Abstract: The present invention provides a method of preparing a stable water soluble solution including a lipophilic bioactive compound such as CoQ10. The method involves providing a non-ionic surfactant; preparing a mixture of the lipophilic bioactive compound and the non-ionic surfactant in a predetermined molar ratio; heating the mixture to a temperature necessary to obtain a clear melt; and adding heated water to the mixture to form the stable solution. The invention includes compositions produced by this method and uses of such compositions. These uses include uses in pharmaceutical, food and cosmetic compositions.
SOLUBLE BIOACTIVE COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to the solubilization of lipophilic bioactive compounds. More particularly, the invention relates to the solubilization of lipophilic bioactive agents using non-ionic surfactant solubilizers. Even more particularly, the present invention relates to methods for preparing water soluble compositions of lipophilic bioactives.

BACKGROUND OF THE INVENTION

Numerous bioactive compounds or bioactives important in the food, pharmaceutical and cosmetic industries are lipophilic and, therefore, insoluble in aqueous solutions. These compounds are used in many different forms for many different purposes. For example, bioactive lipophilic compounds used in the cosmetic industry are often applied to the skin in the form of a cream. Similarly, pharmaceutical uses require dosage forms such as oral, topical or intravenous. Food supplements are usually delivered orally in solid or liquid form. It is recognized, therefore, that there is a pressing need to develop new technologies for improving the bioavailability of these insoluble bioactives. It is also important that any technology for increasing the bioavailability of bioactives produces a composition that is amenable to a broad range of applications. Increasing the bioavailability of these bioactives can be achieved by improving their solubility in aqueous solutions.

Coenzyme Qio ("CoQi_0") is one example of a lipophilic bioactive that is of particular interest as it has applications in the food, cosmetic and pharmaceutical fields. CoQio, also called ubiquinone, is found naturally in the inner membrane of the mitochondria and is involved in electron transfer in oxidative phosphorylation.

Several methods and formulations have been published that describe a variety of approaches to obtaining compositions of CoQio and other lipophilic bioactives having increased bioavailability. For example, US Patent 6,056,971 entitled "Method for enhancing dissolution properties of relatively insoluble dietary supplements and product
incorporating same” discloses a method for enhancing the dissolution properties of relatively insoluble dietary supplements. Specifically claimed is a method for enhancing the bioavailability of CoQ10 from an orally delivered soft gelatine capsule from a uniform, non-aqueous solution produced by mixing a non-ionic surface active agent as a solubilizer with a polyhydric alcohol to form a uniform mixture.

US Patent 6,300,377 entitled "Coenzyme Q products exhibiting high dissolution qualities" discloses a liquid dosage form of CoQ10 for oral, cosmetic, dietary supplement or pharmaceutical dosage form. The formulation is non-aqueous and comprises CoQ10, a polysorbate surfactant, a vegetable oil or triglyceride, a glyceryl ester and optionally a phospholipids such as hydroxylated lecithin or tocopherols to solubilize the CoQ10.

US Patent 6,441,050 entitled "Palatable oral coenzyme Q liquid" discloses a pediatric pharmaceutical liquid dosage form of CoQ10 that is also pleasant-tasting. The formulation is aqueous based and comprises CoQ10, with a polysorbate surfactant, a vegetable oil or triglyceride, a glyceryl ester and optionally a phospholipids such as hydroxylated lecithin to enhance the palatability of CoQ10, a sweetener and water.

US Patent 6,740,338 entitled "Reduced form of Coenzyme Q in high bioavailability stable oral dosage form" discloses a formulation for the reduced form of CoQ10 in combination with a lipid soluble reducing agent effective to maintain the CoQ10 in a reduced state and preferably encapsulated in a soft gelatine capsule.

U.S. Patent 6,616,942 entitled "Coenzyme Q10 formulation and process methodology for soft gel capsules manufacturing" discloses a method and formulation for improving bioavailability of CoQ10 by delivering it in a soft gel capsules containing CoQ10, beta-carotenes, Vitamin E, and medium chain triglycerides in rice bran oil and an optional thickener, such as bee's wax, in a soft gel capsule so that a maximum of the CoQ10 is absorbed by the human body. U.S. patent 6,623,734 entitled "Super absorption coenzyme Q10" also discloses a soft gel capsule method and formulation for delivery of CoQ10 with high bioavailability.
U.S. Patent 7,094,804 entitled "Water free ubiquinone concentrate" discloses a water soluble, essentially water-free CoQ\textsubscript{i,o} concentrate comprising CoQ\textsubscript{i,o}, a light oil containing triglycerides, and an emulsifier such as polysorbate present in at least about 73 weight % of the total weight of the concentrate. A method for preparing the concentrate is also disclosed.

U.S. Patent 5,989,583 entitled "Solid lipid compositions of lipophilic compounds for enhanced oral bioavailability" discloses a dry solid lipid composition for use in food additives or dietary supplements that in one form, comprises CoQ\textsubscript{10}, a lipid or mixture of lipids that are solid at room temperature and a phospholipid.

U.S. Patent application 20030232095 entitled "Nano-sized self-assembled structured liquids" discloses nano-sized self-assembled structured concentrates for use as effective carriers for transferring active components into the human body. The nano-sized self-assembled concentrates are liquid concentrates and comprise an aqueous phase, an oil phase, a surfactant, a co-solvent and co-surfactant.

US patents 6,045,826, 6,191,172 and 6,632,443 disclose methods of improving solubility of lipophilic compounds, such as Coenzyme Q\textsubscript{10}, in aqueous media.

Non-ionic surfactants such as cremophor have been utilized as excipients for injectable pharmaceuticals with mixed results. Such surfactants have also been utilized in compositions with neutraceutical compounds in the presence of solvents, particularly for anything greater than small amounts of insoluble compounds such as CoQ\textsubscript{i,o} (see, e.g., U.S. App. #s 2003/147927, 20040167034, 20060198830, 2007/141090 and PCT App. No. WO 2006/080903, WO 2005/079758 and WO 2007/061752).

Having regard to the above described prior art, there is a need to improve the solubility and bioavailability of lipophilic bioactive compounds such as CoQio-
SUMMARY OF THE INVENTION

The present invention is based on the surprising discovery that the solubility and bioavailability of lipophilic bioactive compounds such as CoQ10 can be greatly improved through the use of non-ionic surfactant solubilizers. In particular, it has been discovered that water soluble and highly bioavailable compositions of CoQ10 can be easily prepared using commercially available non-ionic surfactant solubilizers.

The present invention provides compositions having enhanced dissolution and bioavailability of lipophilic bioactive compounds whereby the bioactive compound is combined with a non-ionic surfactant.

More particularly, the present invention provides compositions having enhanced dissolution and bioavailability of lipophilic bioactive compounds whereby the lipophilic bioactive compound is combined with a non-ionic surfactant having a hydrophilic lipophilic balance of between about 10 and about 20 and wherein the molar ratio of the bioactive lipophilic compound and the non-ionic surfactant is from about 1:0.5 to about 1:25.

The present invention further provides methods for the preparation of lipophilic bioactive compounds having enhanced dissolution and bioavailability whereby the lipophilic bioactive compound is combined with a non-ionic surfactant.

The present invention provides pharmaceutical, food product or cosmetic formulations of CoQio comprising an effective amount of CoQ10 in the form of a water-soluble composition and a pharmaceutically or food or cosmetically acceptable additive or additives or vehicle(s).

