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(57) Abstract

The present invention relates to triglyceride–free pharmaceutical compositions for delivery of hydrophobic therapeutic agents. Compositions of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the surfactants containing the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compositions.

COMPOSITIONS AND METHODS FOR IMPROVED DELIVERY OF HYDROPHOBIC THERAPEUTIC AGENTS

FIELD OF THE INVENTION

The present invention relates to drug delivery systems, and in particular to pharmaceutical compositions for the improved delivery of hydrophobic compounds.

BACKGROUND

Hydrophobic therapeutic agents, *i.e.*, therapeutic compounds having poor solubility in aqueous solution, present difficult problems in formulating such compounds for effective administration to patients. A well-designed formulation must, at a minimum, be capable of presenting a therapeutically effective amount of the hydrophobic compound to the desired absorption site, in an absorbable form. Even this minimal functionality is difficult to achieve when delivery of the hydrophobic therapeutic agent requires interaction with aqueous physiological environments, such as gastric fluids and intestinal fluids. Pharmaceutical compositions for delivery of such hydrophobic therapeutic agents must carry the hydrophobic compound through the aqueous environment, while maintaining the hydrophobic compound in an absorbable form, and avoiding the use of physiologically harmful solvents or excipients.

A number of approaches to formulating hydrophobic therapeutic agents for oral or parenteral delivery are known. One well-known approach uses surfactant micelles to solubilize and transport the therapeutic agent. Micelles are agglomerates of colloidal dimensions formed by amphiphilic compounds under certain conditions. Micelles, and pharmaceutical compositions containing micelles, have been extensively studied and are described in detail in the literature; *see, e.g.*, Remington's Pharmaceutical Sciences, 17th ed. (1985), the disclosure of which is incorporated herein in its entirety. In aqueous solution, micelles can incorporate hydrophobic therapeutic agents in the hydrocarbon core of the micelle, or entangled at various positions within the micelle walls. Although micellar formulations can solubilize a variety of hydrophobic therapeutic agents, the loading capacity of conventional micelle formulations is limited by the solubility of the therapeutic agent in the micelle surfactant. For many hydrophobic therapeutic agents, such solubility is too low to offer formulations that can deliver therapeutically effective doses.

Another conventional approach takes advantage of the increased solubility of hydrophobic therapeutic agents in oils (triglycerides). Hydrophobic therapeutic agents, while poorly soluble in aqueous solution, could be sufficiently lipophilic that therapeutically

effective concentrations of the therapeutic agents can be prepared in triglyceride-based solvents. Thus, one conventional approach is to solubilize a hydrophobic therapeutic agent in a bioacceptable triglyceride solvent, such as a digestible vegetable oil, and disperse this oil phase in an aqueous solution. The dispersion may be stabilized by emulsifying agents and provided in emulsion form. Alternatively, the therapeutic agent can be provided in a water-free formulation, with an aqueous dispersion being formed in the in vivo gastrointestinal environment. The properties of these oil-based formulations are determined by such factors as the size of the triglyceride/therapeutic agent colloidal particles and the presence or absence of surfactant additives.

In simplest form, a triglyceride-containing formulation suitable for delivering hydrophobic therapeutic agents through an aqueous environment is an oil-in-water emulsion. Such emulsions contain the hydrophobic therapeutic agent solubilized in an oil phase which is dispersed in an aqueous environment with the aid of a surfactant. The surfactant may be present in the oil-based formulation itself, or may be a compound provided in the gastrointestinal system, such as bile salts, which are known to be in vivo emulsifying agents. The colloidal oil particles sizes are relatively large, ranging from several hundred nanometers to several microns in diameter, in a broad particle size distribution. Since the particle sizes are on the order of or greater than the wavelength range of visible light, such emulsions, when prepared in an emulsion dosage form, are visibly "cloudy" or "milky" to the naked eye.

Although triglyceride-based pharmaceutical compositions are useful in solubilizing and delivering some hydrophobic therapeutic agents, such compositions are subject to a number of significant limitations and disadvantages. Emulsions are thermodynamically unstable, and colloidal emulsion particles will spontaneously agglomerate, eventually leading to complete phase separation. The tendency to agglomerate and phase separate presents problems of storage and handling, and increases the likelihood that pharmaceutical emulsions initially properly prepared will be in a less optimal, less effective, and poorly-characterized state upon ultimate administration to a patient. Uncharacterized degradation is particularly disadvantageous, since increased particle size slows the rate of transport of the colloidal particle and digestion of the oil component, and hence the rate and extent of absorption of the therapeutic agent. These problems lead to poorly-characterized and potentially harmful changes in the effective dosage received by the patient. Moreover, changes in colloidal emulsion particle size are also believed to render absorption more sensitive to and dependent upon conditions in the gastrointestinal tract, such as pH, enzyme activity, bile components,

and stomach contents. Such uncertainty in the rate and extent of ultimate absorption of the therapeutic agent severely compromises the medical professional's ability to safely administer therapeutically effective dosages.

A further disadvantage of triglyceride-containing compositions is the dependence of therapeutic agent absorption on the rate and extent of lipolysis. Although colloidal emulsion particles can transport hydrophobic therapeutic agents through the aqueous environment of the gastrointestinal tract, ultimately the triglyceride must be digested and the therapeutic agent must be released in order to be absorbed through the intestinal mucosa. The triglyceride carrier is emulsified by bile salts and hydrolyzed, primarily by pancreatic lipase. The rate and extent of lipolysis, however, are dependent upon several factors that are difficult to adequately control. For example, the amount and rate of bile salt secretion affect the lipolysis of the triglycerides, and the bile salt secretion can vary with stomach contents, with metabolic abnormalities, and with functional changes of the liver, bile ducts, gall bladder and intestine. Lipase availability in patients with decreased pancreatic secretory function, such as cystic fibrosis or chronic pancreatitis, may be undesirably low, resulting in a slow and incomplete triglyceride lipolysis. The activity of lipase is pH dependent, with deactivation occurring at about pH 3, so that the lipolysis rate will vary with stomach contents, and may be insufficient in patients with gastric acid hyper-secretion. Moreover, certain surfactants commonly used in the preparation of pharmaceutical emulsions, such as polyethoxylated castor oils, may themselves act as inhibitors of lipolysis. Although recent work suggests that certain surfactant combinations, when used in combination with digestible oils in emulsion preparations, can substantially decrease the lipolysis-inhibiting effect of some common pharmaceutical surfactants (*see*, U.S. Patent No. 5,645,856), such formulations are still subject to the other disadvantages of pharmaceutical emulsions and triglyceride-based formulations.

Yet another approach is based on formation of "microemulsions." Like an emulsion, a microemulsion is a liquid dispersion of oil in water, stabilized by surfactants. The microemulsion particles are smaller than those of an emulsion, rendering the microemulsion essentially optically clear. Microemulsions, however, are thermodynamically stable, and are not subject to the particle agglomeration problems of conventional emulsions. It is generally believed that microemulsions are micelle-like particles, having an essentially micellar structure but containing a distinct oil phase in the micelle "core". These micelle-like particles are often referred to as "swollen micelles", a term which emphasizes their close relationship

to true micellar particles. Despite their close relationship to micelles, microemulsions function quite differently in drug delivery systems. The majority of hydrophobic therapeutic agents are lipophilic, and have greater solubility in triglycerides than in surfactants. As a result, the hydrophobic therapeutic agent in a microemulsion-based delivery system is preferentially solvated in the triglyceride phase, which is in turn encapsulated in the swollen micelle. The preferential partitioning in the triglyceride phase results in higher loading capacities than in comparable micelle-based systems, but at the cost of introducing into the delivery system the lipolysis-dependence and other disadvantages associated with the presence of triglycerides. In addition, the larger size of microemulsion particles, relative to true micelles, results in a slower rate of particle diffusion, and thus a slower rate of therapeutic agent absorption.

Thus, there is a need for pharmaceutical compositions that overcome the limitations of conventional micelle formulations, but without suffering from the disadvantages of triglyceride-containing formulations.

SUMMARY OF THE INVENTION

The present invention provides pharmaceutical compositions for improved delivery of hydrophobic therapeutic agents. In one embodiment, the present invention provides a triglyceride-free pharmaceutical composition including a hydrophobic therapeutic agent and a carrier. The carrier includes a hydrophilic surfactant and a hydrophobic surfactant in amounts such that upon dilution with an aqueous solution such as simulated gastrointestinal fluids the carrier forms a clear aqueous dispersion of the hydrophilic and hydrophobic surfactants containing the hydrophobic therapeutic agent.

In another embodiment, the present invention provides a clear aqueous dispersion containing a hydrophilic surfactant, a hydrophobic surfactant and a hydrophobic therapeutic agent. The dispersion is substantially free of triglycerides.

In another embodiment, the present invention relates to a triglyceride-free pharmaceutical composition which includes a hydrophilic surfactant and a hydrophobic surfactant in amounts such that upon dilution with an aqueous solution a clear aqueous dispersion is formed, a first amount of a hydrophobic therapeutic agent solubilized in the clear aqueous dispersion, and a second amount of the hydrophobic therapeutic agent that remains non-solubilized but dispersed.

According to a first aspect of the invention, there is provided a pharmaceutical composition comprising: (a) a hydrophobic therapeutic agent; and (b) a carrier comprising (i) at least one hydrophilic surfactant and (ii) at least one hydrophobic surfactant, said hydrophilic and hydrophobic surfactants being present in amounts such that upon mixing with an aqueous solution the carrier forms a clear aqueous dispersion of the hydrophilic and hydrophobic surfactants containing the hydrophobic therapeutic agent, wherein the composition is substantially free of triglycerides.

According to a second aspect of the invention, there is provided a dosage form comprising a capsule filled with the above-described pharmaceutical composition, a multiparticulate carrier coated with the above-described pharmaceutical composition or the above-described pharmaceutical composition formulated as a solution, a cream, a lotion, an ointment, a suppository, a spray, an aerosol, a paste or a gel.

According to a third aspect of the invention, there is provided a pharmaceutical composition comprising: (a) at least one hydrophilic surfactant; (b) at least one hydrophobic surfactant; and (c) a hydrophobic therapeutic agent, said pharmaceutical composition being in the form of a clear, aqueous dispersion which is substantially free of glycerol triesters of C_6 to about C_{25} fatty acids.

According to a fourth aspect of the invention, there is provided a pharmaceutical composition comprising: (a) a carrier comprising (i) at least one hydrophilic surfactant and (ii) at least one hydrophobic surfactant, said hydrophilic and hydrophobic surfactants being present in amounts such that upon mixing with an aqueous solution the carrier forms a clear aqueous dispersion of the

hydrophilic and hydrophobic surfactants; (b) a first amount of a hydrophobic therapeutic agent, said first amount being solubilized in the carrier; and (c) a second amount of a hydrophobic therapeutic agent, said second amount not solubilized in the clear aqueous dispersion, said composition being substantially free of glycerol triesters Of C_6 to about C_{25} fatty acids.

According to a fifth aspect of the invention, there is provided a method of treating an animal with a hydrophobic therapeutic agent, the method comprising: administering to the animal a dosage form of a pharmaceutical composition comprising: a hydrophobic therapeutic agent; and a carrier comprised of at least one hydrophilic surfactant and at least one hydrophobic surfactant, said hydrophilic and hydrophobic surfactants being present in amounts such that upon mixing with an aqueous solution the carrier forms a clear aqueous dispersion of the hydrophilic and hydrophobic surfactants containing the hydrophobic therapeutic agent, said composition being substantially free of glycerol triesters of C_6 to about C_{25} fatty acids.

According to a sixth aspect of the invention, there is provided a capsule containing a pharmaceutical composition comprising (a) a hydrophobic therapeutic agent having an intrinsic water solubility of less than about 1 percent by weight and present in a therapeutically effective dosage for oral administration, and (b) a carrier comprised of a hydrophilic surfactant, a hydrophobic surfactant, and a solubilizer selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof and present in an amount of about 1% to about 100% by weight relative to the combined weight of the hydrophilic and hydrophobic surfactants, wherein the hydrophobic surfactant is

present in an amount of about 5% to about 100% by weight relative to the hydrophilic surfactant, and the hydrophilic and hydrophobic surfactants are each present in amounts such that upon dilution with an aqueous solution at an aqueous solution to carrier ratio of 100:1 by weight, the carrier forms a clear aqueous dispersion having an absorbance of less than about 0.1 at a wavelength of about 400 nm, and further wherein the composition is substantially free of water and glycerol triesters of C_6 to about C_{25} fatty acids.

According to a seventh aspect of the invention, there is provided a multiparticulate dosage form for oral administration of a therapeutic agent, comprised of a plurality of beads each coated with a composition comprising (a) a hydrophobic therapeutic agent having an intrinsic water solubility of less than about 1 wt.% at 25°C and present in a therapeutically effective amount for oral administration, and (b) a carrier comprised of (i) at least one hydrophilic surfactant and (ii) at least one hydrophobic surfactant, said hydrophilic and hydrophobic surfactants being present in amounts such that upon dilution with an aqueous solution at an aqueous solution to carrier ratio of 100:1 by weight, the carrier forms a clear aqueous dispersion having an absorbance of less than about 0.1 at a wavelength of about 400 nm, and wherein the composition is substantially free of water and glycerol triesters of C_6 to about C_{25} fatty acids.

According to an eighth aspect of the invention, there is provided a multiparticulate dosage form for oral administration of a therapeutic agent, comprised of a plurality of particles each comprising a composition of (a) a hydrophobic therapeutic agent having an intrinsic water solubility of less than about 1 wt.% at 25°C and present in a therapeutically effective amount for oral administration, and (b) a carrier comprised of (i) at least one hydrophilic surfactant

and (ii) at least one hydrophobic surfactant, said hydrophilic and hydrophobic surfactants being present in amounts such that upon dilution with an aqueous solution at an aqueous solution to carrier ratio of 100:1 by weight, the carrier forms a clear aqueous dispersion having an absorbance of less than about 0.1 at a wavelength of about 400 nm, and wherein the composition is substantially free of water and glycerol triesters Of C_6 to about C_{25} fatty acids.

In another embodiment, the present invention relates to methods of increasing the rate and/or extent of absorption of hydrophobic therapeutic agents by administering to a patient a pharmaceutical composition of the present invention.

These features of the present invention will become more fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to illustrate the manner in which the above-recited and other advantages and objects of the invention are obtained, a more particular description of the invention briefly described above will be rendered by reference to the specific embodiments shown in the appended drawings. Understanding that these drawings depict only typical embodiments of the invention and are not therefore limiting of its scope, the invention will be described and explained with additional specificity and detail through the use of the accompanying drawing, in which:

Figure 1 shows the enhanced bioabsorption of a hydrophobic therapeutic agent in the compositions of the present invention, relative to a commercial formulation.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention overcomes the problems described above characteristic of conventional formulations such as micelle formulations, emulsions, and microemulsions, by providing unique triglyceride-free pharmaceutical compositions. Surprisingly, the present inventors have found that compositions including a combination of a hydrophilic surfactant and a hydrophobic surfactant can solubilize therapeutically effective amounts of hydrophobic therapeutic agents without recourse to the use of triglycerides, thereby avoiding the lipolysis dependence and other disadvantages of conventional formulations. Use of these formulations results in an enhanced rate and/or extent of absorption of the hydrophobic therapeutic agent.

A. Pharmaceutical Compositions

In one embodiment, the present invention provides a pharmaceutical composition including a carrier and a hydrophobic therapeutic agent. The carrier includes a hydrophilic surfactant and a hydrophobic surfactant in amounts such that upon dilution with an aqueous solution the carrier forms a clear aqueous dispersion of the hydrophilic and hydrophobic surfactants containing the hydrophobic therapeutic agent. It is a particular feature of the present invention that the carrier is substantially free of triglycerides, thereby providing surprising and important advantages over conventional, triglyceride-containing formulations.

1. Surfactants

The carrier includes at least one hydrophilic surfactant and at least one hydrophobic surfactant. As is well known in the art, the terms "hydrophilic" and "hydrophobic" are relative terms. To function as a surfactant, a compound must necessarily include polar or charged hydrophilic moieties as well as non-polar hydrophobic (lipophilic) moieties; *i.e.*, a surfactant compound must be amphiphilic. An empirical parameter commonly used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions.

Using HLB values as a rough guide, hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, hydrophobic surfactants are compounds having an HLB value less than about 10.

It should be appreciated that the HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions. For many important surfactants, including several polyethoxylated surfactants, it has been reported that HLB values can differ by as much as about 8 HLB units, depending upon the empirical method chosen to determine the HLB value (Schott, *J. Pharm. Sciences*, 79(1), 87-88 (1990)). Likewise, for certain polypropylene oxide containing block copolymers (PLURONIC® surfactants, BASF Corp.), the HLB values may not accurately reflect the true physical chemical nature of the compounds. Finally, commercial surfactant products are generally not pure compounds, but are complex mixtures of compounds, and the HLB value reported for a particular compound may more accurately be characteristic of the commercial product of which the compound is a major component. Different commercial products having the same primary surfactant component can, and typically do, have different HLB values. In addition, a certain amount of lot-to-lot variability is expected even for a single commercial surfactant product. Keeping these inherent difficulties in mind, and using HLB values as a guide, one skilled in the art can readily identify surfactants having suitable hydrophilicity or hydrophobicity for use in the present invention, as described herein.

The hydrophilic surfactant can be any hydrophilic surfactant suitable for use in pharmaceutical compositions. Such surfactants can be anionic, cationic, zwitterionic or non-ionic, although non-ionic hydrophilic surfactants are presently preferred. As discussed

above, these non-ionic hydrophilic surfactants will generally have HLB values greater than about 10. Mixtures of hydrophilic surfactants are also within the scope of the invention.

Similarly, the hydrophobic surfactant can be any hydrophobic surfactant suitable for use in pharmaceutical compositions. In general, suitable hydrophobic surfactants will have an HLB value less than about 10. Mixtures of hydrophobic surfactants are also within the scope of the invention.

The choice of specific hydrophobic and hydrophilic surfactants should be made keeping in mind the particular hydrophobic therapeutic agent to be used in the composition, and the range of polarity appropriate for the chosen therapeutic agent, as discussed in more detail below. With these general principles in mind, a very broad range of surfactants is suitable for use in the present invention. Such surfactants can be grouped into the following general chemical classes detailed in the Tables below. The HLB values given in the Tables below generally represent the HLB value as reported by the manufacturer of the corresponding commercial product. In cases where more than one commercial product is listed, the HLB value in the Tables is the value as reported for one of the commercial products, a rough average of the reported values, or a value that, in the judgment of the present inventors, is more reliable. It should be emphasized that the invention is not limited to the surfactants in the following Tables, which show representative, but not exclusive, lists of available surfactants.

1.1. Polyethoxylated Fatty Acids

Although polyethylene glycol (PEG) itself does not function as a surfactant, a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful. Among the surfactants of Table 1, preferred hydrophilic surfactants include PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate and PEG-20 oleate. Examples of polyethoxylated fatty acid monoester surfactants commercially available are shown in Table 1.

