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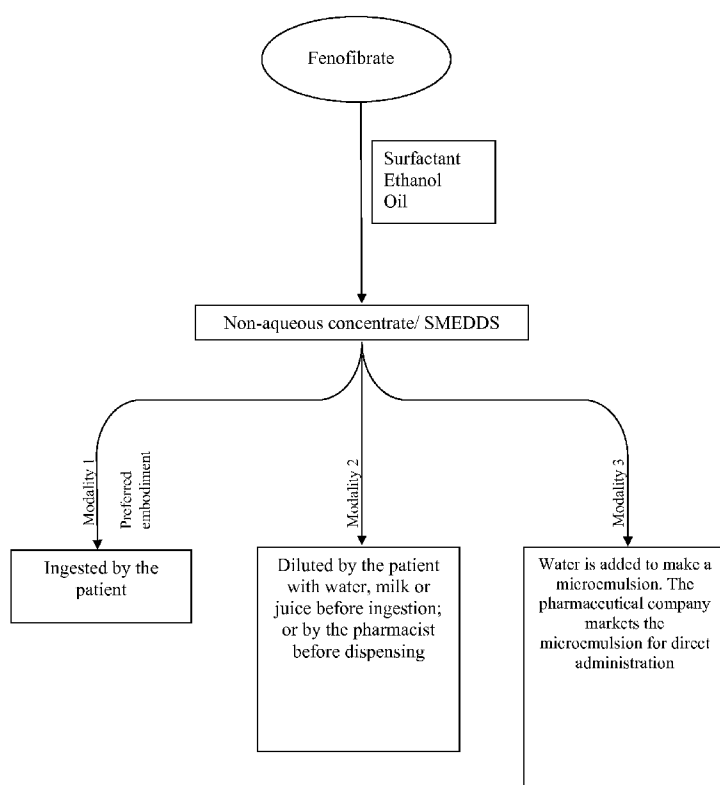
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(54) Title: STABLE, SELF-MICROEMULSIFYING FENOFIBRATE COMPOSITIONS

FIG. 1



(57) Abstract: Stable oral liquid fenofibrate formulations that include a fenofibrate component and a pharmaceutically acceptable liquid carrier that is present in an amount sufficient to solubilize the fenofibrate and that includes a lipophilic component, a surfactant component, at least one monohydric alcohol, and optionally in some embodiments an aqueous component, wherein the formulation is substantially free of an oily phase. Also included are stable liquid fenofibrate formulations including a prophylactically or therapeutically effective amount of fenofibrate and a liquid carrier present in less than 5 ml that is sufficient to maintain dissolution of the fenofibrate under ambient temperature. Methods of preparing and administering such liquid formulations are also included.



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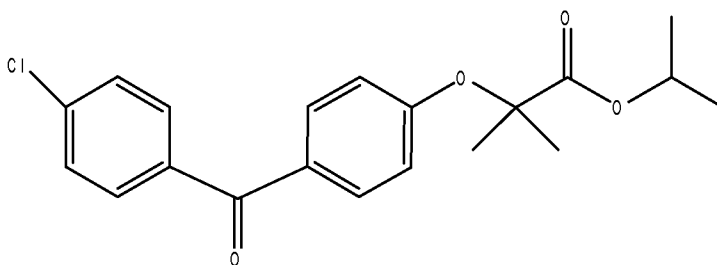
STABLE, SELF-MICROEMULSIFYING FENOFIBRATE COMPOSITIONS

FIELD OF THE INVENTION

The invention relates to stable, bioavailable pharmaceutical compositions of fenofibrate, low-volume liquid fenofibrate formulations, and methods of dosing and manufacturing the same.

BACKGROUND OF THE INVENTION

Fenofibrate is a lipid regulating agent chemically known as 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester. It has the following structure.



Fenofibrate is the ester prodrug of physiologically active fenofibric acid. Following oral administration, fenofibrate is rapidly hydrolyzed by the esterases to its active metabolite and no unchanged fenofibrate is detectable in plasma.

Fenofibrate (CAS Registry #49562-28-9) is a white or almost white crystalline powder, practically insoluble in water, very soluble in methylene chloride, and slightly soluble in alcohol. It has a melting point of 79-82°C and molecular weight of 360.831.

Fenofibrate is stable under ordinary conditions, but sensitive to light.

Fenofibrate is highly hydrophobic with a log P value of 5.575 and aqueous solubility of 0.25 mg/ml at 25°C. It is a Class II compound (low solubility, high permeability) as per the Biopharmaceutics Classification System.

Fenofibrate is well absorbed from the gastrointestinal tract after oral administration, and is rapidly metabolized to fenofibric acid, which is responsible for the pharmacological activity. Fenofibric acid resulting from the hydrolysis of fenofibrate is extensively bound to plasma albumin and is not detectable in plasma as fenofibrate. Also, its absolute bioavailability is not known since it is practically insoluble in aqueous media suitable for injection. Fenofibric acid is excreted predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronides.

Following oral administration of radiolabeled fenofibrate, 60% of the oral dose appeared in urine as fenofibric acid and its glucuronate conjugate, while 25% appeared in feces.

Fenofibric acid produces reductions in total cholesterol, low density lipoprotein cholesterol (LDL-C), apolipoprotein B, total tri-glycerides and tri-glyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and the apolipoproteins apoAI and apoAII. Fenofibrate is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. Fenofibric acid resulting from the hydrolysis of fenofibrate is extensively bound to plasma albumin. The plasma half-life is about 20 hours.

Fenofibric acid has been reported to reduce total cholesterol, low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apoB), total triglycerides, and triglyceride-rich very low density lipoprotein (VLDL); and increase the levels of high density lipoprotein-cholesterol (HDL-C) and apolipoproteins apoAI and apoAII. These effects are deemed helpful in counteracting pro-atherosclerotic conditions, which include high levels of total cholesterol, LDL-C, and apoB; and low levels of HDL-C and proteins involved in its transport complex (apoAI and apoAII). Fenofibric acid is thought to act by the activation of peroxisome proliferator activated receptor α (PPAR α), which leads to the activation of lipoprotein lipase, reduces production of apoprotein C-III (an inhibitor of lipoprotein lipase activity), and increases the synthesis of apoproteins A-I and A-II, and HDL-C.

Fenofibrate is highly hydrophobic and difficult to dissolve in aqueous-based media in concentrations desirable for an oral liquid formulation. High surfactant content in dissolution media is recommended for the dissolution studies of fenofibrate solid dosage forms, indicating low aqueous solubility.

The effects of fenofibric acid have been attributed both *in vivo*, e.g., in transgenic mice, and *in vitro*, e.g., in human hepatocyte cultures, to the activation of peroxisome proliferator activated receptor α (PPAR α). Through PPAR α activation, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase. Fenofibrate also reduces the production of apoprotein C-III, an inhibitor of lipoprotein lipase activity, and PPAR α activation induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol. Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the excretion of uric acid.

Fenofibrate is conventionally marketed as oral solid (tablet and capsule) dosage forms. The brand tablet form of fenofibrate is Tricor[®], which is marketed by Abbott

Laboratories, Illinois. There are a variety of patent documents discussing dosage forms of fenofibrate, which are typically oral and tend to be solid formulations due to low solubility of fenofibrate and consequent difficulty of forming liquid fenofibrate formulations. A few of these are discussed below.

5 U.S. Patent No., 5,45,628 ("the '628 patent") discloses pharmaceutical compositions that are provided for treating hyperlipidemia or hypercholesterolemia or both in a mammal and that contain an effective amount of each of fenofibrate and an excipient containing one or more polyglycolized glycerides. The composition is administered orally as a capsule.

10 U.S. Patent No. 5,145,684 ("the '684 patent") discloses dispersible particles consisting essentially of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm, methods for the preparation of such particles and dispersions containing the particles.

15 U.S. Patent No. 6,375,986 ("the '986 patent") discloses solid dose nanoparticulate compositions comprising a poorly soluble active agent, at least one polymeric surface stabilizer, and dioctyl sodium sulfosuccinate (DOSS).

U.S. Patent No. 6,652,881 ("the '881 patent") discloses compositions comprising micronized fenofibrate, where the compositions reportedly have a dissolution of at
20 least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M sodium lauryl sulfate.

U.S. Patent No. 7,037,529 ("the '529 patent") provides an immediate-release
25 fenofibrate composition comprising (a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 μm , a hydrophilic polymer and, optionally, a surfactant, the polymer making up at least 20% by weight of (a); and (b) optionally one or several outer phase(s) or layer(s).

U.S. Patent No. 7,041,319 ("the '319 patent") provides fenofibrate tablets
30 comprising granulates, wherein the granulates can comprise carrier particles, micronized fenofibrate, and at least one hydrophilic polymer.

U.S. Patent Application Publication No. 2004/0052824 ("the '824 publication") discloses pharmaceutical compositions including micelles containing at least a very lipophilic

principle to enhance bioavailability of active principles insoluble in aqueous solvents called Micellar Improved Drug Delivery Solutions. Specifically, the '824 publication discloses self-microemulsifying formulations with a lipophilic active principle(s) having a log P greater than 2, with a surfactant(s) representing at least 50% by weight of the total composition, with cosurfactant(s) being chosen from good solvents for the active principle(s), where the lipophilic phase is optionally surface-active, and a non-surfactant oily phase representing from 1 to 12% of the total weight of said composition. Many classes of active principles are disclosed, including a variety of hypolipidemic agents such as fenofibrate.

U.S. Patent No. 7,022,337 ("the '337 patent") discloses fibrate self-emulsifying oral formulations having a fibrate solubilizer selected from N-alkyl derivative of 2-pyrrolidone, monoethylene glycol monoethers, diethylene glycol monoethers, higher-ethylene glycol monoethers, polyethylene glycol monoethers, C₈₋₁₂ fatty acid mono- or diesters of propylene glycol, and combinations thereof.

It would be desirable, however, to have suitable stable oral liquid fenofibrate compositions as an additional treatment option, and suitable methods of preparing such compositions. The development of a stable liquid dosage form, with the ease of dose variation and suitable bioavailability, would be desired. The present invention described herein provides such stable, liquid fenofibrate dosage forms.

SUMMARY OF THE INVENTION

The present invention can advantageously meet one or more of these unmet needs of the art by providing the inventive compositions and methods with increased bioavailability of fenofibrate than conventional formulations. The invention relates to a self-microemulsifying drug delivery system (SMEDDS) (herein interchangeably referred to as "SMEDDS" or "SMEDDS/concentrate") of fenofibrate, as well as aqueously diluted formulations of the same referred to herein as a ready-to-use liquid fenofibrate formulation and a microemulsification fenofibrate formulation. By "ready-to-use" and by "microemulsification," it is generally meant a SMEDDS formulation diluted with different amounts of an aqueous component.

Each formulation of the present invention includes a fenofibrate component having a therapeutically or prophylactically effective amount of fenofibrate, or a pharmaceutically acceptable salt or metabolite thereof as well as a pharmaceutically acceptable liquid carrier present in an amount sufficient to solubilize the fenofibrate. In

various embodiments, the liquid carrier includes one or more of a lipophilic component including at least one triglyceride of one or more fractionated vegetable fatty acids including C₈ to C₁₀, a surfactant component, preferably having a HLB value of greater than or equal to 10, including one or more transesterification products of natural or hydrogenated vegetable oil triglyceride, such as a component commonly available under the trade name Labrafil[®], Cremophor[®], and Lauroglycol[®], and at least one monohydric alcohol, preferably an alkanol and more preferably ethanol. Optionally, the formulations may include an aqueous component. In more preferred embodiments, the formulation is at least substantially free of an aqueous phase. In preferred embodiments, at least two, preferably each, of the components selected from the lipophilic, surfactant, and alcohol components, and in other preferred embodiments all three of these components, are present in an amount sufficient to synergistically maintain dissolution of the fenofibrate component, preferably to keep the liquid formulation at least substantially free, more preferably entirely free, of precipitate(s). In more preferred embodiments, the formulation is at least substantially free of an oily phase. In certain embodiments, the formulations are at least substantially stable.

