MICROPARTICLE COMPOSITIONS OF THE TOPOISOMERASE I INHIBITOR 7-TERT-BUTOXYIMINOMETHYLCAMPTOTHECIN

The present invention relates to microparticle compositions in which the active agent is a topoisomerase I inhibitor and pharmaceutical compositions comprising the microparticle compositions that are useful for the treatment and prevention of proliferative diseases including cancer.

Background of the Invention

Camptothecin derivatives are a class of compounds described in U.S. Patent No. 6,242,457. Camptothecin derivatives, such as those disclosed in U.S. Patent No. 6,242,457, present highly specific difficulties in relation to administration generally and galenic compositions in particular, including in particular problems of drug bioavailability because these derivatives have very poor solubility.

Summary of the Invention

In accordance with the present invention it has now surprisingly been found that stable microparticle pharmaceutical compositions with 7-*t*-butoxyiminomethylcamptothecin, have particularly interesting bioavailability characteristics. These novel compositions have been found to meet or substantially reduce the difficulties encountered previously, i.e., poor bioavailability observed for dry formulations of crystalline campothecins and limited drug load observed with microemulsion pre-concentrate formulations. Thus, the invention may achieve effective therapy with tolerable dosage levels of 7-*t*-butoxyiminomethylcamptothecin, and may permit closer standardization and optimization of daily dosage requirements for each individual. Consequently, occurrence of potential undesirable side-effects is diminished and overall cost of therapy may be reduced.

Detailed Description of the Drawings

Figure 1 illustrates *in vitro* dissolution rate profiles.

Figure 2 illustrates *in vivo* dog bioavailability.

Figure 3 illustrates *in vivo* dog bioavailability.

Figure 4 illustrates *in vitro* dissolution rate profiles.

Detailed Description of the Invention

The present invention relates to microparticle compositions comprising a topoisomerase I inhibitor, in particular, 7-*t*-butoxyiminomethylcamptothecin, as the active agent in a vehicle. The present invention also relates to microparticle compositions comprising a topoisomerase I inhibitor, in particular, 7-*t*-butoxyiminomethylcamptothecin, as the active agent, and optionally at least one surface stabilizer in a vehicle. The vehicle is selected from an oily vehicle, a hydrophilic non-aqueous vehicle or a self micro-emulsifying vehicle. In one embodiment, the self micro-emulsifying vehicle further comprises excipients. The microparticle compositions may further comprise a sedimentation inhibitor and also further comprises excipients.

The present invention also relates to pharmaceutical compositions comprising the microparticle compositions of the invention and a pharmaceutically acceptable carrier, as well as any desired excipients.

The unit dose forms of the present invention are, for example, capsules, coated and uncoated tablets, ampoules, vials or bottles. Examples are capsules containing from about 0.1 g to about 5 mg of 7-*t*-butoxyiminomethylcamptothecin.

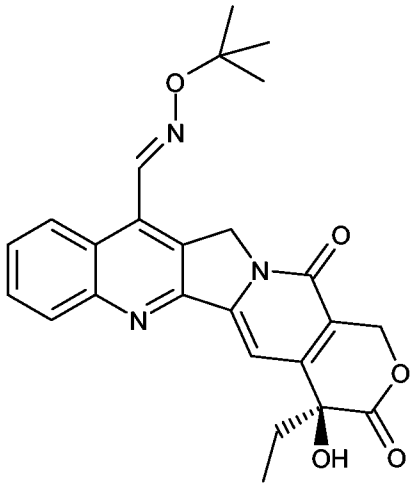
The present invention provides a method of treatment of a subject suffering from a disorder treatable with 7-*t*-butoxyiminomethylcamptothecin comprising administering a therapeutically effective amount of a pharmaceutical composition of the invention to a subject in need of such treatment.

The terms "effective amount" or "pharmaceutically effective amount" of a microparticle formulation, as provided herein, refer to a non-toxic but sufficient amount of the microparticle formulation to provide the desired response and the corresponding therapeutic effect, in an amount sufficient to effect treatment of the subject, as defined below. As will be pointed out below, the exact amount required may vary from subject to subject, depending on the species, age and general condition of the subject, the severity of the condition being treated, the mode of administration. An appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

The phrase "pharmaceutically acceptable" or "pharmacologically acceptable" means a material which is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with the microparticle formulation without causing any undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

I. Active Agent

"Active agent", as used herein, means 7-*t*-butoxyiminomethylcamptothecin which has the following structure known as Compound A:



Compound A

The preferred active agent can be in free or pharmaceutically acceptable salt form, in the form of their possible enantiomers, diastereoisomers and relative mixtures, polymorphs, amorphous, partially amorphous forms, solvates, their active metabolites and prodrugs.

In accordance with the present invention the active agent may be present in an amount by weight from about 0.1% to about 30% by weight of the composition of the invention. The active agent is preferably present in an amount of about 1-10%, most preferably in an amount of about 1% to about 5 % by weight of the composition.

The term "microparticle", as used herein, refers to a particle of the active ingredient that is up to about 15 microns in diameter, more preferably about 0.5 microns to about 5 microns in diameter, most preferably about 1 micron to about 3 microns in diameter.

Microparticle size is readily determined by techniques well-known in the art, laser diffractometry and/or scanning electron microscopy.

The term "microsuspension", as used herein, refers to microparticle compositions comprising a topoisomerase I inhibitor, in particular, 7-*t*-butoxyiminomethylcamptothecin, as the active agent, and optionally at least one surface stabilizer in a vehicle. The microparticle compositions may further comprise a sedimentation inhibitor and also further comprises excipients.

II. Surface Stabilizer

The surface stabilizer enhances the physical stability of the suspension and improves the dispersibility of the suspensions in contact with aqueous, e.g., gastrointestinal fluids. The surface stabilizer also helps to inhibit crystal growth of the active agent in the microsuspension.

Preferred surface stabilizers of the present invention include, but are not limited to, cellulose derivatives, polyvinylpyrrolidone, random copolymers of vinyl pyrrolidone and vinyl acetate, sodium lauryl sulfate, sodium dioctylsulfosuccinate, colloidal or precipitated silicas (e.g., Aerosil® from Degussa or Zeopharm® from Huber) poloxamers (e.g., Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); or a combination thereof. Non-limiting examples of cellulose derivatives include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropylcellulose.

Other surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Surface stabilizers also include nonionic, cationic, ionic and zwitterionic surfactants.

Additional examples of surface stabilizers include gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers, such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially-available Tweens®, such as, e.g., Tween 20® and Tween 80® (ICI Specialty Chemicals)); polyethylene glycols (e.g., Carbowaxs 3550® and

934® (Union Carbide)), polyoxyethylene stearates, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione and triton), poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylene diamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-100®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); *p*-isononylphenoxypoly-(glycidol), also known as Olin-10G® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-*N*-methylglucamide; *n*-decyl &bgr;-D-glucopyranoside; *n*-decyl &bgr;-D-maltopyranoside; *n*-dodecyl &bgr;-D-glucopyranoside; *n*-dodecyl &bgr;-D-maltoside; heptanoyl-*N*-methylglucamide; *n*-heptyl-&bgr;-D-glucopyranoside; *n*-heptyl &bgr;-D-thioglucoside; *n*-hexyl &bgr;-D-glucopyranoside; nonanoyl-*N*-methylglucamide; *n*-noyl &bgr;-D-glucopyranoside; octanoyl-*N*-methylglucamide; *n*-octyl-β-D-glucopyranoside; octyl-β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

Exemplary cationic surface stabilizers are described in Cross and Singer, *Cationic Surfactants: Analytical and Biological Evaluation*, Marcel Dekker (1994); Rubingh, Editor, *Cationic Surfactants: Physical Chemistry*, Marcel Dekker (1991); and Richmond, *Cationic Surfactants: Organic Chemistry*, Marcel Dekker (1990).

Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain [The Pharmaceutical Press (2000)], specifically incorporated by reference. The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

In accordance with the present invention the surface stabilizer is present in an amount by weight from about 0.1% to about 30% by weight of the composition of the invention. The surface stabilizer is preferably present in an amount of about 1% to about 15% by weight of the composition.

III. Vehicle

The vehicles of the present invention may be an oily vehicle; hydrophilic, non-aqueous vehicle; or self micro-emulsifying vehicle.

In accordance with the present invention the vehicle is present in an amount by weight from about 70% to about 99% by weight of the composition of the invention. The vehicle is preferably present in an amount of about 80% to about 98% by weight of the composition, most preferably in an amount of about 90-98%.