The present invention also provides pharmaceutical, food product or cosmetic formulations of lipophilic bioactive compounds comprising an effective amount of the lipophilic bioactive compound in the form of a water-soluble composition and a pharmaceutically or food or cosmetically acceptable additive or additives or vehicles.)
According to one aspect of the present invention, there is provided a method of preparing a stable solution including a lipophilic bioactive compound and water comprising the steps of: providing a non-ionic surfactant; preparing a mixture of the lipophilic bioactive compound and the non-ionic surfactant in a predetermined molar ratio; heating the mixture to a temperature necessary to obtain a clear melt; and adding heated water to the mixture to form the stable solution.

According to another aspect of the present invention, there is provided a method of preparing a stable solution including a lipophilic bioactive compound and water comprising the steps of: providing a non-ionic surfactant; preparing a mixture of the lipophilic bioactive compound and the non-ionic surfactant in a predetermined molar ratio; heating the mixture to a temperature necessary to obtain a clear melt; and formulating with or without acceptable additives into solid dosage forms.

According to another aspect of the present invention, there is provided a use of a non-ionic surfactant for preparing a water soluble solution comprising a lipophilic bioactive compound.

According to yet another aspect of the present invention, there is provided a water soluble pharmaceutical composition comprising a pharmaceutically effective amount of a lipophilic compound and a non-ionic surfactant.

According to another aspect of the present invention, there is provided a water soluble cosmetic composition comprising a cosmetically effective amount of an active lipophilic compound and a non-ionic surfactant.

According to yet another aspect of the present invention, there is provided a water soluble food composition comprising an effective amount of a bioactive lipophilic compound and a non-ionic surfactant.
According to another aspect of the present invention, there is provided a water soluble hair care composition comprising an effective amount of a bioactive lipophilic compound and a non-ionic surfactant.

According to yet another aspect of the present invention, there is provided method of the prophylaxis or treatment of a medical disorder associated with oxidative tissue damages or mitochondrial dysfunctions, said method comprising administering to a human or a warm-blooded animal in need of such prophylaxis or treatment a therapeutically effective amount of a water-soluble composition according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Large proportions of compounds, particularly pharmaceutical and nutraceutical compounds, have poor water solubility. The lipophilic bioactive compounds of the present invention include all those pharmaceutical and bioactives with bioavailability issues as a result of poor aqueous solubility. Examples of pharmaceutical actives include: CoQio, ubiquinones, ubiquinols and sterols for various disorders; amphotericin-B, nystatin, and candicidin antibiotics; anticancer drugs such as taxol and doxorubicin; anesthetics such as propafol; and mixtures thereof. Examples of bioactives for cosmetic and food applications include: ubiquinones, ubiquinols, idebenone, phytosterols, sterols, sterol esters; flavonoids, carotenoids, tocopherols and other phytochemicals, fish oil containing polyunsaturated fatty acids, omega 3 fatty acids, EPA, DHA; carotenoids, such as β-carotene, astaxanthin, canaxanthin, lycopene; squalenes; gamma-tocopherol; curcumin; lignans; lunastatin; leutin; aloe vera; essential oils, such as tea tree, basil, eucalyptus, cedarwood, cypress, lemon, lavender, sage, lemongrass, evening primrose, chamomile, lavender, geranium, rose, neroli, ylang ylang, clary sage, palmarosa, carrot, basil; carrier oils, such as sunflower, walnut, olive, sweet almond, apricot kernel, avocado, borage, caster, coconut, emu, grapeseed, jojoba, kukui, nut, olive, peanut, sesame, safflower, wheat germ; oleoresin; retinoic acid; adapalene; azelaic acid; asiatic acid; fatty acids; polyenoic fatty acids; and mixtures thereof.
The non-ionic surfactant of the present invention is completely miscible with water. Preferably, the surfactant component has a high affinity for and solubility in water, it is bio-compatible (with little to no side effects) and has a melting point close to or below body temperature (about 37°C). Other characteristics of concern preferably include good taste and odor, clarity, low toxicity, and other factors that will be determined by the application of the compound. Various classes of non-ionic surfactants are embraced by the present invention. Preferably, the non-ionic surfactant contains polyethylene glycol (PEG). More specifically, the most preferred PEG-containing surfactant for use in the preparation of the present invention could be defined in several distinct classes. A first class of PEG has a polyoxyethylene moiety and a hydrophobic moiety consisting of saturated or unsaturated alkyl or alkylphenyl groups. A second class of PEG-containing surfactants derived from triglyceride oils, which includes polyoxyethylated vegetable oils. Other classes of non-ionic surfactants are also within the scope of the present invention.

The non-ionic surfactant of the present invention is preferably selected from the group consisting Cremophor RH 40™ (polyoxyyl 40 hydrogenated castor oil), Cremophor EL™ (polyoxyyl 35 castor oil), Cremophor ELPTM (polyoxyyl 35 castor oil), and Solutol HS 15™ (macrogol 15 hydroxystearate), PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-60 castor oil, monostearate (and derivatives thereof), glyceryl laurate, glycercyl stearate, glyceryl oleate, glyceryl monooleate, glyceryl monolaurate, sorbitan monooleate, sorbitan monostearate, sorbitan monopalmitate, sorbitan stearate, nonyl phenols, octyl phenols, caprylocaproyl polyoxyglycerides, lauroyl polyoxyglycerides, stearoyl polyoxyglycerides and d-α-tocopheryl polyethylene glycol succinate, or combinations thereof. More preferably, the non-ionic surfactant is Cremophor RH 40™ (polyoxyyl 40 hydrogenated castor oil), Cremophor EL™ (polyoxyyl 35 castor oil), Cremophor ELPTM (polyoxyyl 35 castor oil), Solutol HS 15™ (macrogol 15 hydroxystearate) or TPGST™ (d-α-tocopheryl polyethylene glycol succinate). Most preferably, the non-ionic surfactant is Cremophor RH 40™ (polyoxyyl 40 hydrogenated castor oil), Cremophor EL™ (polyoxyyl 35 castor oil) or Cremophor ELPTM (polyoxyyl 35 castor oil).
Without limiting the scope of the invention and being bound by theory, it is believed that a number of factors result in the improved dissolution and bioavailability of the present invention. First, mixing the lipophilic bioactive compound with the non-ionic surfactant spontaneously forms micelles including nano-micelles when in contact with water. The formation of nano-micelles improves transient solubilization which improves drug dissolution rates and bioavailability. Second, complex formation of the lipophilic bioactive agent with the non-ionic surfactant improves sustained solubilization. For many poorly water-soluble drugs, transport across the aqueous boundary layer represents the dominant rate-limiting step for drug absorption. Sustained solubilization ensures that the drug will remain solubilized in the gastrointestinal tract for a significant amount of time and, thus, improve transport across the aqueous boundary layer. Finally, reports in the literature demonstrate that surfactants inhibit the Pgp efflux mechanism thereby enhancing absorption of the bioactive.

In a particular embodiment of the present invention, there are provided compositions having enhanced dissolution and bioavailability of lipophilic bioactive compounds whereby the lipophilic bioactive compound is combined with a non-ionic surfactant having a hydrophilic lipophilic balance of between about 10 and about 20 and wherein the molar ratio of the bioactive lipophilic compound and the non-ionic surfactant is from about 1:0.5 to about 1:25. Preferably, the invention composition comprises the molar ratio of the bioactive lipophilic compound and the non-ionic surfactant of from about 1:1 to about 1:10; more preferably from about 1:3 to about 1:5. The ratio is dependent on the particulate bioactive and is the ratio required to obtain complete solubilization of the bioactive in the non-ionic surfactant as a single- or one-phase solution upon cooling. This ratio results in higher levels of the bioactive compounds in solution than existing technologies, in the range of 10% or greater, more typically 20%, 25%, 33%, 50% or greater of the bioactive compound in relation to the percentage of the surfactant.

