Ph. Eur. dissolution test (paddle) employing water with about 0.75% sodium lauryl sulfate as dissolution medium, about 50 rpm and a temperature of about 37°C.

39. A solid dosage form according to claim 38, wherein the dissolution test is carried out after about 1 month of storage at a temperature of about 40°C and a relative humidity of about 75%.

40. A solid dosage form according to claim 34 wherein the concentration of the pharmaceutical composition is between from about 40% w/w to about 100% w/w of the dosage form.
41. A solid dosage form according to claim 34, wherein the concentration of the particulate material is at least about 70% w/w of the dosage form.
42. A solid dosage form according to claim 34 comprising a multiplicity of individual units selected from the group consisting of pellets, beads and granulate.
43. A solid dosage form according to claim 34 in the form of tablets, capsules or sachets.
44. A solid dosage form according to claim 34 in the form of a tablet, optionally coated with a coating selected from the group consisting of film coatings, modified release coatings, enteric coatings, protective coatings and anti-adhesive coatings.
45. A solid dosage form according to claim 34, wherein the active substances are embedded in a matrix that releases at least one of the substances by diffusion.
46. A solid dosage form according to claim 45, wherein the matrix remains substantially intact during the period of drug release.
47. A solid dosage form according to claim 34, wherein the active substances are embedded in a matrix that releases at least one of the substances by erosion.
48. A solid dosage form according to claim 34, wherein the active substances are released from the dosage form by diffusion through a substantially water-insoluble coating.
49. A solid dosage form according to claim 34 in the form of a polydepot dosage form, which - upon administration - disintegrates into a multiplicity of individual units from which the active substances are released.
50. A solid dosage form according to claim 34 having a moisture content of at the most about 2.5% w/w water.
51. A solid dosage form according to claim 34 in unit dosage form, wherein the unit dosage form comprises 120 mg of fenofibrate.
52. A solid dosage form according to claim 34 in unit dosage form, wherein the unit dosage form comprises about 5 mg of simvastatin, or about 10 mg of simvastatin, or about 15 mg of simvastatin, or about 20 mg of simvastatin, or about 30 mg of simvastatin, or about 40 mg of simvastatin, or of a pharmaceutically acceptable salt of simvastatin.
53. A solid dosage form according to claim 34 in unit dosage form, wherein the unit dosage form comprises 120 mg of fenofibrate and an amount of simvastatin or
a pharmaceutically acceptable salt thereof selected from the group consisting of 10 mg, 20 mg, 30 mg and 40 mg.

54. A solid dosage form according to claim 34 in unit dosage form, wherein the weight ratio between fenofibrate and simvastatin (or a pharmaceutically acceptable salt thereof) is less than 15:1.

55. A solid dosage form according to claim 34, wherein the pharmacokinetic profile of the fenofibrate and/or the simvastatin (or a pharmaceutically acceptable salt thereof) is not, when administered to a human, significantly affected by the fed or fasted state of the human.

56. A solid dosage form according to claim 34, wherein the fenofibrate and/or the simvastatin or a pharmaceutically acceptable salt thereof is present in an amount of at least 90%, or at least 95%, or at least 100%, relative to the amount prior to storage, when assayed after 3 months of storage at a temperature of about 40°C and a relative humidity of about 75%.

57. A solid dosage form according to claim 34, which is selected from the group consisting of immediate release formulations, controlled release formulations, delayed release formulations, extended release formulations and mixed immediate release and controlled release formulations.

58. A solid dosage form according to claim 34 comprising an immediate release formulation of fenofibrate and a controlled release or delayed release formulation of simvastatin.

59. A solid dosage form according to claim 34, wherein the solid dosage form is a tablet prepared by compressing a mixture of fenofibrate granulate and entero-coated simvastatin granulate.

60. A solid dosage form according to claim 34, wherein the solid dosage form comprises fenofibrate in a form selected from the group consisting of granulate, granules, grains, beads and pellets, filled into capsules or sachets together with simvastatin or a pharmaceutically acceptable form thereof in a form selected from the group consisting of entero-coated granules, grains, beads and pellets.