Table 1: PEG-Fatty Acid Monoester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG 4-100 monolaurate	Crodet L series (Croda)	>9
PEG 4-100 monooleate	Crodet O series (Croda)	>8
PEG 4-100 monostearate	Crodet S series (Croda), Myrj Series (Atlas/ICI)	>6

PEG 400 distearate	Cithrol 4DS series (Croda)	>10
PEG 100,200,300 monolaurate	Cithrol ML series (Croda)	>10
PEG 100,200,300 monooleate	Cithrol MO series (Croda)	>10
PEG 400 dioleate	Cithrol 4DO series (Croda)	>10
PEG 400-1000 monostearate	Cithrol MS series (Croda)	>10
PEG-1 stearate	Nikkol MYS-1EX (Nikko), Coster K1 (Condea)	2
PEG-2 stearate	Nikkol MYS-2 (Nikko)	4
PEG-2 oleate	Nikkol MYO-2 (Nikko)	4.5
PEG-4 laurate	Mapeg® 200 ML (PPG), Kessco® PEG 200ML (Stepan), LIPOPEG 2L (LIPO Chem.)	9.3
PEG-4 oleate	Mapeg® 200 MO (PPG), Kessco® PEG200 MO (Stepan),	8.3
PEG-4 stearate	Kessco® PEG 200 MS (Stepan), Hodag 20 S (Calgene), Nikkol MYS-4 (Nikko)	6.5
PEG-5 stearate	Nikkol TMGS-5 (Nikko)	9.5
PEG-5 oleate	Nikkol TMGO-5 (Nikko)	9.5
PEG-6 oleate	Algon OL 60 (Auschem SpA), Kessco® PEG 300 MO (Stepan), Nikkol MYO-6 (Nikko), Emulgante A6 (Condea)	8.5
PEG-7 oleate	Algon OL 70 (Auschem SpA)	10.4
PEG-6 laurate	Kessco® PEG300 ML (Stepan)	11.4
PEG-7 laurate	Lauridac 7 (Condea)	13
PEG-6 stearate	Kessco® PEG300 MS (Stepan)	9.7
PEG-8 laurate	Mapeg® 400 ML (PPG), LIPOPEG 4DL(Lipo Chem.)	13
PEG-8 oleate	Mapeg® 400 MO (PPG), Emulgante A8 (Condea)	12
PEG-8 stearate	Mapeg® 400 MS (PPG), Myrj 45	12
PEG-9 oleate	Emulgante A9 (Condea)	>10
PEG-9 stearate	Cremophor S9 (BASF)	>10

PEG-10 laurate	Nikkol MYL-10 (Nikko), Lauridac 10 (Croda)	13
PEG-10 oleate	Nikkol MYO-10 (Nikko)	11
PEG-10 stearate	Nikkol MYS-10 (Nikko), Coster K100 (Condea)	11
PEG-12 laurate	Kessco® PEG 600ML (Stepan)	15
PEG-12 oleate	Kessco® PEG 600MO (Stepan)	14
PEG-12 ricinoleate	(CAS # 9004-97-1)	>10
PEG-12 stearate	Mapeg® 600 MS (PPG), Kessco® PEG 600MS (Stepan)	14
PEG-15 stearate	Nikkol TMGS-15 (Nikko), Koster K15 (Condea)	14
PEG-15 oleate	Nikkol TMGO-15 (Nikko)	15
PEG-20 laurate	Kessco® PEG 1000 ML (Stepan)	17
PEG-20 oleate	Kessco® PEG 1000 MO (Stepan)	15
PEG-20 stearate	Mapeg® 1000 MS (PPG), Kessco® PEG 1000 MS (Stepan), Myrj 49	16
PEG-25 stearate	Nikkol MYS-25 (Nikko)	15
PEG-32 laurate	Kessco® PEG 1540 ML (Stepan)	16
PEG-32 oleate	Kessco® PEG 1540 MO (Stepan)	17
PEG-32 stearate	Kessco® PEG 1540 MS (Stepan)	17
PEG-30 stearate	Myrj 51	>10
PEG-40 laurate	Crodet L40 (Croda)	17.9
PEG-40 oleate	Crodet O40 (Croda)	17.4
PEG-40 stearate	Myrj 52, Emerest® 2715 (Henkel), Nikkol MYS-40 (Nikko)	>10
PEG-45 stearate	Nikkol MYS-45 (Nikko)	18
PEG-50 stearate	Myrj 53	>10
PEG-55 stearate	Nikkol MYS-55 (Nikko)	18
PEG-100 oleate	Crodet O-100 (Croda)	18.8
PEG-100 stearate	Myrj 59, Arlacel 165 (ICI)	19
PEG-200 oleate	Albunol 200 MO (Taiwan Surf.)	>10
PEG-400 oleate	LACTOMUL (Henkel), Albunol 400 MO (Taiwan Surf.)	>10

PEG-600 oleate	Albunol 600 MO (Taiwan Surf.)	>10

1.2 PEG-Fatty Acid Diesters

Polyethylene glycol fatty acid diesters are also suitable for use as surfactants in the compositions of the present invention. Among the surfactants in Table 2, preferred hydrophilic surfactants include PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate and PEG-32 dioleate. Representative PEG-fatty acid diesters are shown in Table 2.

Table 2: PEG-Fatty Acid Diester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-4 dilaurate	Mapeg® 200 DL (PPG), Kessco® PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7
PEG-4 dioleate	Mapeg® 200 DO (PPG),	6
PEG-4 distearate	Kessco® 200 DS (Stepan_	5
PEG-6 dilaurate	Kessco® PEG 300 DL (Stepan)	9.8
PEG-6 dioleate	Kessco® PEG 300 DO (Stepan)	7.2
PEG-6 distearate	Kessco® PEG 300 DS (Stepan)	6.5
PEG-8 dilaurate	Mapeg® 400 DL (PPG), Kessco® PEG 400 DL (Stepan), LIPOPEG 4 DL (Lipo Chem.)	11
PEG-8 dioleate	Mapeg® 400 DO (PPG), Kessco® PEG 400 DO (Stepan), LIPOPEG 4 DO(Lipo Chem.)	8.8
PEG-8 distearate	Mapeg® 400 DS (PPG), CDS 400 (Nikkol)	11
PEG-10 dipalmitate	Polyaldo 2PKFG	>10
PEG-12 dilaurate	Kessco® PEG 600 DL (Stepan)	11.7
PEG-12 distearate	Kessco® PEG 600 DS (Stepan)	10.7
PEG-12 dioleate	Mapeg® 600 DO (PPG), Kessco® 600 DO(Stepan)	10
PEG-20 dilaurate	Kessco® PEG 1000 DL (Stepan)	15
PEG-20 dioleate	Kessco® PEG 1000 DO (Stepan)	13
PEG-20 distearate	Kessco® PEG 1000 DS (Stepan)	12
PEG-32 dilaurate	Kessco® PEG 1540 DL (Stepan)	16

PEG-32 dioleate	Kessco® PEG 1540 DO (Stepan)	15
PEG-32 distearate	Kessco® PEG 1540 DS (Stepan)	15
PEG-400 dioleate	Cithrol 4DO series (Croda)	>10
PEG-400 distearate	Cithrol 4DS series (Croda)	>10

1.3 PEG-Fatty Acid Mono- and Di-ester Mixtures

In general, mixtures of surfactants are also useful in the present invention, including mixtures of two or more commercial surfactant products. Several PEG-fatty acid esters are marketed commercially as mixtures or mono- and diesters. Representative surfactant mixtures are shown in Table 3.

Table 3: PEG-Fatty Acid Mono- and Diester Mixtures

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG 4-150 mono, dilaurate	Kessco® PEG 200-6000 mono, dilaurate (Stepan)	
PEG 4-150 mono, dioleate	Kessco® PEG 200-6000 mono, dioleate (Stepan)	
PEG 4-150 mono, distearate	Kessco® 200-6000 mono, distearate (Stepan)	

1.4 Polyethylene Glycol Glycerol Fatty Acid Esters

Suitable PEG glycerol fatty acid esters are shown in Table 4. Among the surfactants in the Table, preferred hydrophilic surfactants are PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, and PEG-30 glyceryl oleate.

Table 4: PEG Glycerol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-20 glyceryl laurate	Tagat® L (Goldschmidt)	16
PEG-30 glyceryl laurate	Tagat® L2 (Goldschmidt)	16
PEG-15 glyceryl laurate	Glycerox L series (Croda)	15
PEG-40 glyceryl laurate	Glycerox L series (Croda)	15
PEG-20 glyceryl stearate	Capmul® EMG (ABITEC), Aldo® MS-20 KFG (Lonza)	13
PEG-20 glyceryl oleate	Tagat® O (Goldschmidt)	>10
PEG-30 glyceryl oleate	Tagat® O2 (Goldschmidt)	>10

1.5. Alcohol - Oil Transesterification Products

A large number of surfactants of different degrees of hydrophobicity or hydrophilicity can be prepared by reaction of alcohols or polyalcohols with a variety of natural and/or hydrogenated oils. Most commonly, the oils used are castor oil or hydrogenated castor oil, or an edible vegetable oil such as corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, or almond oil. Preferred alcohols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, and pentaerythritol. Among these alcohol-oil transesterified surfactants, preferred hydrophilic surfactants are PEG-35 castor oil (Incrocas-35), PEG-40 hydrogenated castor oil (Cremophor RH 40), PEG-25 trioleate (TAGAT® TO), PEG-60 corn glycerides (Crovol M70), PEG-60 almond oil (Crovol A70), PEG-40 palm kernel oil (Crovol PK70), PEG-50 castor oil (Emalex C-50), PEG-50 hydrogenated castor oil (Emalex HC-50), PEG-8 caprylic/capric glycerides (Labrasol), and PEG-6 caprylic/capric glycerides (Softigen 767). Preferred hydrophobic surfactants in this class include PEG-5 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-9 hydrogenated castor oil, PEG-6 corn oil (Labrafil® M 2125 CS), PEG-6 almond oil (Labrafil® M 1966 CS), PEG-6 apricot kernel oil (Labrafil® M 1944 CS), PEG-6 olive oil (Labrafil® M 1980 CS), PEG-6 peanut oil (Labrafil® M 1969 CS), PEG-6 hydrogenated palm kernel oil (Labrafil® M 2130 BS), PEG-6 palm kernel oil (Labrafil® M 2130 CS), PEG-6 triolein (Labrafil® M 2735 CS), PEG-8 corn oil (Labrafil® WL 2609 BS), PEG-20 corn glycerides (Crovol M40), and PEG-20 almond glycerides (Crovol A40). The latter two surfactants are reported to have HLB values of 10, which is generally considered to be the approximate border line between hydrophilic and hydrophobic surfactants. For purposes of the present invention, these two surfactants are considered to be hydrophobic. Representative surfactants of this class suitable for use in the present invention are shown in Table 5.

Table 5: Transesterification Products of Oils and Alcohols

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-3 castor oil	Nikkol CO-3 (Nikko)	3
PEG-5, 9, and 16 castor oil	ACCONON CA series (ABITEC)	6-7
PEG-20 castor oil	Emalex C-20 (Nihon Emulsion), Nikkol CO-20 TX (Nikko)	11
PEG-23 castor oil	Emulgante EL23	>10

PEG-30 castor oil	Emalex C-30 (Nihon Emulsion), Alkamuls® EL 620 (Rhone-Poulenc), Incrocas 30 (Croda)	11
PEG-35 castor oil	Cremophor EL and EL-P (BASF), Emulphor EL, Incrocas-35 (Croda), Emulgin RO 35 (Henkel)	
PEG-38 castor oil	Emulgante EL 65 (Condea)	
PEG-40 castor oil	Emalex C-40 (Nihon Emulsion), Alkamuls® EL 719 (Rhone-Poulenc)	13
PEG-50 castor oil	Emalex C-50 (Nihon Emulsion)	14
PEG-56 castor oil	Eumulgin® PRT 56 (Pulcra SA)	>10
PEG-60 castor oil	Nikkol CO-60TX (Nikko)	14
PEG-100 castor oil	Thornley	>10
PEG-200 castor oil	Eumulgin® PRT 200 (Pulcra SA)	>10
PEG-5 hydrogenated castor oil	Nikkol HCO-5 (Nikko)	6
PEG-7 hydrogenated castor oil	Simusol® 989 (Seppic), Cremophor WO7 (BASF)	6
PEG-10 hydrogenated castor oil	Nikkol HCO-10 (Nikko)	6.5
PEG-20 hydrogenated castor oil	Nikkol HCO-20 (Nikko)	11
PEG-25 hydrogenated castor oil	Simulsol® 1292 (Seppic), Cerex ELS 250 (Auschem SpA)	11
PEG-30 hydrogenated castor oil	Nikkol HCO-30 (Nikko)	11
PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13
PEG-45 hydrogenated castor oil	Cerex ELS 450 (Auschem Spa)	14
PEG-50 hydrogenated castor oil	Emalex HC-50 (Nihon Emulsion)	14
PEG-60 hydrogenated castor oil	Nikkol HCO-60 (Nikko); Cremophor RH 60 (BASF)	15
PEG-80 hydrogenated castor oil	Nikkol HCO-80 (Nikko)	15

PEG-100 hydrogenated castor oil	Nikkol HCO -100 (Nikko)	17
PEG-6 corn oil	Labrafil® M 2125 CS (Gattefosse)	4
PEG-6 almond oil	Labrafil® M 1966 CS (Gattefosse)	4
PEG-6 apricot kernel oil	Labrafil® M 1944 CS (Gattefosse)	4
PEG-6 olive oil	Labrafil® M 1980 CS (Gattefosse)	4
PEG-6 peanut oil	Labrafil® M 1969 CS (Gattefosse)	4
PEG-6 hydrogenated palm kernel oil	Labrafil® M 2130 BS (Gattefosse)	4
PEG-6 palm kernel oil	Labrafil® M 2130 CS (Gattefosse)	4
PEG-6 triolein	Labrafil® M 2735 CS (Gattefosse)	4
PEG-8 corn oil	Labrafil® WL 2609 BS (Gattefosse)	6-7
PEG-20 corn glycerides	Crovol M40 (Croda)	10
PEG-20 almond glycerides	Crovol A40 (Croda)	10
PEG-25 trioleate	TAGAT® TO (Goldschmidt)	11
PEG-40 palm kernel oil	Crovol PK-70	>10
PEG-60 corn glycerides	Crovol M70(Croda)	15
PEG-60 almond glycerides	Crovol A70 (Croda)	15
PEG-4 caprylic/capric triglyceride	Labrafac® Hydro (Gattefosse),	4-5
PEG-8 caprylic/capric glycerides	Labrasol (Gattefosse),Labrafac CM 10 (Gattefosse)	>10
PEG-6 caprylic/capric glycerides	SOFTIGEN® 767 (Hüls), Glycerox 767 (Croda)	19
Lauroyl macrogol-32 glyceride	GELUCIRE 44/14 (Gattefosse)	14
Stearoyl macrogol glyceride	GELUCIRE 50/13 (Gattefosse)	13
Mono, di, tri, tetra esters of vegetable oils and sorbitol	SorbitoGlyceride (Gattefosse)	<10

Pentaerythrityl tetraisostearate	Crodamol PTIS (Croda)	<10
Pentaerythrityl distearate	Albunol DS (Taiwan Surf.)	<10
Pentaerythrityl tetraoleate	Liponate PO-4 (Lipo Chem.)	<10
Pentaerythrityl tetrastearate	Liponate PS-4 (Lipo Chem.)	<10
Pentaerythrityl tetracaprylate/tetracaprate	Liponate PE-810 (Lipo Chem.), Crodamol PTC (Croda)	<10
Pentaerythrityl tetraoctanoate	Nikkol Pentarate 408 (Nikko)	

Also included as oils in this category of surfactants are oil-soluble vitamins, such as vitamins A, D, E, K, etc. Thus, derivatives of these vitamins, such as tocopheryl PEG-1000 succinate (TPGS, available from Eastman), are also suitable surfactants.

1.6. Polyglycerized Fatty Acids

Polyglycerol esters of fatty acids are also suitable surfactants for the present invention. Among the polyglyceryl fatty acid esters, preferred hydrophobic surfactants include polyglyceryl oleate (Plurol Oleique), polyglyceryl-2 dioleate (Nikkol DGDO), and polyglyceryl-10 trioleate. Preferred hydrophilic surfactants include polyglyceryl-10 laurate (Nikkol Decaglyn 1-L), polyglyceryl-10 oleate (Nikkol Decaglyn 1-O), and polyglyceryl-10 mono, dioleate (Caprol® PEG 860). Polyglyceryl polyricinoleates (Polymuls) are also preferred hydrophilic and hydrophobic surfactants. Examples of suitable polyglyceryl esters are shown in Table 6.

Table 6: Polyglycerized Fatty Acids

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Polyglyceryl-2 stearate	Nikkol DGMS (Nikko)	5-7
Polyglyceryl-2 oleate	Nikkol DGMO (Nikko)	5-7
Polyglyceryl-2 isostearate	Nikkol DGMIS (Nikko)	5-7
Polyglyceryl-3 oleate	Caprol® 3GO (ABITEC), Drewpol 3-1-O (Stepan)	6.5
Polyglyceryl-4 oleate	Nikkol Tetraglyn 1-O (Nikko)	5-7
Polyglyceryl-4 stearate	Nikkol Tetraglyn 1-S (Nikko)	5-6
Polyglyceryl-6 oleate	Drewpol 6-1-O (Stepan), Nikkol Hexaglyn 1-O (Nikko)	9

Polyglyceryl-10 laurate	Nikkol Decaglyn 1-L (Nikko)	15
Polyglyceryl-10 oleate	Nikkol Decaglyn 1-O (Nikko)	14
Polyglyceryl-10 stearate	Nikkol Decaglyn 1-S (Nikko)	12
Polyglyceryl-6 ricinoleate	Nikkol Hexaglyn PR-15 (Nikko)	>8
Polyglyceryl-10 linoleate	Nikkol Decaglyn 1-LN (Nikko)	12
Polyglyceryl-6 pentaoleate	Nikkol Hexaglyn 5-O (Nikko)	<10
Polyglyceryl-3 dioleate	Cremophor GO32 (BASF)	<10
Polyglyceryl-3 distearate	Cremophor GS32 (BASF)	<10
Polyglyceryl-4 pentaoleate	Nikkol Tetraglyn 5-O (Nikko)	<10
Polyglyceryl-6 dioleate	Caprol® 6G20 (ABITEC); Hodag PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)	8.5
Polyglyceryl-2 dioleate	Nikkol DGDO (Nikko)	7
Polyglyceryl-10 trioleate	Nikkol Decaglyn 3-O (Nikko)	7
Polyglyceryl-10 pentaoleate	Nikkol Decaglyn 5-O (Nikko)	3.5
Polyglyceryl-10 septaoleate	Nikkol Decaglyn 7-O (Nikko)	3
Polyglyceryl-10 tetraoleate	Caprol® 10G4O (ABITEC); Hodag PGO-62 (CALGENE), Drewpol 10-4-O (Stepan)	6.2
Polyglyceryl-10 decaisostearate	Nikkol Decaglyn 10-IS (Nikko)	<10
Polyglyceryl-10l decaoleate	Drewpol 10-10-O (Stepan), Caprol 10G10O (ABITEC), Nikkol Decaglyn 10-O	3.5
Polyglyceryl-10 mono, dioleate	Caprol® PGE 860 (ABITEC)	11
Polyglyceryl polyricinoleate	Polymuls (Henkel)	3-20

1.7. Propylene Glycol Fatty Acid Esters

Esters of propylene glycol and fatty acids are suitable surfactants for use in the present invention. In this surfactant class, preferred hydrophobic surfactants include propylene glycol monolaurate (Lauroglycol FCC), propylene glycol ricinoleate (Propymuls),

propylene glycol monooleate (Myverol P-O6), propylene glycol dicaprylate/dicaprate (Captex® 200), and propylene glycol dioctanoate (Captex® 800). Examples of surfactants of this class are given in Table 7.