A. Oily Vehicles

Oily vehicles of the present invention include alone or in combination corn oil, sesame oil, olive oil, paraffin oil, soy bean oil, cottonseed oil, long chain, medium and short chain mono-, di-, trigylcerides and other suitable lipophilic components. Suitable lipophilic components include:

1) Glyceryl mono-C_6-C_{14}-fatty acid esters

These are obtained esterifying glycerol with vegetable oil followed by molecular distillation. Monoglycerides suitable for use in the compositions of the invention include both symmetric (i.e., β-monoglycerides), as well as asymmetric monoglycerides (α-monoglycerides). They also include both uniform glycerides (in which the fatty acid constituent is composed primarily of a single fatty acid), as well as mixed glycerides (i.e., in which the fatty acid constituent is composed of various fatty acids). The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from, e.g., C_8-C_{14}. Particularly suitable are caprylic or lauric acid monoglycerides which are commercially available, e.g., under the trade names Imwitor® 308 or Imwitor® 312, respectively, from, e.g., sasol. For example, Imwitor® 308 comprises at least 80% monoglycerides and exhibits the following additional characterizing data: free glycerol max. 6%, acid value max. 3,

saponification value 245-265, iodine value max. 1, water content max. 1%. Typically it comprises 1% free glycerol, 90% monoglycerides, 7% diglycerides, 1% triglycerides (H. Fiedler, *loc. cit.*, Vol. 1, p. 798). A further example is Capmul MCM C8 from Abitec Corporation.

2) Mixtures of mono- and diglycerides of C_6-C_{18}-fatty acids

These include both symmetric (i.e., β-monoglycerides and α,α[1]-diglycerides), as well as asymmetric mono- and diglycerides (i.e., α-monoglycerides and α,β-diglycerides) and acetylated derivatives thereof. They also include both uniform glycerides (in which the fatty acid constituent is composed primarily of a single fatty acid), as well as mixed glycerides (i.e., in which the fatty acid constituent is composed of various fatty acids) and any derivatives thereof with lactic or citric acid. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from, e.g., C_8-C_{10}. Particularly suitable are mixed caprylic and capric acid mono- and diglycerides as commercially-available, e.g., under the trade name Imwitor® 742 or Imwitor 928 from, e.g., sasol. For example, Imwitor® 742 comprises at least 45% monoglycerides and exhibits the following additional characterizing data: free glycerol max. 2%, acid value max. 2, saponification value 250-280, iodine value max. 1, water max. 2% (H. Fiedler, *loc. cit.*, Vol 1, p. 798). Other suitable mixtures comprise mono/diglycerides of caprylic/capric acid in glycerol as known and commercially-available under, e.g., the trade name Capmul® MCM from, e.g., Abitec Corporation. Capmul® MCM exhibits the following additional characterizing data: acid value 2.5 max., α-mono (as oleate) 80% min., free glycerol 2.5% max., iodine value 1 max., chain length distribution: caproic acid (C6) 3% max., caprylic acid (C8) 75% min., capric acid (C10) 10% min., lauric acid (C12) 1.5% max., moisture (by Karl Fisher) 0.5% max. (manufacturer information). Suitable examples of mono-/di-glcyerides with additional derivatization with lactic or citric acid are those marketed under the brand names of Imwitor 375, 377 or 380 by sasol. Furthermore, the fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from, e.g., C_{16}-C_{18}. A suitable example is Tegin® O (glyceryl oleate) exhibiting the following additional characterizing data: monoglyceride content 55-65%, peroxide value max. 10, water content max. 1%, acid value max. 2, iodine value 70-76, saponification value 158-175, free glycerol max. 2%, (manufacturer information).

3) Glyceryl di-C_6-C_{18}-fatty acid esters

These include symmetric (i.e., α,α^1-diglycerides) and asymmetric diglycerides (i.e., α,β-diglycerides) and acetylated derivatives thereof. They also include both uniform glycerides (in which the fatty acid constituent is composed primarily of a single fatty acid), as well as mixed glycerides (i.e., in which the fatty acid constituent is composed of various fatty acids) and any acetylated derivatives thereof. The fatty acid constituent can include both saturated and unsaturated fatty acids having a chain length of from C_6-C_{18}, e.g., C_6-C_{16}, e.g., C_8-C_{10}, e.g., C_8. Particularly suitable is caprylic diglycerides, which is commercially-available, e.g., under the trade name Sunfat® GDC-S, e.g., from Taiyo Kagaku Co., Ltd. Sunfat® GDC-S has an acid value of about 0.3, a diglyceride content of about 78.8%, and a monoester content of about 8.9.

4) Medium chain fatty acid triglyceride

These include triglycerides of saturated fatty acid having 6-12, e.g., 8-10, carbon atoms. Suitable medium chain fatty acid triglycerides are those known and commercially-available under the trade names Acomed®, Myritol®, Captex®, Neobee® M 5 F, Miglyol® 810, Miglyol® 812, Miglyol® 818, Mazol®, Sefsol® 860, Sefsol® 870; Miglyol® 812 being the most preferred. Miglyol® 812 is a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight of about 520 Daltons. Fatty acid composition = C_6 max. about 3%, C_8 about 50-65%, C_{10} about 30-45%, C_{12} max. 5%; acid value about 0.1; saponification value about 330-345; iodine value max 1. Miglyol® 812 is available from Condea. Neobee® M 5 F is a fractionated caprylic-capric acid triglyceride available from coconut oil; acid value max. 0.2; saponification value about 335-360; iodine value max. 0.5, water content max. 0,15%, D.20 0,930-0,960, nD20 1,448-1,451 (manufacturer information). Neobee® M 5 F is available from Stepan Europe. A further example is Miglyol 829 containing additionally esters with succinic acid.

5) Glyceryl mono-C_{16}-C_{18}-fatty acid esters

These are obtained esterifying glycerol with vegetable oil followed by molecular distillation. Monoglycerides suitable for use in the compositions of the invention include both symmetric (i.e., β-monoglycerides), as well as asymmetric

monoglycerides (α-monoglycerides). They also include both uniform glycerides (in which the fatty acid constituent is composed primarily of a single fatty acid), as well as mixed glycerides (i.e., in which the fatty acid constituent is composed of various fatty acids). The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from, e.g., C_{16}-C_{18}. Suitable examples include GMOrphic by Eastman, Rylo MG20 distilled monoglyceride by Danisco Ingredients, or Monomuls 90-O18 by Henkel. For example, GMOrphic®-80 (glyceryl monooleate) exhibits the following additional characterizing data: monoglyceride content min. 94%, C_{18}:1 content 75% min., peroxide value max. 2.5, C_{18}:2 + C_{18}:3 max. 15%, C_{16}:0 + C_{18}:0 + C_{20}:0 max. 10%, water max. 2%, acid value max. 3, iodine value 65-75, saponification value 155-165, free glycerine max. 1%, hydroxyl number 300-330 (manufacturer information).

6) Mixed mono-, di-, triglycerides

These include mixed mono-, di-, triglycerides that are commercially-available under the trade name Maisine® from Gattefossé. They are transesterification products of corn oil and glycerol. Such products are comprised predominantly of linoleic and oleic acid mono-, di- and triglycerides together with minor amounts of palmitic and stearic acid mono-, di- and triglycerides (corn oil itself being comprised of ca. 56% by weight linoleic acid, 30% oleic acid, ca. 10% palmitic and ca. 3% stearic acid constituents). Physical characteristics are: free glycerol max. 10%, monoglycerides ca. 40%, diglycerides ca. 40%, triglycerides ca. 10% and free oleic acid content ca. 1%. Further physical characteristics are: acid value max. 2, iodine value of 85-105, saponification value of 150-175, mineral acid content = 0. The fatty acid content for Maisine® is typically: palmitic acid ca. 11%, stearic acid ca. 2.5%, oleic acid ca. 29%, linoleic acid ca. 56% and others ca. 1.5% (H. Fiedler, *loc. cit.*, Vol. 2, p. 958; manufacturer information).