The invention also relates to liquid fenofibrate formulations having a therapeutically or prophylactically effective amount of fenofibrate, or a pharmaceutically acceptable salt or metabolite thereof; and about 1 ml up to 7.5 ml of a pharmaceutically acceptable liquid carrier, including an aqueous component, and a hydrophilic surfactant component, a monohydric alcohol, a lipophilic component, or a combination thereof, to maintain dissolution of the fenofibrate under ambient temperature and provide a liquid fenofibrate formulation that is at least substantially stable, or more preferably entirely stable.

Yet another aspect of the invention relates to methods of preparing a stable, orally administered, liquid fenofibrate formulation that includes first adding a solubilizing amount of a surfactant component to a pharmaceutically effective amount of fenofibrate, or a pharmaceutically acceptable salt or metabolite thereof; adding a monohydric alcohol component and lipophilic component to the pharmaceutically effective amount of fenofibrate and the surfactant. In certain embodiments the method includes optionally adding a sufficient amount of an aqueous component to complete solvation of the pharmaceutically effective amount of fenofibrate, the surfactant component, the lipophilic component, and the monohydric alcohol. Preferably, each step is conducted at or about ambient temperature. The effective amount of fenofibrate is preferably from about 10 mg to about 800 mg, and/or preferably the concentration of the pharmaceutically effective amount of fenofibrate, or a salt

or metabolite thereof, is from about 1 mg/ml to about 80 mg/ml, depending on the dilution of the fenofibrate formulations. Embodiments of the SMEDDS concentrate preferably include a range of fenofibrate from about 10 mg/ml to about 80 mg/ml, more preferably from about 20 mg/ml to 70 mg/ml. Embodiments of the diluted SMEDDS formulations generally include a
5 range of fenofibrate from about 1mg/ml to about 20 mg/ml.

One additional aspect of the invention relates to methods of preventing, treating, or managing a lipid or cardiovascular disorder in a mammal which includes orally administering to the mammal a therapeutically or prophylactically effective amount of the stable, liquid fenofibrate formulations disclosed herein.

10 The invention also relates to the use of a fenofibrate component comprising a therapeutically or prophylactically effective amount of fenofibrate, or a pharmaceutically acceptable salt or metabolite thereof to form an oral formulation for the treatment or management of a lipid or cardiovascular disorder in a mammal. This formulation is formed by combining the fenofibrate component with a pharmaceutically acceptable liquid carrier as
15 disclosed herein which is present in an amount sufficient to solubilize the fenofibrate. Another aspect of the invention relates to the use of a therapeutically or prophylactically effective amount of the stable, liquid fenofibrate formulation disclosed herein for the treatment or management of a lipid or cardiovascular disorder in a mammal by oral administration.

20 Any of the embodiments illustrated herein stand independently, and any features or embodiments may be combined in any way, unless expressly excluded, to achieve a preferred embodiment.

BRIEF DESCRIPTION OF THE DRAWINGS

25 Further advantageous features of the present invention will become more apparent with the following detailed description when taken with reference to the accompanying drawings in which:

FIG. 1 illustrates a schematic diagram of various fenofibrate formulations, in accordance with some embodiments of the present invention;

30 FIG. 2 is a graph that illustrates the dissolution profile of certain fenofibrate formulations in 0.75% SDS solution;

FIG. 3 is a graph that illustrates the dissolution profile of certain fenofibrate formulations in 0.1N HCl;

FIG. 4 is a graph that illustrates the dissolution profile of certain fenofibrate formulations in water; and

FIG. 5 is a graph that illustrates the blood levels of fenofibrate as fenofibric acid after administration of certain fenofibrate formulations to dogs.

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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a ready-to-use oral liquid fenofibrate formulation that is at least substantially stable by including a fenofibrate component of a therapeutically or prophylactically effective amount of a fenofibrate component and a pharmaceutically acceptable liquid carrier present in an amount sufficient to solubilize the fenofibrate. The liquid carrier preferably includes a lipophilic component that includes at least one triglyceride of one or more fractionated vegetable fatty acids including C₈ to C₁₀, a surfactant component that includes a transesterification product of natural or hydrogenated vegetable oil triglyceride, at least one monohydric alcohol, and an aqueous component. Each of the lipophilic, surfactant, and aqueous components are present in an amount sufficient to synergistically maintain dissolution of the fenofibrate component. These formulations are typically in the form of a microemulsion, preferably self-emulsifying drug delivery system, that can take the form of a clear solution. The present invention can also provide formulations that are preferably substantially free of added water to provide stable liquid compositions of fenofibrate in a system including a hydrophilic micellar surfactant, hydrophobic lipophilic agent, and a monohydric alcohol.

FIG. 1 illustrates several modalities encompassed by the present invention. The fenofibrate formulations of the present invention are preferably designed to be used with the following modalities: 1) a ready-to-use aqueous drug emulsion or microemulsion; 2) a low-volume dose form (*i.e.*, a ready-to-use concentrate), which can be in a single-dose or a multi-dose container, which is a preferred embodiment of the present invention; and 3) a single-dose or a multi-dose container that is reconstituted or contacted by the patient with a suitable aqueous vehicle, *e.g.*, water, milk, or juice, immediately before administration. In various embodiments of these modalities, it will be readily understood by those of ordinary skill in the art, particularly through the detailed description herein, how to formulate compositions, with or without specific excipients, such as with or without an aqueous solution, to achieve a pharmaceutically suitable liquid formulation of fenofibrate adapted for oral administration.

As defined herein in certain embodiments, "substantially low volume" means at a volume that is lower than, and more preferably substantially lower than, conventional liquid dosing volumes such as 5 ml or one teaspoonful. In certain embodiments, "low volume" is defined as a volume that is less than or equal to about 10 ml, preferably less than or equal to 8 ml, more preferably less than or equal to about 6 ml, and even more preferably less than or equal to about 5 ml. In a most preferred embodiment, "low volume" refers to about 0.5 ml to 4 ml, preferably about 1 ml to 3 ml of formulation. In some embodiments, substantially low volume relative to conventional formulations can be less than the conventional volume by 5% or more, more preferably by about 10% or more, even more preferably by about 15% or more, and most preferably by about 25% or more. In some embodiments, substantially low volume is about 50%, or more, smaller liquid dose volume than a conventional liquid dosage formulation. In some embodiments, substantially low volume refers to a formulation substantially free of added aqueous component or the complete absence of added aqueous component, or even the complete absence of any aqueous component.

"Fenofibrate" is used interchangeably herein with "fenofibrate component," and each is intended to refer to fenofibrate, a pharmaceutically acceptable salt of fenofibrate, and any metabolite of fenofibrate or salt of such a metabolite, or any combination thereof. The fenofibrate active component of the invention can be made in any manner available to those of ordinary skill in the art. An exemplary synthetic route can be derived from U.S. Patent No. 4,739,101 or even from GB patents 1,415,295 and 1,539,897.

The term "pharmaceutically acceptable salt(s)" or "a pharmaceutically acceptable salt thereof" refers to salt(s) prepared from pharmaceutically acceptable non-toxic acid or bases including inorganic acids and bases and organic acids or bases. The pharmaceutically acceptable salts used in the present invention may be amphoteric, may be present in the form of internal salts, or both. Preferably, the term "pharmaceutically acceptable salt" refers to a salt prepared from a pharmaceutically acceptable non-toxic inorganic or organic acid. Suitable non-toxic acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, and p-toluenesulfonic acids. For example, specific pharmaceutically acceptable salts are hydrochloride and maleic acid salts.

The term "about," as used herein, should generally be understood to refer to both numbers in a range of numerals. Moreover, all numerical ranges herein should be understood to include each whole integer within the range.

The term "substantially" means, *e.g.*, not entirely complete, or not entirely absolute. Typically, "substantially" should be understood to refer to at least about 90 percent, preferably at least about 95 percent, and more preferably at least about 99 percent. In one more preferred embodiment, the term "substantially" can refer to at least about 99.5 percent or 99.9 percent. In one example, a composition that is "substantially stable," encompasses dosage forms that do not necessarily exhibit absolute or 100% stability over a defined period of time; instead, the composition may exhibit nearly total stability, such as greater than about 95 percent stability, or 97% stability, or 99.8% stability, over a particular period of time under ambient conditions (unless specified otherwise).

"Stable," as used herein, refers to liquid compositions where the fenofibrate component remains at least substantially dissolved over a long time period, *e.g.*, at least one month, preferably 2 months, and more preferably 3 months, upon aqueous dilution of the SMEDDS/concentrate and at least 18 months for the SMEDDS/concentrate, at a given temperature such as ambient temperature. In preferred embodiments, "stable," with respect to the SMEDDS formulations, typically refers to parameters of 3 months at 40°C or 18 months at 25°C. The term "stable" also refers to liquid compositions where the fenofibrate agent does not degrade to a significant extent at elevated temperatures, *e.g.*, less than about 1.5% of the fenofibrate, and more preferably less than about 0.5% of the fenofibrate, degrades over three months at 40°C. Thus, for example, a stable fenofibrate solution will meet FDA requirements for fenofibrate based on the expected shelf-life of dosages thereof.

Conversely, "substantially free" encompasses amounts that are almost entirely devoid of the referenced characteristic. As used herein with respect to water, substantially free of water is defined as a formulation having a water content less than or equal to 25%, preferably less than or equal to 20%, more preferably less than or equal to 15%, and even more preferably less than or equal to 10% of the total liquid fenofibrate formulation. In certain embodiments, "substantially free" should be understood to refer to less than about 5%, preferably less than about 1% , and more preferably less than about 0.1%. The term may refer to the added water in a formulation, or to all water in the formulation. "Substantially free" may also mean a quantity that is negligible with respect to the safety, effectiveness, and overall quality of the pharmaceutical composition. As used herein, "completely free,"

"entirely free," or "free" is understood to mean an absence of, *i.e.*, less than an analytically detectable amount, and preferably none, of the stated component.

Fenofibrate is sensitive to hydrolysis and expected to degrade in the presence of water. To impart sufficient stability, formulations of the invention are preferably substantially free of water, such as a water content below about 5% v/v, preferably below about 2.5% v/v, and more preferably below about 1% v/v, of the composition. In addition, the active pharmaceutical ingredient used for the formulation should have low impurity content, with regulatory qualification threshold for any unknown impurity not exceeding 0.1% w/w, and preferably not exceeding 0.05% w/w, and more preferably not exceeding 0.01% w/w, of the composition.

The term "amount" includes both a dry quantity of an agent, compound, or component, such as a quantity that is measured or given in milligram (mg) units, and may also refer to a quantity of an agent, compound, or component that is dissolved or otherwise present in a particular volume of a solvent or other liquid reagent and expressed in terms of a concentration, such as mg/ml.

The term "effective amount" includes an amount of an active pharmaceutical agent that is required to obtain prophylactic or therapeutic efficacy against a disease or condition, or a symptom thereof, or to manage a disease or condition, or a symptom thereof. For instance, an "effective amount" or "pharmaceutically effective amount" of fenofibrate includes an amount of fenofibrate, or a salt or metabolite thereof, that is required to obtain efficacy to prevent, treat, or manage cholesterol or the formation or retention thereof, or the symptoms or conditions associated with high cholesterol or a particular type of cholesterol. The term effective amount therefore includes a prophylactically effective amount and a therapeutically effective amount.

