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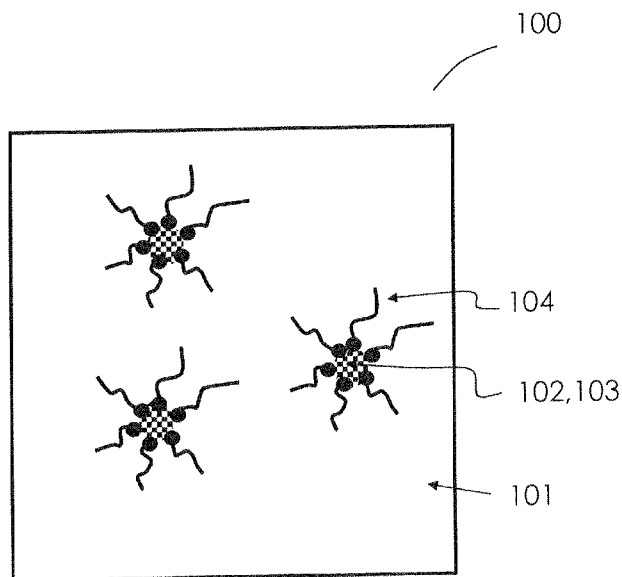


FIG. 1

(57) Abstract: A formulation includes a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component. The stabilizing component can contain D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) and/or at least one emulsifier having a hydrophilic-lipophilic balance (HLB) value of at least 10. In one alternative, the stabilizing component contains a first, polysorbate emulsifier having an HLB value of at least 10, and a second emulsifier having an HLB value of less than 10.



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FORMULATIONS OF HYDROPHILIC COMPOUNDS

TECHNICAL FIELD

[0001] This application relates to formulations generally (*e.g.*, pharmaceuticals or cosmetics), more particularly to formulations suitable for topical application comprising, for example, a hydrophilic compound or compounds in a continuous hydrophobic phase or phases, and associated methods of making and using such formulations.

BACKGROUND

[0002] Many biologically active compounds (*e.g.*, pharmaceutically and/or cosmetically active compounds) are highly hydrophilic. Formulating the biologically active hydrophilic compounds into a stable formulation with a hydrophobic carrier presents considerable challenges. The formulation may be produced by dispersing the biologically active hydrophilic compound in a continuous hydrophobic phase. However, such formulations often have poor stability, toxicity, and tend to phase separate, resulting in a poor shelf stability and inconsistent performance.

SUMMARY OF THE DISCLOSURE

[0003] Described are formulations that may be topically applied and comprise a continuous hydrophobic phase and a hydrophilic phase. In embodiments, a hydrophilic phase may be dispersed throughout the continuous hydrophobic phase. The formulation may comprise at least one hydrophilic compound. The hydrophilic phase can comprise a stabilizing component and a hydrophilic component normally insoluble in the continuous hydrophobic phase at room temperature absent emulsifier. A weight ratio of the stabilizing component to the hydrophilic compound(s) can be at least about 10:1. The stabilizing component may comprise from about 8% to about 30% by weight D- α -tocopheryl polyethylene glycol 1000 succinate ("TPGS") based upon total weight of the stabilizing component, and from about 70% to about 92% by weight at least one emulsifier having a hydrophilic-lipophilic balance (HLB) value of less than 10. The stabilizing component may also comprise from 8% to 30% by weight of a first, polysorbate, emulsifier having a hydrophilic-lipophilic balance ("HLB") value of at least 10, and from 70% to 92% by weight of a second emulsifier having an HLB value of less than 10. The hydrophilic compound comprises a compound that is normally insoluble in the continuous hydrophobic phase at room temperature absent the stabilizing component. The hydrophilic compound is preferably biologically active or otherwise desirable. The hydrophilic component is substantially dissolved in the hydrophilic phase utilizing reverse micelles comprising TPGS and/or the one or more emulsifiers. If the first, polysorbate emulsifier(s) is used, the formulation comprises no more than about

4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10.

[0004] The formulation may be a reverse micelle of the hydrophilic compound(s) in the continuous hydrophobic phase. The hydrophilic compound(s) may be present in the formulations in the form of reverse micelles that are stabilized by the stabilizing component. When including a stabilizing component, the formulation is preferably stable at room temperature, without agitation, for one week or more.

[0005] In embodiments, the formulation may comprise a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound, *e.g.*, green tea extract, epigallocatechin gallate (EGCG), in an amount of at least about 0.1% (preferably at least about 1%) by weight based upon total weight of the topical formulation, and a stabilizing component. The stabilizing component comprises D- α -tocopheryl polyethylene glycol 1000 succinate ("TPGS") in an amount from about 8% to about 30% by weight based upon total weight of the stabilizing component and/or at least one polysorbate emulsifier having an HLB value of less than 10 (preferably about 3 to 9), and at least one emulsifier having an HLB value of less than 10 (preferably about 3 to 8, and more preferably about 3 to 6). A weight ratio of the stabilizing component to the hydrophilic compound(s) in a TPGS-containing formulation is at least about 10:1. Topical formulations containing polysorbate comprise no more than about 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10.