Mixed mono-, di-, triglycerides preferably comprise mixtures of C_8-C_{10}- or C_{12}-C_{20}-fatty acid mono-, di- and triglycerides, especially mixed C_{16}-C_{18}-fatty acid mono-, di- and triglycerides. The fatty acid component of the mixed mono-, di- and triglycerides may comprise both saturated and unsaturated fatty acid residues. Preferably, however, they are predominantly comprised of unsaturated fatty acid residues, in particular, C_{18} unsaturated fatty acid residues. Suitably the mixed mono-, di-, triglycerides comprise

at least 60%, preferably at least 75%, more preferably at least 85% by weight of a C_{18} unsaturated fatty acid (e.g., linolenic, linoleic and oleic acid) mono-, di- and triglycerides. Suitably the mixed mono-, di-, triglycerides comprise less than 20%, e.g., about 15% or 10% by weight or less, saturated fatty acid (e.g., palmitic and stearic acid) mono-, di- and triglycerides. Mixed mono-, di-, triglycerides are preferably predominantly comprised of mono- and diglycerides; e.g., mono- and diglycerides comprise at least 50%, more preferably at least 70% based on the total weight of the lipophilic phase or component. More preferably, the mono- and diglycerides comprise at least 75% (e.g., about 80% or 85% by weight of the lipophilic component. Preferably, monoglycerides comprise from about 25% to about 50%, based on the total weight of the lipophilic component, of the mixed mono-, di-, triglycerides. More preferably from about 30% to about 40% (e.g., 35-40%) monoglycerides are present. Preferably, diglycerides comprise from about 30% to about 60%, based on the total weight of the lipophilic component, of the mixed mono-, di-, triglycerides. More preferably from about 40% to about 55% (e.g., 48-50%) diglycerides are present. Triglycerides suitably comprise at least 5% but less than about 25%, based on the total weight of the lipophilic component, of the mixed mono-, di-, triglycerides. More preferably from about 7.5% to about 15% (e.g., from about 9-12%) triglycerides are present. Mixed mono-, di-, triglycerides may be prepared by admixture of individual mono-, di- or triglycerides in appropriate relative proportion. Conveniently however they comprise transesterification products of vegetable oils, e.g., almond oil, ground nut oil, olive oil, peach oil, palm oil; or, preferably, corn oil, sunflower oil or safflower oil; and most preferably corn oil, with glycerol. Such transesterification products are generally obtained as described in GB 2 257 359 or WO 94/09211. Preferably, some of the glycerol is first removed to give a "substantially glycerol free batch" when soft gelatine capsules are to be made. Purified transesterification products of corn oil and glycerol provide particularly suitable mixed mono-, di- and triglycerides hereinafter referred to as "refined oil" and produced according to procedures described in United Kingdom patent specification GB 2,257,359 or international patent publication WO 94/09211.

7) Acetylated monoglycerides (C_{18})

These include Myvacet 9-45.

8) Propylene glycol monofatty acid esters

The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from, e.g., C_8-C_{12}. Particularly suitable are propylene glycol mono ester of caprylic and lauric acid as commercially-available, e.g., under the trade names Sefsol® 218, Capryol® 90 or Lauroglycol® 90, from, e.g., Nikko Chemicals Co., Ltd. or Gattefossé or Capmul PG-8 from Abitec Corporation. For example, Lauroglycol® 90 exhibits the following additional characterizing data: acid value max. 8, saponification value 200-220, iodine value max. 5, free propylene glycol content max. 5%, monoester content min. 90%; Sefsol® 218 exhibits the following additional characterizing data: acid value max. 5, hydroxy value 220-280 (H. Fiedler, *loc. cit.*, Vol 2, p. 906, manufacturer information).

9) Propylene glycol mono- and di-fatty acid esters

These include Lauroglycol FCC and Capryol PGMC.

10) Propylene glycol di-esters

Propylene glycol di-fatty acid esters, such as propylene glycol dicaprylate (which is commercially-available under the trade name Miglyol® 840 from, e.g., sasol; H. Fiedler, *loc. cit.*, Vol. 2, p. 1008) or Captex 200 from Abitec Corporation.

11) Propylene glycol monoacetate and propylene glycol diacetate

12) Transesterified ethoxylated vegetable oils

These include transesterified ethoxylated vegetable oils, such as those obtained by reacting various natural vegetable oils (e.g., corn oil, maize oil, castor oil, kernel oil, almond oil, ground nut oil, olive oil, soybean oil, sunflower oil, safflower oil and palm oil or mixtures thereof) with polyethylene glycols that have an average molecular weight of from 200-800, in the presence of an appropriate catalyst. These procedures are described in US Patent No. 3,288,824. Transesterified ethoxylated corn oil is particularly preferred.

Transesterified ethoxylated vegetable oils are known and are commercially-available under the trade name Labrafil® (H. Fiedler, *loc. cit.*, Vol. 2, p. 880). Examples are Labrafil® M 2125 CS (obtained from corn oil and having an acid value of less than

about 2, a saponification value of 155-175, an HLB value of 3-4, and an iodine value of 90-110) and Labrafil® M 1944 CS (obtained from kernel oil and having an acid value of about 2, a saponification value of 145-175 and an iodine value of 60-90). Labrafil® M 2130 CS (which is a transesterification product of a C_{12}-C_{18} glyceride and polyethylene glycol and which has a melting point (m.p.) of about 35-40°C, an acid value of less than about 2, a saponification value of 185-200 and an iodine value of less than about 3) may also be used. The preferred transesterified ethoxylated vegetable oil is Labrafil® M 2125 CS which can be obtained, e.g., from Gattefossé, Saint-Priest Cedex, France.

13) Sorbitan fatty acid esters

Such esters include, e.g., sorbitan mono-C_{12}-C_{18}-fatty acid esters, or sorbitan tri-C_{12}-C_{18}-fatty acid esters are commercially-available under the trade mark Span® from, e.g., Uniqema. An especially preferred product of this class is, e.g., Span® 20 (sorbitan monolaurate) or Span® 80 (sorbitan monooleate) (Fiedler, *loc. cit.*, Vol. 2, p. 1430; Handbook of Pharmaceutical Excipients, *loc. cit.*, p. 473).

14) Esterified compounds of fatty acid and primary alcohols

These include esterified compounds of fatty acid having 8-20 carbon atoms and primary alcohol having 2-3 carbon atoms, e.g., isopropyl myristate, isopropyl palmitate, ethyl linoleate, ethyl oleate, ethylmyristate etc., with an esterified compound of linoleic acid and ethanol being particularly preferable, also isopropylmyristat and isopropylpalmitat.

15) Glycerol triacetate or (1,2,3)-triacetin

This is obtained by esterifying glycerin with acetic anhydride. Glycerol triacetate is commercially-available as, e.g., Priacetin® 1580 from Uniqema International, or as Eastman™ Triacetin from Eastman, or from Courtaulds Chemicals Ltd. Glycerol triacetate exhibits the following additional characterizing data: molecular weight 218,03, $D.^{20,3}$ 1,159-1,163, n_D^{20} 1,430-1,434, water content max. 0.2%, viscosity (25°) 17.4 mPa s, acid value max. 0.1, saponification value of about 766-774, triacetin content 97% min. (H. Fiedler, *loc. cit.*, Vol. 2, p. 1580; Handbook of Pharmaceutical Excipients, *loc. cit.*, p. 534, manufacturer information).

16) Acetyl triethyl citrate

This is obtained by esterification of citric acid and ethanol, followed by acetylation with acetic anhydride, respectively. Acetyl triethyl citrate is commercially-available, e.g., under the trade name Citroflex® A-2 from, e.g., Morflex Inc.

17) Tributylcitrate or acetyl tributyl citrate

18) Polyglycerol fatty acid esters

These have, e.g., from 2-10, e.g., 6 glycerol units. The fatty acid constituent can include both saturated and unsaturated fatty acids having a chain length of from, e.g., C_8-C_{18}. Particularly suitable is, e.g., Plurol Oleique CC497 from Gattefossé, having a saponification value of 133-155 and a saponification value of 196-244. Further suitable polyglycerol fatty acid esters include diglyceryl monooleate (DGMO) and Hexaglyn-5-O, as known and commercially-available from, e.g., Nikko Chemicals Co., Ltd.

19) PEG-fatty alcohol ether

This includes Brij 30™ polyoxyethylene(4) lauryl ether.

20) Fatty alcohols and fatty acids

Fatty acids can be obtained by hydrolyzing various animal and vegetable fats or oils, such as olive oil, followed by separation of the liquid acids. The fatty acid/alcohol constituent can include both saturated and mono- or di-unsaturated fatty acids/alcohols having a chain length of from, e.g., C_6-C_{20}. Particularly suitable are, e.g., oleic acid, oleyl alcohol, linoleic acid, capric acid, caprylic acid, caproic acid, tetradecanol, dodecanol or decanol. Oleyl alcohol is commercially-available under the trade mark HD-Eutanol® V from, e.g., Henkel KGaA. Oleyl alcohol exhibits the following additional characterizing data: acid value max. 0.1, hydroxy value of about 210, iodine value of about 95, saponification value max 1, $D.^{20}$ about 0,849, n_D^{20} 1,462, molecular weight 268, viscosity (20°) about 35 mPa s (manufacturer information). Oleic acid exhibits the following additional characterizing data: molecular weight 282,47, $D.^{20}$ 0,895, n_D^{20} 1,45823, acid value 195-202, iodine value 85-95, viscosity (25°) 26 mPa s [H. Fiedler, *loc. cit.*, Vol. 2, p. 1112; Handbook of Pharmaceutical Excipients, 2nd Edition, Wade and Weller, Eds. (1994), Joint

publication of American Pharmaceutical Assoc., Washington, USA and The Pharmaceutical Press, London, England, p. 325].

21) Tocopherol and its derivatives, e.g., acetate

These include Coviox T-70, Copherol 1250, Copherol F-1300, Covitol 1360 and Covitol 1100.