As used herein, the term "patient" (also interchangeably referred to herein as "host" or "subject") refers to any host in need of prevention, management, or therapy related to cholesterol. Preferably, patient includes any animal, which is intended to denote any animal species. In a preferred embodiment, patient refers to any mammal host, such as humans, whales, gorillas, *etc.* In a more preferred embodiment, patient means a human host. A patient can be of any age at which the patient is able to clinically respond to a pharmaceutically effective agent.

The term "manage" includes any action that results in amelioration of cholesterol or another lipid disorder, or a symptom or a condition associated therewith, or

other therapeutic effect that improves the health or well-being of a patient such as the prevention of increase in.

As used herein, the terms "treatment," "treat," "treated," or "treating" refer interchangeably to prophylaxis and/or therapy unless otherwise noted. When used with respect to a chronic disease, for example, the term refers to a prophylactic treatment of the invention which tends to improve the health of the patient and/or affect the target molecules of the pharmaceutical in a beneficial manner, such as the prevention of as large an increase in cholesterol as would occur without the intervention.

The term "pharmaceutically effective amount" has its usual meaning in the art, *i.e.*, an amount of a pharmaceutical that is capable of inducing an *in vivo* and/or clinical response that facilitates management, prophylaxis, or therapy. This term can encompass therapeutic or prophylactic effective amounts, or both.

In one embodiment, the inventive liquid compositions degrade at most about 20% faster than conventional formulations, preferably at most about 10% faster, and more preferably are at least substantially equivalent in stability (or even more stable as discussed herein). Stability is typically measured in the formulations of the present invention by storing samples under various predetermined temperatures, *e.g.*, 40 °C to 50 °C and humidity conditions, *e.g.*, at a relatively high humidity, such as at or below about 75% or at ambient humidity conditions, for a set period of time, *e.g.*, 4 to 12 weeks. In some embodiments, stability is measured at 60% or below at about 25°C. Standard procedures such as HPLC or UV spectroscopic methods are then used to determine the amount of active ingredient remaining before and after storage to compare degradation and stability.

Preferably, the present SMEDDS/concentrate formulation is sufficiently stable to be stored under ambient temperature conditions, *e.g.*, at room temperature of approximately 20°C or 72°F, as well as under cooler conditions including refrigeration. The stability preferably provides a shelf life of at least 120 days, preferably 180 days, more preferably 1 year, and even more preferably at least 18 months even at room temperature. The present formulations exhibit stability even at increased temperatures as further discussed herein.

As used herein, the preferred liquid formulations of the present invention can be prepared as a SMEDDS. Both micellar and microemulsion systems lend themselves to preparation of a concentrate formulation, that can be extemporaneously diluted with the desired aqueous media before administration or before dispensing by the pharmacist. In the

case of microemulsions, the concentrates are known as the SMEDDS. Preferably, there is no need to reconstitute or add additional liquid carrier post-formulation.

As used herein, the term "self-emulsifying" refers to a formulation that is capable of generating an emulsion or microemulsion upon mixing with an aqueous media.

5 In preferred embodiments of the present invention, the SMEDDS/concentrate formulations present fenofibrate in the dissolved form, which is expected to remain solubilized in the microemulsion even upon aqueous dilution should that be desired. As such, in these embodiments, without being bound by theory, the particle size of the active pharmaceutical ingredient, *i.e.*, fenofibrate, used to prepare SMEDDS/concentrate is not
10 believed to be critical to dissolution and bioavailability of the formulation.

Without being bound by theory, the bioavailability of the present invention is expected to be at least similar, or possibly greater, than solid dosage forms of fenofibrate. In certain preferred embodiments, the bioavailability of the fenofibrate formulations of the present invention are within about 20%, preferably about 10%, and more preferably about 5%,
15 of the FDA approved formulations of fenofibrate. In other more preferred embodiments, the bioavailability of fenofibrate in the present formulations exceeds that of FDA approved formulations of fenofibrate.

In addition to solubilization of drug in the aqueous medium, liquid formulations can preferably improve the bioavailability of the drug compared to solid dosage
20 forms, particularly when delivered in SMEDDS. Without being bound by theory, the improvement in bioavailability could be a function of presenting drug in the pre-dissolved form, thus avoiding the step of *in vivo* dissolution from solid particles; digestion of accompanying oil and lipid; increased lymphatic uptake by reduction in the size of bile droplets; inhibition of intestinal efflux of drug mediated by P-glycoprotein; and/or size of the dispersed phase. Without being bound by theory, it is believed that SMEDDS formulations
25 generally have at least about 2 to 10 times, preferably at least about 4 to 10 times higher bioavailability than in tablet or capsule formulations.

The inventive formulations, such as a suitable emulsification form, preferably provides one or more of the following characteristics: 1) it dissolves the drug in a liquid or
30 preferably a solution form; 2) the formulation is substantially or entirely free of precipitation of drug from the liquid formulation, *e.g.*, upon aqueous reconstitution; and/or 3) the formulations exhibit good thermodynamic stability.

The preferred SMEDDS formulations of fenofibrate may be varied, as would be understood by one of ordinary skill in the art as long as the following four functional characteristics are generally satisfied: 1) the drug should be soluble in the formulation under reasonable conditions of agitation; 2) the time taken to dissolve the drug should be reasonable; 3) the formulation should form microemulsion upon reconstitution with water; and 4) the drug precipitation or crystallization upon aqueous reconstitution of the formulation should be absent or delayed and minimum.

The composition of the proposed emulsified liquid formulations of fenofibrate can be varied as long as one or more of the following functional characteristics are satisfied:

1) the drug should maintain dissolution liquid carrier even under reasonable conditions of agitation, *e.g.*, during shipment; 2) the time taken to dissolve the drug should be reasonable, *e.g.*, less than a day, preferably less than about 12 hours, and more preferably within about 30 min. to 4 hours; 3) the formulation should form microemulsion upon contact with an aqueous component.

The present invention includes a pharmaceutically acceptable liquid carrier for oral administration of the formulations of the present invention. The carrier preferably has no pharmaceutical effectiveness without presence of the active pharmaceutical ingredient, *i.e.*, fenofibrate or one or more suitable salts, derivatives, or metabolites thereof. Additionally, it is preferable that the carrier has no adverse interaction of any kind with fenofibrate. The amount of carrier in certain formulation embodiments ranges from about 0.05 ml to about 400 ml per 148 mg dose of fenofibrate. In certain preferred embodiments, without any aqueous solution, the amount of carrier may be from about 0.05 to about 100 ml, preferably 0.1 to 25 ml, and more preferably 1.0 to 10.0 ml in SMEDDS formulations. In some embodiments, the amount of liquid carrier is sufficient to solubilize an effective amount of a fenofibrate in the formulation.

In preferred embodiments, the formulation is substantially free of aqueous solution. Preferred embodiments of the present invention may include a concentrate form, preferably suitable for reconstitution if desired and in some embodiments suitable for low-volume dosing. These formulations tend to have a higher concentration of fenofibrate than ready-to-use formulations described herein.

In certain SMEDDS/concentrate embodiments, the amount of carrier is present in a range from about 1 to about 10 ml, preferably from about 3 to 8 ml, and more preferably from about 2.5 to 6 ml. For example, in a 20mg/ml fenofibrate formulation, about 148mg of

drug will be present in approximately 7.5 ml of carrier. In a 40 mg/ml fenofibrate dose, about 5.0 ml of carrier is present. In a 60 mg/ml fenofibrate formulation, a 148 mg dose will be present in about 2.5ml of carrier.

In accordance with certain embodiments of the present invention, an aqueous microemulsion of the present invention is made, for example, with about a 1:1.25 to 1:2 dilution or a 1:5 to dilution, of SMEDDS/concentrate with aqueous solution. Formulations in accordance with these embodiments have an amount of carrier in the range from about 5 to about 100 ml, preferably from about 10 to 50 ml, more preferably from about 15 to about 40 ml, and even more preferably from about 20 to 35 ml.

A particularly preferable formulation of the present invention includes the self-micellizing (*e.g.*, self-emulsifying) dosage form, which contains only surfactant and monohydric alcohol component, such as to dissolve the drug upon reconstitution and/or dilution with an aqueous phase. In some embodiments, the lipophilic, surfactant, and aqueous components are each present in an amount to synergistically maintain dissolution of the fenofibrate component, preferably over a predominant portion of the shelf-life and more preferably the entire shelf-life of the liquid formulation. By "maintain dissolution" it is meant that small quantities of precipitation occur, but that the drug remains substantially in solution or liquid form. Incorporation of a limited quantity of lipophilic component may be included to inhibit or prevent crystallizing drug out of the formulation over a period of undisturbed storage at room temperature.

The amount of fenofibrate may range from about 25 mg to about 800 mg, preferably from about 50 mg to about 500 mg, and more preferably from about 90 mg to 320 mg, in a formulation of about 5 ml liquid carrier.

In certain SMEDDS embodiments, the amount of fenofibrate is typically about 10 mg/ml to 80 mg/ml, preferably about 15 mg/ml to about 75 mg/ml, and more preferably from about 18 mg/ml to about 60 mg/ml. Some embodiments comprise about 1 to 4% of fenofibrate, preferably 1.5 to 3% fenofibrate, and also preferably 1.75 to 3.5% fenofibrate, weight by volume of the SMEDDS formulation. In preferred embodiments, fenofibrate concentration in the undiluted, non-aqueous concentrate is from about 20 mg/ml to about 60 mg/ml. For example, the fenofibrate concentration of non-aqueous concentrate may be about 20mg/ml, which, in some embodiments, is further diluted, *e.g.*, by 5-times to a final drug concentration in the aqueous solution of 4 mg/ml. In more preferred embodiments, fenofibrate concentration in the undiluted non-aqueous concentrate may be about 40 mg/ml.

In even more preferred embodiments, fenofibrate concentration in the undiluted non-aqueous concentrate may be 60 mg/ml. In yet more preferred embodiments, fenofibrate concentration in the undiluted non-aqueous concentrate may be 80 mg/ml. In some embodiments of the present invention, the concentrations of fenofibrate correspond, preferably based on
5 bioavailability and/or effectiveness, to marketed 45mg and 148mg Tricor[®] tablet formulations.

The formulations of the present invention may be prepared as a ready-to-use form that includes an aqueous component, such as water. In certain preferred embodiments, for aqueous diluted microemulsions, the target dilution of fenofibrate to aqueous solution is between 1:3 to 1:10, preferably 1: 4.0 to 1:7.5, and more preferably 1:45 to 1.6. In some
10 embodiments, the range of fenofibrate in the diluted aqueous microemulsions is from 1 to 35 mg/ml, preferably from 1 to 30 mg/ml, and more preferably from 1-27 mg/ml, and most preferably 3-37 mg/ml. For example, a 1:3 dilution of 10-80 mg/ml fenofibrate would yield 3-27 mg/ml. A 1:10 dilution of 10-80 mg/ml would yield 1-8 mg/ml. Certain embodiments of aqueous fenofibrate comprise less than 2%, preferably less than 1%, and more preferably less
15 than 0.05% fenofibrate.

The formulations of the present invention include a surfactant component. Surfactant serves to facilitate solubilization of a hydrophobic drug, such as fenofibrate. Without being bound by theory, according to the present invention the mechanism of its solubilization appears to be the formation of micelles, swollen micelles, and microemulsion
20 droplets in aqueous solution.

The surfactants used in the present invention are anionic, cationic, non-ionic or zwitterionic. Most preferably the surfactants are non-ionic. In embodiments of the invention, the surfactants have an HLB value greater than 10, preferably greater than 11, and most preferably greater than 12. Examples of suitable surfactants are provided in U.S. Patent
25 Numbers 5,645,856 and 6,096,338, the disclosures of which are incorporated by reference in their entirety herein.