[0006] In certain embodiments, the topical formulation comprises a continuous hydrophobic phase, at least one hydrophilic compound in an amount of at least 0.1% (preferably greater than 1%) by weight based on the total weight of the topical formulation, and a stabilizing component. The stabilizing component may comprise D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) in an amount from about 8% to about 30% by weight based upon total weight of the stabilizing component, and at least one fatty acid monoester of sorbitan. The stabilizing component may also comprise or may alternatively comprise at least one polysorbate emulsifier(s) having an HLB value of at least 10, and at least one fatty acid monoester of sorbitan, wherein from about 8% to about 30% by weight of the stabilizing component is polysorbate emulsifier(s) having an HLB value of at least 10. The topical formulation comprises no more than about 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10.

[0007] In certain embodiments, the topical formulation comprises a continuous hydrophobic phase comprising mineral oil, squalane, or a mixture thereof; a hydrophilic phase comprising propylene glycol; at least about 0.1% by weight of green tea extract, *e.g.*,

epigallocatechin gallate (EGCG) compound based upon total weight of the formulation; and a stabilizing component. A weight ratio of the stabilizing component to the green tea extract compound(s) is at least about 10:1. The stabilizing component comprises D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) in an amount from about 8% to about 30% by weight based upon total weight of the stabilizing component, and one emulsifier having an HLB value of less than 6.

[0008] In certain other embodiments, the topical formulation comprises a continuous hydrophobic phase comprising mineral oil, squalene, or a mixture thereof, a hydrophilic phase in an amount of at least about 1% wt/wt the hydrophilic phase per the continuous hydrophobic phase, at least about 0.1% by weight of the epigallocatechin gallate (EGCG) compound based on total weight of the formulation, and a stabilizing component. The stabilizing component comprises at least one polysorbate emulsifier having an HLB value of at least 10, and at least one emulsifier having an HLB value of less than 10, wherein from about 8% to about 30% by weight of the stabilizing component is polysorbate emulsifier(s) having an HLB value of at least 10. The topical formulation comprises no more than about 4% weight of the polysorbate emulsifier(s) having an HLB value of at least 10.

[0009] In further embodiments, the topical formulation comprises a continuous hydrophobic phase comprising mineral oil, squalene, or a mixture thereof; a propylene glycol hydrophilic phase dispersed throughout said continuous hydrophobic phase; an epigallocatechingallate (EGCG) compound in an amount from 1.0% to 1.7% by weight based upon total weight of the topical formulation; and a stabilizing component in an amount of at least 15% by weight based upon total weight of the topical formulation. The stabilizing component comprises TPGS in an amount of from 8% to 30% by weight based upon total weight of the stabilizing component and at least one fatty acid monoester of sorbitan having an HLB value of less than 6. A weight ratio of the continuous hydrophobic phase to the stabilizing component is no more than 5:1, and the weight ratio of the stabilizing component to the EGCG compound is at least 10:1.

[0010] Further particularly described is a topical formulation comprising a continuous squalene hydrophobic phase, a propylene glycol hydrophilic phase, an epigallocatechin gallate (EGCG) compound in an amount from about 1.0% to about 1.7% by weight based upon total weight of the topical formulation, and a stabilizing component in an amount of at least about 15% weight based upon total weight of the topical formulation. A weight ratio of the continuous squalene hydrophobic phase to the propylene glycol hydrophilic phase is about 10:1. A weight ratio of the continuous squalene hydrophobic phase to the stabilizing component is no more than about 5:1. A weight ratio of the stabilizing component to the EGCG compound is at least about 10:1. The stabilizing component comprises D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) in an amount from

about 8% to about 30% by weight based upon total weight of the stabilizing component, and at least one fatty acid monoester of sorbitan having an HLB value of less than 6.

[0011] Further particularly described is a formulation comprising a continuous squalane hydrophobic phase, a propylene glycol hydrophilic phase, an epigallocatechin gallate (EGCG) compound in an amount from about 1.0% to about 1.7% by weight based on total weight of the formulation, and a stabilizing component. The weight ratio of the continuous squalane hydrophobic phase to the propylene glycol hydrophilic phase is at least about 10:1. The stabilizing component comprises at least one polysorbate emulsifier having an HLB value of at least 10 and at least one fatty acid monoester of sorbitan emulsifier having an HLB value of less than 10. The polysorbate surfactant comprises from about 8% to about 30% by weight based on total weight of the stabilizing component, and no more than about 3.5% by weight based on total weight of the formulation.

[0012] Further described is a topical formulation comprising a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound substantially dissolved in the hydrophilic phase utilizing a stabilizing component comprising TPGS. The continuous hydrophobic phase comprises cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone, ubiquinone, various extracts, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera Biennis* (evening primrose) oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and corn oil. The topical formulation comprises at least about 0.8 mg of the hydrophilic compound(s) per 1 g of the continuous hydrophobic phase.