22) Pharmaceutically acceptable oils

Alternatively the lipophilic component comprises, e.g., a pharmaceutically acceptable oil, preferably with an unsaturated component, such as a vegetable oil.

23) Alkylene polyol ethers or esters

These include C_3-C_5-alkylene triols, in particular, glycerol, ethers or esters. Suitable C_3-C_5-alkylene triol ethers or esters include mixed ethers or esters, i.e., components including other ether or ester ingredients, e.g., transesterification products of C_3-C_5-alkylene triol esters with other mono-, di- or poly-ols. Particularly suitable alkylene polyol ethers or esters are mixed C_3-C_5-alkylene triol/poly-(C_2-C_4-alkylene) glycol fatty acid esters, especially mixed glycerol/polyethylene- or polypropylene-glycol fatty acid esters.

Especially suitable alkylene polyol ethers or esters include products obtainable by transesterification of glycerides, e.g., triglycerides, with poly-(C_2-C_4-alkylene) glycols, e.g., poly-ethylene glycols and, optionally, glycerol. Such transesterification products are generally obtained by alcoholysis of glycerides, e.g., triglycerides, in the presence of a poly-(C-$_2$-C_4-alkylene) glycol, e.g., polyethylene glycol and, optionally, glycerol (i.e., to effect transesterification from the glyceride to the poly-alkylene glycol/glycerol component, i.e., via poly-alkylene glycolysis/glycerolysis).

In general such reaction is effected by reacting the indicated components (glyceride, polyalkylene glycol and, optionally, glycerol) at elevated temperature under an inert atmosphere with continuous agitation.

Preferred glycerides are fatty acid triglycerides, e.g., (C_{10}-C_{22}-fatty acid) triglycerides, including natural and hydrogenated oils, in particular, vegetable oils. Suitable vegetable oils include, e.g., olive, almond, peanut, coconut, palm, soybean and wheat germ oils and, in particular, natural or hydrogenated oils rich in (C_{12}-C_{18}-fatty acid)

ester residues. Preferred polyalkylene glycol materials are polyethylene glycols, in particular, polyethylene glycols having a molecular weight of from ca. 500-4,000, e.g., from ca. 1,000-2,000.

Suitable alkylene polyol ethers or esters include mixtures of C_3-C_5-alkylene triol esters, e.g., mono-, di- and tri-esters in variable relative amount, and poly (C_2-C_4-alkylene) glycol mono- and di-esters, together with minor amounts of free C_3-C_5-alkylene triol and free poly-(C_2-C_5-alkylene) glycol. As hereinabove set forth, the preferred alkylene triol moiety is glyceryl; preferred polyalkylene glycol moieties include polyethylene glycol, in particular, having a molecular weight of from ca. 500-4,000; and preferred fatty acid moieties will be C_{10}-C_{22}-fatty acid ester residues, in particular, saturated C_{10}-C_{22}-fatty acid ester residues.

Particularly suitable alkylene polyol ethers or esters include transesterification products of a natural or hydrogenated vegetable oil and a polyethylene glycol and, optionally, glycerol; or compositions comprising or consisting of glyceryl mono-, di- and tri-C_{10}-C_{22}-fatty acid esters and polyethylene glycol mono- and di-C_{10}-C_{22}-fatty esters (optionally together with, e.g., minor amounts of free glycerol and free polyethylene glycol).

Preferred vegetable oils, polyethylene glycols or polyethylene glycol moieties and fatty acid moieties in relation to the above definitions are as hereinbefore set forth.

Particularly suitable alkylene polyol ethers or esters as described above for use in the present invention include those commercially-available under the trade name Gelucire® from, e.g., Gattefossé, in particular, the products: a) Gelucire® 33/01, which has an m.p. = ca. 33-37°C and a saponification value of ca. 230-255; b) Gelucire® 39/01, m.p. = ca. 37.5-41.5°C, saponification value = ca. 225-245; and c) Gelucire® 43/01, m.p. = ca. 42-46°C, saponification value = ca. 220-240. Products a) to c) above all have an acid value of maximum of 3. The compositions of the invention may include mixtures of such ethers or esters.

24) Hydrocarbons

These include, e.g., squalene, available from, e.g., Nikko Chemicals Co., Ltd.

25) Ethylene glycol esters

These include Monthyle® (ethylene glycol monostearate) available from, e.g., Gattefossé.

26) Pentaerythriol fatty acid esters and polyalkylene glycol ethers

These include, e.g., pentaerythrite-dioleate, -distearate, -monolaurate, -polyglycol ether, and -monostearate, as well as pentaerythrite-fatty acid esters (Fiedler, *loc. cit.*, Vol. 2, pp. 1158-1160, incorporated herein by reference).

Some of these, e.g., (1-3, 5-6, 8-9, 12-13, 19), display surfactant-like behavior and may also be termed co-surfactants.

B. Hydrophilic, Non-Aqueous Vehicle

The hydrophilic, non-aqueous vehicles include, but are not limited to, the following excipients alone or in combination:

1) Polyethylene glycol glyceryl C_6-C_{10}-fatty acid esters

The fatty acid ester may include mono- and/or di- and/or tri-fatty acid esters. It optionally includes both saturated and unsaturated fatty acids having a chain length of from, e.g., C_8-C_{10}. The polyethylene glycols may have, e.g., from 5-10 [CH_2-CH_2-O] units, e.g., 7 units. A particularly suitable fatty acid ester is polyethylene glycol (7) glyceryl monococoate, which is commercially-available, e.g., under the trade name Cetiol® HE, e.g., from Henkel KGaA. Cetiol® HE has a D. (20°) of 1,05, an acid value of less than 5, a saponification value of about 95, a hydroxyl value of about 180 and an iodine value of less than 5 (H. Fiedler, *loc. cit.*, Vol. 1, p. 337) or Lipestrol E-810.

2) *N*-Alkylpyrrolidone

Particularly suitable is, e.g., *N*-methyl-2-pyrrolidone, e.g., as commercially-available under the trade name Pharmasolve™, from e.g. International Specialty Products (ISP). *N*-Methylpyrrolidone exhibits the following additional characterizing data: molecular weight 99,1, D.25 1,027-1,028, purity (as area % by GC) (including methyl isomers) 99.85% min. (H. Fiedler, *loc. cit.*, Vol. 2, p. 1004, manufacturer information).

3) Benzyl alcohol

This is commercially-available from, e.g., Merck or may be obtained by distillation of benzyl chloride with potassium or sodium carbonate. Benzyl alcohol exhibits the following additional characterizing data: molecular weight 108,14, D. 1,043-1,049, nD 1,538-1,541. (H. Fiedler, *loc. cit.*, Vol. 1, p. 238; Handbook of Pharmaceutical Excipients, *loc. cit.*, p. 35).

4) Triethyl citrate

It is obtained esterifying citric acid and ethanol. Triethyl citrate is commercially-available, e.g., under the trade names Citroflex® 2, or in a pharmaceutical grade under the name TEC-PG/N from, e.g., Morflex Inc. Particularly suitable is triethyl citrate which has molecular weight of 276,3, a specific gravity of 1,135-1,139, a refractive index of 1,439-1,441, a viscosity (25°) of 35,2 mPa s, assay (anhydrous basis) 99,0-100,5%, water max. 0,25% (H. Fiedler, *loc. cit.*, Vol. 1, p. 371; Handbook of Pharmaceutical Excipients, *loc. cit.*, p. 540).

Other suitable hydrophilic compounds include transcutol (C_2H_5-[O-(CH_2)$_2$]$_2$-OH); glycofurol (also known as tetrahydrofurfuryl alcohol polyethylene glycol ether); 1,2-propylene glycol; dimethylisosorbide, e.g., Arlasolve from Uniqema; polyethylene glycol, such as 200, 300, 400, 600, etc.; triethylenglycol; ethylacetate; and ethyllactate.

C. Self Micro-emulsifying Vehicles

By using the self-micro-emulsifying media as a milling vehicle instead of a simple oil allows to combine the advantage of a self dispersing system with the benefit of microparticles. "Microemulsion preconcentrate", as used herein, means a composition which spontaneously forms a microemulsion in an aqueous medium, e.g., in water, e.g., on dilution of 1:1 to 1:300, preferably 1:1 to 1:70, but especially 1:1 to 1:10 or in the gastric juices after oral application.

In some embodiments of the compositions of the invention the self micro-emulsifying vehicle comprises one or more of the following lipophilic component and one or more of the following surfactant described below. In other embodiments the self micro-emulsifying vehicle comprises one or more of the following lipophilic component, one or more of the

following one or more of the following hydrophilic component and one or more of the following surfactant described below.