Suitable surfactants may also include a mixture of glycerol-polyethylene glycol ricinoleate, fatty acid esters of polyethylene glycol, polyethylene glycols and ethoxylated glycerol, vegetable oil PEG-6 complexes, generally transesterification products of natural or
30 hydrogenated vegetable oil triglyceride and a polyalkylene polyol, linoleoyl macrogolglycerides, polyoxyethylated oleic glycerides, propylene glycol laurate (e.g., propylene glycol monolaurate), or any combination thereof. Exemplary surfactants include polyoxyethylated apricot kernel oil and ethoxylated persic oil. Preferred surfactants have a

hydrophilic-lipophilic balance value of about 10 to about 15, preferably from about 11 to 14 or about 12 to 15. Some surfactants suitable for the present invention may include Lauroglycol[®] and Labrafil[®], for example, Labrafil[®], both categories of which are manufactured by Gattefosse Pharma, France.

5 A preferred surfactant component includes one of the Cremophor[®] class of surfactants available from BASF, Germany. A more preferred surfactant is Cremophor[®] EL. Cremophor includes a family of nonionic surfactants used to prepare aqueous formulations of hydrophobic substances. Different grades of Cremophor[®] are made by reaction of ethylene oxide with natural oils like castor oil or hydrogenated castor oil. These grades differ in their
10 physical properties and solubilizing capacity. Cremophor[®] EL is produced by the reaction of ethylene oxide with castor oil and it is officially (USP/NF) known as polyoxyl-35-castor oil. Cremophor[®], particularly Cremophor[®] EL, preferably acts as a surfactant that helps form micelles and microemulsion particles upon contact with an aqueous component.

Polyoxyl-35-castor oil can be produced by reaction of ethylene oxide with
15 castor oil in 35:1 molar ratio. The primary portions of Cremophor[®] EL are glycerol-PEG ricinoleate and fatty acid ester(s) of PEG. It also contains lesser quantities of PEGs and ethoxylated glycerol. It has an HLB value of 13.5 (See US 5,444,041).

The surfactant component in SMEDDS/concentrate compositions may generally be present in an amount ranging from about 1 ml to about 5 ml, preferably from
20 about 1.5 ml to about 4 ml, and more preferably from about 2.5 ml to about 3.5 ml, and most preferably from about 2.6 ml to about 3.25 ml, based on a total volume of 5 ml. The percentage of surfactant in the formulation may range from 30 percent to about 70 percent, preferably from about 42.5 percent to about 65 percent and/or from about 46 percent to about 57.5 percent.

25 The surfactant component in aqueous-based, ready-to-use formulations is preferably present in a 100 ml formulation of the present invention in the range from about 7 ml to about 15 ml, and preferably from about 8 ml to about 13 ml. In certain embodiments, for example, Cremophor[®] can be present in the formulation at an amount equivalent to 10 to 13 ml when the density of the Cremophor[®] is at 1.00 g/ml. In some embodiments, the
30 percentage of surfactant by volume of the formulations is about 6 to about 14%, preferably from about 7 to about 12%, and most preferably about 9 to about 11.5%. Preferably, when the surfactant component includes Cremophor[®], the surfactant is not present in an amount sufficient to cause it to act as a solubilizer.

The formulations of the present invention typically include a lipophilic component, such as a triglyceride derived from fractionating a vegetable acid. The lipophilic component serves to provide the hydrophobic environment in the swollen micelles and microemulsion droplets so that extended physical stability of solubilized drug is obtained in the formulation. In the absence of or with the limiting amounts of lipophilic agent in the formulation, precipitation of the drug in the form of crystals is apparent over an extended storage at room temperature or in refrigerator.

A lipophilic component may include any triglyceride, including oil, such as olive oil. Preferably, the lipophilic component, and the formulation as a whole, are substantially free of an oily phase. In preferred embodiments, the lipophilic component includes Miglyol[®], which is a caprylic/capric triglyceride, available commercially from Condea, Cranford, NJ. A more preferred lipophilic component is Miglyol[®] 812. Miglyol[®] includes a family of esters of caprylic and capric acids (derived from coconut oil and palm kernel oil) with glycerin. Different grades of Miglyols[®] differ in the type of oil used and in the replacement of glycerin by propylene glycol. Miglyol[®] 812 is a triglyceride of fractionated vegetable fatty acids C₈ and C₁₀.

The lipophilic component may generally be present in formulations of the present invention in the range from about 0.01 ml to about 2 ml, preferably from about 0.1 ml to about 1.5 ml, and more preferably from 0.25 ml to 1.0 ml, per 5ml of the SMEDDS/concentrate formulation. In other SMEDDS embodiments, the lipophilic component comprises about 3 to 7 percent, preferably 3.5 to 6 percent, more preferably 4 to 5.5 percent, by volume of the formulation.

In ready-to-use formulations, the lipophilic component is present in an amount from about 0.25 ml to about 2.5 ml, preferably from about 0.50 ml to about 2 ml, and more preferably from about 0.75 ml to about 1.50 ml, per total volume of 100 ml. In certain embodiments, 1 ml of lipophilic component is present in 100 ml of total volume. In some embodiments of the aqueous formulations, the lipophilic component comprises about 0.25 to about 1.5% of the formulation, and more preferably from about 0.4% to about 1.25% of the formulation.

The formulations of the present invention include alkanols, and preferably include a monohydric alcohol component, including one or more of methanol, propanol, butanol, pentanol, ethanol, and the like, or any combination thereof. Preferably, the monohydric alcohol component includes ethanol. The alcohol component aids the stability of

the formulations of the present invention. In certain SMEDDS embodiments of the present invention, the monohydric alcohol may generally be present in an amount from about 0.1 ml to about 5 ml, preferably from about 1 ml to about 3.5 ml, and more preferably from about 1.5 to about 2.9 ml, per 5 ml of the formulation. In other SMEDDS embodiments, the monohydric alcohol comprises about 20 to 50%, preferably about 30 to 45%, and more preferably 35 to 47%, by volume of the formulation.

In certain aqueous formulations, the monohydric alcohol may be present in an amount ranging from about 4 ml to about 15 ml, preferably from about 6 ml to about 12 ml, and more preferably from about 7 ml to about 10 ml, per 100 ml of the formulation. The percentage of ethanol, for example, in the aqueous formulations may range from 3 to about 12%, preferably from about 5 to about 10% and/or from about 6 to about 9%.

In certain embodiments, the formulations of the present invention further include an aqueous component, such as water, which can be present in an amount sufficient to top off the formulation to a desired volume such as 100 ml. In preferred embodiments, water is provided q.s. to 100 ml and is thus present at about 60 v/v% to 95 v/v%, preferably about 65 v/v% to 90 v/v%, and more preferably from about 75 v/v% to 90 v/v%.

The present invention may preferably include aqueous fenofibrate formulations having about 2 mg/ml to 6 mg/ml fenofibrate, monohydric alcohol in an amount from about 6 v/v percent to 12 v/v percent, surfactant component in an amount of about 8 v/v percent to 15 v/v percent, a lipophilic component in an amount of about 0.1 v/v percent to 4 v/v percent, and water (q.s. to 100 ml). An exemplary formulation includes 400 mg fenofibrate, 8 ml ethanol, 11 ml Cremophor® EL, 1 ml Miglyol 812®, and water (q.s. to 100 ml).

An exemplary SMEDDS formulation includes 20 mg/ml fenofibrate, 2 ml ethanol, 2.75 ml Cremophor® EL, and 0.25 ml Miglyol 812®, which may but need not be reconstituted with an aqueous component such as water.

Some of the proposed formulations provide fenofibrate in dissolved form, which is expected to remain soluble in the microemulsion whether or not diluted with an aqueous component. Particle size of fenofibrate may be selected to correspond to the time taken to dissolve the drug while preparing the formulations of the present invention, rather than to affect dissolution and bioavailability from the formulation. Namely, smaller particles should dissolve faster but, without being bound by theory, are not expected to substantially affect dissolution or bioavailability. Thus, any suitable size fenofibrate may be selected,

whether micronized or not, if it dissolves in a reasonable amount of time to facilitate preparation of the inventive formulation.

In some embodiments, the formulations of the present invention may additionally include a taste masking agent, flavoring agent, sweetening agent, one or more preservatives, e.g. antimicrobial preservative, or any combination thereof. The flavoring agent, when used in the stable inventive liquid formulation, preferably includes any suitable, sugar-free flavoring agent available to those of ordinary skill in the art in the liquid carrier, typically to enhance patient compliance by making the compositions of the present invention more palatable. The flavoring agent may also or alternatively be one or more substances capable of enhancing taste or aroma of a pharmaceutical composition. Any suitable natural or synthetic flavoring agent can be selected, such as those listed in standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). The flavoring agent is typically selected in type and amount to increase palatability, *e.g.*, by decreasing or eliminating any undesired taste or off-flavors in the taste, *i.e.*, a taste mask, that would otherwise be detectable by the patient to whom the compositions are administered. Examples of a suitable flavoring agent, when used, include one or more of menthol, peppermint, anise, and any fruit flavor, such as one or more of grapefruit, orange, grape, lemon, lime, mango, strawberry, pineapple, or cherry, or a combination thereof.

When an effective amount of fenofibrate is preferably from about 15 mg/ml to 80 mg/ml, and more preferably from about 20 mg/ml to about 60 mg/ml, such a flavoring agent, if present, may be present at a concentration in the composition of about 0.1 mg/ml to 5 mg/ml, preferably about 0.2 mg/ml to 3 mg/ml, and more preferably from about 0.5 mg/ml to 2 mg/ml. In certain embodiments, the flavoring agent may be present in an amount from about 0.1% to 0.6%, and more preferably at about 0.2% to 0.4%, v/v of the pharmaceutical composition. Preservatives may be present in an amount from about 0.01% to 1.0%, preferably at about 0.1% to 0.75%, and more preferably from about 0.2% to 0.5% v/v of the pharmaceutical composition.

Furthermore, a colorant agent, when included, may be provided in an amount sufficient to impart the compositions with a more aesthetic and/or distinctive appearance. Any suitable colorant agent available to those of ordinary skill in the art may be selected. Typically, a colorant agent suitable for inclusion in the present invention includes one or more synthetic organic food additives (*e.g.*, food dyes such as food red dye Nos. 2 and 3, food yellow dye Nos. 4 and 5 and food blue dye Nos. 1 and 2), water-insoluble lake dyes (*e.g.*,

aluminum salts of the above synthetic organic food additives, etc.), and natural pigments (*e.g.*, beta-carotene, chlorophyll, iron oxide red, etc.), or any combination thereof. Suitable colorants include D&C Red No. 33, FD&C Red No. 3, FD&C Red No. 40, D&C Yellow No. 10, and C Yellow No. 6. Any combination of these or any other suitable colorant agent can be included. Such a colorant agent, if present, may be present in a conventional amount.

The present invention also provides a method of manufacturing SMEDDS formulations having fenofibrate, at least one surfactant, one monohydric alcohol, and a lipophilic component. In one step, the surfactant is added to the fenofibrate. In another step, the monohydric alcohol and/or lipophilic component, preferably a component not providing or inducing an oily phase, are added. The SMEDDS/concentrate formulations of the present invention may be ingested by patients, as shown in FIG. 1.

Embodiments of the ready-to-use and self-emulsification formulations typically include dilution of the concentrate formulations with aqueous solution, such as milk, juice, and/or water. Aqueous formulations, as shown in FIG. 1, such as the ready-to-use and self-emulsification forms, may be diluted from about 1.125 to 2 times, and preferably about 1.3 to 1.55 times, particularly for the self-emulsification form and about 2.5 to 7 times, preferably about 3.5 to 5 times for the ready to-use-form.