[0013] Further described is a topical formulation that comprises a continuous hydrophobic phase, a hydrophilic phase comprising propylene glycol, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component. The stabilizing component comprises at least one polysorbate emulsifier having an HLB value of at least 10 and, optionally, at least one emulsifier having an HLB value of less than 10. The continuous hydrophobic phase is a hydrophobic serum composed of cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone, ubiquinone, various extracts, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera Biennis* (evening primrose) oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and corn oil. The topical formulation comprises at least about 0.8 mg of the hydrophilic compound(s) per 1 g of the continuous hydrophobic phase.

[0014] Also described are methods of preparing the formulations, and methods of treating a condition in a subject (*e.g.*, a mammal) in need thereof, wherein the methods comprise topically administering the formulation to the subject.

BRIEF DESCRIPTION OF THE FIGURES

[0015] FIG. 1 depicts a schematic of the spherical reverse micelles formed in the formulations according to one embodiment hereof;

[0016] FIG. 2 depicts a schematic of the non-spherical reverse micelles formed in the formulations according to another embodiment hereof; and

[0017] FIG. 3 depicts a schematic of the cylindrical reverse micelles formed in the formulations according to yet another embodiment hereof.

DETAILED DESCRIPTION

[0018] Described is a formulation for application to a surface (*e.g.*, a biological surface such as skin, endothelial tissue, mucous membrane(s) of the eye, vulva, anus, and nose, the inside of the mouth or other orifice, etc.), wherein the formulation includes a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound (in embodiments, preferably biologically active) substantially dissolved in the hydrophilic phase, and a stabilizing component composed of D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) and/or at least one polysorbate emulsifier having an HLB value of at least 10 and, optionally, at least one emulsifier having an HLB value of less than 10. Also described is a method of incorporating at least one hydrophilic compound into a relatively hydrophobic vehicle, wherein the method includes utilizing a stabilizing component composed of D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) and/or at least one polysorbate emulsifier having an HLB value of at least 10, and, optionally, at least one emulsifier having an HLB value of less than 10, to stabilize a desired amount of the hydrophilic compound(s) in the hydrophobic vehicle.

[0019] The singular forms "a," "an," and "the" as used herein include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a hydrophilic compound" includes reference to one or more of such compounds.

[0020] The term "emulsion" refers to a mixture of two or more liquids wherein one liquid is present as dispersed droplets in another liquid in which it is not soluble or miscible. The emulsion may be a microemulsion or nanoemulsion. The dispersed droplets in emulsion may be in the form of reverse micelles.

[0021] As used herein, the term "microemulsion" refers to a type of emulsion that is thermodynamically stable and comprises dispersed droplets having globule size of less than 100 nanometers.

[0022] The term "reverse micelle" is used herein according to its art-recognized meaning and includes all forms of reverse micelles, including, *e.g.*, spherical reverse micelles, non-spherical

reverse micelles, cylindrical reverse micelles, etc.

[0023] The term "stable" as used herein in connection with the formulations refers to formulations which exhibit no phase separation when kept, without agitation, at room temperature for one week or more.

[0024] The term "HLB" as used herein refers to a hydrophilic-lipophilic balance of a surface-active material (e.g., surfactant, emulsifier). An HLB value of 0 corresponds to a completely hydrophobic (i.e., lipophilic) molecule, and a value of 20 corresponds to a completely hydrophilic (i.e., lipophobic) molecule. The surface-active material having an HLB value of less than 10 is insoluble in water; whereas, the surface-active material having an HLB value of more than 10 is soluble in water.

[0025] As used herein, the term "substantially," in reference to a given property or condition, refers to a degree that one of ordinary skill in the art would understand that the given property or condition is met with a small degree of variance, such as within acceptable measuring tolerances.

[0026] In one embodiment, a formulation comprises a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component. The stabilizing component comprises D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS). The formulation is stable for at least one week at room temperature without agitation. The formulation is composed of stabilized reverse micelles of the hydrophilic compound(s) in the continuous hydrophobic phase.

[0027] In certain embodiments, a formulation comprises a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component. The stabilizing component comprises at least one polysorbate emulsifier having an HLB value of at least 10 and, optionally, at least one emulsifier having an HLB value of less than 10. The formulation is stable for at least one week at room temperature without agitation. The formulation is composed of stabilized reverse micelles of at least one hydrophilic compound in the continuous hydrophobic phase.

[0028] D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS or vitamin E TPGS) is a water-soluble derivative of natural vitamin E, which is formed by esterification of vitamin E succinate with polyethylene glycol (PEG) 1000. TPGS is a nonionic surfactant having an HLB value of 13.2 and a relatively low critical micelle concentration (CMC) of 0.02% w/w. TPGS has an average molecular weight of 1,513 and completely dissolves in water. TPGS is an FDA approved pharmaceutically safe adjuvant, and its oral LD₅₀ is reported to be more than 7 g/kg for young adult rats of both sexes. See, e.g., Guo et al., *The Applications of Vitamin E TPGS in Drug Delivery*, Eur. J. Pharmc. Sci. 49 (2013), 175-186.