According to one aspect of the present invention, there is provided a method of preparing a stable solution including at least one lipophilic bioactive compound and at least one
non-ionic surfactant, comprising the steps of: providing a non-ionic surfactant and the lipophilic bioactive compound in a predetermined molar ratio, and heating the non-ionic surfactant and the lipophilic bioactive compound to a temperature necessary to obtain a clear melt. The lipophilic bioactive compound and the non-ionic surfactant compound can be mixed prior to heating to create the clear melt, or heated separately to each (or in groups) create clear melt solutions. Alternatively, and preferably in certain circumstances and formulations, the lipophilic bioactive compound(s) and non-ionic compounds can be melted separately, combined in an appropriate ratio and the mixture reheated and mixed until a single phase solution results. The melted formulating can occur with or without acceptable additives into solid dosage forms. The invention also includes compositions produced by this method.

The melting point of most compounds are known to those skilled in the art and may depend on factors such as pressure, humidity, and other such factors which trigger melting of compounds. However, in general, the compounds should be heated to such temperature to obtain a clear melt where the components will appear relatively transparent. Alternatively, preparation can occur at lower temperatures but be stirred or agitated for longer periods of time. Depending upon the type of surfactant and bioactive compound, the quantity and the preparation temperature, the time needed to dissolve the components will vary. In addition to heating, it can also be prepared by sonication, microwave, or other mixing method that creates a homogenous liquid or single-phase solution. Suitable manufacturing equipment would include, for example, stainless steel, heating jacketed, pressurized or non-pressurized, lightening mixers.

The temperature range for melting the components is preferably from about 20° C and about 120° C, more preferably about 25° C to about95° C, more preferably about 30° C to about 95° C, more preferably about 35° C to about90° C, more preferably about 40° C to about85° C, more preferably about 45° C to about80° C, and most preferably about 50° C to about70° C. A substantially clear or clear emulsion is formed. The emulsion (of individual components or combinations thereof) stays clear on cooling to room
temperature. The emulsion does not separate into two layers on cooling to room
temperature but remains in a single-phase solution. Sometimes heating to temperatures of
120° C is required (bioactive stability is necessary) but more normally about 50° C to
about 70° C.

5 The mixing or agitation step mixes the components and preferably includes magnetic
stirring, sonication, shaking and vortex agitation, and includes agitators such as orbital
shakers, sonicators, vibrators, and stirrers.

In a particular embodiment of the present invention, a liquid solubilized, bioavailable
form of a lipophilic bioactive agent, which for the purposes of the description of the
preferred embodiment is CoQ10, according to the present invention may be manufactured
by melting CoQ10 and a suitable non-ionic surfactant (as described above) together by
heating a mixture of the two components to around 65° C. The required amount of water
is heated separately to 65° C and slowly added to the melt. A gel forms which is stirred
vigorously for about an hour and slowly the CoQ10 goes into solution to form a bright
red/orange clear solution at a concentration of 50mg/g. Such solution is stable and can
then be used to manufacture creams, drinks, solid oral dosage forms and IV dosage forms
with or without additional materials such as flavours, buffers, preservatives, binders,
fillers etc.

In another particular embodiment of the present invention, solubilised, bioavailable
CoQ10 according to the present invention can be prepared by dissolving the bioactive
lipophilic compound and the solubilizing agent in a predetermined molar ratio in a water-
miscible organic solvent and subsequently diluting the solution with a predetermined
amount of water and then removing the organic solvent from the solution and optionally
an amount of water necessary to achieve a desired concentration of the water-soluble
composition. The solvent and water may be removed by any conventional means known
to the person skilled in the art including, for example, evaporation under reduced
pressure.
A further alternate method of preparing a water soluble composition of a lipophilic bioactive agent such as CoQ₁₀ involves first dissolving the lipophilic bioactive agent and the non-ionic surfactant in a water miscible solvent. The next step is to dilute the resulting solution with a predetermined amount of water. The following step is the removal from the solution of the organic solvent and optionally an amount of water necessary to achieve a desired concentration of the water soluble composition.

The present invention also includes dry formulations of a lipophilic bioactive agent which solubilises in water upon contact. Such dry formulations are prepared by melting for example CoQ₁₀ and a suitable non-ionic surfactant together by heating a mixture of the two components to around 65° C in order to form a melt. Water may optionally be added at this point to form a gel which is stirred vigorously for about an hour and slowly the CoQ₁₀ goes into solution to form a bright red/orange clear solution at a concentration of 50mg/g. The water is then removed by lyophilisation or other methods known in the art. Dry formulations may need additional ingredients such as polyethylene glycol 600, polyethylene glycol 400 or polypropylene glycol to stabilize the complex. They can be filled into hard or soft gelatin capsules or mixing with traditional standard tableting excipients and compressed into tablets. The liquid complex may also be lyophilized and filled into capsules or vials or compressed into tablets with or without additional materials. The dry formulation is useful for example in the preparation of oral dosage forms such as tablets and capsules. The lipophilic bioactive agent is solubilized upon ingestion where it is readily absorbed.

Pharmaceutical formulations required in a sterile format can be preferably subjected to heat or filter sterilization.

The composition of solubilised bioavailable bioactive lipophilic compound of the present invention, and in particular CoQ₁₀, can be used in the preparation of pharmaceutical dosage forms known in the art including topical, oral, parenteral, suppository and aerosol. Routes of administration include intravenous, oral, topical, rectal, parenteral (injectable), local, inhalant and epidural administration. The compositions of the invention may also
be conjugated to transport molecules or included in transport modalities such as vesicles and micelles to facilitate transport of the molecules. The compositions of the invention may also be conjugated to transport molecules, monoclonal antibodies or transport modalities such as vesicles and micelles. Pharmaceutical compositions including the compounds of the present invention can be administered to humans or animals.

The compositions of the present invention are also used to prepare cosmetic preparations, including hair care products, known in the art including creams, gels or liquid preparations such as aerosols and mists. In addition, the cosmetic preparations include foam baths, oil baths, oil moisturizers, sun protection agents, lotions, baby care products, gels or ointments and, oil bodies, emulsifiers, hyperfatting agents, pearl lustre waxes, consistency substances, thickening agents, polymers, silicon compounds, fats, waxes, stabilizing agents, biogenic active substances, deodorants, agents against dandruff, film forming agents, swelling agents, UV light protection factors, antioxidants, inorganic colour pigments, hydrotropes, preservatives, insect repellents, self tanning agents, perfume oils, and colouring agents. A person skilled in the art will appreciate that cosmetics of the present invention also include: skin-care creams, serums, lotions, powders, perfumes, lipsticks, fingernail polishes, eye and facial makeup, permanent waves, hair colors, hair shampoo, hair conditioners, deodorants, bath oils, bubble baths, and many other types of products. Cosmetic compositions including the compounds of the present invention can be administered to humans or animals.

The compositions of the present invention are also used to prepare food formulations known in the art including dry solid, wet semi-solid and liquid formulations. Foods of the present invention include liquid and solid dietary supplements, liquid and solid nutritional supplements, functional foods, functional drinks, and many other types of products. Food compositions including the compounds of the present invention can be administered to humans or animals.

In a particular embodiment of the present invention, the composition comprising a non-ionic surfactant and bioactive compound is a nutritional supplement or nutraceutical.
prepared as a dietary supplement. For example, the composition can be prepared in a hard or soft gelatin capsules by means known in the art. The composition can also be added to drinks or beverages, or in other palatable solution. Preferably, the non-ionic surfactant will have palatable characteristics or masked with flavoring.