In a preferred embodiment, the order of the manufacturing steps is helpful to providing stability, wherein a portion of the surfactant component is added to the fenofibrate first, a portion of the monohydric alcohol and/or lipophilic component are added next, in any order, and when appropriate for the diluted formulations of the present invention, the aqueous component such as is added to the mixture. The portion combined with the solution during preparation may be 40%, half, 60%, 80%, or all the amount of the specified component. In preferred embodiments, no heat is added to any step of the method of manufacture. In certain embodiments, the process of manufacturing is conducted at ambient temperature, and more preferably room temperature.

In certain embodiments, the formulation of the present invention that is reconstituted with water, whether prepackaged or added by a third party prior to ingestion/administration is also referred to as a "ready-to-use" aqueous microemulsion formulation.

The following example provides one embodiment of preparing the formulations of the present invention. Cremophor[®] EL is added to fenofibrate. Miglyol[®] 812 is then added to the fenofibrate mixture. Subsequently, the ethanol is added. Lastly, water is

added to the mixture. The amount of fenofibrate and excipients is consistent with the amounts provided above.

In some embodiments, the present invention includes methods of preventing, treating, or managing a lipid or cardiovascular disorder in a mammal which includes orally administering to the mammal a therapeutically or prophylactically effective amount of any of the stable, liquid fenofibrate formulations disclosed herein. Additionally, the present invention may be administered in low doses relative to conventional doses of Tricor[®]. A preferred administration regimen may include providing a patient in need of cholesterol treatment with a pharmaceutically effective amount of fenofibrate in accordance with the FDA approved labeling for fenofibrate. Preferably, low volume dose regimens of fenofibrate are substantially free of water, buffer, and/or aqueous solution or other aqueous component.

EXAMPLES

The invention is further defined by reference to the following illustrative examples that may be used to prepare or administer the compositions of the present invention. These examples are for illustrative purposes only, and are not to be construed as limiting the appended claims.

Example 1a: Ready-To-Use Formulation of the Invention

In certain embodiments, the fenofibrate ready-to-use formulation can be prepared having the following components:

Fenofibrate	4 mg/ml
Ethanol	7-12%
Surfactant	10-15%
Lipophilic Component	1-4%
Water	q.s. to 100%

An exemplary embodiment of a ready-to-use fenofibrate formulation can include the following components:

Fenofibrate	400mg (4 mg/ml)		
Ethanol	8 ml	(8% v/v)	(density: 0.791 g/ml)
Cremophor EL	11ml	(11% v/v)	(density: 1.055 g/ml)
Miglyol 812	1 ml	(1% v/v)	(density: 0.945 g/ml)
Water q.s. to	100 ml	(80% v/v)	(density: 1g/ml)
(80 ml of water added to q.s. to 100 ml final volume)			

Example 1b: Additional Formulations of the Invention

In other embodiments, fenofibrate was formulated into a SMEDDS having a non-aqueous concentrate of lipid (Miglyol[®] 812), monohydric alcohol (ethanol), and surfactant (Cremophor[®] EL) with the following three exemplary aqueous-free compositions:

I

Fenofibrate	20 mg/ml	100mg/5 ml	2% w/v
Ethanol	0.4 ml/ml	2 ml /5 ml	40% v/v
Cremophor [®] EL	0.55 ml/ml	2.75 ml/5 ml	55% v/v
Miglyol [®] 812	0.05 ml/ml	0.25 ml/5 ml	5% v/v

II

Fenofibrate	40 mg/ml	200 mg/5 ml	4% w/v
Ethanol	0.4 ml/ml	2 ml/5 ml	40% v/v
Cremophor [®] EL	0.55 ml/ml	2.75 ml/5 ml	55% v/v
Miglyol [®] 812	0.05 ml/ml	0.25 ml/5 ml	5% v/v

III

Fenofibrate	60 mg/ml	300 mg/5 ml	6% w/v
Ethanol	0.4 ml/ml	2 ml/5 ml	40% v/v
Cremophor [®] EL	0.55 ml/ml	2.75 ml/5 ml	55% v/v
Miglyol [®] 812	0.05 ml/ml	0.25 ml/5 ml	5% v/v

Example 2: Stability Testing of Various Formulations

Several batches of SEDDS/SMEDDS formulations were prepared for evaluation of chemical stability. The composition of these formulations is listed in Table 1.

Table 1. Fenofibrate Formulations - initial evaluation of chemical stability.

B.No.	Ingredient	Qty	%	Claim/Dil
Example 2.1	Fenofibrate	100mg		22mg/ml
	Labrafil	2.05ml	45%	5.5 times
	Olive Oil	2.5ml	55%	
Example 2.2	Fenofibrate	100mg		20mg/ml
	EtOH	0.45ml	9%	5 times
	Labrafil	2.05ml	41%	
	Olive Oil	2.5ml	50%	
Example 2.3	Fenofibrate	100mg		20mg/ml
	EtOH	0.45ml	9%	5 times
	Labrafil	2.05ml	41%	
	Grape Seed Oil	2.5ml	50%	

B.No.	Ingredient	Qty	%	Claim/Dil
Example 2.4	Fenofibrate	100mg		20mg/ml
	EtOH	0.45ml	9%	5 times
	Labrafil	2.05ml	41%	
	Wheat Germ Oil	2.5ml	50%	
Example 2.5	Fenofibrate	100mg		20mg/ml
	EtOH	2ml	40%	5 times
	PS80	2ml	40%	
	Olive Oil	1ml	20%	
Example 2.6	Fenofibrate	100mg		20mg/ml
	EtOH	2ml	40%	5 times
	PS 80	2.25ml	45%	
	Span 40	0.25ml	5%	
	Olive Oil	0.5ml	10%	
Example 2.7	Fenofibrate	100mg		25mg/ml
	EtOH	2ml	50%	6.25 times
	Pl oleique	1ml	25%	
	Olive oil	1ml	25%	
Example 2.8	Fenofibrate	100mg		25mg/ml
	EtOH	2ml	50%	6.25 times
	Cr CO 40	1ml	25%	
	Olive Oil	1ml	25%	
Example 2.9	Fenofibrate	100mg		25mg/ml
	EtOH	2ml	50%	6.25 times
	Cr EL	1ml	25%	
	Olive Oil	1ml	25%	
Example 2.10	Fenofibrate	100mg		25mg/ml
	EtOH	2ml	50%	6.25 times
	Cr RH 40	1ml	25%	
	Olive Oil	1ml	25%	
Example 2.11	Fenofibrate	100mg		25mg/ml
	EtOH	2ml	50%	6.25 times
	Labrafil	2ml	50%	
Example 2.12	Fenofibrate	100mg		20mg/ml
	EtOH	2ml	40%	5 times
	Cr EL	3ml	60%	
Example 2.13	Fenofibrate	100mg		20mg/ml
	EtOH	2ml	40%	5 times
	Cr CO 40	2.75ml	55%	
	Miglyol	0.25ml	5%	

B.No.	Ingredient	Qty	%	Claim/Dil
Example 2.14	Fenofibrate	100mg		20mg/ml
	EtOH	2ml	40%	5 times
	Cr EL	2.75ml	55%	
	Miglyol	0.25ml	5%	
Example 2.15	Fenofibrate	100mg		20mg/ml
	EtOH	2ml	40%	5 times
	Cr RH 40	2.75ml	55%	
	Miglyol	0.25ml	5%	
Example 2.16	Fenofibrate	100mg		20mg/ml
	EtOH	2ml	40%	5 times
	PS 80	2.75ml	55%	
	Miglyol	0.25ml	5%	
Example 2.17	Fenofibrate	100mg		22mg/ml
	EtOH	2ml	44%	5.5 times
	Cr EL	2.25ml	50%	
	Cr WO 7	0.25ml	6%	
Example 2.18	Fenofibrate	100mg		22mg/ml
	EtOH	2ml	44%	5.5 times
	Cr EL	2.25ml	50%	
	Labrafil	0.25ml	6%	
Example 2.19	Fenofibrate	100mg		22mg/ml
	EtOH	2ml	44%	5.5 times
	Cr EL	2.25ml	50%	
	LG	0.25ml	6%	
Example 2.20	Fenofibrate	100mg		22mg/ml
	EtOH	2ml	44%	5.5 times
	Cr RH 40	2.25ml	50%	
	Cr WO 7	0.25ml	6%	
Example 2.21	Fenofibrate	100mg		20mg/ml
	PS 80	4ml	80%	5 times
	LG	1ml	20%	
Example 2.22	Fenofibrate	100mg		
	EtOH	0.45ml	9%	2%
	Labrafil	2.05ml	41%	8%
	Olive Oil	2.5ml	50%	10%
	Water to 25ml			80%

B.No.	Ingredient	Qty	%	Claim/Dil
Example 2.23	Fenofibrate	100mg		
	EtOH	2ml	40%	8%
	Cr EL	3ml	60%	12%
	Water to 25ml			80%
Example 2.24	Fenofibrate	100mg		
	EtOH	2ml	40%	8%
	Cr EL	2.75ml	55%	11%
	Miglyol	0.25ml	5%	1%
	Water to 25ml			80%
Example 2.25	Fenofibrate	100mg		
	EtOH	2ml	40%	8%
	Cr CO40	2.75ml	55%	11%
	Miglyol	0.25ml	5%	1%
	Water to 25ml			80%
Example 2.26	Fenofibrate	100mg		
	EtOH	2ml	40%	8%
	PS 80	2.75ml	55%	11%
	Miglyol	0.25ml	5%	1%
	Water to 25ml			80%

Note: Abbreviation below the batch number indicates the type of formulation.
Abbreviations: SEDDS, Self-emulsifying drug delivery system; SMEDDS,
Self-microemulsifying drug delivery system; Cr, Cremophor; EtOH, ethanol;
Pl, plurool; PS 80, polysorbate 80

These formulations were packed in 1 oz HDPE bottle packs for stability evaluation at 40°C for 1, 2, and 3 months, with corresponding 25°C and 4°C samples as controls. Samples were tested under a stability indicating reverse phase gradient HPLC method using UV detection.

The samples, *i.e.*, 1 month and 2 month samples at 40° C were analyzed for assay. The data is reported in Table 2 as a percentage of the label claim. As used herein, the label claim indicates the concentration, *e.g.*, mg/ml, of drug added to the formulation. The initial amount mg/ml is typically 100%.

Table 2. Chemical stability data of fenofibrate-base formulations for assay.

B.No.	Assay as % of claim (2 month)	Assay as % of claim (1 month)	% Fall in Assay (2-1 month)
Example 2.1	102.7	104.7	-1.93
Example 2.2	105.9	105.0	0.9
Example 2.3	102.9	103.6	-0.70
Example 2.4	105.0	103.8	1.2
Example 2.5	108.6	105.3	3.38
Example 2.6	105.1	101.0	4.1
Example 2.7	110.0	103.1	6.91
Example 2.8	119.8	104.1	15.6
Example 2.9	107.5	105.1	2.41
Example 2.10	118.1	105.9	12.3
Example 2.11	135.7	103.4	32.32
Example 2.12	107.6	106.0	1.5
Example 2.13	107.9	105.6	2.31
Example 2.14	108.3	106.2	2.0
Example 2.15	110.7	107.4	3.30
Example 2.16	95.9	103.6	-7.7
Example 2.17	113.8	111.9	1.93
Example 2.18	109.5	104.7	4.8
Example 2.19	112.3	104.2	8.11
Example 2.20	118.3	111.3	7.0
Example 2.21	101.5	101.8	-0.30

The variations in assay data from 100% of $\pm 5\%$ were attributed to variations in the amount of drug added during batch preparation, while variations greater than $\pm 5\%$ were attributable to variation during sample preparation. Sample preparation and HPLC peak resolution for this product required optimization for each individual formulation since a lipidic component was used in these products.