Table 7: Propylene Glycol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Propylene glycol monocaprylate	Capryol 90 (Gattefosse), Nikkol Sefsol 218 (Nikko)	<10
Propylene glycol monolaurate	Lauroglycol 90 (Gattefosse), Lauroglycol FCC (Gattefosse)	<10
Propylene glycol oleate	Lutrol OP2000 (BASF)	<10
Propylene glycol myristate	Mirpyl	<10
Propylene glycol monostearate	ADM PGME-03 (ADM), LIPO PGMS (Lipo Chem.), Aldo® PGHMS (Lonza)	3-4
Propylene glycol hydroxy stearate		<10
Propylene glycol ricinoleate	PROPYMULS (Henkel)	<10
Propylene glycol isostearate		<10
Propylene glycol monooleate	Myverol P-O6 (Eastman)	<10
Propylene glycol dicaprylate/dicaprate	Captex® 200 (ABITEC), Miglyol® 840 (Hüls), Neobee® M-20 (Stepan)	>6
Propylene glycol dioctanoate	Captex® 800 (ABITEC)	>6
Propylene glycol caprylate/caprate	LABRAFAC PG (Gattefosse)	>6
Propylene glycol dilaurate		>6
Propylene glycol distearate	Kessco® PGDS (Stepan)	>6
Propylene glycol dicaprylate	Nikkol Sefsol 228 (Nikko)	>6
Propylene glycol dicaprate	Nikkol PDD (Nikko)	>6

1.8. Mixtures of Propylene Glycol Esters - Glycerol Esters

In general, mixtures of surfactants are also suitable for use in the present invention. In particular, mixtures of propylene glycol fatty acid esters and glycerol fatty acid esters are suitable and are commercially available. One preferred mixture is composed of the oleic acid esters of propylene glycol and glycerol (Arlacel 186). Examples of these surfactants are shown in Table 8.

Table 8: Glycerol/Propylene Glycol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Oleic	ATMOS 300, ARLACEL 186 (ICI)	3-4
Stearic	ATMOS 150	3-4

1.9. Mono- and Diglycerides

A particularly important class of surfactants is the class of mono- and diglycerides. These surfactants are generally hydrophobic. Preferred hydrophobic surfactants in this class of compounds include glyceryl monooleate (Peceol), glyceryl ricinoleate, glyceryl laurate, glyceryl dilaurate (Capmul® GDL), glyceryl dioleate (Capmul® GDO), glyceryl mono/dioleate (Capmul® GMO-K), glyceryl caprylate/caprate (Capmul® MCM), caprylic acid mono/diglycerides (Imwitor® 988), and mono- and diacetylated monoglycerides (Myvacet® 9-45). Examples of these surfactants are given in Table 9.

Table 9: Mono- and Diglyceride Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Monopalmitolein (C16:1)	(Larodan)	<10
Monoelaidin (C18:1)	(Larodan)	<10
Monocaproin (C6)	(Larodan)	<10
Monocaprylin	(Larodan)	<10
Monocaprin	(Larodan)	<10
Monolaurin	(Larodan)	<10
Glyceryl monomyristate (C14)	Nikkol MGM (Nikko)	3-4
Glyceryl monooleate (C18:1)	PECEOL (Gattefosse), Hodag GMO-D, Nikkol MGO (Nikko)	3-4
Glyceryl monooleate	RYLO series (Danisco), DIMODAN series (Danisco), EMULDAN (Danisco), ALDO® MO FG (Lonza),	3-4

		EMULDAN (Danisco), ALDO® MO FG (Lonza), Kessco GMO (Stepan), MONOMULS® series (Henkel), TEGIN O, DREWMULSE GMO (Stepan), Atlas G-695 (ICI), GMOrphic 80 (Eastman), ADM DMG-40, 70, and 100 (ADM), Myverol (Eastman)	
Glycerol monooleate/linoleate	OLICINE (Gattefosse)		3-4
Glycerol monolinoleate	Maisine (Gattefosse), MYVEROL 18-92, Myverol 18-06 (Eastman)		3-4
Glyceryl ricinoleate	Softigen® 701 (Hüls), HODAG GMR-D (Calgene), ALDO® MR (Lonza)		6
Glyceryl monolaurate	ALDO® MLD (Lonza), Hodag GML (Calgene)		6.8
Glycerol monopalmitate	Emalex GMS-P (Nihon)		4
Glycerol monostearate	Capmul® GMS (ABITEC), Myvaplex (Eastman), IMWITOR® 191 (Hüls), CUTINA GMS, Aldo® MS (Lonza), Nikkol MGS series (Nikko)		5-9
Glyceryl mono-,dioleate	Capmul® GMO-K (ABITEC)		<10
Glyceryl palmitic/stearic	CUTINA MD-A, ESTAGEL-G18		<10
Glyceryl acetate	Lamegin® EE (Grünau GmbH)		<10
Glyceryl laurate	Imwitor® 312 (Hüls), Monomuls® 90-45 (Grünau GmbH), Aldo® MLD (Lonza)		4
Glyceryl citrate/lactate/oleate/ linoleate	Imwitor® 375 (Hüls)		<10
Glyceryl caprylate	Imwitor® 308 (Hüls), Capmul® MCMC8 (ABITEC)		5-6
Glyceryl caprylate/caprate	Capmul® MCM (ABITEC)		5-6
Caprylic acid mono,diglycerides	Imwitor® 988 (Hüls)		5-6
Caprylic/capric glycerides	Imwitor® 742 (Hüls)		<10
Mono-and diacetylated monoglycerides	Myvacet® 9-45, Myvacet® 9-40, Myvacet® 9-08 (Eastman), Lamegin® (Grünau)		3.8-4
Glyceryl monostearate	Aldo® MS, Arlacel 129 (ICI), LIPO GMS (Lipo Chem.), Imwitor® 191 (Hüls), Myvaplex (Eastman)		4.4
Lactic acid esters of mono,diglycerides	LAMEGIN GLP (Henkel)		<10

Dicaproin (C6)	(Larodan)	<10
Dicaprin (C10)	(Larodan)	<10
Dioctanoin (C8)	(Larodan)	<10
Dimyristin (C14)	(Larodan)	<10
Dipalmitin (C16)	(Larodan)	<10
Distearin	(Larodan)	<10
Glyceryl dilaurate (C12)	Capmul® GDL (ABITEC)	3-4
Glyceryl dioleate	Capmul® GDO (ABITEC)	3-4
Glycerol esters of fatty acids	GELUCIRE 39/01 (Gattefosse), GELUCIRE 43/01 (Gattefosse)	1
	GELUCIRE 37/06 (Gattefosse)	6
Dipalmitolein (C16:1)	(Larodan)	<10
1,2 and 1,3-diolein (C18:1)	(Larodan)	<10
Dielaidin (C18:1)	(Larodan)	<10
Dilinolein (C18:2)	(Larodan)	<10

1.10. Sterol and Sterol Derivatives

Sterols and derivatives of sterols are suitable surfactants for use in the present invention. These surfactants can be hydrophilic or hydrophobic. Preferred derivatives include the polyethylene glycol derivatives. A preferred hydrophobic surfactant in this class is cholesterol. A preferred hydrophilic surfactant in this class is PEG-24 cholesterol ether (Solulan C-24). Examples of surfactants of this class are shown in Table 10.

Table 10: Sterol and Sterol Derivative Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Cholesterol, sitosterol, lanosterol		<10
PEG-24 cholesterol ether	Solulan C-24 (Amerchol)	>10
PEG-30 cholestanol	Nikkol DHC (Nikko)	>10
Phytosterol	GENEROL series (Henkel)	<10
PEG-25 phyto sterol	Nikkol BPSH-25 (Nikko)	>10

PEG-5 soya sterol	Nikkol BPS-5 (Nikko)	<10
PEG-10 soya sterol	Nikkol BPS-10 (Nikko)	<10
PEG-20 soya sterol	Nikkol BPS-20 (Nikko)	<10
PEG-30 soya sterol	Nikkol BPS-30 (Nikko)	>10

1.11. Polyethylene Glycol Sorbitan Fatty Acid Esters

A variety of PEG-sorbitan fatty acid esters are available and are suitable for use as surfactants in the present invention. In general, these surfactants are hydrophilic, although several hydrophobic surfactants of this class can be used. Among the PEG-sorbitan fatty acid esters, preferred hydrophilic surfactants include PEG-20 sorbitan monolaurate (Tween-20), PEG-20 sorbitan monopalmitate (Tween-40), PEG-20 sorbitan monostearate (Tween-60), and PEG-20 sorbitan monooleate (Tween-80). Examples of these surfactants are shown in Table 11.

Table 11: PEG-Sorbitan Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-10 sorbitan laurate	Liposorb L-10 (Lipo Chem.)	>10
PEG-20 sorbitan monolaurate	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
PEG-4 sorbitan monolaurate	Tween-21 (Atlas/ICI), Crillet 11 (Croda)	13
PEG-80 sorbitan monolaurate	Hodag PSML-80 (Calgene); T-Maz 28	>10
PEG-6 sorbitan monolaurate	Nikkol GL-1 (Nikko)	16
PEG-20 sorbitan monopalmitate	Tween-40 (Atlas/ICI), Crillet 2 (Croda)	16
PEG-20 sorbitan monostearate	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
PEG-4 sorbitan monostearate	Tween-61 (Atlas/ICI), Crillet 31 (Croda)	9.6
PEG-8 sorbitan monostearate	DACOL MSS (Condea)	>10

PEG-6 sorbitan monostearate	Nikkol TS106 (Nikko)	11
PEG-20 sorbitan tristearate	Tween-65 (Atlas/ICI), Crillet 35 (Croda)	11
PEG-6 sorbitan tetrastearate	Nikkol GS-6 (Nikko)	3
PEG-60 sorbitan tetrastearate	Nikkol GS-460 (Nikko)	13
PEG-5 sorbitan monooleate	Tween-81 (Atlas/ICI), Crillet 41 (Croda)	10
PEG-6 sorbitan monooleate	Nikkol TO-106 (Nikko)	10
PEG-20 sorbitan monooleate	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15
PEG-40 sorbitan oleate	Emalex ET 8040 (Nihon Emulsion)	18
PEG-20 sorbitan trioleate	Tween-85 (Atlas/ICI), Crillet 45 (Croda)	11
PEG-6 sorbitan tetraoleate	Nikkol GO-4 (Nikko)	8.5
PEG-30 sorbitan tetraoleate	Nikkol GO-430 (Nikko)	12
PEG-40 sorbitan tetraoleate	Nikkol GO-440 (Nikko)	13
PEG-20 sorbitan monoisostearate	Tween-120 (Atlas/ICI), Crillet 6 (Croda)	>10
PEG sorbitol hexaoleate	Atlas G-1086 (ICI)	10
PEG-6 sorbitol hexastearate	Nikkol GS-6 (Nikko)	3

1.12. Polyethylene Glycol Alkyl Ethers

Ethers of polyethylene glycol and alkyl alcohols are suitable surfactants for use in the present invention. Preferred hydrophobic ethers include PEG-3 oleyl ether (Volpo 3) and PEG-4 lauryl ether (Brij 30). Examples of these surfactants are shown in Table 12.

Table 12: Polyethylene Glycol Alkyl Ethers

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-2 oleyl ether,oleth-2	Brij 92/93 (Atlas/ICI)	4.9
PEG-3 oleyl ether,oleth-3	Volpo 3 (Croda)	<10
PEG-5 oleyl ether,oleth-5	Volpo 5 (Croda)	<10

PEG-10 oleyl ether,oleth-10	Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12
PEG-20 oleyl ether,oleth-20	Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15
PEG-4 lauryl ether, laureth-4	Brij 30 (Atlas/ICI)	9.7
PEG-9 lauryl ether		>10
PEG-23 lauryl ether, laureth-23	Brij 35 (Atlas/ICI)	17
PEG-2 cetyl ether	Brij 52 (ICI)	5.3
PEG-10 cetyl ether	Brij 56 (ICI)	13
PEG-20 cetyl ether	Brij 58 (ICI)	16
PEG-2 stearyl ether	Brij 72 (ICI)	4.9
PEG-10 stearyl ether	Brij 76 (ICI)	12
PEG-20 stearyl ether	Brij 78 (ICI)	15
PEG-100 stearyl ether	Brij 700 (ICI)	>10

1.13. Sugar Esters

Esters of sugars are suitable surfactants for use in the present invention. Preferred hydrophilic surfactants in this class include sucrose monopalmitate and sucrose monolaurate. Examples of such surfactants are shown in Table 13.

Table 13: Sugar Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Sucrose distearate	SUCRO ESTER 7 (Gattefosse), Crodesta F-10 (Croda)	3
Sucrose distearate/monostearate	SUCRO ESTER 11 (Gattefosse), Crodesta F-110 (Croda)	12
Sucrose dipalmitate		7.4
Sucrose monostearate	Crodesta F-160 (Croda)	15
Sucrose monopalmitate	SUCRO ESTER 15 (Gattefosse)	>10
Sucrose monolaurate	Saccharose monolaurate 1695 (Mitsubishi-Kasei)	15

1.14. Polyethylene Glycol Alkyl Phenols

Several hydrophilic PEG-alkyl phenol surfactants are available, and are suitable for use in the present invention. Examples of these surfactants are shown in Table 14.

Table 14: Polyethylene Glycol Alkyl Phenol Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-10-100 nonyl phenol	Triton X series (Rohm & Haas), Igepal CA series (GAF, USA), Antarox CA series (GAF, UK)	>10
PEG-15-100 octyl phenol ether	Triton N-series (Rohm & Haas), Igepal CO series (GAF, USA), Antarox CO series (GAF, UK)	>10

1.15. Polyoxyethylene-Polyoxypropylene Block Copolymers

The POE-POP block copolymers are a unique class of polymeric surfactants. The unique structure of the surfactants, with hydrophilic POE and hydrophobic POP moieties in well-defined ratios and positions, provides a wide variety of surfactants suitable for use in the present invention. These surfactants are available under various trade names, including Synperonic PE series (ICI); Pluronic® series (BASF), Emkalyx, Lutrol (BASF), Supronic, Monolan, Pluracare, and Plurodac. The generic term for these polymers is "poloxamer" (CAS 9003-11-6). These polymers have the formula:

$$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$$

where "a" and "b" denote the number of polyoxyethylene and polyoxypropylene units, respectively.

Preferred hydrophilic surfactants of this class include Poloxamers 108, 188, 217, 238, 288, 338, and 407. Preferred hydrophobic surfactants in this class include Poloxamers 124, 182, 183, 212, 331, and 335.

Examples of suitable surfactants of this class are shown in Table 15. Since the compounds are widely available, commercial sources are not listed in the Table. The compounds are listed by generic name, with the corresponding "a" and "b" values.

Table 15: POE-POP Block Copolymers

COMPOUND	a, b values in $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$	HLB
Poloxamer 105	a = 11 b = 16	8

Poloxamer 108	a = 46 b = 16	>10
Poloxamer 122	a = 5 b = 21	3
Poloxamer 123	a = 7 b = 21	7
Poloxamer 124	a = 11 b = 21	>7
Poloxamer 181	a = 3 b = 30	
Poloxamer 182	a = 8 b = 30	2
Poloxamer 183	a = 10 b = 30	
Poloxamer 184	a = 13 b = 30	
Poloxamer 185	a = 19 b = 30	
Poloxamer 188	a = 75 b = 30	29
Poloxamer 212	a = 8 b = 35	
Poloxamer 215	a = 24 b = 35	
Poloxamer 217	a = 52 b = 35	
Poloxamer 231	a = 16 b = 39	
Poloxamer 234	a = 22 b = 39	
Poloxamer 235	a = 27 b = 39	
Poloxamer 237	a = 62 b = 39	24
Poloxamer 238	a = 97 b = 39	
Poloxamer 282	a = 10 b = 47	
Poloxamer 284	a = 21 b = 47	
Poloxamer 288	a = 122 b = 47	>10
Poloxamer 331	a = 7 b = 54	0.5
Poloxamer 333	a = 20 b = 54	
Poloxamer 334	a = 31 b = 54	
Poloxamer 335	a = 38 b = 54	
Poloxamer 338	a = 128 b = 54	
Poloxamer 401	a = 6 b = 67	
Poloxamer 402	a = 13 b = 67	
Poloxamer 403	a = 21 b = 67	
Poloxamer 407	a = 98 b = 67	

1.16. Sorbitan Fatty Acid Esters

Sorbitan esters of fatty acids are suitable surfactants for use in the present invention. Among these esters, preferred hydrophobic surfactants include sorbitan monolaurate (Arlacel 20), sorbitan monopalmitate (Span-40), sorbitan monooleate (Span-80), sorbitan monostearate, and sorbitan tristearate. Examples of these surfactants are shown in Table 16.

Table 16: Sorbitan Fatty Acid Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Sorbitan monolaurate	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI)	8.6
Sorbitan monopalmitate	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6.7
Sorbitan monooleate	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4.3
Sorbitan monostearate	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4.7
Sorbitan trioleate	Span-85 (Atlas/ICI), Crill 45 (Croda), Nikkol SO-30 (Nikko)	4.3
Sorbitan sesquioleate	Arlacel-C (ICI), Crill 43 (Croda), Nikkol SO-15 (Nikko)	3.7
Sorbitan tristearate	Span-65 (Atlas/ICI) Crill 35 (Croda), Nikkol SS-30 (Nikko)	2.1
Sorbitan monoisostearate	Crill 6 (Croda), Nikkol SI-10 (Nikko)	4.7
Sorbitan sesquistearate	Nikkol SS-15 (Nikko)	4.2

1.17. Lower Alcohol Fatty Acid Esters

Esters of lower alcohols (C_2 to C_4) and fatty acids (C_8 to C_{18}) are suitable surfactants for use in the present invention. Among these esters, preferred hydrophobic surfactants include ethyl oleate (Crodamol EO), isopropyl myristate (Crodamol IPM), and isopropyl palmitate (Crodamol IPP). Examples of these surfactants are shown in Table 17.

Table 17: Lower Alcohol Fatty Acid Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Ethyl oleate	Crodamol EO (Croda), Nikkol EOO (Nikko)	<10
Isopropyl myristate	Crodamol IPM (Croda)	<10
Isopropyl palmitate	Crodamol IPP (Croda)	<10

Ethyl linoleate	Nikkol VF-E (Nikko)	<10
Isopropyl linoleate	Nikkol VF-IP (Nikko)	<10

1.18. Ionic Surfactants

Ionic surfactants, including cationic, anionic and zwitterionic surfactants, are suitable hydrophilic surfactants for use in the present invention. Preferred anionic surfactants include fatty acid salts and bile salts. Specifically, preferred ionic surfactants include sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium cholate, and sodium taurocholate. Examples of such surfactants are shown in Table 18 below. For simplicity, typical counterions are shown in the entries in the Table. It will be appreciated by one skilled in the art, however, that any bioacceptable counterion may be used. For example, although the fatty acids are shown as sodium salts, other cation counterions can also be used, such as alkali metal cations or ammonium. Unlike typical non-ionic surfactants, these ionic surfactants are generally available as pure compounds, rather than commercial (proprietary) mixtures. Because these compounds are readily available from a variety of commercial suppliers, such as Aldrich, Sigma, and the like, commercial sources are not generally listed in the Table.