In each case, an effective amount of the solubilized and bioavailable lipophilic bioactive compound is added to the formulation in a therapeutically effective amount along with any additional acceptable additive or vehicle selected from, for example, solvents, adjuvants, sweeteners, fillers, colourants, flavouring agents, lubricants, binders, moisturizing agents, preservatives and mixtures thereof as the case may be.

CoQio can be used in the treatment of certain ailments including hypercholesteremia, infectious diseases and cancers. For example, a pharmaceutical preparation for use in the treatment of hypercholesterolemia according to the present invention comprises a therapeutically effective amount of solubilised composition CoQio and a pharmaceutically acceptable carrier. Similarly, the present invention includes a pharmaceutical composition for the treatment of a fungal infection comprising a therapeutically effective amount of a solubilised composition of CoQio and a macrolide polyene antibiotic as the bioactive lipophilic compound, in conjunction with a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are known and understood by person skilled in the art.

CoQio and other lipophilic bioactive compounds are also useful ingredients in cosmetics, including hair care products, for alleviating a number of skin conditions.

CoQio and other lipophilic bioactive compounds can also be delivered through food compositions for health and therapeutic benefits.

The manufacture of the fill formulations of the present invention requires standard mixing and heating equipment known by persons skilled in the art, while conventional emulsion methods require high energy input and shearing during processing. The fill formulations
of the present invention are also physically stable without recrystallization during storage. Stable shelf life is critical for commercialization.

Solubility and dissolution are the limiting factors in bioavailability of coenzyme Q\textsubscript{10}. These factors have been successfully overcome by the present invention. Therefore, the bioavailability of the formulations of the present invention is has higher bioavailability than prior art formulations. The principle, methodology and formulations developed in this application are not limited to coenzyme Q\textsubscript{10}. They are also applicable to other poorly water-soluble pharmaceutical active ingredients for improving dissolution and bioavailability.

EXAMPLE 1

Preparation of a fish oil beverage. Cremophor RH 40 (100g) is heated to around 60\textdegree C until a clear liquid results. Fish oil (25g) is heated to around 50\textdegree C until a clear liquid results. Cremophor RH 40 and fish oil are combined in an appropriate ratio and the mixture reheated to around 50\textdegree C and mixed until a single phase solution results. 5g of the mixture is added to 500g of spring water and the mixture stirred vigorously until the complex disperses and a clear solution results. A solution containing 1g of fish oil in 500 ml of spring water results. Alternatively the fish oil complex can be added to Gatorade, Propel or other sports drink.

EXAMPLE 2

Preparation of a CoQi\textsubscript{0} beverage. Cremophor RH 40 (100g) is heated to around 60\textdegree C until a clear liquid results. CoQi\textsubscript{0} (25g) is heated to around 60\textdegree C until a clear liquid results. Cremophor RH 40 and CoQi\textsubscript{0} are combined in an appropriate ratio and the mixture reheated 60\textdegree C and mixed until a single phase solution results. 2.5g of the mixture is added to 500g of spring water and the mixture stirred vigorously until the complex disperses and a clear solution results. A solution containing 500 mg of CoQio in 500 ml of water results. Alternatively the CoQio can be added to beer, Gatorade, Propel or other sports drinks or beverage.
EXAMPLE 3

Preparation of an Oleo resin beverage. Cremophor RH 40 (100g) is heated to around 60°C until a clear liquid results. Oleo resin (25g) is heated to around 60°C until a clearer liquid results. Cremophor RH 40 and Oleo resin are combined in an appropriate ratio and the mixture reheated to around 60°C and mixed until a single phase solution results. 2.5g of the mixture is added to 500g of spring water and the mixture stirred vigorously until the complex disperses and a clear solution results. A solution containing 500 mg of Oleo resin in 500 ml of water results. Alternatively the oleo resin can be added to Gatorade, Propel or other sports drinks.

EXAMPLE 4

Preparation of an avocado oil beverage. Cremophor RH 40 (100g) is heated to around 60°C until a clear liquid results. Avocado oil (25g) is heated to around 60°C until a clear liquid results. Cremophor RH 40 and Oleoresin are combined in an appropriate ratio and the mixture reheated 60°C and mixed until a single phase solution results. 2.5g of the mixture is added to 500g of spring water and the mixture stirred vigorously until the complex disperses and a clear solution results. A solution containing 500 mg of avocado oil in 500 ml of water results. Alternatively the avocado oil can be added to Gatorade, Propel or other sports drinks.

EXAMPLE 5

Preparation of a fish oil capsule. Cremophor RH 40 (100g) is heated to around 60°C until a clear liquid results. Fish oil (25g) is heated to around 50°C until a clear liquid results. Cremophor RH 40 and fish oil are combined in an appropriate ratio and the mixture reheated to 50°C and mixed until a single phase solution results. 1g of the mixture while warm is added to a "000" hard gelatine capsule and allowed to cool. A capsule containing 200 mg of water soluble fish oil results. Alternatively the fish oil complex can be encapsulated in a soft gelatine capsule.
EXAMPLE 6

Preparation of a CoQi0 capsule. Cremophor RH 40 (75g) is heated up to 120\(^{\circ}\)C until a clear liquid results. CoQi0 (25g) is heated to around 60\(^{\circ}\)C until a clear liquid results. Cremophor RH 40 and CoQi0 are combined in an appropriate ratio and the mixture reheated up to 120\(^{\circ}\)C and mixed until a single phase solution results. The mixture is allowed to cool to room temperature and the cycle repeated until a stable complex is achieved. 1g of the mixture while warm is added to a "000" hard gelatine capsule and allowed to cool. A capsule containing 300 mg of water soluble CoQio results. Alternatively the CoQi0 complex can be encapsulated in a soft gelatine capsule.

EXAMPLE 7

Preparation of a Vitamin E capsule. Cremophor RH 40 (100g) is heated to around 60\(^{\circ}\)C until a clear liquid results. Vitamin E (25g) is heated to around 60\(^{\circ}\)C until a clear liquid results. Cremophor RH 40 and vitamin E are combined in an appropriate ratio and the mixture reheated to 60 \(^{\circ}\)C and mixed until a single phase solution results. 1g of the mixture while warm is added to a "000" hard gelatine capsule and allowed to cool. A capsule containing 200 mg of water soluble vitamin E results. Alternatively the vitamin E complex can be encapsulated in a soft gelatine capsule.

EXAMPLE 8

Preparation of a Oleo resin capsule. Cremophor RH 40 (100g) is heated to around 60\(^{\circ}\)C until a clear liquid results. Oleo resin (25g) is heated to around 60\(^{\circ}\)C until a clear liquid results. Cremophor RH 40 and Oleo resin are combined in an appropriate ratio and the mixture reheated to 60\(^{\circ}\)C and mixed until a single phase solution results. 1g of the mixture while warm is added to a "000" hard gelatine capsule and allowed to cool. A capsule containing 200 mg of water soluble Oleo resin results. Alternatively the Oleo resin complex can be encapsulated in a soft gelatine capsule.
EXAMPLE 9

Preparation of a avocado oil capsule. Cremophor RH 40 (100g) is heated to around 60°C until a clear liquid results. Avocado oil (25g) is heated to around 60°C until a clear liquid results. Cremophor RH 40 and avocado oil are combined in an appropriate ratio and the mixture reheated to 60°C and mixed until a single phase solution results. 1g of the mixture while warm is added to a "000" hard gelatine capsule and allowed to cool. A capsule containing 200 mg of water soluble avocado oil results. Alternatively the avocado oil complex can be encapsulated in a soft gelatine capsule.