In addition to the results of the preliminary assay in Table 2, which did not indicate significant fall in fenofibrate concentration over a 2-month period, the chromatograms did not show any significant impurity peaks. These data indicated good stability of non-aqueous SEDDS/SMEDDS concentrate formulations of fenofibrate.

The ready-to-use formulations showed drug crystallization at room temperature, which was more pronounced at 4°C storage for a 1-month period. The drug precipitation also led to loss in assay, as seen for batch 199-91, in Table 3.

Table 3. Assay of ready-to-use fenofibrate formulations at 4 mg/ml concentration after 1M storage at 4, 25, 40° C.

B.No.	Type of Formulation	Assay at 4°C	Assay at 25°C	Assay at 40°C
Example 2.22	SEDDS	101.9	103.6	103.9
Example 2.23	Reconstituted SMEDDS	na	na	105.6
Example 2.24	Reconstituted SMEDDS	31.4	83.4	104.0
Example 2.25	Reconstituted SMEDDS	na	na	104.2
Example 2.26	Reconstituted SMEDDS	na	na	103.6

Abbreviations: na, not analyzed

These data indicated the need to improve formulation with respect to drug precipitation by crystallization upon reconstitution. No crystallization or precipitation was observed in any samples when they were formulated and preserved as SEDDS/SMEDDS concentrates.

Table 4. Composition of different formulations to improve physical stability of reconstituted SMEDDS formulation at 4° and 25°C.

B.No.	Fenofibrate (mg)	Ethanol (ml)	Cremophor® EL (ml)	Miglyol® 812 (ml)
Example A	500	10	13.75	1.25
Example B	500	10	12.5	2.5
Example C	500	10	11.25	3.75
Example D	500	10	15	0
Example E	500	10	17.25	4
Example F	500	10	18.75	2.5
Example G	500	10	20	1.25
Example H	500	10	18.5	1.5
Example I	500	10	17.25	1.5

No precipitates appeared in any SMEDDS/ concentrate samples. Upon reconstitution with water, formulation 'Example C' had milky white appearance indicating large particle size of dispersed phase and formulation 'Example E' was slightly cloudy – which increased in opacity to become milky white over several weeks. All other formulations were

optically clear upon reconstitution. All the formulations were stored at 4°C and 25°C in non-aqueous concentrate form as well as after 1:5 reconstitution with water. The formulations were observed for possible precipitation of fenofibrate crystals upon undisturbed storage for 5 months. These observations are summarized in Table-5. Formulation 'Example D' was the most unstable in that the precipitation appeared most rapidly, while formulations 'Example A' and 'Example G' showed many small crystals at 4°C over a period of time. Samples 'Example B', 'Example H', and 'Example I' showed fewer, large crystals at 4°C indicating slower crystallization. Formulations 'C', 'Example E', and 'Example F' were essentially free of any crystalline precipitates at both 4° and 25°C. These results indicated that the propensity for drug precipitation by crystallization was dependent on the content of Miglyol® and Cremophor® in the formulation. Therefore, formulations 'Example C' and 'Example E' were considered the best formulations for a ready-to-use aqueous-based self-emulsifying systems and formulation 'Example F' was considered the best choice for a ready-to-use aqueous-based self-microemulsifying system.

Table 5. Results of formulation trials to improve physical stability of reconstituted SMEDDS formulation at 4° and 25°C.

B.No.	Temperature (°C)	Precipitation observed?	
		Concentrate	Reconstituted
Example A	4	No	Yes*
	25	No	Yes**
Example B	4	No	Yes**
	25	No	Yes**
Example C	4	No	No
	25	No	No
Example D	4	No	Yes*
	25	No	Yes*
Example E	4	No	No
	25	No	No
Example F	4	No	No
	25	No	No
Example G	4	No	Yes*
	25	No	No
Example H	4	No	Yes**
	25	No	No
Example I	4	No	Yes**
	25	No	No

*, many small crystals; **, fewer large crystals

The concentration of fenofibrate in SMEDDS concentrate (as per Example A) was sought to be increased from 20 mg/ml to 40 mg/ml or 60 mg/ml. Fenofibrate was soluble in the current SMEDDS/concentrate formulation without any changes. Upon dilution of 1 ml of formulation into 100 ml water, the samples dissolved well to give a clear solution. Upon
5 undisturbed storage of diluted samples at room temperature, however, drug precipitates/crystals appeared in all solutions with higher relative amount of precipitates with increasing drug concentration. These studies indicated that while the SMEDDS/concentrate formulations could be prepared as a solution up to 60 mg/ml and did not immediately precipitate out of solution, they did have the tendency to crystallize over a substantial period
10 of undisturbed storage. Precipitation from solution in the stomach is known to adversely affect bioavailability.

Example 3: Precipitation of Inventive Formulation in Simulated Gastric Fluid

Drug precipitation *in vivo* could compromise the advantage of oral
15 bioavailability of a self-emulsifying dosage form. To assess the tendency of the SMEDDS formulation at 60 mg/ml concentration to precipitate *in vivo*, 0.8 ml of formulation (300 mg Fenofibrate, 2 ml ethanol, 2.75 ml Cremophor[®], and 0.25 ml Miglyol[®]) (equivalent to 48 mg strength of Tricor[®] tablets) was added to 50 ml (estimated gastric fluid volume) of simulated gastric fluid (2g NaCl + 3.2g pepsin + 7 ml HCl + q.s. water to 1000 ml) and equivalent HCl
20 and HCl + NaCl solutions.

Testing indicated that the formulations of the present invention did not show a tendency to precipitate for the first 1 hour of incubation after dilution at 37°C and orbital rotation at 100 rpm. Very fine and few particles appeared after 2 hours of incubation. There was no significant difference between the three media used for the precipitation study. Based
25 on this experiment, it was concluded that the formulations of the present invention would not likely precipitate in the stomach upon oral ingestion.

Example 4: Solubility of Inventive Formulation

To evaluate whether any individual component can dissolve the amount of drug
30 in the formulation, fenofibrate solubility was evaluated in individual excipients under agitation conditions relevant to pharmaceutical manufacturing. Two hundred or 300 mg fenofibrate from the 3 vendors was mixed with 2 ml ethanol, 2.75 ml Cremophor[®] EL, 3.75 ml Cremophor[®] EL, or 0.25 ml Miglyol[®] 812 in scintillation vials by spinning at room temperature for 4 days. None of the excipients used in the formulation could dissolve the drug

by itself. The drug also did not dissolve in Cremophor[®] EL alone (solubility < 9 mg/ml) or in Cremophor[®] EL micelles in water (solubility < 1 mg/ml).

These results indicated that the fenofibrate SMEDDS concentrate formulation was not achievable based on the concept of solubilization of the drug in one excipient, with addition of other excipients for distinct functional roles.

Example 5: Solubility Testing

Several small-scale pre-formulation experiments were conducted to test the role and requirement of each excipient towards developing viable formulation choices based on desired characteristics, *i.e.*, drug solubilization in the SEDDDS/ SMEDDS concentrate formulation and physical stability upon reconstitution. These trials are summarized in the following:

Table 6.

#	Ingredient 1	Ingredient 2	Ingredient 3	Observations
C3	0.45ml EtOH	2.05ml Labrafil	2.5ml Olive oil	Did not dissolve with #1, dissolves fastest when all components are added, SEDDS, no crystallization
C4	2ml EtOH	2ml Labrafil	1ml Olive oil	clear solution, SEDDS, no crystallization
C5	2ml EtOH	2.5ml Labrafil	0.5ml Olive oil	clear solution, SEDDS
C6	2ml EtOH	2ml Tmaz80	1ml Olive oil	cloudy solution, SEDDS, no crystallization
C7	2ml EtOH	2.25gTmaz80+0.25g Span40	1ml Olive oil	cloudy solution, SEDDS, no crystallization
C13	2ml EtOH	2g RH60	1g Olive oil	clear solution after #2, milky white dispersion after #3
C28	2ml EtOH	2g Labrasol	-	SEDDS, foam, lots crystallization
C33	2ml EtOH	2g Lauroglycol 90	-	oil separation and white particle precipitation
C34	2ml EtOH	2g Labrafil M 1944 Cs	-	SEDDS, less foam than 28 (creamish), no crystallization
58	2ml EtOH	2.5g CO40	0.5g Miglyol	slightly cloudy SMEDDS/SEDDS, no crystallization
C59	2ml EtOH	2g EL	Simethicone	particulate precipitation
60				Error
61	2ml EtOH	2g EL	0.5g Labrafil	slightly cloudy SMEDDS/SEDDS, little crystallization
113-4	2ml EtOH	2.75ml EL	0.25ml Miglyol	dissolves, SMEDDS, little crystallization
115	2ml EtOH	2.75ml EL	0.25ml Miglyol	SMEDDS

Abbreviations: Labrafil[®], Labrafil[®] M 1944 Cs; EtOH, ethanol; EL, Cremophor[®] EL; RH40, Cremophor[®] RH40; RH60, Cremophor[®] RH60; A20, Cremophor[®] A20; A6, Cremophor[®] A6; WO7, Cremophor[®] WO7; GS32, glyceryl stearate 32; A25, Cremophor[®] A25; GMS, glyceryl monostearate; Miglyol[®], Miglyol[®] 812; PEG, polyethylene glycol; PG, propylene glycol

Example 6: Solubility Testing of Cremophor[®] as a potential solubilizer

As shown in the table below, in the formulations of the present invention, Cremophor[®] EL alone can not solubilize the amount of drug in water throughout the concentration range from 1 mg/ml to 50 mg/ml. The range of drug concentrations in the formulations of the present invention that can be solubilized in the amount of Cremophor[®] used was tested from 1 mg/ml to 200 mg/ml (our target concentration 60 mg/ml). Only 1 mg/ml dissolved. The amount of Cremophor[®] used in the SMEDDS/Concentrate formulation was not able to dissolve the drug concentration (in final formulation) throughout the range 5 mg/ml to 200 mg/ml.

Table 7.

**Calculation for solubility study of fenofibrate
range of concentration around which Cremophor® can dissolve API**

Formulation (SMEDDS/Concentrate 60mg/ml)	
Fenofibrate	300mg
Ethanol	2ml
Cremophor® EL	2.75ml
Miglyol® 812	0.25ml
TOTAL	5ml

60mg/ml fenofibrate in formulation
eq. to 109.1mg/ml fenofibrate in Cremophor® EL

mg/ml Fenofibrate in formulation	mg/ml Fenofibrate in Cremophor® EL	mg	ml	mg/ml	Dissolve?
1	1.82	36.4	20	1.82	Yes
5	9.09	90.9	10	9.09	No
10	18.18	90.9	5	18.18	No
20	36.36	181.8	5	36.36	No
40	72.73	363.6	5	72.73	No
60	109.09	545.5	5	109.09	NO
80	145.45	727.3	5	145.45	NO
100	181.82	909.1	5	181.82	No
200	363.64	1818.2	5	363.64	No

Calculation for solubility study of fenofibrate
range of concentration around which Cremophor® micelles can dissolve API

Formulation (ready-to-use 4mg/ml)

Fenofibrate	300mg	4mg in
Ethanol	2ml	0.03
Cremophor® EL	2.75ml	0.04
Miglyol® 812	0.25ml	0.00
Water	70ml	0.93

TOTAL 75ml 1ml

mg/ml Fenofibrate in formulation	mg		ml		Total	mg	Cremophor® ml	Water ml	Total ml	Dissolve?
	Feno		Cremophor®	Water						
1	1		0.04	0.93	1.0	10.31	0.38	9.62	10	No
2	2		0.04	0.93	1.0	20.62	0.38	9.62	10	No
4	4		0.04	0.93	1.0	41.24	0.38	9.62	10	No
8	8		0.04	0.93	1.0	82.47	0.38	9.62	10	No
10	10		0.04	0.93	1.0	103.09	0.38	9.62	10	No
20	20		0.04	0.93	1.0	206.19	0.38	9.62	10	No
35	35		0.04	0.93	1.0	360.82	0.38	9.62	10	No
50	50		0.04	0.93	1.0	515.46	0.38	9.62	10	No
Mix at room temperature										

Example 7. Solubility of fenofibrate in Individual Components

To evaluate whether any individual component can dissolve the amount of drug in the formulation, fenofibrate solubility was evaluated in individual excipients under agitation conditions relevant to pharmaceutical manufacturing. Two hundred or 300mg fenofibrate from the 3 vendors was mixed with 2 ml ethanol, 2.75 ml Cremophor[®] EL, 3.75 ml Cremophor[®] EL, or 0.25 ml Miglyol[®] 812 in scintillation vials by spinning at room temperature for 4 days. None of the excipients used in the formulation could dissolve the drug by itself. The drug also did not dissolve in Cremophor[®] EL alone (solubility < 9 mg/ml) or in Cremophor[®] EL micelles in water (solubility < 1 mg/ml).