Table 18: Ionic Surfactants

COMPOUND	HLB
FATTY ACID SALTS	>10
Sodium caproate	
Sodium caprylate	
Sodium caprate	
Sodium laurate	
Sodium myristate	
Sodium myristolate	
Sodium palmitate	
Sodium palmitoleate	
Sodium oleate	18
Sodium ricinoleate	
Sodium linoleate	
Sodium linolenate	
Sodium stearate	

Sodium lauryl sulfate (dodecyl)	40
Sodium tetradecyl sulfate	
Sodium lauryl sarcosinate	
Sodium dioctyl sulfosuccinate [sodium docusate (Cytec)]	
BILE SALTS	>10
Sodium cholate	
Sodium taurocholate	
Sodium glycocholate	
Sodium deoxycholate	
Sodium taurodeoxycholate	
Sodium glycodeoxycholate	
Sodium ursodeoxycholate	
Sodium chenodeoxycholate	
Sodium taurochenodeoxycholate	
Sodium glyco cheno deoxycholate	
Sodium cholylsarcosinate	
Sodium N-methyl taurocholate	
PHOSPHOLIPIDS	
Egg/Soy lecithin [Epikuron™ (Lucas Meyer), Ovothin™ (Lucas Meyer)]	
Lyso egg/soy lecithin	
Hydroxylated lecithin	
Lysophosphatidylcholine	
Cardiolipin	
Sphingomyelin	
Phosphatidylcholine	
Phosphatidyl ethanolamine	
Phosphatidic acid	
Phosphatidyl glycerol	
Phosphatidyl serine	
PHOSPHORIC ACID ESTERS	
Diethanolammonium polyoxyethylene-10 oleyl ether phosphate	
Esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride	

CARBOXYLATES

Ether carboxylates (by oxidation of terminal OH group of fatty alcohol ethoxylates)

Succinylated monoglycerides [LAMEGIN ZE (Henkel)]

Sodium stearyl fumarate

Stearoyl propylene glycol hydrogen succinate

Mono/diacetylated tartaric acid esters of mono- and diglycerides

Citric acid esters of mono-, diglycerides

Glyceryl-lacto esters of fatty acids (CFR ref. 172.852)

Acyl lactylates:

lactylic esters of fatty acids
calcium/sodium stearoyl-2-lactylate
calcium/sodium stearoyl lactylate

Alginate salts

Propylene glycol alginate

SULFATES AND SULFONATES

Ethoxylated alkyl sulfates

Alkyl benzene sulfones

α-olefin sulfonates

Acyl isethionates

Acyl taurates

Alkyl glyceryl ether sulfonates

Octyl sulfosuccinate disodium

Disodium undecylenamideo-MEA-sulfosuccinate

CATIONIC Surfactants >10

Hexadecyl triammonium bromide

Decyl trimethyl ammonium bromide

Cetyl trimethyl ammonium bromide

Dodecyl ammonium chloride

Alkyl benzyldimethylammonium salts

Diisobutyl phenoxyethoxydimethyl benzylammonium salts

Alkylpyridinium salts

Betaines (trialkylglycine):

Lauryl betaine (N-lauryl,N,N-dimethylglycine)

Ethoxylated amines:

Polyoxyethylene-15 coconut amine

1.19 Surfactant Concentrations

The hydrophilic and hydrophobic surfactants are present in the pharmaceutical compositions of the present invention in amounts such that upon dilution with an aqueous solution, the carrier forms a clear, aqueous dispersion of the hydrophilic and hydrophobic surfactants, containing the hydrophobic therapeutic agent. The relative amounts of hydrophilic and hydrophobic surfactants are readily determined by observing the properties of the resultant dispersion; *i.e.*, when the relative amounts of the hydrophobic and hydrophilic surfactants are within a suitable range, the resultant aqueous dispersion is optically clear. When the relative amount of hydrophobic surfactant is too great, the resulting dispersion is visibly "cloudy", resembling a conventional emulsion or multiple phase system. Although a visibly cloudy solution may be potentially useful for some applications, such a system would suffer from many of the same disadvantages as conventional prior art formulations, as described above.

A convenient method of determining the appropriate relative concentrations for any hydrophilic surfactant - hydrophobic surfactant pair is as follows. A convenient working amount of a hydrophilic surfactant is provided, and a known amount of a hydrophobic surfactant is added. The surfactants are stirred to form a homogeneous mixture, with the aid of gentle heating if desired. The resulting mixture is diluted with purified water to prepare an aqueous dispersion. Any dilution amount can be chosen, but convenient dilutions are those within the range expected *in vivo*, about a 10 to 250-fold dilution. The aqueous dispersion is then assessed qualitatively for optical clarity. The procedure can be repeated with incremental variations in the relative amount of hydrophobic surfactant added, to determine the maximum relative amount of hydrophobic surfactant that can be present for a given surfactant pair.

Alternatively, the optical clarity of the aqueous dispersion can be measured using standard quantitative techniques for turbidity assessment. One convenient procedure to measure turbidity is to measure the amount of light of a given wavelength transmitted by the solution, using, for example, a UV-visible spectrophotometer. Using this measure, optical clarity corresponds to high transmittance, since cloudier solutions will scatter more of the incident radiation, resulting in lower transmittance measurements. If this procedure is used, care should be taken to insure that the surfactant mixture does not itself absorb light of the chosen wavelength, as any true absorbance necessarily reduces the amount of transmitted light and falsely increases the quantitative turbidity value. In the absence of chromophores at

the chosen wavelength, suitable dispersions at a dilution of 10X should have an apparent absorbance of less than about 0.3, preferably less than about 0.2, and more preferably less than about 0.1. At a dilution of 100X, suitable dispersions should have an apparent absorbance of less than about 0.1, preferably less than about 0.05, and more preferably less than about 0.01.

A third method of determining optical clarity and carrier diffusivity through the aqueous boundary layer is to quantitatively measure the size of the particles of which the dispersion is composed. These measurements can be performed on commercially available particle size analyzers, such as, for example, a Nicomp particle size analyzer available from Particle Size Systems, Inc., of Santa Barbara, CA. Using this measure, clear aqueous dispersions according to the present invention have average particle sizes much smaller than the wavelength of visible light, whereas dispersions containing excessive relative amounts of the hydrophobic surfactant have more complex particle size distributions, with much greater average particle sizes. It is desirable that the average particle size be less than about 100 nm, preferably less than about 50 nm, more preferably less than about 30 nm, and still more preferably less than about 20 nm. It is also preferred that the particle size distribution be mono-modal. As is shown in more detail in the Examples herein, dispersions having an undesirably large relative amount of hydrophobic surfactant typically display bimodal particle size distributions, such distributions having a small particle size component, typically less than about 30 nm, and a large particle size component, typically on the order of 100 nm or more. It should be emphasized that these particle sizes are appropriate for the carrier particles in aqueous solution, in the absence of a hydrophobic therapeutic agent. It is expected that the presence of the hydrophobic therapeutic agent may result in an increase in the average particle size.

Other methods of determining optical clarity or particle size can be used as desired. Such methods are well know to those skilled in the art.

It should be emphasized that any or all of the available methods may be used to ensure that the resulting aqueous dispersions possess the requisite optical clarity. For convenience, however, the present inventors prefer to use the simple qualitative procedure; *i.e.*, simple visible observation. However, in order to more fully illustrate the practice of the present invention, all three of the above measures are used to assess the dispersion clarity in the Examples herein.

Although it should be understood that any aqueous dispersion having the properties described above is within the scope of the present invention regardless of the specific relative amounts of hydrophobic and hydrophilic surfactants, it is expected that the amount of hydrophobic surfactant will generally be less than about 200% by weight, based on the amount of hydrophilic surfactant, and more specifically, in the range of about 1% to 200%. Further, based on observations reported in the Examples herein, it is expected that the amount of hydrophobic surfactant will generally be less than about 100%, and more specifically in the range of about 5% to about 100% by weight, or about 10% to about 100% by weight, based on the amount of hydrophilic surfactant. For some particular surfactant combinations, cloudy solutions result when the amount of hydrophobic surfactant is greater than about 60% by weight, based on the amount of hydrophilic surfactant. A preferred range for these surfactants is about 1% to about 60%, preferably about 5% to about 60%, and more preferably about 10% to about 60%. Addition of optional excipients as described below can further increase the maximum relative amount of hydrophobic surfactant that can be used.

Other considerations well known to those skilled in the art will further inform the choice of specific proportions of hydrophobic and hydrophilic surfactants. These considerations include the degree of bioacceptability of the surfactants, and the desired dosage of hydrophobic therapeutic agent to be provided. In some cases, the amount of hydrophobic surfactant actually used in a pharmaceutical composition according to the present invention will be less than the maximum that can be used, and it should be apparent that such compositions are also within the scope of the present invention.

2. Hydrophobic Therapeutic Agents

Hydrophobic therapeutic agents suitable for use in the pharmaceutical compositions of the present invention are not particularly limited, as the carrier is surprisingly capable of solubilizing and delivering a wide variety of hydrophobic therapeutic agents. Hydrophobic therapeutic agents are compounds with little or no water solubility. Intrinsic water solubilities (*i.e.*, water solubility of the unionized form) for hydrophobic therapeutic agents usable in the present invention are less than about 1% by weight, and typically less than about 0.1% or 0.01% by weight. Such therapeutic agents can be any agents having therapeutic or other value when administered to an animal, particularly to a mammal, such as drugs, nutrients, and cosmetics (cosmeceuticals). It should be understood that while the invention is described with particular reference to its value in the form of aqueous dispersions, the invention is not so limited. Thus, hydrophobic drugs, nutrients or cosmetics which derive

their therapeutic or other value from, for example, topical or transdermal administration, are still considered to be suitable for use in the present invention.

Specific non-limiting examples of hydrophobic therapeutic agents that can be used in the pharmaceutical compositions of the present invention include the following representative compounds, as well as their pharmaceutically acceptable salts, isomers, esters, ethers and other derivatives:

analgesics and anti-inflammatory agents, such as aloxiprin, auranofin, azapropazone, benorylate, capsaicin, celecoxib, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, leflunomide, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, rofecoxib, sulindac, tetrahydrocannabinol, tramadol and tromethamine;

antihelminthics, such as albendazole, bephenium hydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel embonate, praziquantel, pyrantel embonate and thiabendazole;

anti-arrhythmic agents, such as amiodarone HCl, disopyramide, flecainide acetate and quinidine sulfate;

anti-asthma agents, such as zileuton, zafirlukast, terbutaline sulfate, montelukast, and albuterol;

anti-bacterial agents, such as alatrofloxacin, azithromycin, baclofen, benzathine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, dirithromycin, doxycycline, erythromycin, ethionamide, furazolidone, grepafloxacin, imipenem, levofloxacin, lorefloxacin, moxifloxacin HCl, nalidixic acid, nitrofurantoin, norfloxazin, ofloxacin, rifampicin, rifabutine, rifapentine, sparfloxacin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim, trovafloxacin, and vancomycin;

anti-viral agents, such as abacavir, amprenavir, delavirdine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, and stavudine;

anti-coagulants, such as cilostozol, clopidogrel, dicumarol, dipyridamole, nicoumalone, oprelvekin, phenindione, ticlopidine, and tirofiban;

anti-depressants, such as amoxapine,. bupropion, citalopram, clomipramine, fluoxetine HCl, maprotiline HCl, mianserin HCl, nortriptyline HCl, paroxetine HCl, Sertraline HCl, trazodone HCl, trimipramine maleate, and venlafaxine HCl;

anti-diabetics, such as acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, glimepiride, miglitol, pioglitazone, repaglinide, rosiglitazone, tolazamide, tolbutamide and troglitazone;

anti-epileptics, such as beclamide, carbamazepine, clonazepam, ethotoin, felbamate, fosphenytoin sodium, lamotrigine, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone, phenytoin, phensuximide, primidone, sulthiame, tiagabine HCl, topiramate, valproic acid, and vigabatrin;

anti-fungal agents, such as amphotericin, butenafine HCl, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, oxiconazole, terbinafine HCl, terconazole, tioconazole and undecenoic acid;

anti-gout agents, such as allopurinol, probenecid and sulphinpyrazone;

anti-hypertensive agents, such as amlodipine, benidipine, benezepril, candesartan, captopril, darodipine, dilitazem HCl, diazoxide, doxazosin HCl, enalapril, eposartan, losartan mesylate, felodipine, fenoldopam, fosenopril, guanabenz acetate, irbesartan, isradipine, lisinopril, minoxidil, nicardipine HCl, nifedipine, nimodipine, nisoldipine, phenoxybenzarnine HCl, prazosin HCl, quinapril, reserpine, terazosin. HCl, telmisartan, and valsartan;

anti-malarials, such as arnodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl, mefloquine HCl, proguanil HCl, pyrimethamine and quinine sulfate;

anti-migraine agents, such as dihydroergotamine mesylate, ergotamine tartrate, frovatriptan, methysergide maleate, naratriptan HCl, pizotifen maleate, rizatriptan benzoate, sumatriptan succinate, and zolmitriptan;

anti-muscarinic agents, such as atropine, benzhexol HCL, biperiden, ethopropazine HCL, hyoscyamine, mepenzolate bromide, oxyphencyclimine HCl and tropicamide;

anti-neoplastic agents and immunosuppressants, such as aminoglutethimide,

amsacrine, azathioprine, bicalutamide, bisantrene, busulfan, camptothecin, capecitabine, chlorambucil, cyclosporin, dacarbazine, ellipticine, estramustine, etoposide, irinotecan, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, mofetil mycophenolate, nilutamide, paclitaxel, procarbazine HCl, sirolimus, tacrolimus, tamoxifen citrate, teniposide, testolactone, topotecan HCl, and toremifene citrate;

anti-protozoal agents, such as atovaquone, benznidazole, clioquinol, decoquinate, diiodohydroxyquinoline, diloxanide furoate, dinitolmide, furazolidone, metronidazole, nimorazole, nitrofurazone, ornidazole and tinidazole;

anti-thyroid agents, such as carbimazole, paracalcitol, and propylthiouracil;

anti-tussives, such as benzonatate;

anxiolylics, sedatives, hypnotics and neuroleptics, such as alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, chlorprothixene, clonazepam, clobazam, clotiazepam, clozapine, diazepam, droperidol, ethinamate, flunanisone, flunitrazepam, triflupromazine, fluphenthixol decanoate, fluphenazine decanoate, flurazepam, gabapentin, haloperidol, lorazepam, lormetazeparn, medazepam, meprobamate, mesoridazine, methaqualone, methylphenidate, midazolam, molindone, nitrazepam, olanzapine, oxazepam, pentobarbitone, perphenazine pimozide, prochlorperazine, pseudoephedrine, quetiapine, risperidone, sertindole, sulpiride, temazepam, thioridazine, triazolam, zolpidem, and zopiclone;

ß-Blockers, such as acebutolol, alprenolol, atenolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol and propranolol;

cardiac inotropic agents, such as amrinone, digitoxin, digoxin, enoximone, lanatoside C and medigoxin;

corticosteroids, such as beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, fluocortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone;

diuretics, such as acetazolamide, amiloride, bendroflumethiazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, frusemide, metolazone, spironolactone

and triamterene.

anti-parkinsonian agents, such as bromocriptine mesylate, lysuride maleate, pramipexole, ropinirole HCl, and tolcapone,

gastro-intestinal agents, such as bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, lansoprazole, loperamide, mesalazine, nizatidine, omeprazole, ondansetron HCl, rabeprazole sodium, ranitidine HCl and sulphasalazine;

histamine H_1- and H_2-receptor antagonists, such as acrivastine. astemizole, chlopheniramine, cinnarrizine, cetrizine, clemastine fumarate, cyclizine, cyproheptadine HCl, dexchlorpheniramine, dimenhydrinate, fexofenadine, flunarizine HCl, loratadine, meclizine HCI, oxatomide, and terfenadine;

keratolytics, such as acetretin, calciprotriene, calcifediol, calcitriol, cholecalciferol, ergocalciferol, etretinate, retinoids, targretin, and tazarotene;

lipid regulating agents, such as atorvastatin, bezafibrate, cerivastatin, ciprofibrate, clofibrate, fenofibrate, fluvastatin, gemfibrozil, pravastatin, probucol, and sirnvastatin;

muscle relaxants, such as dantrolene sodium and tizanidine HCl;

nitrates and other anti-anginal agents, such as amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate and pentaerythritol tetranitrate;

nutritional agents, such as calcitriol, carotenes, dihydrotachysterol, essential fatty acids, non-essential fatty acids, phytonadiol, vitamin A, vitamin B_2, vitamin D, vitamin E and vitamin K;

opioid analgesics, such as codeine, dextropropoxyphene, diamorphine, dihydrocodeine, fentanyl, meptazinol, methadone, morphine, nalbuphine and pentazocine;

sex hormones, such as clomiphene citrate, cortisone acetate, danazol, dehydroepiandrosterone, ethynyl estradiol, finasteride, fludrocortisone, fluoxymesterone, medroxyprogesterone acetate, megestrol acetate, mestranol, methyltestosterone, norethisterone, norgestrel, oestradiol, conjugated estrogens, progesterone, rimexolone, stanozolol, stilbestrol, testosterone and fibolone;

stimulants, such as amphetamine, dexamphetamine, dexfenfluramine, fenfluramine and mazindol;

and others, such as becaplermin, donepezil HCI, L-thryroxine, methoxsalen,

verteporfin, physostigmine, pyridostigmine, raloxifene HCl, sibutramine HCl, sildenafil citrate, tacrine, tamsulosin HCl, and tolterodine.

Preferred hydrophobic therapeutic agents include sildenafil citrate, amlodipine, tramadol, celecoxib, rofecoxib, oxaprozin, nabumetone, ibuprofen, terbenafine, itraconazole, zileuton, zafirlukast, cisapride, fenofibrate, tizanidine, nizatidine, fexofenadine, loratadine, famotidine, paricalcitol, atovaquone, nabumetone, tetrahydrocannabinol, megestrol acetate, repaglinide, progesterone, rimexolone, cyclosporin, tacrolimus, sirolimus, teniposide, paclitaxel, pseudoephedrine, troglitazone, rosiglitazone, finasteride, vitamin A, vitamin D, vitamin E, and pharmaceutically acceptable salts, isomers and derivatives thereof. Particularly preferred hydrophobic therapeutic agents are progesterone and cyclosporin.

It should be appreciated that this listing of hydrophobic therapeutic agents and their therapeutic classes is merely illustrative. Indeed, a particular feature, and surprising

advantage, of the compositions of the present invention is the ability of the present compositions to solubilize and deliver a broad range of hydrophobic therapeutic agents, regardless of functional class. Of course, mixtures of hydrophobic therapeutic agents may also be used where desired.