EXAMPLE 10

Preparation of a CoQi0/Vitamin E beverage. Cremophor RH 40 (40g) is heated to around 60°C until a clear liquid results. CoQi0 (5g) and vitamin E (5g) are mixed and heated to around 60°C until a clear liquid results. Cremophor RH 40 and the bioactive mixture are combined in an appropriate ratio and the mixture reheated to around 60°C and mixed until a single-phase solution results. 10g of the mixture is added to 500g of spring water and the mixture stirred vigorously until the complex disperses and a clear solution results. A solution containing 1g of CoQi0 and 1 g of vitamin E in 500 ml of spring water results. Alternatively the CoQi0/vitamin E complex can be added to Gatorade, Propel or other sports drink.

EXAMPLE 11

Preparation of a CoQi0/avocado oil beverage. Cremophor RH 40 (40g) is heated to around 60°C until a clear liquid results. CoQi0 (5g) and avocado oil (5g) are mixed and heated to around 60°C until a clear liquid results. Cremophor RH 40 and the bioactive mixture are combined in an appropriate ratio and the mixture reheated 60°C and mixed until a single phase solution results. 10g of the mixture is added to 500g of spring water and the mixture stirred vigorously until the complex disperses and a clear solution results. A solution containing 1g of CoQi0 and 1 g of avocado oil in 500 ml of spring water
results. Alternatively the CoQi₀/avocado oil complex can be added to Gatorade, Propel or other sports drink.

EXAMPLE 12

Preparation of a CoQi₀/avocado oil/vitamin E beverage. Cremophor RH 40 (60g) is heated to around 60°C until a clear liquid results. CoQi₀ (5g), avocado oil (5g) and vitamin E (5g) are mixed and heated to around 60°C until a clear liquid results. Cremophor RH 40 and the bioactive mixture are combined in an appropriate ratio and the mixture reheated to around 60°C and mixed until a single phase solution results. 10g of the mixture is added to 500g of spring water and the mixture stirred vigorously until the complex disperses and a clear solution results. A solution containing 750 mg of CoQIO, 750 mg of avocado oil and 750 mg of vitamin E in 500 ml of spring water results. Alternatively the CoQio/avocado oil complex can be added to Gatorade, Propel or other sports drink.

EXAMPLE 13

Preparation of a CoQi₀/avocado oil/vitamin E moisturizing cream. Cremophor EL (60g) is heated to around 60°C until a clear liquid results. CoQio (5g), avocado oil (5g) and vitamin E (5g) are mixed and heated to around 60°C until a clear liquid results. Cremophor EL and the bioactive mixture are combined in an appropriate ratio and the mixture reheated to around 60°C and mixed until a single phase solution results. 40g of the mixture is added to 60g of moisturizing cream to produce a cosmetic cream with 1% of each bioactive.

EXAMPLE 14

Preparation of a CoQi₀/avocado oil/vitamin E body spray. Cremophor EL (40g) is heated to around 60°C until a clear liquid results. CoQio (4g), avocado oil (8g) and vitamin E (6g) are mixed and heated to around 60°C until a clear liquid results. Cremophor EL and the bioactive mixture are combined in an appropriate ratio and the mixture reheated to
60°C and mixed until a single phase solution results. 20g of the mixture is added to 500g of spring water and the mixture stirred vigorously until the complex disperses and a clear solution results. The solution containing 0.08% CoQio, 0.16% avocado oil and 0.12% vitamin E is filled into a spray bottle to produce an enriched body spray.

EXAMPLE 15

Preparation of a CoQi o/Vitamin E capsule. Cremophor RH 40 (40g) is heated to around 60°C until a clear liquid results. CoQi o (5g) and vitamin E (5g) are mixed and heated to around 60°C until a clear liquid results. Cremophor RH 40 and the bioactive mixture are combined in an appropriate ratio and the mixture reheated 60°C and mixed until a single phase solution results. 1g of the mixture while warm is added to a "000" hard gelatine capsule and allowed to cool. A capsule containing 100 mg of water soluble CoQi o and 100 mg of water soluble vitamin E results. Alternatively the complex can be encapsulated in a soft gelatine capsule.

EXAMPLE 16

Preparation of a CoQi o/avocado oil capsule. Cremophor RH 40 (40g) is heated to around 60°C until a clear liquid results. CoQi o (5g) and avocado oil (5g) are mixed and heated to around 60°C until a clear liquid results. Cremophor RH 40 and the bioactive mixture are combined in an appropriate ratio and the mixture reheated 60°C and mixed until a single phase solution results. 1g of the mixture while warm is added to a "000" hard gelatine capsule and allowed to cool. A capsule containing 100 mg of water soluble CoQi o and 100 mg of water soluble avocado oil results. Alternatively the complex can be encapsulated in a soft gelatine capsule.

EXAMPLE 17

Preparation of a CoQi o/avocado oil/vitamin E capsule. Cremophor RH 40 (60g) is heated to around 60°C until a clear liquid results. CoQi o (5g), avocado oil (5g) and vitamin E (5g) are mixed and heated to around 60°C until a clear liquid results.
Cremophor EL and the bioactive mixture are combined in an appropriate ratio and the mixture reheated to 60°C and mixed until a single phase solution results. 1g of the mixture while warm is added to a "000" hard gelatine capsule and allowed to cool. A capsule containing 67 mg of water soluble CoQ_{10}, 67 mg of water soluble avocado oil and 67 mg of water soluble vitamin E results. Alternatively the complex can be encapsulated in a soft gelatine capsule.

Various embodiments of the present invention having been thus described in detail by way of example, it will be apparent to those skilled in the art that variations and modifications may be made without departing from the invention. The invention includes all such variations and modifications as fall within the scope of the appended claims.

Having thus described the present invention in detail, it will be obvious to those skilled in the art that various changes or modifications may be made without departing from the scope of the invention defined in the appended claims and described in the specification.
I CLAIM:

1. A method of preparing a stable solution including a lipophilic bioactive compound and water comprising the steps of:

   providing a non-ionic surfactant;

   preparing a mixture of the lipophilic bioactive compound and the non-ionic surfactant in a predetermined molar ratio;

   heating the mixture to a temperature necessary to obtain a clear melt; and

   adding heated water to the mixture to form the stable solution.

2. A method of preparing a stable complex including a lipophilic bioactive compound comprising the steps of:

   providing a non-ionic surfactant;

   preparing a mixture of the lipophilic bioactive compound and the non-ionic surfactant in a predetermined molar ratio;

   heating the mixture to a temperature necessary to obtain a clear melt.

3. A method according to claim 1 or 2 wherein the lipophilic bioactive compound is selected from the group consisting of: ubiquinones, ubiquinols and sterols; amphotericin-B, nystatin, and candididin antibiotics; anticancer drugs such as taxol and doxorubicin; anesthetics such as propafol; phytosterols, sterols, sterol esters; fish oil containing polyunsaturated fatty acids, omega 3 fatty acids, EPA, DHA; carotenoids, such as β-carotene, astaxanthin, canaxanthin, lycopene; squalenes; gamma-tocopherol; curcumin; lignans; lunastatin; leutin; aloe vera; essential oils such as tea tree, basil, eucalyptus, cedarwood, cypress, lemon, lavender, sage, lemongrass, evening primrose, chamomile, lavender, geranium, rose, neroli, ylang ylang, clary sage, palmarosa, carrot, basil; carrier oils such as sunflower, walnut, olive, sweet almond, apricot kernel, avocado, borage,
caster, coconut, emu, grapeseed, jojaba, kukui, nut, olive, peanut, sesame, safflower, wheat germ; oleoresin; retinoic acid; adapalene; azelaic acid; asiatic acid; fatty acids; polyenoic fatty acids; and mixtures thereof.