(I) Surfactants

Surfactants may be complex mixtures containing side products or unreacted starting products involved in the preparation thereof, e.g., surfactants made by polyoxyethylation may contain another side product, e.g., polyethylene glycol. Each surfactant preferably has a hydrophilic-lipophilic balance (HLB) value of 8-17, especially 10-17. The HLB value is preferably the mean HLB value.

Suitable surfactants include:

1) Reaction products of a natural or hydrogenated castor oil and ethylene oxide

The natural or hydrogenated castor oil may be reacted with ethylene oxide in a molar ratio of from about 1:35 to about 1:60, with optional removal of the polyethylene-glycol component from the products. Various such surfactants are commercially-available. Particularly suitable surfactants include polyethyleneglycol-hydrogenated castor oils available under the trade name Cremophor®; Cremophor® RH 40, which has a saponification value of about 50-60, an acid value less than about 1, a water content (Fischer) less than about 2%, an n_D^{60} of about 1.453-1.457 and an HLB of about 14-16; and Cremophor® RH 60, which has a saponification value of about 40-50, an acid value less than about 1, an iodine value of less than about 1, a water content (Fischer) of about 4.5-5.5%, an n_D^{60} of about 1.453-1.457 and an HLB of about 15-17.

An especially preferred product of this class is Cremophor® RH40. Other useful products of this class are available under the trade names Nikkol® (e.g., Nikkol® HCO-40 and HCO-60), Mapeg® (e.g., Mapeg® CO-40h), Incrocas® (e.g., Incrocas® 40), Tagat® (e.g., polyoxyethylene-glycerol-fatty acid esters, e.g., Tagat® RH 40) and Simulsol OL-50 (PEG-40 castor oil, which has a saponification value of about 55-65, an acid value of max. 2, an iodine value of 25-35, a water content of max. 8%, and an HLB of about 13, available from Seppic). These surfactants are further described in H. Fiedler, *loc. cit.*

Other suitable surfactants of this class include polyethyleneglycol castor oils, such as that available under the trade name Cremophor® EL, which has a molecular weight

(by steam osmometry) of about 1630, a saponification value of about 65-70, an acid value of about 2, an iodine value of about 28-32 and an n_D^{25} of about 1.471.

2) Polyoxyethylene-sorbitan-fatty acid esters

These include mono- and trilauryl, palmityl, stearyl and oleyl esters of the type known and commercially-available under the trade name Tween® (H. Fiedler, *loc. cit.*, p. 1615 ff) from Uniqema including the products:

- Tween® 20 [polyoxyethylene(20)sorbitanmonolaurate],
- Tween® 21 [polyoxyethylene(4)sorbitanmonolaurate],
- Tween® 40 [polyoxyethylene(20)sorbitanmonopalmitate],
- Tween® 60 [polyoxyethylene(20)sorbitanmonostearate],
- Tween® 65 [polyoxyethylene(20)sorbitantristearate],
- Tween® 80 [polyoxyethylene(20)sorbitanmonooleate],
- Tween® 81 [polyoxyethylene(5)sorbitanmonooleate], and
- Tween® 85 [polyoxyethylene(20)sorbitantrioleate].

Especially preferred products of this class are Tween® 20 and Tween® 80.

3) Polyoxyethylene fatty acid esters

These include polyoxyethylene stearic acid esters of the type known and commercially-available under the trade name Myrj® from Uniqema (H. Fiedler, *loc. cit.*, Vol. 2, p. 1042). An especially preferred product of this class is Myrj® 52 having a D25 of about 1.1., a m.p. of about 40-44°C, an HLB value of about 16.9, an acid value of about 0-1 and a saponification value of about 25-35.

4) Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers or poloxamers

These include the type known and commercially-available under the trade names Pluronic® and Emkalyx® (H. Fiedler, *loc. cit.*, Vol. 2, p. 1203). An especially preferred product of this class is Pluronic® F68 (poloxamer 188) from BASF, having a m.p. of about 52°C and a molecular weight of about 6,800-8,975. A further preferred product of this class is Synperonic® PE L44 (poloxamer 124) from Uniqema.

5) Polyoxyethylene mono esters of a saturated C_{10}-C_{22}

These include C_{18}-substituted, e.g., hydroxy fatty acid, e.g., 12 hydroxy stearic acid PEG ester, e.g., of PEG about, e.g., 600-900, e.g., 660 Daltons MW, e.g., Solutol® HS 15 from BASF, Ludwigshafen, Germany. According to the BASF technical leaflet MEF 151E (1986) comprises about 70% polyethoxylated 12-hydroxystearate by weight and about 30% by weight unesterified polyethylene glycol component. Solutol HS 15 has a hydrogenation value of 90-110, a saponification value of 53-63, an acid number of max. 1, and a max. water content of 0.5% by weight.

6) Polyoxyethylene alkyl ethers

These include polyoxyethylene glycol ethers of C_{12}-C_{18}-alcohols, e.g. Polyoxyl 2-, 10- or 20-cetyl ether or Polyoxyl 23-lauryl ether, or polyoxyl 20-oleyl ether, or Polyoxyl 2-, 10-, 20- or 100-stearyl ether, as known and commercially-available, e.g., under the trade mark Brij® from Uniqema. An especially preferred product of this class is, e.g., Brij® 35 (Polyoxyl 23 lauryl ether) or Brij® 98 (Polyoxyl 20 oleyl ether) (H. Fiedler, *loc. cit.*, Vol. 1, p. 259; Handbook of Pharmaceutical Excipients, *loc. cit.*, p. 367). Similarly suitable products include polyoxyethylene-polyoxypropylene-alkyl ethers, e.g., polyoxyethylene-polyoxypropylene-ethers of C_{12}-C_{18}-alcohols, e.g., polyoxyethylen-20-polyoxypropy-lene-4-cetylether which is known and commercially-available under the trade mark Nikkol PBC® 34 from, e.g., Nikko Chemicals Co., Ltd. (H. Fiedler, *loc. cit.*, Vol. 2, p. 1239). Polyoxypropylene fatty acid ethers, e.g., Acconon® E are also suitable.

7) Sodium alkyl sulfates and sulfonates, and sodium alkyl aryl sulfonates

These include sodium lauryl sulfate, which is also known as sodium dodecyl sulfate and commercially-available, e.g., under the trade name Texapon K12® from Henkel KGaA.

8) Water soluble tocopheryl polyethylene glycol succinic acid esters (TPGS)

These include those with a polymerisation number ca. 1,000 or 400, e.g., available from Eastman Fine Chemicals Kingsport, TX, USA.

9) Polyglycerol fatty acid esters

These include those with, e.g., from 10-20, e.g., 10 glycerol units. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain

length of from, e.g., C_8-C_{18}. Particularly suitable is, e.g., decaglycerylmonolaurat or decaglycerylmonomyristat, as known and commercially-available under the trade mark Decaglyn® 1-L or Decaglyn® 1-M or Decaglyn 1-O, respectively, from, e.g., Nikko Chemicals Co., Ltd (H. Fiedler, *loc. cit.*, Vol. 2, p. 1228).

10) Alkylene polyol ethers or esters

These include C_3-C_5-alkylene triols, in particular, glycerol, ethers or esters. Suitable C_3-C_5-alkylene triol ethers or esters include mixed ethers or esters, i.e., components including other ether or ester ingredients, e.g., transesterification products of C_3-C_5-alkylene triol esters with other mono-, di- or poly-ols. Particularly suitable alkylene polyol ethers or esters are mixed C_3-C_5-alkylene triol/poly-(C_2-C_4-alkylene) glycol fatty acid esters, especially mixed glycerol/polyethylene- or polypropylene-glycol fatty acid esters.

Especially suitable alkylene polyol ethers or esters include products obtainable by transesterification of glycerides, e.g., triglycerides, with poly-(C_2-C_4-alkylene) glycols, e.g., poly-ethylene glycols and, optionally, glycerol.

Such transesterification products are generally obtained by alcoholysis of glycerides, e.g., triglycerides, in the presence of a poly-(C_2-C_4-alkylene) glycol, e.g., polyethylene glycol and, optionally, glycerol (i.e., to effect transesterification from the glyceride to the poly-alkylene glycol/glycerol component, i.e., via poly-alkylene glycolysis/glycerolysis). In general such reaction is effected by reacting the indicated components (glyceride, polyalkylene glycol and, optionally, glycerol) at elevated temperature under an inert atmosphere with continuous agitation.

Preferred glycerides are fatty acid triglycerides, e.g., C_{10}-C_{22}-fatty acid triglycerides, including natural and hydrogenated oils, in particular, vegetable oils. Suitable vegetable oils include, e.g., olive, almond, peanut, coconut, palm, soybean and wheat germ oils and, in particular, natural or hydrogenated oils rich in C_{12}-C_{18}-fatty acid ester residues.