61. A method of manufacturing the solid oral dosage form of claim 34 comprising the steps of: i) Bringing a vehicle in liquid form, if applicable, ii) maintaining the liquid vehicle of (i) at a temperature below the melting point of the fenofibrate
and/or the simvastatin or a pharmaceutically acceptable salt thereof, iii) dissolving the desired amount of fibrate and simvastatin in the vehicle of (ii) to obtain a solution, iv) spraying the resulting solution of (iii) onto a solid carrier having a temperature below the melting point of the vehicle to obtain a composition, v) mechanically working the resulting composition of (iv) to obtain particles, i.e. a particulate material, and vi) optionally subjecting the particulate material to conventional methods for preparing solid dosage forms.

62. A method of manufacturing the solid oral dosage form of claim 34 comprising the steps of: A) obtaining a particulate material comprising fenofibrate comprising: i) Bringing a vehicle in liquid form, to obtain a liquid vehicle, ii) maintaining the liquid vehicle of i) at a temperature below the melting point of fenofibrate or a pharmaceutically acceptable salt thereof, iii) dissolving the desired amount of fenofibrate in the vehicle of ii) to obtain a solution, iv) spraying the resulting solution of iii) onto a solid carrier having a temperature below the melting point of the vehicle to obtain a composition, v) mechanically working the resulting composition of iv) to obtain particles, i.e. a particulate material containing fenofibrate, B) obtaining a particulate material containing simvastatin comprising the steps of: i) Bringing a vehicle in liquid form to obtain a liquid vehicle, ii) maintaining the liquid vehicle of i) at a temperature below the melting point of simvastatin or a pharmaceutically acceptable salt thereof, iii) dissolving the desired amount of simvastatin in the vehicle of ii) to obtain solution, iv) spraying the resulting solution of iii) onto a solid carrier having a temperature below the melting point of the vehicle to obtain a composition, v) mechanically working the resulting composition of iv) to obtain particles, i.e. a particulate material containing simvastatin, followed by the steps of: C) Mixing the particulate material containing fenofibrate and the particulate material containing simvastatin, and D) optionally subjecting the particulate material to conventional methods for preparing solid dosage forms.

63. The method according to claim 62, wherein a particulate material containing simvastatin of step B) is obtained prior to obtaining a particulate material containing fenofibrate.
64. The method according to claim 62, wherein a particulate material containing simvastatin of step B) is obtained simultaneously with obtaining a particulate material containing fenofibrate.

65. The method according to claim 62, wherein a particulate material containing simvastatin of step B) is obtained after obtaining a particulate material containing fenofibrate.

66. A method of manufacturing the solid oral dosage form of claim 34 comprising the steps of: A) obtaining a particulate material comprising fenofibrate comprising i) bringing vehicle in liquid form to obtain a liquid vehicle, ii) maintaining the liquid vehicle of i) at a temperature below the melting point of fenofibrate or a pharmaceutically acceptable salt thereof, iii) dissolving the desired amount of fenofibrate in the vehicle of ii) to obtain a solution, iv) spraying the resulting solution of iii) onto a solid carrier having a temperature below the melting point of the vehicle to obtain composition, v) mechanically working the resulting composition of iv) to obtain particles, i.e. a particulate material containing fenofibrate, b) micronizing simvastatin or a pharmaceutically acceptable salt thereof, if applicable, followed by the steps of: C) Mixing the particulate material containing fenofibrate and micronized simvastatin, and D) optionally subjecting the particulate material to conventional methods for preparing solid dosage forms.

67. A method of manufacturing the solid oral dosage form of claim 34 comprising the steps of: i) Bringing the vehicle for fibrate in liquid form, if applicable, ii) maintaining the liquid vehicle at a temperature below the melting point of the fibrate or a pharmaceutically acceptable salt thereof, iii) dissolving the desired amount of fibrate in the vehicle, iv) spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle, v) mechanically working the resulting composition to obtain particles, i.e. a particulate material containing fibrate, and, prior to or simultaneous with or after applying steps i) to v), vi) bringing the vehicle for simvastatin in liquid form, if applicable, vii) dissolving or dispersing the desired amount of simvastatin in the vehicle, viii) spraying the resulting solution onto a solid carrier having a temperature below the melting point of the vehicle, ix) mechanically working the resulting composition to obtain particles, i.e. a
particulate material containing simvastatin, x) subjecting the particles to enteric coating, followed by the steps of xi) mixing the particulate material containing fenofibrate and the entero-coated particulate material containing simvastatin, and xii) optionally subjecting the particulate material to conventional methods for preparing solid dosage forms, for example compression into tablets or filling into capsules or sachets.