4. A method according to claim 1 or 2 wherein the lipophilic bioactive compound is CoQ10.

5. A method according to any one of claims 1-4 wherein the non-ionic surfactant is selected from the group consisting of polyoxyl 40 hydrogenated caster oil, polyoxyl 35 caster oil, macrogol 15 hydroxystearate, caprylocaproyl polyoxyglycerides, lauroyl polyoxyglycerides, stearoyl polyoxyglycerides and \( \alpha \)-tocopheryl polyethylene glycol succinate; and mixtures thereof.

6. A method according to any one of claims 1-5 wherein the non-ionic surfactant is selected from the group consisting of polyoxyl 40 hydrogenated caster oil and polyoxyl 35 caster oil; and mixtures thereof.

7. A method according to any one of claims 1-5 wherein the non-ionic surfactant is selected from the group consisting of macrogol 15 hydroxystearate and \( \alpha \)-tocopheryl polyethylene glycol succinate; and mixtures thereof.

8. A method according to claim 1 or 2, wherein the molar ratio of the bioactive lipophilic compound and the non-ionic surfactant is from about 1:0.5 to about 1:25.

9. A method according to claim 1, wherein the mixture is heated to about 65°C.

10. Use of a non-ionic surfactant for preparing a water soluble lipophilic bioactive composition.

11. Use according to claim 10 wherein the lipophilic bioactive compound is selected from the group consisting of: ubiquinones, ubiquinols and sterols; amphotericin-B, nystatin, and candidin antibiotics; anticancer drugs such as taxol and doxorubicin; anesthetics such as propafol; idebenone, phytosterols, sterols, sterol esters; fish oil.
containing polyunsaturated fatty acids, omega 3 fatty acids, EPA, DHA; carotenoids, such as β-carotene, astaxanthin, canthaxanthin, lycopene; squalenes; gamma-tocopherol; curcumin; lignans; lunastatin; leutin; aloe vera; essential oils such as tea tree, basil, eucalyptus, cedarwood, cypress, lemon, lavender, sage, lemongrass, evening primrose, chamomile, lavender, geranium, rose, neroli, ylang ylang, clary sage, palmarosa, carrot, basil; carrier oils such as sunflower, walnut, olive, sweet almond, apricot kernel, avocado, borage, caster, coconut, emu, grapeseed, jojoba, kukui, nut, olive, peanut, sesame, safflower, wheat germ; oleoresin; retinoic acid; adapalene; azelaic acid; asiatic acid; fatty acids; polyenoic fatty acids; and mixtures thereof.

12. Use according to claim 10 or 11 wherein the lipophilic bioactive compound is CoQ10.

13. Use according to any one of claims 10 to 12 wherein the non-ionic surfactant is selected from the group consisting of polyoxyl 40 hydrogenated castor oil, polyoxyl 35 castor oil, macrogol 15 hydroxy stearate, caprylocaproyl polyoxyglycerides, huroyl polyoxyglycerides, stearoyl polyoxyglycerides and d-α-tocopheryl polyethylene glycol succinate; and mixtures thereof.

14. Use according to any one of claims 10-12 wherein the non-ionic surfactant is selected from the group consisting of polyoxyl 40 hydrogenated castor oil and polyoxyl 35 castor oil; and mixtures thereof.

15. Use according to any one of claims 10-12 wherein the non-ionic surfactant is selected from the group consisting of macrogol 15 hydroxy stearate and d-α-tocopheryl polyethylene glycol succinate; and mixtures thereof.

16. A pharmaceutical water soluble composition comprising an effective amount of a lipophilic compound and a non-ionic surfactant.

17. A pharmaceutical composition according to claim 16 further comprising a pharmaceutically acceptable additive or vehicle selected from the group consisting of
solvents, adjuvants, sweeteners, fillers, colourants, flavouring agents, lubricants, binders, moisturizing agents, preservatives and mixtures thereof.

18. A pharmaceutical composition according to claim 16, in a form suitable for topical, oral, parenteral, or inhaled administration and in a form suitable for patch and aerosol delivery.

19. A pharmaceutical composition according to claim 16, wherein the composition is lyophilized for topical application, oral delivery, or parenteral administration.

20. A cosmetic water soluble composition comprising an effective amount of a lipophilic compound and a non-ionic surfactant.

21. A cosmetic composition according to claim 20 further comprising a cosmetically acceptable additive or vehicle selected from the group consisting of solvents, adjuvants, sweeteners, fillers, colourants, flavouring agents, lubricants, binders, moisturizing agents, preservatives and mixtures thereof.

22. A hair care water soluble composition comprising an effective amount of a lipophilic compound and a non-ionic surfactant.

23. A hair care composition according to claim 22 further comprising a cosmetically acceptable additive or vehicle selected from the group consisting of solvents, adjuvants, sweeteners, fillers, colourants, flavouring agents, lubricants, binders, moisturizing agents, preservatives and mixtures thereof.

24. A food water soluble composition comprising an effective amount of a bioactive lipophilic compound and a non-ionic surfactant.

25. A food composition according to claim 24 further comprising a food acceptable additive or vehicle selected from the group consisting of solvents, adjuvants, sweeteners, fillers, colourants, flavouring agents, lubricants, binders, moisturizing agents, preservatives and mixtures thereof.
26. A composition according to claim 20, 22 or 24, in a form suitable for topical, oral, parenteral, or inhaled administration and in a form suitable for patch and aerosol delivery.

27. A method of the prophylaxis or treatment of a medical disorder associated with oxidative tissue damages or mitochondrial dysfunctions, said method comprising administering to a human or a warm-blooded animal in need of such prophylaxis or treatment a therapeutically effective amount of a water-soluble composition according to any one of claims 16-25.

28. A method according to claim 27, wherein the disorder is selected from the group consisting of heart diseases, ischemia/reperfusion tissue damages, neurodegenerative disorders and mitochondrial encephalomyelopathies.

28. Use of the pharmaceutical composition according to claim 16 or 17 for the treatment of an ailment in a human or warm blooded animal.

29. Use of the pharmaceutical composition according to claim 16 or 17 for the treatment of a fungal infection, wherein a macrolide polyene antibiotic is the bioactive lipophilic compound, in conjunction with a pharmaceutically acceptable diluent or carrier.

30. Use of the pharmaceutical composition according to claim 16 or 17 for the treatment of a cancer or neurogenerative diseases or cardiovascular diseases.

31. Use of the pharmaceutical composition according to claim 16 or 17 for the treatment of a condition associated with high cholesterol and high blood pressure.

32. A method of the prophylaxis or treatment of a condition associated with a deficiency in a lipophilic compound.

33. Use of cosmetic, hair care and food compositions according to claim 26 for the treatment of a condition in a human or warm blooded animal.
34. A method of preparing a stable complex including a lipophilic bioactive compound comprising the steps of:

- providing a non-ionic surfactant;
- preparing a mixture of the lipophilic bioactive compound and the non-ionic surfactant in a predetermined molar ratio in a water-miscible organic solvent;
- diluting the mixture with a predetermined amount of water; and
- removing the organic solvent from the mixture and optionally an amount of water necessary to achieve a desired concentration of the water-soluble composition.