[0029] In certain embodiments, the formulation comprises a continuous hydrophobic phase, a

hydrophilic phase, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component. A weight ratio of the stabilizing component to the hydrophilic compound(s) is at least about 10:1. The stabilizing component comprises D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) in an amount from about 8% to about 30% by weight based upon total weight of the stabilizing component, and at least one emulsifier having an HLB value of less than 10 (preferably about 3 to 8, and more preferably about 3 to 6).

[0030] In certain other embodiments, the formulation may comprise a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component composed of at least one polysorbate emulsifier having an HLB value of at least 10 and at least one emulsifier having an HLB value of less than 10. About 8% to about 30% by weight of the stabilizing component is polysorbate emulsifier(s) having an HLB value of at least 10. The formulation comprises no more than about 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10. The formulation may be in the form of nanoemulsion of the hydrophilic compound(s) in the continuous hydrophobic phase.

[0031] In certain embodiments, the formulation may comprise a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component composed of at least one polysorbate emulsifier having an HLB value of at least 10. The formulation may be in the form of microemulsion of the hydrophilic compound(s) in the continuous hydrophobic phase.

[0032] In the embodiment depicted in FIG. 1, a formulation 100 that may be topically applied comprises a continuous hydrophobic phase 101, a hydrophilic phase 102, at least one hydrophilic compound 103 substantially dissolved in the hydrophilic phase 102, and a stabilizing component 104. In FIG. 1, due to their hydrophilicity, the hydrophilic phase 102 and the hydrophilic compound(s) 103 may form spherical reverse micelles dispersed in the continuous hydrophobic phase 101. The stabilizing component 104 is composed of surface-active compounds to stabilize the dispersed spherical reverse micelles in the continuous hydrophobic phase 101.

[0033] In the embodiment depicted in FIG. 2, a formulation 200 that may come into contact with a subject comprises a continuous hydrophobic phase 201, a hydrophilic phase 202, at least one hydrophilic compound 203 substantially dissolved in the hydrophilic phase 202, and a stabilizing component 204. The hydrophilic phase 202 and the hydrophilic compound(s) 203 form dispersed non-spherical reverse micelles when they are mixed with the continuous hydrophobic phase 101. The stabilizing component 204 enhances the stability of the dispersed non-spherical reverse micelles in the continuous hydrophobic phase 201.

[0034] In the embodiment depicted in FIG. 3, a formulation 300 that may come into contact

with a subject comprises a continuous hydrophobic phase 301, a hydrophilic phase 302, at least one hydrophilic compound 303 substantially dissolved in the hydrophilic phase 302, and a stabilizing component 304. Upon mixing a solution of the hydrophilic compound(s) 303 in the hydrophilic phase 302 with the continuous hydrophobic phase 301, cylindrical reverse micelles are formed and dispersed in the continuous hydrophobic phase 301. The stabilizing component 304 facilitates the dispensability and enhances the stability of cylindrical reverse micelles in the continuous hydrophobic phase 301.

[0035] Although FIGS. 1-3 show three different structures of reverse micelles, it is understood that other structures of reverse micelles may be formed in the formulations. Such differently configured micelles may be present in the same formulation or at different times or temperatures of the formulation. A particular formulation hereof may contain all such depicted reverse micelles.

[0036] Hydrophilic Compounds

[0037] Various biologically active (e.g., pharmaceutically active and/or cosmetically active) hydrophilic compounds may be used. Alternatively or in addition, hydrophilic compounds such as scents, or colorants, or insect repellants may be used, which are not biologically active in the subject. Examples of biologically active hydrophilic compounds may include, but not be limited to, green tea extract, grape seed extract, fruit extract, polyphenol compounds, or mixtures thereof.

[0038] In embodiments, the hydrophilic compound includes green tea extract. Green tea itself though is a complex composition of polyphenols. Green tea extract is derived from green tea leaves (*Camellia sinensis*), and contains various antioxidant ingredients—mainly green tea catechins (GTC). GTC itself comprises four major epicatechin derivatives; *i.e.*, epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG). Other components of green tea include flavonoids, such as kaempferol, quercetin, and myricetin. Studies suggest that green tea polyphenols may help prevent skin cancer with direct (topical) application to the skin. *See, e.g.*, Katiyar et al., "Green tea and skin," *Arch Dermatol.* 136:989-994 (2000). Evidence also exists that green tea constituents helps protect the skin from sun damage. *See, e.g.*, Katiyar et al., "Polyphenolic antioxidant (-)-epigallocatechin-3-gallate from green tea reduces UVB-induced inflammatory responses and infiltration of leukocytes in human skin," *Photochem Photobiol.* 69:148-153 (1999); Katiyar et al., "Protection against ultraviolet-B radiation-induced local and systemic suppression of contact hypersensitivity and edema responses in C3H/HeN mice by green tea polyphenols," *Photochem Photobiol.* 62:855-861 (1995); and Elmets et al., "Cutaneous photoprotection from ultraviolet injury by green tea polyphenols," *J Am. Acad Dermatol.* 44:425-432 (2001). *See, also*, Chiu et al.,

"Double-blinded, placebo-controlled trial of green tea extracts in the clinical and histologic appearance of photoaging skin," *Dermatol Surg.* 31 :855-860 (2005). Furthermore, one percent (1 % w/w) epigallocatechin gallate (EGCG—derived from green tea) topical formulations has been suggested as being useful for treating acne.