68. A method of treating hyperlipidemia comprising administering to a human in need of such treatment a solid pharmaceutical composition in particulate form comprising a vehicle, an effective amount of simvastatin or a pharmaceutically acceptable salt thereof, and an effective amount of fenofibrate exhibiting a bioavailability which is at least bioequivalent to a 130 mg Antara® tablet, the bioequivalency being established by a 90% confidence interval of between 0.80 and 1.25 for AUC, when administered to a human.

69. A method of treating hypercholesterolemia comprising administering to a human in need of such treatment a solid pharmaceutical composition in particulate form comprising a vehicle, an effective amount of simvastatin or a pharmaceutically acceptable salt thereof, and an effective amount of fenofibrate exhibiting a bioavailability which is at least bioequivalent to a 130 mg Antara® tablet, the bioequivalency being established by a 90% confidence interval of between 0.80 and 1.25 for AUC, when administered to a human.

70. Use of fenofibrate of an analog thereof and simvastatin or a pharmaceutically acceptable salt thereof for preparing a medicament for treatment of hypercholesterolemia or hyperlipidemia in a mammal, wherein the medicament comprises a vehicle, an effective amount of simvastatin or a pharmaceutically acceptable salt thereof, and an effective amount of fenofibrate exhibiting a bioavailability which is at least bioequivalent to a 130 mg Antara® tablet, the bioequivalency being established by a 90% confidence interval of between 0.80 and 1.25 for AUC, when administered to a human.

71. Use of a pharmaceutical composition according to claim 1 for manufacturing a medicament for treatment of hyperlipidemia in humans in need thereof.

72. Use of a pharmaceutical composition according to claim 1 for manufacturing a medicament for treatment of hypercholesterolemia in humans in need thereof.
Plasma concentration of Fenofibrate 160 mg [ng/ml] - Means
Lipanthyl®, fed state (N=24) vs. Lipanthyl fasted state (N=23)
LCP-Feno fed state (N=24) vs. LCP-Feno fasted state (N=24)
Plasma concentration of Fenofibrate 160 mg [ng/ml] - Means

Concentration [ng/ml]

Time [h]

-- fasted state, Test---fed state, Test
**INTERNATIONAL SEARCH REPORT**

**International application No**
PCT/DK2005/050003

**A. CLASSIFICATION OF SUBJECT MATTER**

|----------|----------|------------|------------|----------|

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

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, PAJ, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<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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</thead>
<tbody>
<tr>
<td>P,X</td>
<td>WO 2005/034908 A (LIFECYCLE PHARMA A/S; HOLM, PER; NORLING, TOMAS) 21 April 2005 (2005-04-21) examples 4,8,9 claims 1,12,16,22,25,28,37</td>
<td>1-72</td>
</tr>
<tr>
<td>X</td>
<td>WO 02/067901 A (RTF PHARMA INC) 6 September 2002 (2002-09-06) examples 1,4 claims 1,4,16</td>
<td>1-72</td>
</tr>
<tr>
<td>X</td>
<td>WO 03/013608 A (GALEPHAR M/F; VANDERBIST, FRANCIS; DEBOECK, ARTHUR; BAUDIER, PHILIPPE;) 20 February 2003 (2003-02-20) cited in the application example 1 claims 1,5,26</td>
<td>1-72</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

*"A"* document defining the general state of the art which is not considered to be of particular relevance

*"E"* earlier document but published on or after the international filing date

*"L"* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

*"O"* document referring to an oral disclosure, use, exhibition or other means

*"P"* document published prior to the international filing date but later than the priority date claimed

*"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 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

15 February 2006

Date of mailing of the international search report

27/02/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5819 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer

Hedegaard, A
<table>
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