35. A method of preparing a single-phase solution comprising the steps of:

- pre-treating at least one non-ionic surfactant;
- pre-treating at least one lipophilic bioactive compound;
- preparing a mixture of the lipophilic bioactive compound and the non-ionic surfactant in a predetermined molar ratio necessary to produce a single phase solution; and
- heating the mixture to a temperature necessary to obtain a clear melt and cooling to form the single-phase solution.

36. The method of claim 35, wherein the heating and cooling of the combined mixture is repeated to form the single-phase solution.

37. The method of claim 35, wherein the lipophilic compound and non-ionic surfactant is agitated together to form the single-phase solution.

38. The method of claim 35, wherein the single-phase solution is added to water or other beverage.
39. The method of Claim 38 where the solution is filter sterilized, heat sterilized or pasteurized.

40. The method of claim 35, wherein the mixture is filled into a hard or soft gelatine capsule.

41. The method of claim 38, wherein the mixture is lyophilized for topical, oral or parenteral administration.

42. The method of claim 35, wherein the mixture is formulated into a compressed tablet, conventional capsule or IV formulation.

43. The method of claim 35, wherein the surfactant is melted to its melting point to form a liquid surfactant mixture and and the bioactive compound is melted to its melting point to form a liquid bioactive compound mixture.

44. The method of claim 35, wherein the liquid mixtures are combined, mixed and reelted until a single phase solution results.

45. The method of claim 35, wherein the lipophilic bioactive compound is selected from the group consisting of: ubiquinones, ubiquinols and sterols; amphotericin-B, nystatin, and candidicidin antibiotics; anticancer drugs such as taxol and doxorubicin; anesthetics such as propafol; phytosterols, sterols, sterol esters; fish oil containing polyunsaturated fatty acids, omega 3 fatty acids, EPA, DHA; carotenoids, such as β-carotene, astaxanthin, canaxanthin, lycopene; squalenes; gamma-tocopherol; curcumin; lignans; lunastatin; leutin; aloe vera; essential oils, such as tea tree, basil, eucalyptus, cedarwood, cypress, lemon, lavender, sage, lemongrass, evening primrose, chamomile, lavender, geranium, rose, neroli, ylang ylang, clary sage, palmarosa, carrot, basil; carrier oils, such as sunflower, walnut, olive, sweet almond, apricot kernel, avocado, borage,
caster, coconut, emu, grapeseed, jojaba, kukui, nut, olive, peanut, sesame, safflower, wheat germ; oleoresin; retinoic acid; adapalene; azelaic acid; asiatic acid; fatty acids; polyenoic fatty acids; and mixtures thereof.

46. The method of claim 42, including two or more lipophilic bioactive compounds.

47. The method of claim 42, wherein the lipophilic bioactive compound is CoQ10.

48. The method of claim 42, wherein the lipophilic bioactive compound is fish oil.

49. The method of claim 35, wherein the non-ionic surfactant contains polyethylene glycol (PEG).

40. The method of claim 44, wherein the non-ionic surfactant is selected from the group consisting of Cremophor RH 40™ (polyoxyl 40 hydrogenated castor oil), Cremophor EL™ (polyoxyl 35 castor oil), Cremophor ELP™ (polyoxyl 35 castor oil), and Solutol HS 15™ (macrogol 15 hydroxystearate), PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-60 castor oil, monostearate (and derivatives thereof), glyceryl laurate, glyceryl stearate, glyceryl oleate, glyceryl monooleate, glyceryl monolaurate, sorbitan monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan stearate, nonyl phenols, octyl phenols, caprylocaproyl polyoxyglycerides, lauroyl polyoxyglycerides, stearoyl polyoxyglycerides and 1-α-tocopheryl polyethylene glycol succinate, or combinations thereof.

41. The method of claim 35, including two or more lipophilic bioactive compounds.

42. The method of claim 35, wherein the non-ionic surfactant is cremophor.
43. The method of claim 40, wherein the lipophilic bioactive compound is selected from vitamin E, vitamin A, vitamin K, and vitamin D, and prodrugs or derivatives thereof.

44. The method of claim 35, wherein the single-phase solution is formulated for cosmetic, pharmaceutical, nutritional, dietary or supplemental applications.

45. A single-phase composition comprising at least one non-ionic surfactant and at least one lipophilic bioactive compound prepared by the method of claim 1.

46. A single-phase solution comprising:
   at least one non-ionic surfactant, and
   at least one lipophilic bioactive compound,
   wherein the molar ratio of the bioactive lipophilic compound and the non-ionic surfactant is from about 1:0.5 to about 1:25.

47. The single-phase solution of claim 46, wherein the lipophilic bioactive compound is selected from the group consisting of: ubiquinones, ubiquinols and sterols; amphotericin-B, nystatin, and candididin antibiotics; anticancer drugs such as taxol and doxorubicin; anesthetics such as propafol; phytosterols, sterols, sterol esters; fish oil containing polyunsaturated fatty acids, omega 3 fatty acids, EPA, DHA; carotenoids, such as β-carotene, astaxanthin, canaxanthin, lycopene; squalenes; gamma-tocopherol; curcumin; lignans; lunastatin; leutin; aloe vera; essential oils, such as tea tree, basil, eucalyptus, cedarwood, cypress, lemon, lavender, sage, lemongrass, evening primrose, chamomile, lavender, geranium, rose, neroli, ylang ylang, clary sage, palmarosa, carrot, basil; carrier oils, such as sunflower, walnut, olive, sweet almond, apricot kernel, avocado, borage, caster, coconut, emu, grapeseed, jojoba, kukui, nut, olive, peanut, sesame, safflower, wheat germ; oleoresin; retinoic acid; adapalene; azelaic acid; asiatic acid; fatty acids; polyenoic fatty acids; and mixtures thereof.
48. The single-phase solution of claim 47, including two or more lipophilic bioactive compounds.

49. The single-phase solution of claim 47, wherein the lipophilic bioactive compound is CoQio.

50. The single-phase solution of claim 47, wherein the lipophilic bioactive compound is fish oil.

51. The single-phase solution of claim 47, wherein the non-ionic surfactant contains polyethylene glycol (PEG).

52. The single-phase solution of claim 51, wherein the non-ionic surfactant is selected from the group consisting of Cremophor RH 40™ (polyoxyl 40 hydrogenated castor oil), Cremophor EL™ (polyoxyl 35 castor oil), Cremophor ELP™ (polyoxyl 35 castor oil), and Solutol HS 15™ (macrogol 15 hydroxystearate), PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-60 castor oil, monostearate (and derivatives thereof), glyceryl laurate, glyceryl stearate, glyceryl oleate, glyceryl monooleate, glyceryl monolaurate, sorbitan monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan stearate, nonyl phenols, octyl phenols, caprylocaproyl polyoxyglycerides, lauroyl polyoxyglycerides, stearyl polyoxyglycerides and α-tocopherol polyethylene glycol succinate, or combinations thereof.

53. The single-phase solution of claim 46, including two or more lipophilic bioactive compounds.

54. The single-phase solution of claim 46, wherein the non-ionic surfactant is cremophor.
55. The single-phase solution of claim 46, wherein the bioactive compound is at least 15% of the single-phase solution.

56. The single-phase solution of claim 46, wherein the single-phase solution is added to water or other beverage.

57. The single-phase solution of claim 46, wherein the mixture is filled into a hard or soft gelatine capsule.

58. The single-phase solution of claim 57, wherein the lipophilic bioactive compound is selected from vitamin E, vitamin A, vitamin K, and vitamin D, and prodrugs or derivatives thereof.