3. Solubilizers

If desired, the pharmaceutical compositions of the present invention can optionally include additional compounds to enhance the solubility of the hydrophobic therapeutic agent in the carrier system. Examples of such compounds, referred to as "solubilizers", include:

alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives;

ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol, available commercially from BASF under the trade name Tetraglycol) or methoxy PEG (Union Carbide);

amides, such as 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, and polyvinylpyrrolidone;

esters, such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof;

and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide (Arlasolve DMI (ICI)), N-methyl pyrrolidones (Pharmasolve (ISP)), monooctanoin, diethylene glycol monoethyl ether (available from Gattefosse under the trade name Transcutol), and water.

Mixtures of solubilizers are also within the scope of the invention. Except as indicated, these compounds are readily available from standard commercial sources.

Preferred solubilizers include triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol

200-600, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

The amount of solubilizer that can be included in compositions of the present invention is not particularly limited. Of course, when such compositions are ultimately administered to a patient, the amount of a given solubilizer is limited to a bioacceptable amount, which is readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in access of bioacceptable amounts in order to maximize the concentration of hydrophobic therapeutic agent, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a concentration of 50%, 100%, 200%, or up to about 400% by weight, based on the amount of surfactant. If desired, very small amounts of solubilizers may also be used, such as 25%, 10%, 5%, 1% or even less. Typically, the solubilizer will be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

4. Other Additives

Other additives conventionally used in pharmaceutical compositions can be included, and these additives are well known in the art. Such additives include antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants odorants, opacifiers, suspending agents, binders, and mixtures thereof. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

5. Dosage Forms

The pharmaceutical compositions of the present invention can be provided in the form of a solution preconcentrate; *i.e.*, a composition as described above, and intended to be dispersed with water, either prior to administration, in the form of a drink, or dispersed *in vivo*. Alternatively, the compositions can be provided in the form of a diluted preconcentrate (*i.e.*, an aqueous dispersion), a semi-solid dispersion or a solid dispersion. If desired, the compositions may be encapsulated in a hard or soft gelatin capsule, a starch capsule or an enteric coated capsule. The term "enteric coated capsule" as used herein means a capsule coated with a coating resistant to acid; *i.e.*, an acid resistant enteric coating. Although solubilizers are typically used to enhance the solubility of a hydrophobic therapeutic agent, they may also render the compositions more suitable for encapsulation in hard or soft gelatin

capsules. Thus, the use of a solubilizer such as those described above is particularly preferred in capsule dosage forms of the pharmaceutical compositions. If present, these solubilizers should be added in amounts sufficient to impart to the compositions the desired solubility enhancement or encapsulation properties.

Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration, in the form of a triglyceride-free cream, lotion, ointment, suppository, gel or the like. If such a formulation is desired, other additives may be included, such as are well-known in the art, to impart the desired consistency and other properties to the formulation. The compositions of the present invention can also be formulated as a spray or an aerosol. In particular, the compositions may be formulated as a sprayable solution, and such formulation is particularly useful for spraying to coat a multiparticulate carrier, such as a bead. Such multiparticulate carriers are well known in the art.

6. Preparation of Pharmaceutical Compositions

The pharmaceutical compositions of the present invention can be prepared by conventional methods well known to those skilled in the art. Of course, the specific method of preparation will depend upon the ultimate dosage form. For dosage forms substantially free of water, *i.e.*, when the composition is provided in a pre-concentrated form for later dispersion in an aqueous system, the composition is prepared by simple mixing of the components to form a pre-concentrate. The mixing process can be aided by gentle heating, if desired. For compositions in the form of an aqueous dispersion, the pre-concentrate form is prepared, then the appropriate amount of purified water is added. Upon gentle mixing, a clear aqueous dispersion is formed. If any water-soluble additives are included, these may be added first as part of the pre-concentrate, or added later to the clear aqueous dispersion, as desired.

In another embodiment, the present invention includes a multi-phase dispersion. In this embodiment, a pharmaceutical composition includes a carrier which forms a clear aqueous dispersion upon mixing with an aqueous solution, and an additional amount of non-solubilized hydrophobic therapeutic agent. Thus, the term "multi-phase" as used herein to describe these compositions of the present invention means a composition which when mixed with an aqueous solution forms a clear aqueous phase and a particulate dispersion phase. The carrier is as described above, and can include any of the surfactants, hydrophobic therapeutic

agents, solubilizers and additives previously described. An additional amount of hydrophobic therapeutic agent is included in the composition. This additional amount is not solubilized by the carrier, and upon mixing with an aqueous system is present as a separate dispersion phase. The additional amount is optionally a milled, micronized, or precipitated form. Thus, upon dilution, the composition contains two phases: a clear aqueous dispersion of the hydrophilic and hydrophobic surfactants containing a first, solubilized amount of the hydrophobic therapeutic agent, and a second, non-solubilized amount of the hydrophobic therapeutic agent dispersed therein. It should be emphasized that the resultant multi-phase dispersion will not have the optical clarity of a dispersion in which the hydrophobic therapeutic agent is fully solubilized, but will appear to be cloudy, due to the presence of the non-solubilized phase. Such a formulation may be useful, for example, when the desired dosage of a hydrophobic therapeutic agent exceeds that which can be solubilized in the carrier of the present invention. The formulation may also contain additives, as described above.

One skilled in the art will appreciate that a hydrophobic therapeutic agent may have a greater solubility in the pre-concentrate carrier than in the aqueous dispersion, so that meta-stable, supersaturated solutions having apparent optical clarity but containing a hydrophobic therapeutic agent in an amount in excess of its solubility in the aqueous dispersion can be formed. Such super-saturated solutions, whether characterized as clear aqueous dispersions (as initially formed) or as multi-phase solutions (as would be expected if the meta-stable state breaks down), are also within the scope of the present invention.

The multi-phase formulation can be prepared by the methods described above. A pre-concentrate is prepared by simple mixing of the components, with the aid of gentle heating, if desired. It is convenient to consider the hydrophobic therapeutic agent as divided into two portions, a first solubilizable portion which will be solubilized by the carrier and contained within the clear aqueous dispersion upon dilution, and a second non-solubilizable portion which will remain non-solubilized. When the ultimate dosage form is non-aqueous, the first and second portions of the hydrophobic therapeutic agent are both included in the pre-concentrate mixture. When the ultimate dosage form is aqueous, the composition can be prepared in the same manner, and upon dilution in an aqueous system, the composition will form the two phases as described above, with the second non-solubilizable portion of the hydrophobic therapeutic agent dispersed or suspended in the aqueous system, and the first solubilizable portion of the hydrophobic therapeutic agent solubilized in the mixed surfactant

carrier. Alternatively, when the ultimate dosage form is aqueous, the pre-concentrate can be prepared including only the first, solubilizable portion of the hydrophobic therapeutic agent. This pre-concentrate can then be diluted in an aqueous system to form a clear aqueous dispersion, to which is then added the second, non-solubilizable portion of the hydrophobic therapeutic agent to form a multi-phase aqueous composition.

The amount of hydrophobic therapeutic agent included in the pharmaceutical compositions of the present invention can be any amount desired by the formulator, up to the maximum amount that can be solubilized or suspended in a given carrier system. In general, the amount of hydrophobic therapeutic agent will be about 0.1% to about 60% by weight, based on the total weight of the pharmaceutical composition. In another aspect of the invention, described below, excess hydrophobic therapeutic agent can also be added, in a multi-phase dispersion.

B. Methods of Improved Delivery

In another aspect, the present invention relates to methods of improving delivery of hydrophobic therapeutic agents in an animal by administering to the animal a dosage form of the pharmaceutical compositions described herein. Preferably the animal is a mammal, and more preferably, a human. It has been found that the pharmaceutical compositions of the present invention when administered to an animal enable the hydrophobic therapeutic agent contained therein to be absorbed more rapidly than in conventional pharmaceutical compositions. Thus, in this aspect the invention relates to a method of increasing the rate of and/or extent of bioabsorption of a hydrophobic therapeutic agent by administering the hydrophobic therapeutic agent to an animal in the pharmaceutical compositions described herein.

C. Characteristics of the Pharmaceutical Compositions

The dispersions formed upon dilution of the pharmaceutical compositions of the present invention have the following characteristics:

Rapid formation: upon dilution with an aqueous solution, the carrier forms a clear dispersion very rapidly; *i.e.*, the clear dispersion appears to form instantaneously.

Optical clarity: the dispersions are essentially optically clear to the naked eye, and show no readily observable signs of heterogeneity, such as turbidity or cloudiness. More quantitatively, dispersions of the pharmaceutical compositions of the present invention show a mono-modal distribution of very small particles sizes, typically 20 nm or less in average diameter; absorbances of less than about 0.3, typically less than about 0.1, at 10X dilution;

and absorbances of less than about 0.1, typically less than about 0.01, at 100X dilution, as described more fully in the Examples herein. In the multi-phase embodiment of the compositions described herein, it should be appreciated that the optical clarity of the aqueous carrier dispersion phase will be obscured by the dispersed particulate non-solubilized hydrophobic therapeutic agent.

Robustness to dilution: the dispersions are surprisingly stable to dilution in aqueous solution, including aqueous solutions simulating physiological fluids such as enzyme-free simulated gastric fluid (SGF) and enzyme-free simulated intestinal fluid (SIF). The hydrophobic therapeutic agent remains solubilized for at least the period of time relevant for absorption.

Triglyceride-free: It is a particular feature of the present invention that the pharmaceutical compositions are substantially triglyceride-free. The term "triglyceride" as used herein means glycerol triesters of C_6 to about C_{25} fatty acids. Unlike conventional compositions such as oil-based solutions, emulsions, and microemulsions, which rely on the solubilizing power of triglycerides, the present compositions surprisingly solubilize hydrophobic therapeutic agents using combinations of substantially triglyceride-free surfactants.

As used herein, the term "substantially triglyceride-free" means compositions which contain triglycerides, if at all, only as minor components or impurities in surfactant mixtures. It is well known in the art that commercially available surfactants often are complex mixtures of compounds. For example, one preferred surfactant is Capmul® GMO-K, a widely-used blend of glyceryl mono- and dioleates. Due to difficulties in separating complex product mixtures, however, a typical lot of Capmul® GMO-K, as reported by the manufacturer's certificate of analysis, contains the following distribution of glyceryl esters, in percent by weight based on the total weight of glyceryl esters:

Palmitic acid	3.3%
Stearic acid	4.0%
Oleic acid	81.0%
Linoleic acid	9.7%
Linolenic acid	0.3%

In addition, the surfactant mixture in the particular lot reported contains 0.10% water and 0.95% free, unesterified glycerol. These specific percentages are expected to vary, lot-by-lot, as well, and it is expected that commercial surfactant products will generally possess similar

variability, regardless of the specific major component and the specific manufacturer. Thus, the present invention does not include surfactants which contain triglycerides as an intended component. Indeed, such surfactants are not common, since triglycerides themselves have no surfactant properties. However, it should be appreciated that the present invention does not exclude the use of surfactant products which contain small amounts of triglycerides as impurities or as unreacted starting material. It is expected that commercial mixtures suitable for use in the present invention may contain as much as 5% triglycerides by weight as unintended components. Thus, "substantially triglyceride-free" should be understood as meaning free of added triglycerides, and containing less than 5%, preferably essentially 0%, triglyceride impurities.

Without wishing to be bound by theory, it is believed that the observed properties of the clear, aqueous dispersions formed by the compositions of the present invention are consistent with, and best explained by, the formation of mixed micelles of the hydrophobic and hydrophilic surfactants, with the hydrophobic therapeutic agent solubilized by the micelles. It should be emphasized that these dispersions are characterized by the properties described herein, regardless of the precise microscopic physical form of the dispersed particles. Nevertheless, in order to more fully explain the invention, and to illustrate its unexpected and important advantages, the following discussion is offered in terms consistent with the theoretical principles believed to be correct.

It is believed that the hydrophobic and hydrophilic surfactants form mixed micelles in aqueous solution. In this model, each micelle is composed of molecules (or ions) of both the hydrophilic and hydrophobic surfactants. Depending upon the detailed three-dimensional structure of the hydrophobic therapeutic agent, its distribution of polar moieties, if any, its polarizability in local regions, and other molecule-specific and complex factors, the hydrophobic therapeutic agent may be distributed in any part of the micelle, such as near the outer, more hydrophilic region, near the inner, more hydrophobic region, or at various points in between. Further, it is known that micelles exist in dynamic equilibrium with their component molecules, and it is expected that this equilibrium will include dynamic redistribution of the hydrophobic therapeutic agent.

As discussed above, triglyceride-containing formulations suffer the disadvantage that bioabsorption of the hydrophobic therapeutic agents contained therein is dependent upon enzymatic degradation (lipolysis) of the triglyceride components. The pharmaceutical compositions of the present invention, however, are substantially free of triglycerides, and

thus do not depend upon lipolysis to enable release of the hydrophobic therapeutic agent for bioabsorption. The hydrophobic therapeutic agent is in a dynamic equilibrium between the free compound in solution and the solubilized compound, thus promoting rapid release.

The unique pharmaceutical compositions of the present invention present a number of significant and unexpected advantages, including:

Efficient transport: The particle sizes in the aqueous dispersions of the present invention are much smaller, typically less than 20 nm, than the larger particles characteristic of vesicular, emulsion or microemulsion phases, and the particle size distribution is mono-modal and narrow. This reduced and more uniform size enables more efficient drug transport through the intestinal aqueous boundary layer, and through the absorptive brush border membrane. More efficient transport to absorptive sites leads to improved and more consistent absorption of hydrophobic therapeutic agents.

Non-dependence on lipolysis: The lack of triglyceride components provides pharmaceutical compositions not dependent upon lipolysis, and upon the many poorly characterized factors which affect the rate and extent of lipolysis, for effective presentation of a hydrophobic therapeutic agent to an absorptive site. Such factors include the presence of composition components which may inhibit lipolysis; patient conditions which limit production of lipase, such as pancreatic lipase secretory diseases; and dependence of lipolysis on stomach pH, endogenous calcium concentration, and presence of co-lipase or other digestion enzymes. The lack of lipolysis dependence further provides transport which does not suffer from any lag time between administration and absorption caused by the lipolysis process, enabling a more rapid onset of therapeutic action and better bioperformance characteristics. In addition, pharmaceutical compositions of the present invention can make use of hydrophilic surfactants which might otherwise be avoided or limited due to their potential lipolysis inhibiting effects.

Non-dependence on bile and meal fat contents: Due to the higher solubilization potential over bile salt micelles, the present compositions are less dependent on endogenous bile and bile related patient disease states, and meal fat contents. These advantages overcome meal-dependent absorption problems caused by poor patient compliance with meal-dosage restrictions.

Superior solubilization: The surfactant combinations used in compositions of the present invention enable superior loading capacity over conventional micelle formulations. In addition, the particular combination of surfactants used can be optimized for a specific

hydrophobic therapeutic agent to more closely match the polarity distribution of the therapeutic agent, resulting in still further enhanced solubilization.

Faster dissolution and release: Due to the robustness of compositions of the present invention to dilution, the hydrophobic therapeutic agents remain solubilized and thus do not suffer problems of precipitation of the therapeutic agent in the time frame relevant for absorption. In addition, the therapeutic agent is presented in small particle carriers, and is not limited in dilution rate by entrapment in emulsion carriers. These factors avoid liabilities associated with the poor partitioning of lipid solubilized drug in to the aqueous phase, such as large emulsion droplet surface area, and high interfacial transfer resistance, and enable rapid completion of the critical partitioning step.

Consistent performance: Aqueous dispersions of the present invention are thermodynamically stable for the time period relevant for absorption, and can be more predictably reproduced, thereby limiting variability in bioavailability-- a particularly important advantage for therapeutic agents with a narrow therapeutic index.

Efficient release: The compositions of the present invention are designed with components that help to keep the hydrophobic therapeutic agent solubilized for transport to the absorption site, but readily available for absorption, thus providing a more efficient transport and release.

Less prone to gastric emptying delays: Unlike triglyceride-containing formulations, the present compositions are less prone to gastric emptying delays, resulting in faster absorption. Further, the particles in dispersions of the present invention are less prone to unwanted retention in the gastro-intestinal tract.

Small size: Because of the small particle size in aqueous dispersion, the pharmaceutical compositions of the present invention allow for faster transport of the hydrophobic therapeutic agent through the aqueous boundary layer.

These and other advantages of the present invention, as well as aspects of preferred embodiments, are illustrated more fully in the Examples which follow.

EXAMPLES

Example 1: Preparation of Compositions

A simple pre-concentrate of a hydrophobic surfactant and a hydrophilic surfactant is prepared as follows. Predetermined weighed amounts of hydrophilic and hydrophobic surfactants are stirred together to form a homogeneous mixture. For surfactant combinations that are poorly miscible, the mixture can be gently heated to aid in formation of the homogeneous mixture. A chosen hydrophobic therapeutic agent in a predetermined amount is added and stirred until solubilized. Optionally, solubilizers or additives are included by simple mixing.

To form an aqueous dispersion of the pre-concentrate, a predetermined amount of purified water, buffer solution, or aqueous simulated physiological solution, is added to the pre-concentrate, and the resultant mixture is stirred to form a clear, aqueous dispersion.

Example 2: Surfactant Combinations Giving Clear Aqueous Dispersions

Surfactant mixtures giving clear, aqueous dispersions were prepared according to the method of Example 1. Seven hydrophilic surfactants and sixteen hydrophobic surfactants were used to produce approximately one hundred clear aqueous dispersions suitable for use in the present invention. For simplicity, no hydrophobic therapeutic agent was included in these compositions, since it is believed that the presence of the hydrophobic therapeutic agent does not substantially affect the clear, aqueous nature of composition. For the same reason, these compositions were free of additional solubilizers and other additives.

Multiple solutions were prepared for each surfactant combination, to determine the approximate maximum amount of hydrophobic therapeutic agent giving a clear aqueous dispersion with a given amount of hydrophilic therapeutic agent. Thus, for each gram of the hydrophilic surfactant, a predetermined amount of hydrophobic agent was used to prepare a 10X aqueous dispersion. If the dispersion appeared to be optically clear, a new dispersion was prepared according to Example 1, using a larger amount of hydrophobic surfactant. Similarly, if the dispersion appeared to be cloudy, a new dispersion was prepared using a smaller amount of hydrophobic surfactant. The results are shown in Table 19.

TABLE 19: Surfactant Combinations Giving Clear Dispersions

Hydrophilic Surfactant / Hydrophobic Surfactant	PEG-35 Castor Oil (Incroc as 35)	PEG-40H Castor Oil (Cremophor RH-40)	Polysorbate-20 (Tween 20)	Polysorbate 80 (Tween 80)	PEG-60 Corn Oil (Crovol M-70)	PEG-8 Capric /Caprylic (Labrasol)	PEG-25 Glyceryl trioleate (TagatTO)
Glyceryl/ Propylene Glycol Oleate (Arlacel 186)	20	20	20	8	15	25	10
Glyceryl Oleate (Peceol)	15	40	10	12	10	35	10
Acetylated Monoglycerides (Myvacet 9-45)	80	80	20	15	10	10	10
PEG-6 Corn Oil (Labrafil M2125CS)	50	95	10	10	20	10	10
Sorbitan Monooleate (Span 80)	25	65	5	5	20	15	10
Sorbitan Monolaurate (Arlacel 20)	30	20	20	10	15	30	10
Polyglyceryl oleate (Plurol Oleique CC497)	10	5	35	10	10	35	10
Propylene Glycol Laurate (Lauroglycol FCC)	10	55	35	20	15	35	10
Glyceryl Caprylate / Caprate (Capmul MCM)	10	50	20	25	25	20	10

PEG-20 Corn Oil (Crovol M-40)	35	40	40	25	30	90	10
PEG-20 Almond Oil (Crovol A-40)	30	35	40	25	30	90	10
Mono/diglycerides of Caprylic Acid (Imwitor 988)	50	50	60	25	25	30	10
PEG-4-lauryl ether (Brij 30)	40	45	95	70	*	90	10
PEG-3-oleyl ether (Volpo 3)	20	30	25	20	20	25	10
Glyceryl mono/dioleate (Capmul GMO-K)	*	10	*	*	10	25	10
Ethyl Oleate (Crodamol EO)	40	60	10	10	60	10	10

* This combination was not tested.