In the SMEDDS concentrate, as well as the diluted formulations, the fenofibrate component is solubilized with at least the surfactant, with the incorporation of the lipophilic phase to reduce the tendency for drug precipitation or crystallization.

Example 8. Comparison of in-vitro and in-vivo release of Fenofibrate

The following fenofibrate formulations were selected for use as shown in Table 8:

Ingredient	Qty/ml	Qty (%)
Fenofibrate	20 or 60 mg	2 or 6% w/v
Ethanol	0.4 ml	40% v/v
Cremophor EL	0.55 ml	55% v/v
Miglyol 812	0.05 ml	5% v/v

Certain optimized formulations are shown in Tables 9 and 10 for the different amounts of the fenofibrate:

Table 9: Formulation 20

Ingredient	Qty/ 5ml
Fenofibrate (20mg)	100 mg
Ethanol	1.56 g
Cremophor EL	2.86 g
Miglyol 812	0.24g

Table 10: Formulation 60

Ingredient	Qty/ 5ml
Fenofibrate (60mg)	300 mg
Ethanol	1.5 g
Cremophor EL	2.74 g
Miglyol 812	0.224g

Although fenofibrate is highly soluble in Cremophor EL, alcohol is added to reduce viscosity and improve the solubility of the drug. The time taken for the fenofibrate to dissolve completely in the other components is around 1 hr. Evaporation of alcohol was observed during this process despite taking precautions against it. To maintain the concentration of alcohol in the formulation a small amount of alcohol was set aside and used to make up 100% weight. Also, the formulations were filtered through a 0.45 μ filter to remove contamination. The results before and after filtration are shown in Table 11.

Table 11: Assay and impurities of Fenofibrate SMEDDS before and after filtration

Lot number	Assay (mg/ml)	% Recovery	%Total impurities [#]
Before Filtration			
Formulation 20	20.2	101.0	0.011
Formulation 60	59.5	99.2	0.055
After Filtration			
Formulation 20	20.2	101.0	NP*
Formulation 60	58.8	98.0	0.053

*Not Performed

[#]Impurities calculated as % of label claim

The two fenofibrate formulations with concentrations of 20 mg/ml and 60mg/ml were then tested for stability. The formulations were stored at accelerated and room temperature conditions and tested for stability at 1 month, 2 month and 3 month time intervals. Stability of the SMEDDS concentrates was assessed by comparing various parameters. All formulations showed stable results at all conditions, as shown by the results summarized in Tables 12 to 15.

Table 12: Three month Assay and impurity summary for Fenofibrate SMEDDS concentrate

Sample ID	Time	temperature	Assay (mg/mL)	% Recovery	Total Imp (%)
Formulation 20	0	RT	20.20	101.0	0.011
Formulation 20	0	RT	59.50	99.2	0.055
Formulation 20	1M	4 ⁰ C	20.21	101.1	0.042
Formulation 20	1M	25 ⁰ C	20.19	101.0	0.040
Formulation 20	1M	40 ⁰ C	20.26	101.3	0.087
Formulation 60	1M	4 ⁰ C	59.55	99.3	0.060
Formulation 60	1M	25 ⁰ C	59.80	99.7	0.060
Formulation 60	1M	40 ⁰ C	59.86	99.8	0.072
Formulation 20	2M	4 ⁰ C	20.18	100.9	0.044
Formulation 20	2M	25 ⁰ C	20.29	101.5	0.056
Formulation 20	2M	40 ⁰ C	20.37	101.9	0.097
Formulation 60	2M	4 ⁰ C	59.91	99.9	0.062
Formulation 60	2M	25 ⁰ C	59.34	98.9	0.060
Formulation 60	2M	40 ⁰ C	59.72	99.5	0.061
Formulation 20	3M	4 ⁰ C	20.20	101.0	0.058
Formulation 20	3M	25 ⁰ C	20.34	101.7	0.070
Formulation 20	3M	40 ⁰ C	20.35	101.8	0.069
Formulation 60	3M	4 ⁰ C	59.19	98.7	0.063
Formulation 60	3M	25 ⁰ C	59.06	98.4	0.058
Formulation 60	3M	40 ⁰ C	59.61	99.4	0.060

Table 13: Three month pH summary for Fenofibrate SMEDDS concentrate

Sample ID	Temp	1M	2M	3M
Formulation 20	initial	8.97	N/A	N/A
Formulation 20	4 ⁰ c	8.87	8.95	8.98
Formulation 20	25 ⁰ C	8.94	8.85	9.01
Formulation 20	40 ⁰ C	8.90	8.75	8.49
Formulation 60	initial	9.02	N/A	N/A
Formulation 60	4 ⁰ c	8.91	8.91	9.09
Formulation 60	25 ⁰ C	8.89	9.01	8.96
Formulation 60	40 ⁰ C	8.74	8.62	8.42

Table 14: Three month summary of % Moisture content in Fenofibrate SMEDDS concentrate

Sample ID	Time/	1M	2M	3M
	Temp	% Moisture content		
Formulation 20	initial	1.37	N/A	N/A
Formulation 20	4 ⁰ c	1.50	1.51	1.50
Formulation 20	25 ⁰ C	1.54	1.57	1.61
Formulation 20	40 ⁰ C	1.63	1.78	1.94
Formulation 60	initial	1.77	N/A	N/A
Formulation 60	4 ⁰ c	1.86	1.87	1.93
Formulation 60	25 ⁰ C	1.54	1.89	2.00
Formulation 60	40 ⁰ C	2.05	2.14	2.25

Table 15: Three month summary of % Alcohol content in Fenofibrate SMEDDS concentrate

Sample ID	Time/	1M	2M	3M
	Temp	% recovery of Alcohol		
Formulation 20	initial	104.2	N/A	N/A
Formulation 20	4 ⁰ c	104.2	103.6	
Formulation 20	25 ⁰ C	103.8	103.5	104.9
Formulation 20	40 ⁰ C	103.0	102.9	102.8
Formulation 60	initial	103.5	N/A	N/A
Formulation 60	4 ⁰ c	103.5	103.8	103.9
Formulation 60	25 ⁰ C	102.8	103.5	103.8
Formulation 60	40 ⁰ C	102.3	101.9	101.5

The release rate of the active from the formulation was assessed by conducting dissolution experiments for Formulation 20 and Formulation 60 using 0.75%SDS, water and 0.1N HCl as dissolution media. These formulations were compared to Tricor® tablets (48mg) and the percent drug release profiles are presented herewith in Figures 2-4. The fenofibrate SMEDDS concentrate was proven to be stable under accelerated conditions.

The addition of the surfactant SDS (Sodium Dodecyl sulphate) enhanced the solubility of the drug in the dissolution media. Although the profile of all three formulations look equivalent, 0.75% SDS caused rapid release of the drug (75 – 100% in 10 minutes) and the resulting dissolution profile could not be interpreted. The dissolution experiments were then repeated using water and 0.1N HCl. Further method development experiments were required in order to obtain a clear dissolution profile. However, it is clear from the current experiments that the SMEDDS formulation provides faster release of the drug into the stomach fluids.

To explore the possibility of improved bioavailability from one or both SMEDDS formulation options, a single dose oral 3-way cross over pharmacokinetic study was conducted in 6 beagle dogs. Single doses of fenofibrate SMEDDS concentrate 20mg/ml (test article – week 1),

Tricor® tablets 48mg (Reference article – week 2) and fenofibrate SMEDDS concentrate 60mg/ml (test article – week 3) were administered to 6 dogs and their blood samples were collected at regular time intervals and assayed for fenofibrate.

The blood samples thus obtained were transferred to an independent contract lab for the assay of fenofibrate. The pharmacokinetic release profiles and the bioavailability are presented in Figure 5 and Table 16. The plasma concentrations were averaged in 6 dogs at each time point.

Table 16: Bioavailability of Fenofibrate

Parameter	Tricor	20mg/mL	60mg/mL
AUC (µg.h/mL)0-24h	21.25	29.12	28.01
Cmax (µg/mL)	2.77	4.07	3.95
Tmax (h)	1	1	1

The pharmacokinetic study clearly indicated improvement in the bioavailability of fenofibrate. Around 40% increase in the Cmax and the AUC (bioavailability) were observed.

Although preferred embodiments of the invention have been described in the foregoing description and figures, it will be understood that the invention is not limited to the specific embodiments disclosed herein but is capable of numerous modifications by one of ordinary skill in the art. It will be understood that the materials used and the chemical and pharmaceutical details may be slightly different or modified from the descriptions herein without departing from the methods and compositions disclosed and taught by the present invention.

THE CLAIMS

What is claimed is:

1. A ready-to-use oral liquid fenofibrate formulation comprising:
a fenofibrate component comprising a therapeutically or prophylactically effective amount of fenofibrate, or a pharmaceutically acceptable salt or metabolite thereof;
and
a pharmaceutically acceptable liquid carrier present in an amount sufficient to solubilize the fenofibrate, comprising:
a lipophilic component comprising at least one triglyceride of one or more fractionated vegetable fatty acids including C₈ to C₁₀;
a surfactant component wherein the surfactant has a HLB value of greater than 10; and
at least one monohydric alcohol;
wherein each of the lipophilic, surfactant, and alcohol component are present in an amount sufficient to maintain dissolution of the fenofibrate component,
wherein the formulation is at least substantially stable and substantially free of an oily phase.
2. The formulation of claim 1, wherein the liquid carrier further comprises an aqueous component in an amount sufficient to aqueously dilute each of the lipophilic, surfactant, and alcohol components by a factor of about 3 to 5.
3. The formulation of claim 1, wherein the surfactant comprises a transesterification product of natural or hydrogenated vegetable oil triglyceride.
4. The formulation of claim 1, wherein the fenofibrate is present in an amount of about 10 mg/ml to about 80 mg/ml and preferably about 20 mg/ml to about 60 mg/ml.
5. The formulation of claim 1, wherein the monohydric alcohol is ethanol present in an amount of about from about 1.5 to about 2.5 ml, per 5 ml of the formulation.

6. The formulation of claim 1, wherein surfactant is a one or a mixture of glycerol-polyethylene glycol ricinoleate, fatty acid esters of polyethylene glycol, polyethylene glycols and ethoxylated glycerol and is present in an amount of from about 1.5 ml to about 4 ml.

7. The formulation of claim 1, wherein the lipophilic component is present in an amount of about 0.25 ml to 1.0 ml, per 5ml of the formulation.

8. A transparent fenofibrate formulation according to any of claims 1 to 7, optionally containing a sweetening agent, flavoring agent, colorant agent, or a combination thereof.