Preferred polyalkylene glycol materials are polyethylene glycols, in particular, polyethylene glycols having a molecular weight of from ca. 500-4,000, e.g., from ca. 1,000-2,000.

Suitable alkylene polyol ethers or esters include mixtures of C_3-C_5-alkylene triol esters, e.g., mono-, di- and tri-esters in variable relative amount, and poly-(C_2-C_4-alkylene) glycol mono- and di-esters, together with minor amounts of free C_3-C_5-alkylene triol and free poly-(C_2-C_5-alkylene) glycol. As hereinabove set forth, the preferred alkylene triol moiety is glyceryl; preferred polyalkylene glycol moieties include polyethylene glycol, in particular, having a molecular weight of from ca. 500-4,000; and preferred fatty acid moieties will be C_{10}-C_{22}-fatty acid ester residues, in particular, saturated C_{10}-C_{22}-fatty acid ester residues.

Particularly suitable alkylene polyol ethers or esters include transesterification products of a natural or hydrogenated vegetable oil and a polyethylene glycol and, optionally, glycerol; or compositions comprising or consisting of glyceryl mono-, di- and tri-C_{10}-C_{22}-fatty acid esters and polyethylene glycol mono- and di-C_{10}-C_{22}-fatty esters (optionally together with, e.g., minor amounts of free glycerol and free polyethylene glycol).

Preferred vegetable oils, polyethylene glycols or polyethylene glycol moieties and fatty acid moieties in relation to the above definitions are as hereinbefore set forth.

11) Polyethylene glycol glyceryl fatty acid esters

The fatty acid ester may include mono- and/or di- and/or tri-fatty acid ester. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from, e.g., C_{12}-C_{18}. The polyethylene glycols may have, e.g., from 10-40 [CH_2-CH_2-O] units, e.g., 15 or 30 units. Particularly suitable is polyethylene glycol (15) glyceryl monostearat which is commercially-available, e.g., under the trade name TGMS®-15, e.g., from Nikko Chemicals Co., Ltd. Other suitable glyceryl fatty acid esters include polyethylene glycol (30) glyceryl monooleate which is commercially-available, e.g., under the trade name Tagat® O, e.g., from Goldschmidt (H. Fiedler, *loc. cit.*, Vol. 2, pp. 1502-1503), and Tagat O2 (polytheylene glycol (20) glycerol monooleate, as well as Tagat L (polytheylene glycol (30) glycerol monolaurate) and Tagat L2 (polytheylene glycol (20) glycerol monolaurate), all, e.g., from Goldschmidt (H. Fiedler, *loc. cit.*, Vol. 2, pp. 1502-1503). A further suitable polyethylene glycol glyceryl fatty acid ester is Tagat TO.

12) Sterols and derivatives thereof

These include cholesterols and derivatives thereof, in particular, phytosterols, e.g., products comprising sitosterol, campesterol or stigmasterol, and ethylene oxide adducts thereof, e.g., soya sterols and derivatives thereof, e.g., polyethylene glycol sterols, e.g., polyethylene glycol phytosterols or polyethylene glycol soya sterols. The polyethylene glycols may have, e.g., from 10-40 [CH_2-CH_2-O] units, e.g., 25 or 30 units. Particularly suitable is polyethylene glycol (30) phytosterol which is commercially-available, e.g., under the trade name Nikkol BPS®-30, e.g., from Nikko Chemicals Co., Ltd. Further suitable is polyethylene glycol (25) soya sterol which is commercially-available, e.g., under the trade name Generol® 122 E 25, e.g., from Henkel (H. Fiedler, *loc. cit.*, Vol. 1, p. 680).

13) Transesterified, polyoxyethylated caprylic-capric acid glycerides

These include those that are commercially available under the trade name Labrasol® from, e.g., Gattefossé. Labrasol® has an acid value of max. 1, a saponification value of 90-110, and an iodine value of max. 1 (H. Fiedler, *loc. cit.*, Vol. 2, p. 880).

14) Sugar fatty acid esters

These include those of C_{12}-C_{18}-fatty acids, e.g., sucrose monolaurate, e.g., Ryoto L-1695®, which is commercially-available from, e.g., Mitsubishi-Kasei Food Corp., Tokyo, Japan.

15) PEG sterol ethers

These include those having, e.g., from 5-35 [CH_2-CH_2-O] units, e.g., 20-30 units., e.g., Solulan® C24, which is commercially-available from, e.g., Amerchol.

16) Dioctylsodiumsulfosuccinate

This is commercially-available under the trade mark Aerosol OT® from, e.g., American Cyanamid Co. (H. Fiedler, *loc. cit.*, Vol. 1, p. 118), or di-[2-ethylhexyl]-succinate (H. Fiedler, *loc. cit.*, Vol. 1, p. 487).

17) Phospholipids

These include in particular lecithins (H. Fiedler, *loc. cit.*, Vol. 2, p. 910, 1184). Suitable lecithins include, in particular, soya bean lecithins.

18) Salts of fatty acids, fatty acid sulfates and sulfonates

These include those of, e.g., C_6-C_{18}-fatty acids, -fatty acid sulfates and sulfonates, as known and commercially-available from, e.g., Fluka.

19) Salts of acylated amino acids

These include those of C_6-C_{18}-acylated amino acids, e.g., sodium lauroyl sarcosinate, which is commercially-available from, e.g., Fluka.

20) Medium or long-chain alkyl, e.g., C_6-C_{18}-ammonium salts

These include C_6-C_{18}-acylated amino acids, e.g., cetyl trimethyl ammonium bromide, which is commercially-available from, e.g., E. Merck AG.

(II) Lipophilic components are described above

(III) Hydrophilic components

Examples of hydrophilic components of the present invention include, but are not limited to:

1) Polyethylene glycol glyceryl C_6-C_{10} fatty acid esters

The fatty acid ester may include mono- and/or di- and/or tri-fatty acid esters. It optionally includes both saturated and unsaturated fatty acids having a chain length of from, e.g., C_8-C_{10}. The polyethylene glycols may have, e.g., from 5-10 [CH_2-CH_2-O] units, e.g., 7 units. A particularly suitable fatty acid ester is polyethylene glycol (7) glyceryl monococoate, which is commercially-available, e.g., under the trade name Cetiol® HE, e.g., from Henkel KGaA. Cetiol® HE has a D. (20°) of 1,05, an acid value of less than 5, a saponification value of about 95, a hydroxyl value of about 180 and an iodine value of less than 5 (H. Fiedler, *loc. cit.*, Vol. 1, p. 337) or Lipestrol E-810.

2) *N*-Alkylpyrrolidone

Particularly suitable is, e.g., *N*-methyl-2-pyrrolidone, e.g., as commercially-available under the trade name Pharmasolve™ from, e.g., International Specialty Products (ISP). *N*-Methylpyrrolidone exhibits the following additional characterizing data:

molecular weight 99,1, D.25 1,027-1,028, purity (as area % by GC) (including methyl isomers) 99.85% min. (H. Fiedler, *loc. cit.*, Vol. 2, p. 1004, manufacturer information).

3) Benzyl alcohol

This is commercially-available from, e.g., Merck or may be obtained by distillation of benzyl chloride with potassium or sodium carbonate. Benzyl alcohol exhibits the following additional characterizing data: molecular weight 108,14, D. 1,043-1,049, nD 1,538-1,541 (H. Fiedler, *loc. cit.*, Vol. 1, p. 238; Handbook of Pharmaceutical Excipients, *loc. cit.*, p. 35).

4) Triethyl citrate

It is obtained esterifying citric acid and ethanol. Triethyl citrate is commercially-available, e.g., under the trade names Citroflex® 2, or in a pharmaceutical grade under the name TEC-PG/N from, e.g., Morflex Inc. Particularly suitable is triethyl citrate which has molecular weight of 276,3, a specific gravity of 1,135-1,139, a refractive index of 1,439-1,441, a viscosity (25°) of 35,2 mPa s, assay (anhydrous basis) 99,0-100,5%, water max. 0,25% (H. Fiedler, *loc. cit.*, Vol. 1, p. 371; Handbook of Pharmaceutical Excipients, *loc. cit.*, p. 540).

Other suitable hydrophilic compounds include transcutol (C_2H_5-[O-$(CH_2)_2$]$_2$-OH); glycofurol (also known as tetrahydrofurfuryl alcohol polyethylene glycol ether); 1,2-propylene glycol, dimethylisosorbide, e.g., Arlasolve from Uniqema; polyethylene glycol, such as 200, 300, 400, 600, etc.; triethylenglycol; ethylacetate; and ethyllactate.

An example of the self-micro-emulsifying media includes hydrogenated polyoxyl castor oil, corn oil, mono-, di-, triglycerides, propyleneglycol 1,2 and ethanol.

An example of the self-micro-emulsifying media includes hydrogenated polyoxyl castor oil, corn oil, mono-, di-, triglycerides and propyleneglycol 1,2.