Each entry in the Table represents the approximate maximum number of grams of hydrophobic surfactant per 100 g of hydrophilic surfactant giving acceptable optical clarity. The numbers in the Table are illustrative only, and it is expected that further optimization of the surfactant systems with solubilizers, co-surfactants, and other additives will give still higher numbers.

Example 3: Compositions Containing Solubilizers

The procedure of Example 2 was repeated for compositions containing PEG-40 hydrogenated castor oil (Cremophor RH 40) as the hydrophilic surfactant, with eight different hydrophobic surfactants, and four different solubilizers, to study the effect of solubilizer on the relative amounts of hydrophobic and hydrophilic surfactants giving clear aqueous dispersions. In each case, the amount of solubilizer was held constant at 20% by weight, based on the total weight of the two surfactants. The results are shown in Table 20. As in Example 2, the numbers in the Table represent the approximate maximum number of grams

of hydrophobic surfactant per 100 g of hydrophilic surfactant giving a clear aqueous dispersion. For convenience, the corresponding entries from Table 19 (with no solubilizer present) are reproduced in Table 20 in the column labeled "none."

Table 20: Effect of Solubilizer on Hydrophobic Surfactant Amounts

Hydrophobic Surfactant	Hydrophilic Surfactant (Cremophor RH40) + 20% Solubilizer				
	(None)	Triacetin	Ethanol	PEG-400	Glycofurol
Glyceryl/ Propylene Glycol Oleate (Arlacel 186)	20	28	25	25	25
Glyceryl Oleate (Peceol)	40	40	42	40	44
Sorbitan Monooleate (Span 80)	65	40	40	25	30
Sorbitan Monolaurate (Span 20)	20	65	*	*	65
PEG-6 Corn Oil (Labrafil M2125CS)	95	95	*	95	*
Acetylated Monoglyceride (Myvacet 9-45)	80	80	80	80	80
Ethyl Oleate (Crodamol EO)	60	60	60	*	60
Mono/diglycerides of Caprylic Acid (Imwitor 988)	50	80	*	*	75

* This combination was not tested.

As is clear from the data in the Table, the effect of added solubilizer on the relative amount of hydrophobic surfactant that can be used varies considerably. For some surfactant combinations, the added solubilizer has a dramatic effect on the amount of hydrophobic surfactant (*e.g.*, Span 20, Imwitor 988). In other systems, the effect is moderate (Arlacel 186, Peceol) or negligible (Crodamol EO, Myvacet 9-45). In the one case of Span 80, the presence of the solubilizer actually decreases the amount of hydrophobic surfactant that can be used.

Example 4: Compositions Containing Solubilizers

Example 3 was repeated, this time choosing a single hydrophobic surfactant (Arlacel 186) and three different hydrophilic surfactants, with addition of either ethanol or triacetin (20% by weight, based on the total weight of the two surfactants). The results are shown in Table 21. The corresponding entry from Table 19 (with no solubilizer present) is included in Table 21 for reference.

Table 21: Effect of Solubilizer on Hydrophobic Surfactant Amounts

Hydrophilic Surfactant	Hydrophobic Surfactant (Arlacel 186) + 20% Solubilizer		
	(None)	Ethanol	Triacetin
PEG-60 Corn Oil (Crovol M-70)	15	20	20
PEG-35 Castor Oil (Incrocas 35)	20	25	25
Polysorbate 20 (Tween 20)	20	25	25

In each case, a moderate increase (20%) in the relative amount of hydrophobic surfactant was observed.

Example 5: Effect of Solubilizer Concentration

The procedure of Example 3 was repeated, with the following differences. A single hydrophilic surfactant (Cremophor RH-40) and hydrophobic surfactant (Arlacel 186) were chosen, to examine the effect of increased solubilizer concentration. For each of the four solubilizers tested at 20% concentrations in Example 3 (Table 20) plus an additional solubilizer (propylene glycol), compositions were tested at a solubilizer concentration of 50% by weight, based on the total weight of the surfactant pair. As in each of the previous examples, the numbers in Table 22 represent the maximum hydrophobic surfactant concentration giving a clear aqueous dispersion. Note that the "0" column in Table 22 reproduces the numbers shown in Table 19 (no solubilizer), and the "20%" column reproduces the numbers in Table 20, with the value for propylene glycol also supplied.

Table 22: Effect of Solubilizer Concentration on Hydrophobic Surfactant Amounts*

Solubilizer	Weight Percent of Solubilizer		
	0	20	50
PEG-400	20	25	25
Propylene Glycol	20	28	30
Triacetin	20	28	25
Ethanol	20	25	30
Glycofurol	20	25	30

* for an Arlacel 186 (hydrophobic) - Cremophor RH-40 (hydrophilic) surfactant pair

As the Table shows, increasing the amount of solubilizer has a small to moderate effect on the amount of hydrophobic surfactant that can be present in a clear aqueous dispersion. It should be appreciated that the data equivalently show that very large amounts of solubilizer can be used, without detrimental effect on the ability of the surfactant system to form a clear, aqueous dispersion.

Example 6: Effect of High Solubilizer Concentration and Solubilizer Mixtures

Example 5 was repeated, using the same surfactant pair, but with an 80% concentration of solubilizer, based on the total weight of the surfactants. The 80% solubilizer was either PEG-400, or a mixture of PEG-400 and one of three alcohols or polyols. The results are shown in Table 23, with the numbers in the Table having the same meaning as in the previous Examples.

Table 23: Large Solubilizer Concentrations and Solubilizer Mixtures*

(no solubilizer)	80% PEG-400	60% PEG-400 + 20% Glycerol	60% PEG-400 + 20% Propylene Glycol	60% PEG-400 + 20% Isopropanol
20	25	25	25	25

* for an Arlacel 186 (hydrophobic) - Cremophor RH-40 (hydrophilic) surfactant pair

It is clear from the data in the Table that very high concentrations of solubilizers, as well as mixtures of solubilizers, can be used effectively in the clear aqueous dispersions of the present invention.

Examples 7-12: Average Particle Size

In order to more quantitatively characterize the clear aqueous dispersions of the present invention, particle sizes were measured for several compositions of the present invention. For simplicity, the measurement were made for the dispersed carrier, in the absence of a hydrophobic therapeutic agent. In this Example, formulations were prepared as in Example 1, and diluted to form 10X or 100X aqueous dispersions. Each of the resulting dispersions was observed to be optically clear to the naked eye. Average particle sizes were measured with a Nicomp Particle Size Analyzer (Particle Size Systems, Inc., Santa Barbara, CA). The results of these measurements are shown in Table 24.

Table 24: Average Particle Size

Example No.	Formula		Surfactant Ratio*	Dilution	Observation	Particle Size (nm) ± S.D.**
7	Tween 80 Lauroglycol FCC	520 mg 50 mg	9.6	100X	very clear solution	6.5 ± 1.1
8	Tween 80 Capmul MCM	500 mg 73 mg	15	10X	very clear solution	8.1 ± 1.6
9	Cremophor RH-40 Peceol	530 mg 150 mg	28	100X	clear solution	12.4 ± 3.0
10	Cremophor RH-40 Plurol Oleique CC497	500 mg 10 mg	2.0	100X	clear solution	14.7 ± 3.0
11	Cremophor RH-40 Lauroglycol FCC	550 mg 200 mg	36	100X	clear solution	14.3 ± 2.5
12	Cremophor RH-40 Capmul MCM	500 mg 200 mg	40	100X	clear solution	12.6 ± 2.9

* grams of hydrophobic surfactant per 100 g of hydrophilic surfactant

** standard deviation

As the data show, the compositions of the present invention produce clear, aqueous dispersions, with no visible cloudiness. The particle size distribution shows very small

particles, with average diameters of from about 6 to about 15 nm. The distribution is mono-modal, with a standard deviation of approximately 20%, indicating a highly uniform distribution of very small particles. This particle size distribution is consistent with a solution of particles of micellar structure, although the invention is not limited by any particular theoretical framework.

Comparative Examples C1-C5: Optical Clarity and Particle Sizes of Compositions Not Forming Clear Aqueous Dispersions

For comparison to the clear aqueous dispersions of the present invention, several compositions were prepared having hydrophobic surfactant concentrations higher than those suitable for forming clear aqueous dispersions. These compositions were prepared by weighing the components and mixing well, with gentle warming. The compositions were then diluted 10X to form dispersions, and these dispersions were subjected to the particle size measurements as described in Example 7. The results are shown in Table 25. For direct comparison with the compositions of the present invention, Examples 7, 9, 10, 11 and 12 are shown next to the corresponding comparative compositions.

Table 25: Optical Clarity and Particle Size

Example No.	Surfactants	Surfactant Ratio*	Observation	Particle Size (nm)**	
				Mean 1	Mean 2
C1	Tween 80 Lauroglycol FCC	67	milky solution	26.6	209
7	Tween 80 Lauroglycol FCC	9.6	very clear solution	6.5	---
C2	Cremophor RH-40 Peceol	67	milky solution	25	116
9	Cremophor RH-40 Peceol	28	clear solution	8.1	---
C3	Cremophor RH-40 Plurol Oleique CC497	67	milky solution	16.5	102
10	Cremophor RH-40 Plurol Oleique CC497	2.0	clear solution	12.4	---

C4	Cremophor RH-40 Lauroglycol FCC	69	hazy solution	17.1	45.3
11	Cremophor RH-40 Lauroglycol FCC	36	clear solution	14.3	
C5	Cremophor RH-40 Capmul MCM	67	milky solution	11.6	176
12	Cremophor RH-40 Capmul MCM	40	clear solution	12.6	---

* grams of hydrophobic surfactant per 100 g of hydrophilic surfactant

** two means are reported for bimodal distributions

In addition to the compositions shown in the Table, compositions containing Tween 80 and Plurol Oleique CC497, Tween 80 and Peceol, and Tween 80 and Capmul MCM were prepared at a surfactant ratio of 67 g hydrophobic surfactant per 100 g hydrophilic surfactant. Particle sizes were not measured for these compositions, but each was observed to form a milky or hazy aqueous dispersion.

As the data show, compositions having excessive amounts of hydrophobic surfactant form milky or hazy solutions, whereas those of the present invention form clear solutions. In addition, the particle size distributions of the milky solutions are bimodal, in contrast to the mono-modal solutions of the corresponding clear solutions. These bimodal particle size distributions show a first mode having a small mean particle size of about 12 to about 27 nm, and a second mode having particle sizes of up to more than 200 nm. Thus, compositions having excessive hydrophobic surfactant are heterogeneous (multi-phasic), non-clear dispersions, having a complex bimodal distribution of particles of two distinct size ranges. In contrast, compositions of the present invention are homogeneous (single phase), clear dispersion, having a mono-modal distribution of very small particle sizes.

Examples 13-42: Spectroscopic Characterization of Optical Clarity

The optical clarity of aqueous dispersions of the present invention was measured spectroscopically. Compositions were prepared according to Example 1, and diluted to 10X and 100X solutions. The specific compositions measured also include a solubilizer, to further illustrate preferred aspects of the invention. In addition, several of the compositions illustrate compositions according to the present invention wherein either the hydrophilic surfactant

(Examples 20 and 27) or the hydrophobic surfactant (Examples 41 and 42) itself is a mixture of surfactants.

The absorbance of each solution was measured at 400.2 nm, using a purified water standard, and the results are shown in Table 26.

Table 26: Spectroscopic Characterization of Optical Clarity

Example No.	Formulation		Absorbance (400.2 nm)	
			10X	100X
13	Cremophor RH-40 Myvacet 9-45 Ethyl Alcohol	430 mg 310 mg 210 mg	0.407	0.099
14	Cremophor RH-40 Peceol Ethyl Alcohol	610 mg 160 mg 200 mg	0.299	0.055
15	Cremophor RH-40 Span 80 Triacetin	540 mg 260 mg 220 mg	0.655	0.076
16	Incrocas 35 Myvacet 9-45 Ethyl Alcohol	470 mg 250 mg 220 mg	0.158	0.038
17	Incrocas 35 Imwitor 988 Triacetin	510 mg 220 mg 200 mg	0.064	0.009
18	Tween 20 Lauroglycol FCC Glycofurol	570 mg 140 mg 220 mg	0.031	0.003
19	Crovol M70 Crovol M40 Ethyl Alcohol	610 mg 120 mg 200 mg	0.049	0.006
20	Cremophor RH-40 Labrasol Capmul GMO-K Triacetin	250 mg 250 mg 110 mg 100 mg	0.028	0.008
21	Cremophor RH-40 Lauroglycol FCC Ethyl Alcohol	220 mg 200 mg 75 mg	0.114	0.018

22	Tween 80 Capmul MCM Ethyl Alcohol	170 mg 30 mg 38 mg	0.050	0.008
23	Cremophor RH-40 Capmul MCM Ethyl Alcohol	550 mg 80 mg 53 mg	0.029	0.006
24	Cremophor RH-40 Peceol Ethyl Alcohol	230 mg 70 mg 54 mg	0.187	0.020
25	Cremophor RH-40 Plurol Oleique CC497 Ethyl Alcohol	500 mg 10 mg 11 mg	0.028	0.005
26	Tween 80 Lauroglycol FCC Ethyl Alcohol	180 mg 20 mg 37 mg	0.036	0.003
27	Tween 80 Labrasol Arlacel 186 Ethyl Alcohol	420 mg 330 mg 54 mg 140 mg	0.036	0.009
28	Tagat O2 PGMG-03 Ethyl Alcohol	500 mg 50 mg 100 mg	0.077	0.005
29	Incrocas 35 Gelucire 44/14 Triacetin	250 mg 150 mg 94 mg	0.053	0.005
30	Cremophor RH-40 Labrafil Ethyl Alcohol	270 mg 170 mg 100 mg	0.232	0.047
31	Crovol M-70 Labrafil Triacetin	380 mg 50 mg 100 mg	0.064	0.011
32	Cremophor RH-40 Peceol Triacetin	300 mg 110 mg 110 mg	0.163	0.034
33	Tween 20 Lauroglycol FCC	340 mg 110 mg	0.038	0.005

	Glycofurol	100 mg		
34	Incrocas-35 Labrafil Ethyl Alcohol	310 mg 110 mg 100 mg	0.101	0.020
35	Cremophor RH-40 Span 80 Triacetin	300 mg 130 mg 100 mg	0.908	0.114
36	Cremophor RH-40 Arlacel 186 Propylene Glycol	510 mg 58 mg 55 mg	0.039	0.008
37	Cremophor RH-40 Peceol Propylene Glycol	510 mg 140 mg 58 mg	0.440	0.100
38	Cremophor RH-40 Labrafil M2125CS Propylene Glycol	500 mg 400 mg 88 mg	0.411	0.107
39	Cremophor RH-40 Span 80 Propylene Glycol	550 mg 220 mg 78 mg	0.715	0.106
40	Cremophor RH-40 Crodamol Propylene Glycol	500 mg 280 mg 100 mg	0.547	0.147
41	Cremophor RH-40 Labrafil M2125CS Span 80 Ethyl Alcohol	550 mg 340 mg 200 mg 110 mg	0.419	0.055
42	Cremophor RH-40 Labrafil M2125CS Crovol M-40 Ethyl Alcohol	500 mg 270 mg 280 mg 100 mg	0.293	0.260

Ideally, a clear aqueous dispersion should have a very high transmittance, indicating little scattering of light by large particles. Absorbance and transmittance are related by the simple expression

$$A = -\log T$$

where A is absorbance, and T is the transmittance expressed as a decimal. Thus, preferred solutions of the present invention will have small absorbances. As noted above, in the

absence of true absorption (due to chromophores in solution), suitable clear aqueous dispersions of the present invention should have an absorbance at 10X dilution of less than about 0.3.

The data in Table 26 show 30 solutions, 22 of which have absorbances less than about 0.3 at 10X dilution. Of these solutions, 3 have absorbances between 0.2 and 0.3, 5 have absorbances between 0.1 and 0.2, and 14 have absorbances less than 0.1. Thus, for the majority of the solutions, absorbance provides an adequate measure of optical clarity.

Solutions having absorbances greater than 0.3 may still be suitable for use in the present invention, as these are observed to have acceptable optical clarity by visual examination. For these relatively high absorbance solutions, this simple spectroscopic measure of optical clarity is inadequate, and other methods are more well-suited to assessing optical clarity, such as visual observation and particle size. As an example, Example 37, which shows an absorbance of 0.440, has a surfactant ratio of 27, well below the value of 40 shown in Table 19, and is observed to be a clear solution. This same composition, without the additional solubilizer, is shown in Example 9 at a surfactant ratio of 28 to have a mono-modal, narrow particle size distribution, at an average particle size of 12.4 nm. It should be appreciated that direct particle size measurement and absorbance measurement are different ways of assessing optical clarity, and provide alternative criteria for quantifying clarity. However, it is believed that the simple, qualitative visual observation of optical clarity is a sufficient measure of suitable clarity for use in the present invention, particularly so since compositions outside the scope of the invention show marked and unmistakable cloudiness without recourse to quantitative measurement (*See, e.g.*, Comparative Example 1).

Comparative Examples C6-C12: Spectroscopic Characterization of Compositions Not Forming Clear Aqueous Dispersions

For comparison to the clear aqueous dispersions of the present invention, compositions observed to be milky or cloudy were characterized by absorption, as in Examples 13-42. Where available, results for comparable solutions from Examples 13-42 are reproduced for comparison. In such cases, where a given surfactant combination is presented in Examples 13-42 more than once (with different solubilizer concentrations), the composition having the lowest solubilizer concentration is chosen, to facilitate more direct comparison. The results are shown in Table 27.