[0039] In one embodiment, the hydrophilic compound includes at least one polyphenol compound.

[0040] The term "polyphenol" has been defined differently. For example, under one widely accepted definition, the White-Bate-Smith-Swain-Haslam (WBSSH) definition, polyphenols are generally moderately water-soluble compounds, typically with molecular weights of about 500 Da to about 4000 Da, having, *e.g.*, more than 12 phenolic hydroxyl groups, and about 5 to 7 aromatic rings per 1000 Da. Under the proposed "Quideau definition" of polyphenols, "[t]he term 'polyphenol' should be used to define compounds exclusively derived from the shikimate/phenylpropanoid and/or the polyketide pathway, featuring more than one phenolic unit and deprived of nitrogen-based functions." As used herein, the term "polyphenol" is to be used inclusively.

[0041] Non-limiting examples of polyphenol compounds include epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin (EC), epicatechin gallate (ECG), and catechin.

[0042] In certain embodiments, the hydrophilic compound may include those compounds, available from, *e.g.*, Silab S.A. of Saint Viance, France, selected from the group consisting of: hydrolyzed pepper fruit extract (*Piper nigrum*) (Retilactyl D®); hydrolyzed soy protein (Ridulisse C®, Ridulisse C® Bio, Pro-Coll-One+®, or Raffermin®); peppermint extract (*Mentha piperita*) (Calmiskin®); lotus (*Nelumbo nucifera*) (Pro-Sveltyl®); coriander (*Coriandrum sativum*) (Affiness® compound that may also contains orange extract); *Verbena officinalis* extract (Vitalayer®); and *Helianthus annuus* (sunflower) seed extract (Antiglyskin® or Helioxine®).

[0043] In certain embodiments, the hydrophilic compound may include, for example, (supplier in parenthesis): Alistin (DD Chemco), Chlorellagen DP (DD Chemco), Depollutine (Devereaux), Derm SRC (DD Chemco), Dragosine (Symrise), Ellagi-C (Devereaux), Hydrolite S P (Symrise), IBR Dormins (Israeli Biotechnology Research, Ltd.), Kaden berry extracts (Symrise), Matrixyl synthe 6 (Croda), Matrixyl 3000 (Croda), Micromeral (BASF), Milk Peptide Complex (Devereaux), Mitostime L (DD Chemco), Minythis (DD Chemco) Muciliance fruit (Devereaux), Phytosan-K (Devereaux), Pholsine (DD Chemco), Pinoxide (DD Chemco), Quicklift (BASF), Scoparlane BPC (DD Chemco), Seanergilium (BASF), Silox Apple (BASF), Slimbuster L (DD Chemco), SymMatrix (Tri-K), SymPeptide (Symrise), SymVital (Tri-K), Thiotaine® L- ergothioneine (DD Chemco), or Ursolisome (BASF).