9. A method of treating or managing a lipid or cardiovascular disorder in a mammal which comprises orally administering to the mammal a therapeutically or prophylactically effective amount of the stable, liquid fenofibrate formulation according to any of claims 1 to 8.

10. Use of a therapeutically or prophylactically effective amount of the stable, liquid fenofibrate formulation according to any of claims 1 to 8 for the treatment or management of a lipid or cardiovascular disorder in a mammal by oral administration.

11. A method of preparing a stable, orally administered, liquid fenofibrate formulation which comprises:

first adding a surfactant component to a pharmaceutically effective amount of fenofibrate, or a pharmaceutically acceptable salt or metabolite thereof;

adding a monohydric alcohol component and lipophilic component to the pharmaceutically effective amount of fenofibrate and the surfactant to form the liquid fenofibrate formulation, wherein the surfactant component, alcohol component, and lipophilic component are collectively present in an amount sufficient to solubilize and maintain dissolution of the fenofibrate.

12. The method of claim 11, which further comprises adding a sufficient amount of an aqueous component to the liquid fenofibrate formulation to increase solvation of

the pharmaceutically effective amount of fenofibrate, the surfactant component, the lipophilic component, and the monohydric alcohol.

13. The method of claim 11 or 12, wherein each step is conducted at ambient temperature and the effective amount of fenofibrate is from about 200 mg to 600 mg or from about 20 mg/ml to 60 mg/ml.

14. The method of any of claims 11 to 13, wherein the amount of surfactant component ranges from about 1 ml to 15 ml, the amount of monohydric alcohol is from about 1 ml to 12 ml, and the amount of lipophilic component is from about 0.1 ml to 1.5 ml.

15. Use of a fenofibrate component comprising a therapeutically or prophylactically effective amount of fenofibrate, or a pharmaceutically acceptable salt or metabolite thereof to form an oral formulation for the treatment or management of a lipid or cardiovascular disorder in a mammal; which comprises combining the fenofibrate component with a pharmaceutically acceptable liquid carrier present in an amount sufficient to solubilize the fenofibrate, wherein the liquid carrier comprises:

a lipophilic component comprising at least one triglyceride of one or more fractionated vegetable fatty acids including C₈ to C₁₀;

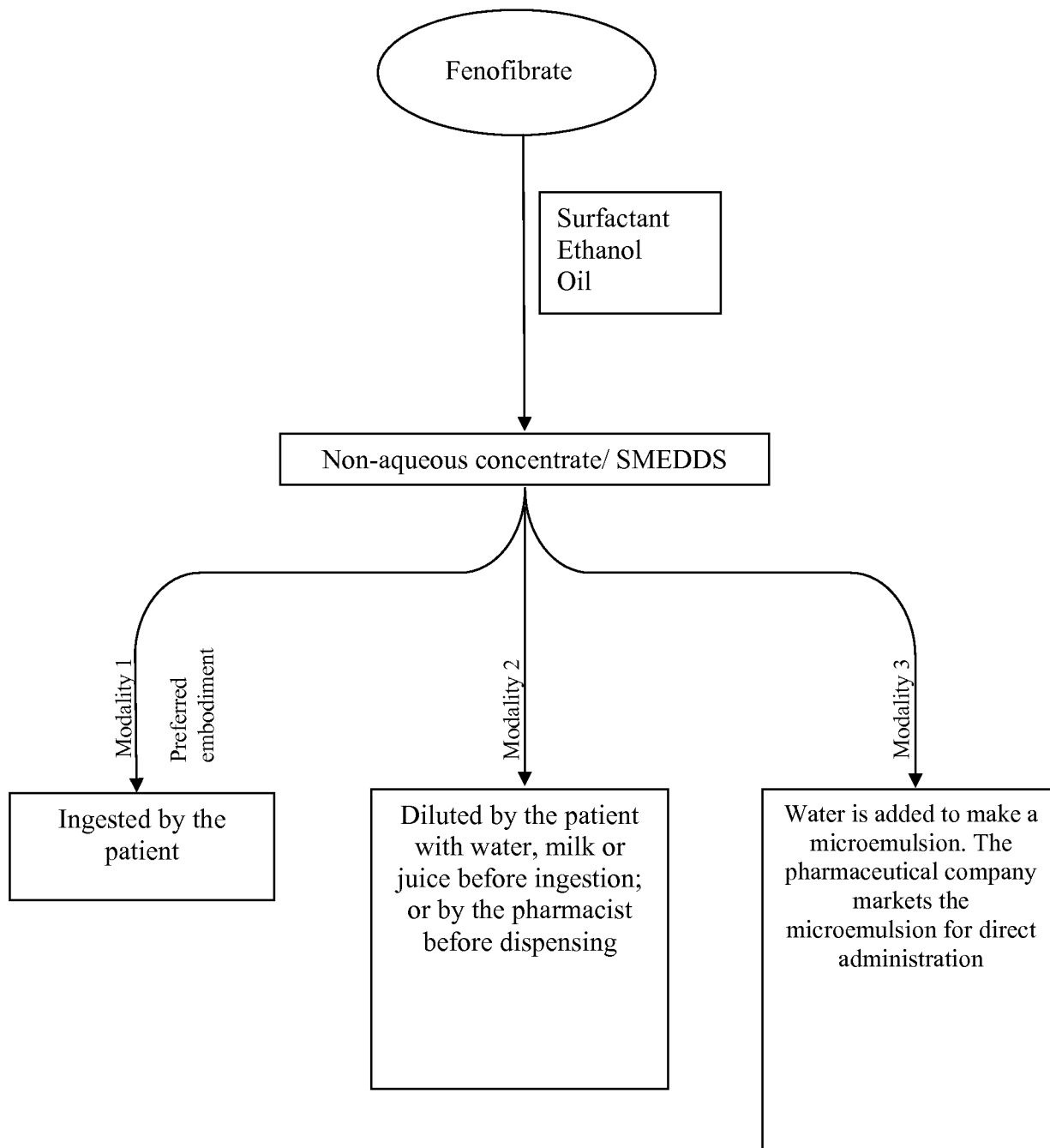
a surfactant component wherein the surfactant has a HLB value of greater than 10; and

at least one monohydric alcohol;

wherein each of the lipophilic, surfactant, and alcohol component are present in an amount sufficient to maintain dissolution of the fenofibrate component,

wherein the formulation is at least substantially stable and substantially free of an oily phase.

1/3

FIG. 1

2/3

FIG. 2

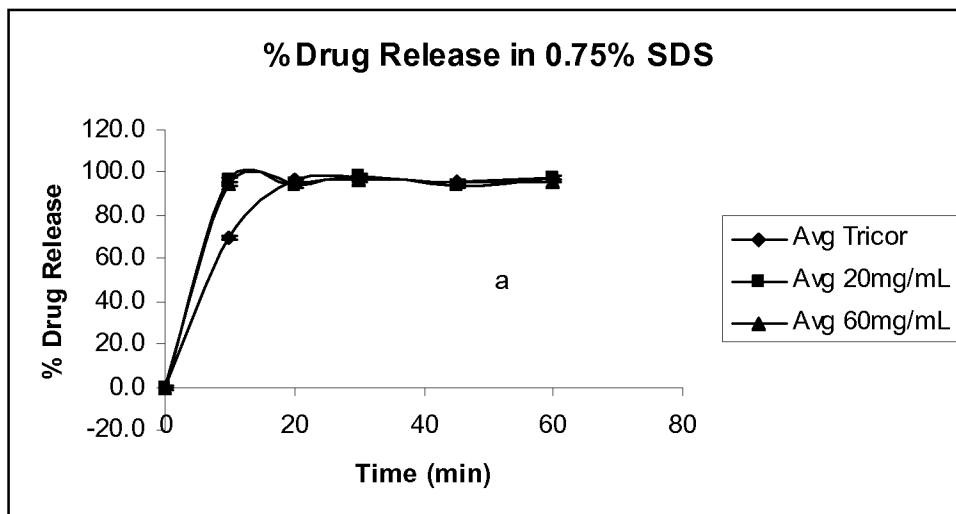
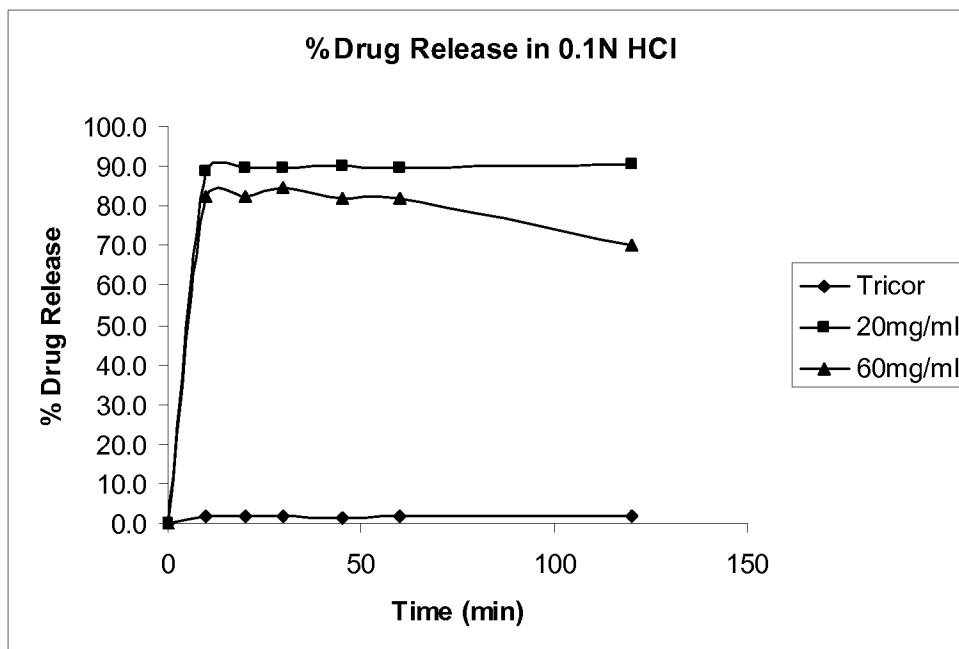


FIG. 3



3/3

FIG. 4

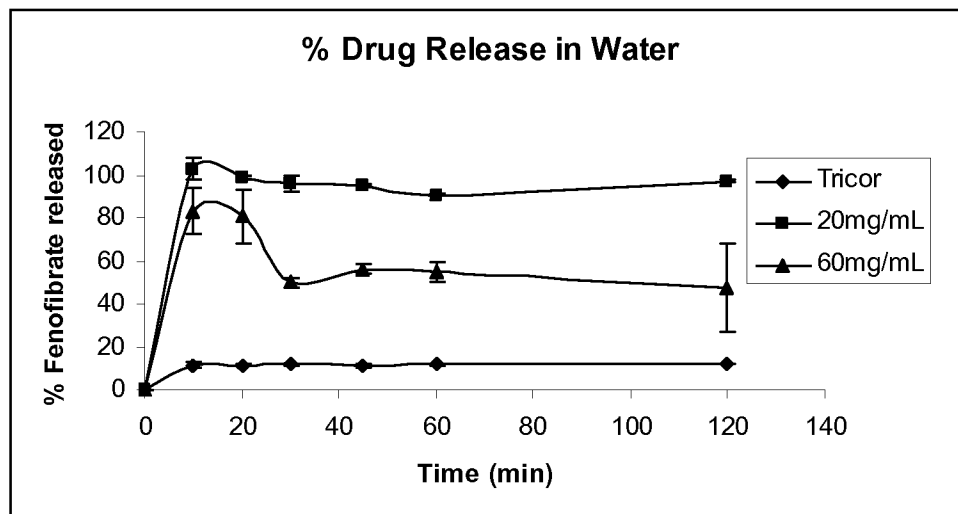


FIG. 5