Table 27: Comparative Spectroscopic Characterization

Example No.	Formulation		Absorbance (400.2 nm)	
			10X	100X
C6	Tween 80 Lauroglycol FCC	100 mg 67 mg	2.938	2.827
26	Tween 80 Lauroglycol FCC Ethyl Alcohol	180 mg 20 mg 37 mg	0.036	0.003
C7	Tween 80 Capmul MCM	100 mg 67 mg	0.980	0.932
22	Tween 80 Capmul MCM Ethyl Alcohol	170 mg 30 mg 38 mg	0.050	0.008
C8	Cremophor RH-40 Plurol Oleique CC497	100 mg 67 mg	2.886	1.595
25	Cremophor RH-40 Plurol Oleique CC497 Ethyl Alcohol	500 mg 10 mg 11 mg	0.028	0.005
C9	Cremophor RH-40 Peceol	100 mg 67 mg	2.892	1.507
24	Cremophor RH-40 Peceol Ethyl Alcohol	230 mg 70 mg 54 mg	0.187	0.020
C10	Cremophor RH-40 Capmul MCM	100 mg 67 mg	1.721	0.491
23	Cremophor RH-40 Capmul MCM Ethyl Alcohol	550 mg 80 mg 53 mg	0.029	0.006
C11	Tween 80 Plurol Oleique CC497	100 mg 67 mg	1.585	1.357
C12	Tween 80 Peceol	100 mg 67 mg	2.849	2.721

The data in the Table demonstrate that the clear aqueous dispersions of the present invention show very different absorptive behavior from compositions having excessive hydrophobic surfactant concentrations, having apparent absorbances (through scattering losses) lower by at least a factor of ten, and in some cases by a factor of more than one hundred.

Examples 43 and 44: Solubility of a Polyfunctional Hydrophobic Therapeutic Agent

The enhanced solubility of a typical polyfunctional hydrophobic therapeutic agent, cyclosporin, in the pharmaceutical compositions of the present invention was measured using a conventional "shake flask" method. Compositions were prepared and diluted to 10X and 100X as in Example 1, without including the therapeutic agent. The solutions were then provided with an excess of cyclosporin, and agitated to allow the cyclosporin to achieve an equilibrium partitioning between the solubilized phase and the non-solubilized dispersion phase. Concentration of the solubilized cyclosporin was then determined using standard HPLC techniques, optimized for the quantitative detection of cyclosporin. The results are shown in Table 28.

Table 28: Solubility of Cyclosporin in Clear Aqueous Dispersions

Example No.	Carrier Composition		Solubility (μg/mL)	
			10X Dilution	100X Dilution
43	Cremophor RH-40 Myvacet 9-45 Ethyl Alcohol	430 mg 321 mg 210 mg	13,205	1,008
44	Cremophor RH-40 Span 80 Triacetin	540 mg 260 mg 220 mg	11,945	1,127

This Example demonstrates the dramatically enhanced solubility of a hydrophobic therapeutic agent in the pharmaceutical compositions of the present invention.

Comparative Examples C13-C16: Solubility of a Polyfunctional Hydrophobic Therapeutic Agent

For comparison, the solubility experiment of Examples 43-44 was performed on four standard aqueous solutions. The first comparison solution was purified water with no additives. Next, a standard simulated intestinal fluid (SIF) was used, to simulate the in vivo

conditions to be encountered by the hydrophobic therapeutic agent. A third solution was prepared with simulated intestinal fluid, plus an additional aliquot of 20 mM sodium taurocholate (a bile salt); this solution is designated SIFB in Table 29. Finally, a fourth solution was prepared with simulated intestinal fluid, 20 mM sodium taurocholate, and 5 mM lecithin; this solution is designated SIFBL. The 20 mM bile salt and 5 mM lecithin concentrations are believed to be representative of the average concentration of these compounds encountered in the gastrointestinal tract. As in the previous Examples, these comparison solutions were equilibrated with cyclosporin using the shake flask method, and analyzed by HPLC. The results of these measurements are presented in Table 29.

Table 29: Solubility of Cyclosporin in Aqueous Solutions

Example No.	Solution	Solubility (μg/mL)
C13	Water	6
C14	SIF	6
C15	SIFB	49
C16	SIFBL	414
43-44 (average at 10X)	present invention	12,575

As the Table indicates, the solubility of the polyfunctional hydrophobic therapeutic agent in the compositions of the present invention is far greater than its solubility in aqueous and gastrointestinal aqueous solutions.

Examples 45-49: Solubility of a Lipophilic Hydrophobic Therapeutic Agent

The enhanced solubility of a typical lipophilic hydrophobic therapeutic agent, progesterone, in the pharmaceutical compositions of the present invention was measured as described in Examples 43-44. The results are shown in Table 30.

Table 30: Solubility of Progesterone in Clear Aqueous Dispersions

Example No.	Carrier Composition		Solubility (μg/mL)	
			10X Dilution	100X Dilution
45	Cremophor RH-40 Arlacel 186 Propylene Glycol	1000 mg 120 mg 110 mg	1100	200
46	Cremophor RH-40 Peceol Propylene Glycol	1000 mg 240 mg 120 mg	1240	140
47	Cremophor RH-40 Labrafil M2125CS Propylene Glycol	1000 mg 800 mg 180 mg	1760	190
48	Cremophor RH-40 Span 80 Propylene Glycol	1000 mg 350 mg 140 mg	1360	160
49	Cremophor RH-40 Crodamol EO Propylene Glycol	1000 mg 600 mg 160 mg	1720	190

This Example demonstrates the dramatically enhanced solubility of a hydrophobic therapeutic agent in the pharmaceutical compositions of the present invention.

Comparative Examples C17-C20: Solubility of a Lipophilic Hydrophobic Therapeutic Agent

For comparison, the solubility experiment of Comparative Examples C13-C16 was repeated, using progesterone instead of cyclosporin. The results of these measurements are presented in Table 31.

Table 31: Solubility of Progesterone in Aqueous Solutions

Example No.	Solution	Solubility (μg/mL)
C17	Water	6
C18	SIF	7-10
C19	SIFB	32-40

C20	SIFBL	80
45-49 (average at 10X)	Present invention	1436

As the Table indicates, the solubility of the lipophilic hydrophobic therapeutic agent in the compositions of the present invention is far greater than its solubility in aqueous and gastrointestinal aqueous solutions.

Examples 50-57: Aqueous Dilution Stability
of Compositions Containing a Polyfunctional Hydrophobic Therapeutic Agent

Compositions according to the present invention were prepared, with a typical polyfunctional hydrophobic therapeutic agent, cyclosporin, as the therapeutic agent. The compositions were prepared as described in Example 1, except that the ingredients were added in the order listed in Table 32. The pre-concentrates were diluted 100X with purified water, and a visual observation was made immediately after dilution. The solutions were then allowed to stand 6 hours to assess dilution stability, then the cyclosporin concentration in solution was measured, using a drug-specific HPLC assay. The results are shown in Table 32.

Table 32: Dilution Stability of Polyfunctional Therapeutic Agents

Example No.	Composition		Observation	Cyclosporin Concentration*
50	Cremophor RH-40 Myvacet 9-45 Ethyl Alcohol Cyclosporin	430 mg 310 mg 210 mg 99 mg	clear solution	121
51	Cremophor RH-40 Peceol Ethyl Alcohol Cyclosporin	610 mg 160 mg 200 mg 100 mg	clear solution	99
52	Cremophor RH-40 Span 80 Triacetin Cyclosporin	540 mg 260 mg 220 mg 97 mg	clear solution	114
53	Incrocas 35 Myvacet 9-45 Ethyl Alcohol	470 mg 250 mg 220 mg	clear solution	96

	Cyclosporin	100 mg		
54	Cremophor RH-40 Arlacel 186 Propylene Glycol Ethanol Cyclosporin	660 mg 120 mg 100 mg 100 mg 100 mg	clear solution	105
55	Cremophor RH-40 Arlacel 186 Propylene Glycol Cyclosporin	550 mg 120 mg 450 mg 100 mg	clear solution	102
56	Cremophor RH-40 Arlacel 186 Propylene Glycol Ethanol Cyclosporin	580 mg 120 mg 100 mg 100 mg 100 mg	clear solution	108
57	Gelucire 44/14 Incrocas 35 Glycofurol Cyclosporin	120 mg 200 mg 100 mg 100 mg	clear solution (at 37 °C)	108

* as a percentage of the initial cyclosporin concentration

The data in the Table indicate that large amounts of a polyfunctional hydrophobic therapeutic agent can be solubilized in the compositions of the present invention to produce clear, aqueous dispersions. These dispersions show no instability effects, such as hydrophobic therapeutic agent precipitation or particle agglomeration, upon standing.

Examples 58-74: Aqueous Dilution Stability of Compositions Containing a Lipophilic Hydrophobic Therapeutic Agent

Compositions according to the present invention were prepared, with a typical lipophilic hydrophobic therapeutic agent, progesterone, as the therapeutic agent. The compositions were prepared and analyzed as in Examples 50-57, and the results are shown in Table 33.

Table 33: Dilution Stability of Lipophilic Therapeutic Agents

Example No.	Composition		Observation	Progesterone Concentration*
58	Cremophor RH-40 Arlacel 186 Propylene Glycol Progesterone	1000 mg 120 mg 110 mg 48 mg	very clear solution	99.1
59	Cremophor RH-40 Peceol Propylene Glycol Progesterone	1000 mg 240 mg 120 mg 48 mg	very clear solution	99.3
60	Cremophor RH-40 Labrafil Propylene Glycol Progesterone	1000 mg 800 mg 180 mg 45 mg	very clear solution	100.2
61	Cremophor RH-40 Span 80 Propylene Glycol Progesterone	1000 mg 350 mg 140 mg 50 mg	very clear solution	97.2
62	Cremophor RH-40 Crodamol EO Propylene Glycol Progesterone	1000 mg 600 mg 160 mg 48 mg	very clear solution	98.4
63	Cremophor RH-40 Labrafil M2125CS Ethyl Alcohol Progesterone	540 mg 350 mg 200 mg 42 mg	clear solution	104.4
64	Cremophor RH-40 Ethyl Oleate Ethyl Alcohol Progesterone	570 mg 260 mg 200 mg 42 mg	very slight tang blue color solution	106.1
65	Cremophor RH-40 Peceol Triacetin Progesterone	600 mg 210 mg 210 mg 42 mg	very slight tang blue color solution	104.6
66	Cremophor RH-40 Capmul MCM Triacetin Progesterone	600 mg 200 mg 200 mg 44 mg	very clear solution	97.7

67	Cremophor RH-40 Span 80 Triacetin Progesterone	590 mg 270 mg 210 mg 41 mg	clear solution	102.3
68	Crovol M-70 Labrafil M2125CS Triacetin Progesterone	760 mg 100 mg 200 mg 43 mg	very clear solution	104.6
69	Tween 20 Imwitor 988 Triacetin Progesterone	610 mg 300 mg 200 mg 45 mg	very slight tang blue color solution	98.0
70	Tween 20 Lauroglycol FCC Glycofurol Progesterone	670 mg 170 mg 200 mg 43 mg	very clear solution	96.3
71	Incrocas 35 Labrafil M2125CS Ethyl Alcohol Progesterone	620 mg 220 mg 200 mg 43 mg	very clear solution	99.5
72	Incrocas 35 Span 20 Ethyl Alcohol Progesterone	660 mg 160 mg 210 mg 41 mg	very clear solution	105.9
73	Cremophor RH-40 Arlacel 186 Propylene Glycol Progesterone	980 mg 130 mg 110 mg 110 mg	very clear supernatant	103.7
74	Cremophor RH-40 Labrafil Propylene Glycol Progesterone	520 mg 400 mg 110 mg 100 mg	very clear supernatant	103.1

* as a percentage of the initial progesterone concentration

The data in the Table indicate that a lipophilic hydrophobic therapeutic agent can be solubilized in the compositions of the present invention to produce clear, aqueous dispersions. These dispersions show no instability effects, such as hydrophobic therapeutic agent precipitation or particle agglomeration, upon standing.

Example 75: Enhancement of Bioabsorption

Studies were performed to establish that the clear aqueous dispersions of the present invention facilitate an increased rate of bioabsorption of the hydrophobic therapeutic agent contained therein. The studies used a rat model with perfused intestinal loop along with cannulation of the mesenteric vein. This unique methodology enabled assessment of the "true" absorption potential free of any systemic metabolic interference.

A representative preconcentrate of the present invention containing a cyclosporin hydrophobic therapeutic agent was used. The composition had the following formulation:

Cyclosporine	0.140 g
Cremophor RH-40	0.41 g
Arlacel 186	0.29 g
Sodium taurocholate	0.26 g
Propylene glycol	0.46 g

For this experiment, the preconcentrate was diluted with an isotonic aqueous HEPES buffer rather than purified water. The resultant solution was spiked with radioactive active and perfused through isolated ileal lumen segment of known length and diameter. Loss of radioactivity from the lumenal side and appearance of radioactivity in the mesenteric blood from the other side was monitored as an indicator of absorption.

Experimental Details:

Young adult (275-300 g) male Sprague Dawley rats were used. The procedures were consistent with those reported by Winne et al., "In vivo studies of mucosal-serosal transfer in rat jejunum", Naunyn-Schmeideberg's Arch. Pharmacol., 329, 70 (1985).

Jugular vein cannulation: the animal was anesthetized using 2% halothane in 98% oxygen via a halothane vaporizer (Vapomatic, A.M. Bickford, Inc., NY). An opening in the jugular vein was made with a 21 ga needle and a jugular cannula consisting of a 4 cm segment of silastic tubing connected to polyethylene tubing was inserted in the jugular vein and secured with cyanoacrylate glue. For the donor rat, approximately 20 mL of blood was freshly collected in the presence of heparin (1,000 units) and the collected blood was infused at a rate of 0.2 mL/min through the jugular vein in the experimental rat to replenish blood sampling.

Intestine cannulation: after the animal was anesthetized, its body temperature was maintained at 37 °C using a heating pad. A vertical midline incision of approximately 3 cm was made through the skin to expose the small intestine. Approximately 6-10 cm segment of

ileum was located. Using electro-cautery, a small incision was made at the ends of the segment and the lumenal contents were flushed with saline maintained at 37 °C. Two 1.5 cm notched pieces of Teflon tubing were inserted into the intestinal lumen at each incision and tightened using 4-0 silk. A warm isotonic buffer was passed through the intestine using a 50-mL syringe. These Teflon cannula were used to perfuse the drug solution through the isolated intestinal segment using a syringe pump.

Mesenteric vein cannulation: the mesenteric vein draining blood from the resulting isolated mesenteric cascade venules was then cannulated using a 24 ga IV catheter and secured in place using 4-0 silk sutures. The cannula was then connected to a polyethylene tubing 25 cm long where the blood was collected in a vial kept under the animal level. Blood samples were collected continuously over 60 min. The infusion of blood via the jugular vein was initiated to replenish blood loss. The animal was then killed by a lethal injection of Phenobarbital after completion of the experiment.

The experiment was performed twice using the compositions of the present invention as the drug carrier, and twice using a commercial cyclosporin microemulsion formulation for comparison (NeOral®). For each formulation, the results of the two trials were averaged. The results are presented graphically in Figure 1.

Figure 1 shows the accumulated radioactivity ($\mu Ci/cm^2 \mu Ci$) in mesenteric blood as a function of time, over the course of 60 minutes, for the pharmaceutical compositions of the present invention (filled squares) and a commercial cyclosporin formulation (filled circles). As the Figure shows, the bioabsorption of the hydrophobic therapeutic agent exceeds that of the commercial formulation at the earliest measurement point, and continues to increase relative to the commercial formulation over the course of the measurement interval. At the final measurement point (60 min), the bioabsorption of the hydrophobic therapeutic agent from the compositions of the present invention exceeds that of the commercial formulation by nearly 100%.

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed is:

CLAIMS

1. A pharmaceutical composition comprising:

(a) a hydrophobic therapeutic agent; and

(b) a carrier comprising

(i) at least one hydrophilic surfactant and

(ii) at least one hydrophobic surfactant,

said hydrophilic and hydrophobic surfactants being present in amounts such that upon mixing with an aqueous solution the carrier forms a clear aqueous dispersion of the hydrophilic and hydrophobic surfactants containing the hydrophobic therapeutic agent, wherein the composition is substantially free of triglycerides.

2. The pharmaceutical composition of claim 1, wherein the hydrophobic surfactant is present in an amount of less than 200%, 100%, or 60% by weight, relative to the amount of the hydrophilic surfactant.

3. The pharmaceutical composition of claim 1, wherein the hydrophilic surfactant comprises at least one non-ionic hydrophilic surfactant having an HLB value greater than or equal to 10.

4. The pharmaceutical composition of claim 1, wherein the hydrophilic surfactant comprises at least one ionic surfactant.

5. The pharmaceutical composition of claim 3, which further comprises at least one ionic surfactant.

6. The pharmaceutical composition of claim 3, wherein the non-ionic surfactant is selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures thereof.

7. The pharmaceutical composition of claim 6, wherein the non-ionic hydrophilic surfactant comprises a reaction product of a polyol and a mono glyceride, diglyceride, triglyceride, or a mixture thereof.

8. The pharmaceutical composition of claim 6, wherein the non-ionic hydrophilic surfactant comprises a transesterification product of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

9. The pharmaceutical composition of claim 7 or claim 8, wherein the polyol is glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol or a mixture thereof.

10. The pharmaceutical composition of claim 3, wherein the hydrophilic surfactant is PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryllaurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-I 0 laurate, PEG-'30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, or a mixture thereof.

11. The pharmaceutical composition of claim 3, wherein the hydrophilic surfactant is PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides,

polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a poloxamer, or a mixture thereof.

12. The pharmaceutical composition of claim 4, wherein the ionic surfactant is selected from the group consisting of alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyllactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated monoglycerides; citric acid esters of mono- and di-glycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof, phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate and mixtures thereof.

13. The pharmaceutical composition of claim 4, wherein the ionic surfactant is selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyllactylate,succinylated monoglycerides, mono- and di-acetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono- and di-glycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, chenodeoxycholate, glycodeoxycholate, glycochenodeoxycholate, taurochenodeoxycholate, ursodeoxycholate, tauroursodeoxycholate, glycoursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, and salts and mixtures thereof.

14. The pharmaceutical composition of claim 1 wherein the hydrophobic surfactant is a compound or mixture of compounds having an HLB value less than 10.

15. The pharmaceutical composition of claim 14, wherein the hydrophobic surfactant is selected from the group consisting of alcohols; polyoxyethylene alkylethers;

fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acid esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

16. The pharmaceutical composition of claim 14, wherein the hydrophobic surfactant is selected from the group consisting of lower alcohol fatty acids esters; polypropylene glycol fatty acid esters; propylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene vegetable oils; and mixtures thereof.

17. The pharmaceutical composition of claim 14, wherein the glycerol fatty acid ester is a monoglyceride, diglyceride, or a mixture thereof.

18. The pharmaceutical composition of claim 17, wherein the fatty acid of the glycerol fatty acid ester is a C_6 to C_{20} fatty acid or a mixture thereof.

19. The pharmaceutical composition of claim 14, wherein the hydrophobic surfactant comprises a transesterification product of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

20. The pharmaceutical composition of claim 15, wherein the polyol is polyethylene glycol, sorbitol, propylene glycol, pentaerythritol or a mixture thereof.

21. The pharmaceutical composition of claim 14, wherein the hydrophobic surfactant is selected from the group consisting of myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid; PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil;

PEG 5-10 hydrogenated castor oil; PEG 6-20 com oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; PEG-4 capric/caprylic triglyceride, mono-, di-, tri-, and tetra-esters of vegetable oil and sorbitol; pentaerythrityl distearate, tetrastearate, isostearate, oleate, caprylate, and caprate; polyglyceryl 2-4 oleate, stearate, and isostearate; polyglyceryl 4-10 pentaoleate; polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-10 trioleate; polyglyceryl-3 distearate; propylene glycol mono- and di-esters of a C_6 to C_{20} fatty acid; monoglycerides of a C_6 to C_{20} fatty acid; acetylated monoglycerides; acetylated monoglycerides of a C_6 to C_{20} fatty acid; diglycerides of a C_6 to C_{20} fatty acid; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; cholesterol; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetrastearate and hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono- and tri-oleate; sorbitan mono- and tri-stearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PEG-2 cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate; isopropyl myristate; isopropyl palmitate; ethyllinoleate; isopropyllinoleate; poloxamers; and mixtures thereof.