Another example of the self-micro-emulsifying media includes hydrogenated polyoxyl castor oil, corn oil, mono-, di and triglycerides, polyethylene glycol 400 and ethanol.

Another example of the self-micro-emulsifying media includes hydrogenated polyoxyl castor oil, corn oil, mono-, di and triglycerides and polyethylene glycol 400.

Another example of the self-micro-emulsifying media includes vitamin E TPGS, dimethyl isosorbide, triethylcitrate and ethanol.

Another example of the self-micro-emulsifying media includes vitamin E TPGS, dimethyl isosorbide and triethylcitrate.

Another example of the self-micro-emulsifying media includes hydrogenated polyoxyl castor oil, C_8/C_{10}-mono-/diglycerides, triethylcitrate and ethanol.

Another example of the self-micro-emulsifying media includes hydrogenated polyoxyl castor oil, C_8/C_{10}-mono-/diglycerides and triethylcitrate.

Another example of the self-micro-emulsifying media includes hydrogenated polyoxyl castor oil, lineoyl macrogol-6 glycerides, propyleneglycol and ethanol.

Another example of the self-micro-emulsifying media includes hydrogenated polyoxyl castor oil, lineoyl macrogol-6 glycerides and propyleneglycol.

IV. Sedimentation Inhibitor

The microparticle compositions of the present invention may further comprise a sedimentation inhibitor which significantly enhances the viscosity. Examples of the sedimentation inhibitor are oleogel formers which include, but are not limited to, precipitated or colloidal silica (e.g., Aerosil 200® or 300®), Bentonit, zinc/aluminium stearate and certain copolymers, such as ethylene/propylene/styrene copolymer, butylene/ethylene/styrene copolymer (e.g., Versagel® MP), hydrogenated styrene/isoprene copolymer and hydrogenated styrene/butadiene copolymer).

Another example of the sedimentation inhibitors are waxes and solid excipients, e.g., surfactants, lipophilic or hydrophilic excipients, e.g., polyethylene glycol of higher molecular weight (2,000, 4,000, ...) or alkylene polyol ethers or esters, e.g., Gelucire 44/14.

The sedimentation inhibitor can be either added during milling or after the milling procedure.

V. Pharmaceutical Compositions and Methods of Treatment

The pharmaceutical compositions of the present invention comprising the microparticle compositions of the present invention can be administered as oral suspensions

in multidose or single dose containers or filled in hard or soft gelatin capsules. The microparticles of the present invention may also be absorbed on a carrier and compressed into hard tablets. Examples of suitable carriers are precipitated and colloidal silicas (e.g., Zeopharm 80®, 600® or 5170® from Huber Corp., Aerosil 200® or 300®, Aeroperl 300® from Degussa), as well as sugar spheres or cellulose derivative spheres (e.g., Celphere® from Asahi-Kasei or Cellets® from Syntapharm).

Certain embodiments of the pharmaceutical compositions of the present invention include additives, e.g., antioxidants, antimicrobial agents, enzyme inhibitors, stabilizers, preservatives, flavors, sweeteners and other components, such as those described in H. Fiedler, *loc. cit.*

Preferred antioxidants include ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT), alpha-tocopherol.

Preferred stabilizers include an organic acid, e.g., citric acid, fumaric acid, maleic acid, tartaric acid, ascorbic acid and phosphoric acid.

The dose of the active agent in the compositions of the invention is of the same order as, or up to half, that used in known compositions containing the active agent. The compositions of the invention show activity at concentrations from about 0.1 mg to about 40 mg/day of active agent, preferably from about 0.1 mg to about 20 mg/day, e.g., most preferably from about 0.1 to about 5 mg/day of active agent.

A typical dose for the active agent is from 0.1-5 mg/day for treating proliferative diseases or diseases that are associated with or triggered by persistent angiogenesis.

A proliferative disease is mainly driven by tumor(s) disease (or cancer) (and/or any metastases). The inventive compositions are particularly useful for treating a tumor which is a breast cancer, lung cancer, gastrointestinal cancer, including esophageal, gastric, small bowel, large bowel and colorectal cancer, glioma, sarcoma, such as those involving bone, cartilage, soft tissue, muscle, blood and lymph vessels, ovarian cancer, myeloma, female cervical cancer, endometrial cancer, head and neck cancer, mesothelioma, renal cancer, ureter, bladder and urethral cancers, prostate cancer, skin cancers and melanoma. In particular, the inventive compositions are particularly useful for treating:

(i) a breast tumor; a lung tumor, e.g., non-small cell and small cell lung cancer; a gastrointestinal tumor, e.g., a colorectal tumor; or a genitourinary tumor, e.g., a prostate tumor;

(ii) a proliferative disease that is refractory to the treatment with other chemotherapeutics; or

(iii) a tumor that is refractory to treatment with other chemotherapeutics due to multidrug resistance. In a broader sense of the invention, a proliferative disease may furthermore be a hyperproliferative condition, such as a leukemia, lymphoma and multiple myeloma.

These additives or ingredients may comprise about 0.05-5% by weight of the total weight of the composition. Antioxidants, antimicrobial agents, enzyme inhibitors, stabilizers or preservatives typically provide up to about 0.05-2% by weight based on the total weight of the composition. Sweetening or flavouring agents typically provide up to about 0.5% or 1% by weight based on the total weight of the composition.

The microparticle compositions of the present invention can be prepared by milling techniques including, but not limited to, wet-milling including wet ball milling, high pressure homogenization, microfluidization or precipitation techniques.

Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

Example 1 **Microparticle Compositions**

The wet co-milling was performed in a ball mill using glass beads (3 mm in ∅). Seven (7) hours milling time at 3,200 rpm were employed. Alternatively, the microsuspensions can be prepared using other mills and/or milling conditions (rotation speed, concentration of ingredients, time, beads – material and size).

Table 1: Illustration of Microparticle Compositions of the Present Invention

Trial	Drug load	Vehicle, %	Surface Stabilizer, %
1	2%	Corn oil, 98%	
2	2%	Corn oil, 92%	HPMC 3 cps, 6%
3	2%	Corn oil, 96%	Colloidal silica, 2%
4	2%	Corn oil, 90%	HPMC 3 cps, 6% Pluronic F68®, 2%
5	2%	Corn oil, 94%	Colloidal silica, 2% Pluronic F68®, 2%
6	2%	Corn oil, 92%	Povidone K30, 6%
7	2%	Corn oil, 90%	Povidone K30, 6% SDS, 2%
8	2%	Self-micro-emulsifying system 1*, 98%	
9	2%	Self-micro-emulsifying system 1*, 92%	HPMC 3 cps, 6%
10	2%	Corn oil, 87% + 3% Aerosil 200 (thickener)	HPMC 3 cps, 6% Pluronic F68®, 2%
11	4%	Self-micro-emulsifying system 1*, 93% + 3% Aerosil 200 (thickener)	
12	4%	Corn oil, 88%	HPMC 3 cps, 6% Pluronic F68®, 2%
13	4%	Self-micro-emulsifying system 2*, 96%	
14	4%	Self-micro-emulsifying system 1*, 96%	

* Composition (w/w, %):

Self-micro-emulsifying system 1: 36% corn oil mono-, di- and triglycerides, 45% polyethylene glycol 40 hydrogenated castor oil (Cremophor RH40), 9% propylene glycol, 10% ethanol abs.

Self-micro-emulsifying system 2: 40% corn oil mono-, di- and triglycerides, 49% polyethylene glycol 40 hydrogenated castor oil (Cremophor RH40), 10% propylene glycol.

The particle size distribution of 7-*t*-butoxyiminomethylcamptothecin after milling was measured using either laser light scattering or light microscope. The results are given in Table 2.

Table 2: Particle Size Distribution after Milling

Trial	x 10 (µm)	x 50 (µm)	x 90 (µm)
1	0.5	1.2	3.0
2	0.5	1.3	3.2
3	0.4	1.1	2.9
4	2.4	12.2	51.5
5	0.4	1.3	4.4
6	4.1	13.8	25.8
7	3.7	13.5	26.6
8*		Very fine particles, <1 – approx. 3 µm	
9*		Very fine particles, <1 – approx. 3 µm, few irregular shaped particles, ∅ up to 120 µm**	
10	4.9	14.3	68.2
11	0.6	1.5	4.4
12	1.8	11.9	85.3
13	0.6	1.4	3.2
14	0.8	2.4	5.0

* Particle size distribution determined by light microscopy.

** The larger irregular shaped particles could be identified as excipient particles, while the small particles are drug substance particles.

Example 2 **Dissolution Rate/Bioavailability**

The results from the technical trials and from the *in vivo* dog study clearly demonstrated:

1) Increased bioavailability as compared to powder mixtures of crystalline 7-t-butoxyiminomethylcamptothecin.