59. The single-phase solution of claim 46 formulated for cosmetic, pharmaceutical, nutritional, dietary or supplemental applications.

60. A method of preparing a stable complex including a lipophilic bioactive compound comprising the steps of:
providing at least one non-ionic surfactant;
providing at least one lipophilic bioactive compound;
preparing a mixture of the lipophilic bioactive compound and the non-ionic surfactant in a predetermined molar ratio in a water-miscible organic solvent wherein the molar ratio of the bioactive lipophilic compound and the non-ionic surfactant is from about 1:0.5 to about 1:25;
diluting the mixture with a predetermined amount of water; and
removing the organic solvent from the mixture and optionally an amount of water necessary to achieve a desired concentration of the water-soluble composition.
INTERNATIONAL SEARCH REPORT

International application No
PCT/CA2008/000336

A CLASSIFICATION OF SUBJECT MATTER
According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database (*), Delphion (*), PubMed (*), Google Scholar (*), Scopus (*)
(* Hypophil*, solubiliz*, surfactant, coenzyme Q, CoQ10, vitamin E, fish oil, Cremophor)

C DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<tr>
<td>X</td>
<td>US 6,045,826 (H BOROWY-BOROWSKI et al) 4 Apr 2000 (04-04-2000) cited in the application see entire document, and particularly col 3, line 25 - col 4, line 10, col 4, line 29 - col 7, line 64, col 8, lines 1-25, claims 1-45, examples 5-11</td>
<td>1-28, 28*, 29-47, 49, 40<em>49</em>, 51*-60*</td>
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<tr>
<td>X</td>
<td>WO 05/079758 (S B HARRIS et al) 1 September 2005 (01-09-2005) cited in the application see entire document, and particularly pages 7-8, 14-17, claims 1, 2, 4-10, 21, 25, 43-60, examples 1, 2</td>
<td>1-11, 13, 15-26, 33, 46*, 47*, 50*-52*, 54*-57*, 59*</td>
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<td>X</td>
<td>CA 2,313,024 (A K MISHRA et al) 17 June 1999 (17-06-1999) see entire document, and particularly pages 6-13, claims, example 2</td>
<td>2, 3, 5, 6, 8, 10, 11, 13, 14, 16-26, 28*, 33, 35-46, 48, 49, 40*-42*, 44*-48*, 50*-57*, 59*</td>
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</table>

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents
A document defining the general state of the art which is not considered to be of particular relevance
E earlier application or patent but published on or after the international filing date
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
O document referring to an oral disclosure use exhibition or other means
P document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
10 June 2008 (10-06-2008)

Date of mailing of the international search report
22 July 2008 (22-07-2008)

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### DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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| X        | WO 06/080903 (S B HARRIS et al)  
3 August 2006 (03-08-2006)  
cited in the application  
see entire document, and particularly  
pages 7, 10-13, 18-21, claims, examples 8, 9 | 1-6, 8, 10-14, 16-26, 28*, 33, 35-45, 47, 49, 40*, 42*, 44*, 46*, 47*, 49*, 51*, 52*, 54*-57*, 59* |
| X        | S NAZZAL et al “Analysis of ubidecarenone (CoQ10) aqueous samples using reversed phase liquid chromatography”  
PHARMAZIE, vol 56, no 5, May 2001,  
pages 394-396  
page 394, sect 2, page 395, sect 4 3 4 5 | 1-6, 8, 10-14, 16-26, 28, 28*, 30, 31, 33, 46*, 47*, 49*, 51*, 52*, 54*-57*, 59* |
| X        | EP 0179,583 (D G POPE et al)  
30 April 1986 (30-04-1986)  
see entire document, and particularly  
claims 1-9, page 4, formulation 6, pages 9-10, examples 7-9 | 1-8, 10-12, 16-26, 35-45, 40*, 46*, 47*, 52*, 55*, 59* |
| X        | CA 2,442,151 (K FUIH et al)  
14 November 2002 (14-11-2002)  
see entire document, and particularly  
claims 1-5, 12-18, example 2 | 10-14, 16-26, 46*, 47*, 49*, 52*, 55*, 59* |
| X        | EP 1,464,341 (A. CAMPANA et al)  
6 October 2004 (06-10-2004)  
see entire document, and particularly  
page 2, lines 15-16, page 3, line 50 - page 4, line 15, claims 1-9, examples 1-10 | 10-13, 15-26, 28*, 33, 46*, 47*, 49*, 52*, 55*, 59* |
| X        | WO 02/056709 (D ROWE et al)  
see entire document, and particularly  
pages 7-9, example 1, claims, examples 1, 2 | 10, 11, 13, 14, 16-26, 33, 46*-48*, 50*-59* |

**Notes:**  
- the numbering of the second claim 28 of page 25 has been modified as claim 28*, because there are two claims 28;  
- the numbering of claims 40-60 of pages 28-31 has been modified as claims 40*, 60*, because these claims are not numbered consecutively to claim 49 of page 28.
The claims are directed to two alleged inventions, corresponding to the following independent claims defining the two different methods of preparing a stable complex/solution including a lipophilic bioactive compound. Claims 1, 2 and 35 for the method of Group A, and claims 34 and 60* for the method of Group B. The only feature linking these groups is the presence of a lipophilic compound and a non-ionic surfactant in the composition, in a predetermined molar ratio. This feature is already known in the art, see for example documents D7-D9. Since this feature is known, it cannot be relied upon to link the independent claims into a single general inventive concept.

The remaining independent claims, defining compositions and uses thereof, have been searched on the basis of being derived from any one of the present alleged inventive methods of preparing the stable lipophilic compound solution.
INTERNATIONAL SEARCH REPORT

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos 27, 28, 32 because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 27, 28, 32 are directed to a method of treatment of the human or animal body, the search has been carried out based on the alleged effects of the compounds and composition thereof.

2. Claim Nos 1-3, 5-11, 13-46, 49, 40M2*, 44M8*, 51*-57*, 59* and 60* because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

   Claims 1-3, 5-11, 13-46, 49, 40*-42*, 44*-48*, 51*-57*, 59* and 60* relate to a use or a method of using so many different compounds arising from the expression "lipophilic bioactive compound", that a meaningful search of the claims is rendered impossible. The subject-matter of these claims is not adequately supported in the description. Consequently, a limited search has been established for the parts of the application which appear to be clear and supported under PCT Articles 5 and 6, namely a method of solubilizing a lipophilic compound with a nonionic surfactant. More specifically, the following lipophilic compounds selected from the examples 1-15 within the disclosure for which the method is tested have been searched: the focus has been directed to the lipophilic agents Coenzyme Q10, Vitamin E and fish oil.

3. Claim Nos because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 64(a).

This International Searching Authority found multiple inventions in this international application, as follows:

Group A: claims 1-9, 35-45*, and (partially) claims 10-33 and 46*-59* are directed to a method of preparing a stable lipophilic bioactive compound solution, by mixing a lipophilic bioactive compound with a non-ionic surfactant and heating the mixture to obtain a clear melt, and to compositions and uses thereof.

Group B: claims 34, 60*, and (partially) claims 34-33 and 46*-59* are directed to a method of preparing a stable lipophilic bioactive compound solution, by mixing a lipophilic bioactive compound with a non-ionic surfactant in a water-soluble organic solvent, diluting the mixture with water and by removing the organic solvent and optionally the water, to obtain a water-soluble composition, and to uses and compositions thereof. See Continuation on Supplemental page

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claim Nos.

Remark on Protest: The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

No protest accompanied the payment of additional search fees.
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