[0044] Further examples of the hydrophilic compounds may include, but are not limited to, those available from, e.g., Silab S.A. of Saint Viance, France, such as those selected from the group consisting of *Saccharomyces cerevisiae* extract, *Withania somnifera* root extract, butylene glycol and hydrolyzed *Coriandrum sativum* fruit extract and *Citrus aurantium dulcis* (orange) fruit extract, *Helianthus annuus* (sunflower) seed extract, *Taraxacum officinale* (dandelion) extract, hydrolyzed *Viola tricolor* extract, *Pyrus malus* (apple) fruit extract (e.g., Bioprotectyl®), hydrolyzed *Celosia cristata* extract and hydrolyzed *Prunella vulgaris* extract, hydrolyzed *Citrus aurantium dulcis* fruit extract, hydrolyzed *Candida saitoana* extract (e.g., Celldetox®), *Lindera strychnifolia* root extract, *Triticum vulgare* (wheat germ) extract, *Secale cereale* (rye) seed extract, hydrolyzed sesame extract, *Tropaeolum majus* flower extract, *Spiraea ulmaria* extract, hydrolyzed sweet almond protein, *Salix Alba* (willow) leaf extract (e.g., Astressyl®), *Mentha piperita* (peppermint) extract, *Triticum vulgare* (wheat) germ extract, butylene glycol and *Butyrospermum parkii* (shea butter) seedcake extract, hydrolyzed lupine protein octenylsuccinate, hydrolyzed *Cucurbita pepo* (pumpkin) seedcake, hydrolyzed *Opuntia ficus indica* flower extract, *Medicago sativa* (alfalfa) seed extract and hydrolyzed lupine protein, *Lentinus edodes* extract, hydrolyzed *Ceratonia siliqua* seed extract, *Gossypium hirsutum* (cotton) extract, *Helianthus annuus* (sunflower) seed extract, *Jasminum officinale* (jasmine) flower extract (e.g., Helisun®), hydrolyzed *Manihot esculenta* tuber extract, butylene glycol and *Iris florentina* root extract, hydrolyzed wheat protein, hydrolyzed *Myrtus communis* leaf extract, butylene glycol and *Boerhavia diffusa* root extract, *Cynara scolymus* (artichoke) leaf extract, yeast extract, hydrolyzed rice protein, *Nasturtium officinale* extract, *Avena sativa* (oat) kernel extract, *Tropaeolum majus* flower/leaf/stem extract, *Lens esculenta* (lentil) seed extract (including oligosaccharides thereof), *Cyperus esculentus* tuber extract, *Prunus amygdalus dulcis* (sweet almond) seed extract, hydrolyzed soy fiber, *Pichia anomala* extract, butylene glycol and *Nelumbo nucifera* leaf extract, yeast extract, butylene glycol and *Artemisia abrotanum* extract, hydrolyzed soy flour, *Castanea sativa* (chestnut) seed extract, propylene glycol and *Citrus aurantium amara* (bitter orange) flower extract, hydrolyzed pepper fruit extract, hydrolyzed soy protein, butylene glycol and *Spiraea ulmaria* extract, hydrolyzed linseed extract, butylene glycol and *Peumus boldus* leaf extract, red algae (*Kappaphycus alvarezii*) galactans, *Pichia anomala* (including biopeptides thereof) extract, sulfated galactans of *Hypnea musciformis* (e.g., Deglysome®), *Glycine soja* hydrolyzed soy protein (e.g., Ridulisse C® and/or Pro-Coll-One+®), *Oryza sativa* extract (e.g., Nutripeptides®), *Cyperus esculentus* tuber extract (e.g., Papilactyl

D®), *Piper nigrum* hydrolyzed pepper fruit extract (e.g., Retilactyl D®), *Verbena officinalis* extract (e.g., Vitalayer®), butylene glycol and *Peumus boldus* leaf extract, butylene glycol and *Peumus boldus* leaf extract, seed extract (e.g., SMS Anti-wrinkle®), hydrolyzed *Cicer* seed extract, *Triticum Vulgare* (wheat) germ extract, hydrolyzed pea, butylene glycol and *Silybum Marianum* extract, hydrolyzed lupine protein, *Kappaphycus alvarezii* (red algae) extract, *Triticum vulgare* (wheat) protein, yeast extract (e.g., Toniskin® and/or Unflamagyl®), *Cichorium intybus* (chicory) root extract, *Prunus persica* (peach) leaf extract, *Verbena officinalis* extract, *Medicago sativa* (alfalfa) extract, *Paeonia albiflora* root extract, *Palmaria palmata* extract, hydrolyzed millet, butylene glycol and triethanolamine and *Punica granatum* extract, glycerin and *Prunus amygdalus dulcis* (sweet almond) extract, hydrolyzed sweet almond seedcake, butylene glycol and *Fumaria officinalis* extract, butylene glycol and *Camellia sinensis* leaf extract, soytrimonium chloride, or combinations of any thereof.

[0045] Moreover, examples of the hydrophilic compounds may include, but not be limited to, proteins, peptides, nucleic acids, or hydrophilic drugs (characterized chemically by having a relatively low octanol/water partition coefficient) such as vancomycin, phenobarbital, antibiotics such as ampicillin, streptomycin, aminoglycosides, and the penicillins, theophylline, polysaccharides, non-ADEK vitamins, digoxin, atenolol, paclitaxel, 5-fluorouracil, inulin, lithium, ara-C, gemcitabine, propranolol, tramadol, diltiazem, etc.

[0046] The amount of, e.g., hydrophilic compounds in the formulations depends on various factors, such as the desired dosage of the hydrophilic compounds, the types of hydrophilic solvents, the types of continuous hydrophobic phase, and the types of stabilizing components. It is also appreciated that the amount of hydrophilic compounds in the formulations may also depend on the nature of the conditions for which treatment is required.

[0047] In certain embodiments, the formulation may comprise at least about 0.1% by weight, preferably at least about 1% by weight, of the hydrophilic compound(s) based upon total weight of the formulations. In certain embodiments, the formulations may comprise at least about 0.1% g/g of the hydrophilic compound(s) per the continuous hydrophobic phase. Thus, for example the amount of the hydrophilic compound can vary from about 0.01%, 0.05%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5% or 1.0% to about 1.5%, 2.0%, 3.0%, 4.0%, 5.0%, 6.0%, 10% or even higher.