2) Smaller doses of 7-*t*-butoxyiminomethylcamptothecin required to obtain the same bioavailability as compared to conventional forms of 7-*t*-butoxyiminomethylcamptothecin.

3) Good redispersibility of the microparticles of 7-*t*-butoxyiminomethylcamptothecin present in the compositions following oral administration.

4) increased rate of dissolution as compared to conventional crystalline forms of 7-*t*-butoxyiminomethylcamptothecin.

5) Improved performance characteristics for oral administration, such as higher dose loading and thus lower formulation volumes, i.e., smaller capsules.

Figure 1 of the present invention describes the *in vitro* dissolution rate profiles (USP2, 1,000 mL, 0.3% SDS, 50 rpm, 37°C). It can be seen that all microparticle formulations show improved dissolution and resuspendability behavior compared to the crystalline drug substance. Especially significant increase in dissolution rate was observed for Trials 4 and 5 containing corn oil and Pluronic F68® as surface stabilizer and Trials 8, 9, 11 and 13 using self-microemulsifiying vehicles as milling media.

The bioavailability of 7-*t*-butoxyiminomethylcamptothecin is compared as it is determinable after administration of unmilled drug substance in a dry powder formulation (hard capsule) and of a composition according to the present invention.

Administered form: 0.5 mg 7-*t*-butoxyiminomethylcamptothecin per capsule and dog.

The composition according to the present invention corresponds to Trials 4 and 8 in Example 1.

Six (6) dogs completed the study. Each of the dogs received all three formulations. Blood samples for the determination of 7-*t*-butoxyiminomethylcamptothecin in plasma were taken before dosing, and then 10 minutes, 30 minutes, 45 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours, 3 hours, 4 hours, 6 hours, 10 hours and 24 hours after drug intake. The individual concentrations of 7-*t*-butoxyiminomethylcamptothecin in heparinized plasma were determined for each sample by a liquid chromatography/tandem mass spectroscopy in positive electrospray ionization mode (positive ESI-LC/MS-MS). Heparinized plasma samples were prepared for analysis by liquid-liquid extraction and evaporation of the supernatant to dryness before reconstitution in the injection medium. The limit of quantification was 0.1 ng/mL.

Figures 2 and 3 of the present invention describes the *in vivo* dog bioavailability (0.5 mg 7-*t*-butoxyiminomethylcamptothecin/dog, beagle dogs, 6 dogs). A significant increase in bioavailability was observed for the two microparticle formulations (Figure 2) compared to the one observed for a dry mixture containing crystalline compound A (Figure 3). The microparticle suspension compositions tested correspond to Trials 4 and 8 in Table 1.

Example 3 **Scale-Up**

To demonstrate the scale-up ability of the wet co-milling process, a 2 L batch was processed in a ball mill using glass beads (1 mm in ∅). In continuous mode, processing time was 72 hours/batch while the suspension remained 7 hours in the milling chamber at 3,200 rpm. Alternatively, the microparticle formulation can be prepared using other mills and/or milling conditions (rotation speed, concentration of ingredients, time, beads – material and size).

Table 3: Illustration of Microparticle Compositions During Scale-Up

Trial	Drug load	Vehicle, %	Corresponding Small Scale Trial
15	4%	Self-micro-emulsifying system 1*, 96%	14
16	2%	Self-micro-emulsifying system 1*, 98%	8
17	2%	Self-micro-emulsifying system 2*, 98%	13 (with 4% drug load)

* Composition (w/w, %):

Self-micro-emulsifying system 1: 36% corn oil mono-, di- and triglycerides, 45% polyethylene glycol 40 hydrogenated castor oil (Cremophor RH40), 9% propylene glycol, 10% ethanol abs.

Self-micro-emulsifying system 2: 40% corn oil mono-, di- and triglycerides, 49% polyethylene glycol 40 hydrogenated castor oil (Cremophor RH40), 10% propylene glycol.

The particle size distribution of the compound after milling was measured using either laser light scattering. The results are given in Table 4. Particle size of small scale and 2l scale batches were in the same range.

Table 4: Particle Size Distribution after Milling

Trial	x 10 (µm)	x 50 (µm)	x 90 (µm)
15	0.8	1.9	4.3
16	0.7	1.9	4.6
17	0.6	2.3	3.5

Figure 4 of the present invention describes the *in vitro* dissolution rate profiles (USP2, 1,000 mL, 0.3% SDS, 50rpm, 37°C) of the scale-up trial batches 15 compared to the small scale batch 14. Dissolution rate profiles were comparable.

Example 4 **Final Dosage Form**

Microparticle formulation 16 and 17 were diluted with the self-micro emulsifying system used also to prepare the milled product. In some cases Aerosil 200 was added. The resulting diluted microparticle formulation were either filled in soft gelatin capsules (18, 19) or in hard gelatin capsules (20, 21). The composition of these dosage forms is summarized in Table 5.

Table 5: Composition of Exemplary Final Dosage Forms

Example	18	19	20	21
Microsuspension	1% of example 16	1% of example 16	1% of example 17	1% of example 17
Self-micro-emulsifying system 1*	9%			
Self-micro-emulsifying system 1* with 3% Aerosil 200		9%		
Self-micro-emulsifying system 2*			9%	
Self-micro-emulsifying system 2* with 3% Aerosil 200				9%
Total fill suspension	250 mg	250 mg	250 mg	250 mg
Hard gelatin capsule (size 1)			250 mg of diluted microparticle formulation/hard gelatin capsule	
Soft gelatin capsules	250 mg of diluted microparticle formulation/soft gelatin capsule			

* Composition (w/w, %):

Self-micro-emulsifying system 1: 36% corn oil mono-, di- and triglycerides, 45% polyethylene glycol 40 hydrogenated castor oil (Cremophor RH40), 9% propylene glycol, 10% ethanol abs.

Self-micro-emulsifying system 2: 40% corn oil mono-, di- and triglycerides, 49% polyethylene glycol 40 hydrogenated castor oil (Cremophor RH40), 10% propylene glycol.

CLAIMS

1. A pharmaceutical composition comprising microparticles of 7-*t*-butoxyiminomethylcamptothecin in a vehicle and optionally at least one surface stabilizer.

2. The pharmaceutical composition according to Claim 1, wherein the vehicle is selected from an oily vehicle, a hydrophilic non-aqueous vehicle or a self micro-emulsifying vehicle.

3. The pharmaceutical composition according to Claim 1, wherein the microparticles are up to about 15 microns.

4. The pharmaceutical composition according to Claim 3, wherein the microparticles are about 1 micron to about 5 microns.

5. The pharmaceutical composition according to Claim 1, wherein the at least one surface stabilizer is selected from hydroxymethyl propyl cellulose, polyvinylpyrrolidone, Pluronic F68®, sodium dodecyl sulphate or colloidal silica.

6. The pharmaceutical composition according to Claim 2, wherein the oily vehicle is selected from one or more corn oil, sesame oil, olive oil, paraffin oil, soy bean oil, cottonseed oil, long chain, medium and short chain mono-, di-, triglycerides and other suitable lipophilic components.

7. The pharmaceutical composition according to Claim 2, wherein the hydrophilic non-aqueous vehicle comprises of one or more of the following excipients polyethylene glycol glyceryl C_6-C_{10}-fatty acid esters, *N*-alkylpyrrolidone, benzyl alcohol or triethyl citrate.

8. The pharmaceutical composition according to Claim 2, wherein the self micro-emulsifying vehicle comprises of one or more lipophilic component, one or more surfactants, and optionally one or more hydrophilic components.

9. The pharmaceutical composition according to Claim 8, wherein the self micro-emulsifying vehicle comprises corn oil mono-, di- and triglycerides, polyethylene glycol Polyoxyl 40 hydrogenated castor oil, propylene glycol and optionally ethanol.

10. The pharmaceutical composition according to Claim 1, further comprising a sedimentation inhibitor.

11. The pharmaceutical composition according to Claim 9, wherein the sedimentation inhibitor is colloidal silica.

12. A microparticle of 7-*t*-butoxyiminomethylcamptothecin.

13. The microparticle according to Claim 12, which is up to about 15 microns in diameter.

14. The microparticle according to Claim 13 which is about 1 micron to about 5 microns.

15. The microparticle according to Claim 12, produced by milling, high pressure homogenization or precipitation techniques.

16. A method of treating a proliferative disease in a patient in need of such treatment comprising administering the pharmaceutical composition according to Claim 1.

17. The method according to Claim 16, wherein the proliferative disease is breast cancer, lung cancer, gastrointestinal cancer, large bowel and colorectal cancer, glioma, sarcoma, ovarian cancer, myeloma, cervical cancer, endometrial cancer, head and neck cancer, mesothelioma, renal cancer, prostate cancer, cancer of the uterus, bladder and urethral, skin cancer and melanoma.