22. The pharmaceutical composition of claim 14, wherein the hydrophobic surfactant is selected from the group consisting of oleic acid; lauric acid; glyceryl monocaprate; glyceryl monocaprylate; glyceryl monolaurate; glyceryl monooleate; glyceryl dicaprate; glyceryl dicaprylate; glyceryl dilaurate; glyceryl dioleate; acetylated monoglycerides; propylene glycol oleate; propylene glycollaurate; polyglyceryl-3 oleate; polyglyceryl-6 dioleate; PEG-6 corn oil; PEG-20 com oil; PEG-20 almond oil; sorbitan monooleate; sorbitan monolaurate; POE-4 lauryl ether; POE-3 oleyl ether; ethyl oleate; poloxamers; and mixtures thereof.

23. The pharmaceutical composition of claim 1, wherein the clear aqueous dispersion has a particle size distribution having an average particle size of less than 100 nm.

24. The pharmaceutical composition of claim 23, wherein the clear aqueous dispersion has a particle size distribution having an average particle size of less than 50 nm.

25. The pharmaceutical composition of claim 24, wherein the clear aqueous dispersion has a particle size distribution having an average particle size of less than 20 nm.

26. The pharmaceutical composition of claim 1, wherein the clear aqueous dispersion has an absorbance of less than 0.1 at 400 nm when the carrier is diluted with an aqueous solution in an aqueous solution to carrier ratio of 100: 1 by weight.

27. The pharmaceutical composition of claim 26, wherein the clear aqueous dispersion has an absorbance of less than 0.01 at 400 nm when the carrier is diluted with an aqueous solution in an aqueous solution to carrier ratio of 100: 1 by weight.

28. The pharmaceutical composition of claim 1, wherein the hydrophobic therapeutic agent has an intrinsic water solubility of less than 1% by weight at 25°C.

29. The pharmaceutical composition of claim 28, wherein the hydrophobic therapeutic agent has an intrinsic water solubility of less than 0.1 % by weight at 25°C.

30. The pharmaceutical composition of claim 29, wherein the hydrophobic therapeutic agent has an intrinsic water solubility of less than 0.01 % by weight at 25°C.

31. The pharmaceutical composition of claim 1, wherein the therapeutic agent is a drug, a vitamin, a nutritional supplement, a cosmeceutical, or a mixture thereof.

32. The pharmaceutical composition of claim 1, wherein the therapeutic agent is a polyfunctional hydrophobic drug, a lipophilic drug, a pharmaceutically acceptable salt, isomer or derivative thereof, or a mixture thereof.

33. The pharmaceutical composition of claim 31,wherein the therapeutic agent is selected from the group consisting of analgesics, anti-inflammatory agents, antihelminthics, anti-arrhythmic agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, antimalarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, erectile dysfunction improvement agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anxiolytic agents, sedatives, hypnotics, neuroleptics, β-blockers, cardiac inotropic agents, corticosteroids, diuretics, anti-parkinsonian agents, gastro-intestinal agents, histamine H_1-and H_2-receptor antagonists, keratolytics, lipid regulating agents, anti-anginal agents, nutritional agents, opioid analgesics, sex hormones, stimulants, muscle relaxants, anti-osteoporosis agents, anti-obesity agents, cognition enhancers, anti-

urinary incontinence agents, nutritional oils, anti-benign prostate hypertrophy agents, essential fatty acids, non-essential fatty acids, and mixtures thereof.

34. The pharmaceutical composition of claim 31,wherein the therapeutic agent is tramadol, celecoxib, etodolac, rofecoxib, oxaprozin, leflunomide, diclofenac, nabumetone, ibuprofen, flurbiprofen, tetrahydrocannabinol, capsaicin, ketorolac, albendazole, ivermectin, amiodarone, zileuton, zafirlukast, albuterol, montelukast, azithromycin, ciprofloxacin, clarithromycin, dirithromycin, rifabutine, rifapentine, trovafloxacin, baclofen, ritanovir, saquinavir, nelfinavir, efavirenz, dicumarol, tirofiban, cilostazol, ticlopidine, clopidogrel, oprevelkin, paroxetine, sertraline, venlafaxine, bupropion, clomipramine, miglitol, repaglinide, glimepiride, pioglitazone, rosiglitazone, troglitazone, glyburide, glipizide, glibenclamide, carbamezepine, fosphenytoin, tiagabine, topiramate, lamotrigine, vigabatrin, amphotericin B, butenafine, terbinafine, itraconazole, fluconazole, miconazole, ketoconazole, metronidazole, griseofulvin, nitrofurantoin, spironolactone, lisinopril, benazepril, nifedipine, nilsolidipine, telmisartan, irbesartan, eposartan, valsartan, candesartan, minoxidil, terazosin, halofantrine, mefloquine, dihydroergotamine, ergotamine, frovatriptan, pizofetin, sumatriptan, zolmitriptan, naratriptan, rizatriptan, aminoglutethemide, busulfan, cyclosporin, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecin, topotecan, nilutamide, bicalutamide, pseudoephedrine, toremifene, atovaquone, metronidazole, furazolidone, paracalcitol, benzonatate, midazolam, zolpidem, gabapentin, zopiclone, digoxin, beclomethasone, budesonide, betamethasone, prednisolone, cisapride, cimetidine, loperamide, famotidine, lansoprazole, rabeprazole, nizatidine, omeprazole, cetrizine, cinnarizine, dexchlorpheniramine, loratadine, clemastine, fexofenadine, chlorpheniramine, acetretin, tazarotene, calcipotriene, calcitriol, targretin, ergocalciferol, cholecalciferol, isotretinoin, tretinoin, calcifediol, fenofibrate, probucol, gemfibrozil, cerivastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, tizanidine, dantrolene, isosorbide dinitrate, a carotene, dihydrotachysterol, vitamin A, vitamin D, vitamin E, vitamin K, an essential fatty acid source, codeine, fentanyl, methadone, nalbuphine, pentazocine, clomiphene, danazol, dehydroepiandrosterone, medroxyprogesterone, progesterone, rimexolone, megestrol acetate, estradiol, finasteride, mefepristone, amphetamine, L-thryroxine, tamsulosin, methoxsalen, tacrine, donepezil, raloxifene, verteporfrin, sibutramine,

pyridostigmine, a pharmaceutically acceptable salt, isomer, or derivative thereof, or a mixture thereof.

35. The pharmaceutical composition of claim 1, wherein the hydrophobic therapeutic agent is selected from the group consisting of sildenafil citrate, amlodipine, tramadol, celecoxib, rofecoxib, oxaprozin, nabumetone, ibuprofen, terbinafine, itraconazole, zileuton, zafirlukast, cisapride, fenofibrate, tizanidine, nizatidine, fexofenadine, loratadine, famotidine, paracalcitol, atovaquone, nabumetone, tetrahydrocannabinol, megestrol acetate, repaglinide, progesterone, rimexolone, cyclosporine, tacrolimus, sirolimus, teniposide, paclitaxel, pseudoephedrine, troglitazone, rosiglitazone, finasteride, vitamin A, vitamin D, vitamin E, pharmaceutically acceptable salts, isomers and derivatives thereof, and mixtures thereof.

36. The pharmaceutical composition of claim 1, which further comprises a solubilizer.

37. The pharmaceutical composition of claim 36, wherein the solubilizer is selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof.

38. The pharmaceutical composition of claim 37, wherein the alcohol or polyol is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose, cyclodextrins and cyclodextrin derivatives, and mixtures thereof

39. The pharmaceutical composition of claim 37, wherein the amide is selected from the group consisting of 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, polyvinylpyrrolidone, and mixtures thereof

40. The pharmaceutical composition of claim 37, wherein the ester is selected from the group consisting of ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl

tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof, and mixtures thereof

41. The pharmaceutical composition of claim 36, wherein the solubilizer is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediol , glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose, cyclodextrins, ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propy lene glycol diacetate, s-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof, 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-methylpyrrolidone, N-ethylpyrrolidone, N-hydroxyethyl pyrrolidone, N-octylpyrrolidone, N-laurylpyrrolidone, dimethylacetamide, polyvinylpyrrolidone, glycofurol, methoxy PEG, and mixtures thereof.

42. The pharmaceutical composition of claim 36, wherein the solubilizer is selected from the group consisting of ethanol, isopropanol, benzyl alcohol, ethylene glycol, propylene glycol, 1,3-butanediol, glycerol, pentaerythritol, sorbitol, glycofurol, transcutol, dimethyl isosorbide, polyethylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, hydroxypropyl cyclodextrins, sulfobutyl ether derivatives of cyclodextrins, ethyl propionate, tributylcitrate, triethylcitrate, ethyl oleate, ethyl caprylate, triacetin, β-butyrolactone and isomers thereof, 2-pyrrolidone, N-methylpyrrolidone, N-ethylpyrrolidone, N-hydroxyethylpyrrolidone, N-octylpyrrolidone, N-laurylpyrrolidone, dimethylacetamide, polyvinylpyrrolidone, and mixtures thereof

43. The pharmaceutical composition of claim 36, wherein the solubilizer is triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpynolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-600, glycoffirol, diethylene glycol monoethyl ether, propylene glycol, dimethyl isosorbide, or a mixture thereof.

44. The pharmaceutical composition of claim 36, wherein the solubilizer is

triacetin, ethanol, polyethylene glycol 400, glycofurol, propylene glycol or a mixture thereof.

45. The pharmaceutical composition of claim 36, wherein the solubilizer is present in the composition in an amount of 400%, 200%, 100%, 50%, 25% or less by weight, based on the total weight of the surfactants.

46. The pharmaceutical composition of claim 1, which further comprises an antioxidant, a preservative, a chelating agent, a viscomodulator, a tonicifier, a flavorant, a colorant, an odorant, an opacifier, a suspending agent, a binder, or a mixture thereof.

47. The pharmaceutical composition of claim 1 in the form of a preconcentrate, a diluted preconcentrate, a semi-solid dispersion, a solid dispersion, or a sprayable solution.

48. A dosage form comprising a capsule filled with the pharmaceutical composition of claim 1.

49. A dosage form comprising a multiparticulate carrier coated with the pharmaceutical composition of claim 1.

50. A dosage form comprising the pharmaceutical composition of claim 1 formulated as a solution, a cream, a lotion, an ointment, a suppository, a spray, an aerosol, a paste or a gel.

51. The dosage form of claim 48, wherein the capsule is a hard gelatin capsule, a soft gelatin capsule, a starch capsule or an enteric coated capsule.

52. The pharmaceutical composition of claim 1, which further comprises water or an aqueous buffer.

53. The pharmaceutical composition of claim 1, which further comprises an additional amount of a hydrophobic therapeutic agent, said additional amount not solubilized in the carrier.

54. The pharmaceutical composition of claim 1 wherein the hydrophobic therapeutic agent further comprises:

(c) a first amount of a hydrophobic therapeutic agent, said first amount being solubilized in the carrier; and

(d) a second amount of a hydrophobic therapeutic agent, said second amount not solubilized in the clear aqueous dispersion.

55. The pharmaceutical composition of claim 1, wherein the composition is contained in a capsule and wherein the hydrophobic therapeutic agent has an intrinsic water solubility of less than 1 percent by weight and is present in a therapeutically effective dosage for oral administration, and wherein the carrier further comprises a solubilizer selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and mixtures thereof and present in an amount of 1% to 100% by weight relative to the combined weight of the hydrophilic and hydrophobic surfactants, wherein the hydrophobic surfactant is present in an amount of 5% to 100% by weight relative to the hydrophilic surfactant, and the hydrophilic and hydrophobic surfactants are each present in amounts such that upon dilution with an aqueous solution at an aqueous solution to carrier ratio of 100: 1 by weight, the carrier forms a clear aqueous dispersion having an absorbance of less than 0.1 at a wavelength of 400 nm, and further wherein the composition is free of water and glycerol triesters of C_6 to C_{25} fatty acids.

56. The capsule of claim 55, wherein the hydrophobic surfactant is selected from the group consisting of monoglycerides, diglycerides, acetylated monoglycerides, acetylated diglycerides, propylene glycol mono-fatty acid esters, propylene glycol di-fatty acid esters, and mixtures thereof.

57. The capsule of claim 55, wherein the solubilizer is an alcohol, a polyol, or a mixture thereof.

58. The capsule of claim 57, wherein the solubilizer is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinyl alcohol, hydroxypropyl methylcellulose, cyclodextrins, and mixtures thereof.

59. The capsule of claim 55, wherein the hydrophobic surfactant is present in an amount of less than 60% by weight relative to the amount of the hydrophilic surfactant.

60. The capsule of claim 55, wherein the solubilizer is present in an amount of 5% to 25% by weight relative to the combined weight of the hydrophilic and hydrophobic surfactants.

61. The dosage form of claim 51, coated with an enteric coating.

62. The capsule of claim 55, coated with an enteric coating.

63. The pharmaceutical composition of claim 1, wherein the composition is a coating on a multiparticulate dosage form for oral administration of a therapeutic agent, and the hydrophobic therapeutic agent has an intrinsic water solubility of less than 1 wt.% at 25°C and is present in a therapeutically effective amount for oral administration, and the hydrophilic and hydrophobic surfactants are present in amounts such that upon dilution with an aqueous solution at an aqueous solution to carrier ratio of 100: 1 by weight, the carrier forms a clear aqueous dispersion having an absorbance of less than 0.1 at a wavelength of 400 nm, and wherein the composition is free of water and glycerol triesters of C_6 to C_{25} fatty acids.

64. The composition of claim 1, wherein the composition is a multiparticulate dosage form for oral administration of a therapeutic agent, comprised of a plurality of particles and wherein the hydrophobic therapeutic agent has an intrinsic water solubility of less than 1 wt.% at 25°C and is present in a therapeutically effective amount for oral administration, and wherein the hydrophilic and hydrophobic surfactants are present in amounts such that upon dilution with an aqueous solution at an aqueous solution to carrier ratio of 100: 1 by weight, the carrier forms a clear aqueous dispersion having an absorbance of less than 0.1 at a wavelength of 400 nm, and wherein the composition is free of water and glycerol triesters of C_6 to C_{25} fatty acids.

65. The dosage form of claim 51, wherein the hydrophobic therapeutic agent is fenofibrate.

66. The capsule of claim 55, wherein the hydrophobic therapeutic agent is

fenofibrate.

67. The multiparticulate dosage form of claim 63 or claim 64, wherein the hydrophobic therapeutic agent is fenofibrate.

68. The capsule of claim 55, wherein the hydrophobic therapeutic agent is cerivastatin, pravastatin, simvastatin, fluvastatin, or atorvastatin.

69. The multiparticulate dosage form of claim 63 or claim 64, wherein the hydrophobic therapeutic agent is cerivastatin, pravastatin, simvastatin, fluvastatin, or atorvastatin.

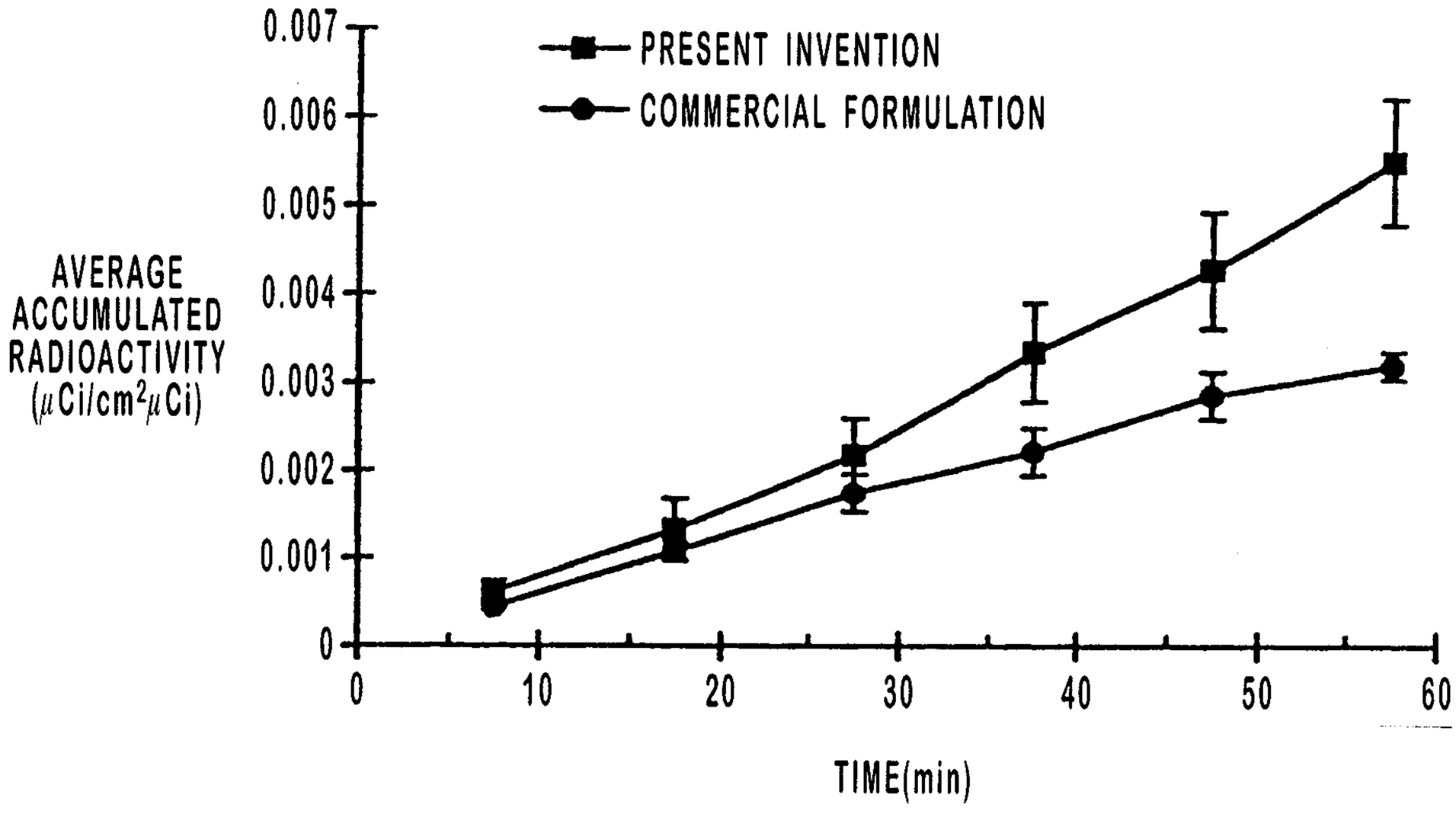
PRESENT INVENTION
COMMERCIAL FORMULATION
AVERAGE ACCUMULATED RADIOACTIVITY (μCi/cm²μCi)
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0
0
10
20
30
40
50
60
TIME(min)

FIG. 1