[0048] Hydrophilic Phase

[0049] The hydrophilic phase may include one or more hydrophilic solvents. Various non-toxic pharmaceutically and/or cosmetically acceptable hydrophilic solvents may be used to

substantially dissolve the hydrophilic compound(s). Examples of such hydrophilic solvents may include, but are not limited to, water, ethanol, dimethyl sulfoxide (DMSO), propylene glycol (PG), and polyethylene glycol (PEG) at different molecular weights (*e.g.*, PEG 400 and PEG 800). These hydrophilic solvents can sometimes serve as humectants for the hydrophilic compounds, such as a pharmaceutically active ingredient, to be included in certain embodiments of the formulation. Thus, other humectants known to those having ordinary skill in the art can also be incorporated into the hydrophilic phase.

[0050] The hydrophilic solvent may be present in the formulations in an amount sufficient to provide a stable dispersed phase of the hydrophilic compound in the continuous hydrophobic phase. Thus, for example, the amount of hydrophilic solvent can vary from about 0.5%, 1.0%, 2.0%, 3.0%, 4.0% or 5.0% to about 7.0%, 8.0%, 9.0%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60% or 65%.

[0051] Stabilizing Component

[0052] The stabilizing component may comprise TPGS and/or at least one polysorbate emulsifier having an HLB value of at least 10 (“polysorbate emulsifier”) and, optionally, at least one emulsifier having an HLB value of less than 10 (preferably from 3 to 8, and more preferably from 3 to 6).

[0053] In particular embodiment, a weight ratio of the stabilizing component to the hydrophilic compound(s) is at least about 10:1.

[0054] In certain embodiments, the stabilizing component comprises at least one polysorbate emulsifier having an HLB value of at least 10 (preferably from about 12 to about 20), and the emulsifier having an HLB value of less than 10. About 8% to about 30% by weight of the stabilizing component is polysorbate emulsifier(s) having an HLB value of at least 10. The formulation comprises no more than about 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10.

[0055] The polysorbate emulsifier(s) having an HLB value of at least 10 accounts for about 8% to about 30% by weight based on total weight the stabilizing component, and no more than about 4% by weight based on total weight of the formulation. Examples of the polysorbate emulsifiers (*i.e.*, PEG sorbitan fatty acid esters) may include, but not be limited to, PEG-20 sorbitan monolaurate having an HLB value of 17 (*e.g.* polysorbate 20, TWEEN 20 from Croda, Inc.) PEG-20 sorbitan monopalmitate having an HLB value of 16 (*e.g.* TWEEN 40 from Croda, Inc.); PEG-20 sorbitan monostearate having an HLB value of 15 (*e.g.* TWEEN 60 from Croda, Inc.); and PEG-20 sorbitan monooleate having an HLB value of 15 (*e.g.* polysorbate 80, TWEEN 80 from Croda, Inc.)

[0056] In certain embodiments, the formulations comprise the stabilizing component in an amount of at least about 10% by weight based upon total weight of the formulations. In some embodiments, the formulation includes PEG-20 sorbitan monooleate having an HLB value of 15 (e.g. polysorbate 80, TWEEN 80 from Croda, Inc.) as the polysorbate emulsifier having an HLB value of at least 10.

[0057] In certain embodiments, a weight ratio of the continuous hydrophobic phase to the stabilizing component is no more than about 25:1. Thus, for example, the ratio can be from about 1:1, 2:1, 3:1, 4:1 or 5:1 to about 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 15:1, 20:1 or 25:1.

[0058] In certain embodiments, the stabilizing component comprises TPGS in an amount from about 0.1%, 0.5%, 1.0% or 2.0% to about 2.0%, 3.0%, 5.0%, 10%, 20% or 30% by weight based upon total weight of the stabilizing component, and at least one emulsifier having an HLB value of less than 10.

[0059] The emulsifier having an HLB value of less than 10 ("low HLB emulsifier") may include a cationic surfactant, an anionic surfactant, an amphoteric surfactant, a non-ionic surfactant, or a mixture thereof. In certain embodiments, the low HLB emulsifier may include a surfactant having an HLB value of about 3 to about 9.

[0060] The low HLB emulsifier may include a compound selected from the group consisting of fatty acid monoesters of glycerol, fatty acid diesters of glycerol, fatty acid monoesters of propylene glycol, fatty acid diesters of propylene glycol, fatty acid monoesters of sorbitan, fatty acid diesters of sorbitan, fatty acid triesters of sorbitan, and triglyceride.

[0061] The emulsifiers having an HLB value of less than 10 ("low HLB emulsifiers") may include a compound selected from the group consisting of fatty acid monoesters of glycerol, fatty acid diesters of glycerol, fatty acid monoesters of propylene glycol, fatty acid diesters of propylene glycol, fatty acid monoesters of sorbitan, and fatty acid diesters of sorbitan.

[0062] Examples of the fatty acid mono- and di-esters of glycerols may include, but not be limited to, IMWITOR® 742 surfactant having an HLB value of less than 10, which is a mixture of mono- and di-glycerides of caprylic and capric acids from Sasol Olefins and Surfactants GmbH; IMWITOR® 988 surfactant having an HLB value of about 5 to 6, which is a mixture of mono- and di-glycerides of caprylic acid from Sasol Olefins and Surfactants GmbH; IMWITOR® 308 surfactant having an HLB value of about 5 to 6, which is a mixture of mono- and di-glycerides of caprylic acid with more than about 80% monoglycerides from Sasol Olefins and Surfactants GmbH; IMWITOR® 191 surfactant having an HLB value of about 4.4, which is glyceryl monostearate from Huls AG/Huls America; CAPMUL® MCM surfactant having an HLB

value of about 5 to 6, which is monoglyceride of caprylic and capric acid from ABITEC Corporation; CAPMUL® GM0-50 surfactant having an HLB value of less than 10, which is glyceryl monooleate from ABITEC Corporation; CAPMUL® GDL surfactant having an HLB value of about 3 to 4, which is glyceryl dilaurate from ABITEC Corporation; MAISINE® 35-1 surfactant having an HLB value of about 3 to 4, which is glyceryl monolinoleate from Gattefosse Corporation; and PECEOL™ surfactant having an HLB value of about 3 to 4, which is glyceryl monooleate from Gattefosse Corporation.

[0063] Examples of the fatty acid mono- and di-esters of propylene glycol may include, but not be limited to, CAPTEX® 200 having an HLB value of more than 6, which is propylene glycoldicaprylate/dicaprate from ABITEC Corporation; Miglyo® 840 surfactant having an HLB value of about more than 6, which is propylene glycol dicaprylate/dicaprate from Sasol Olefins and Surfactants GmbH; Neobee® M-20 surfactant having an HLB value of about more than 6, which is propylene glycol dicaprylate/dicaprate from Stepan Company; LAUROGLYCOL™ surfactant having an HLB value of about less than 10, which is propylene glycol monolaurate from Gattefosse Corporation; MIRPYL® surfactant having an HLB value of about less than 10, which is propylene glycol monolaurate; CAPMUL® PG8 surfactant having an HLB value of about 4, which is propylene glycol monocaprylate with up to about 5% propylene glycol dicaprylate from ABITEC Corporation.

[0064] Examples of the fatty acid mono- and di-esters of sorbitan may include, but not be limited to, sorbitan monooleate such as SPAN™ 80 surfactant having an HLB value of about 4.3 from Croda Inc.; sorbitan monopalmitate such as SPAN™ 40 surfactant having an HLB value of about 6.7 from Croda Inc.; sorbitan monolaurate such as SPAN™ 20 surfactant having an HLB value of about 8.6 from Croda Inc.; sorbitan monostearate such as SPAN™ 60 surfactant having an HLB value of about 4.7 from Croda Inc.; sorbitan sesquioleate such as SPAN™ 83 surfactant from Croda Inc.; sorbitan monoisostearate such as SPAN™ 120 surfactant from Croda Inc.; and sorbitan sesquistearate such as NIKKOL® SS-15 surfactant having an HLB value of about 4.2 from Nikkol Chemicals Co., Ltd.

[0065] The triglycerides may be medium chain (C6-C12) triglycerides, long chain (C14-C20) triglycerides, or a mixture thereof. Examples of the medium chain (C6-C12) triglycerides may include, but not be limited to, fractionated coconut oils; MIGLYOL® 812 compound having an HLB value of about 1 from Sasol Olefins and Surfactants GmbH that contains 56% caprylic (C8) and 36% capric (C10) triglycerides; MIGLYOL® 810 compound having an HLB value of about 1 from Sasol Olefins and Surfactants GmbH that contains 68% caprylic (C8) and 28% capric (C10) triglycerides; NEOBEE® M5 compound having an HLB value of about 1 from Stepan Company, which is

caprylic/capric triglyceride; CAPTEX® 300 and 355 compounds having an HLB value of about 1 from ABITEC Corporation that is glyceryl tricaprylate/tricaprate; and CRODAMOL™ GTCC compound having an HLB value of about 1 from Croda Inc that is glyceryl tricaprylate/tricaprate. Examples of the long chain triglycerides (C14-C20) triglycerides may include, but not be limited to, vegetable oils such as safflower, corn, soybean, olive, cotton seed, sunflower seed, arachis, palm and rapeseed oils.

[0066] In certain embodiments, the formulation includes a fatty acid monoester sorbitan, particularly sorbitan monooleate (*e.g.*, SPAN™ 80 surfactant having an HLB value of about 4.3), as at least one of the low HLB emulsifier.

[0067] In certain embodiments, the stabilizing component in the formulation comprises TPGS emulsifier and at least one low HLB emulsifier including sorbitan monooleate.

[0068] In certain embodiments, the stabilizing component in the formulation may comprise at least one low HLB emulsifier including sorbitan monooleate, and at least one polysorbate emulsifier having an HLB value of at least 10 including PEG-20 sorbitan monooleate.

[0069] Continuous Hydrophobic Phase

[0070] The continuous hydrophobic phase may include one or more pharmaceutically and/or cosmetically acceptable hydrophobic solvents.

[0071] Non-limiting examples of hydrophobic solvents include, but not be limited to, mineral oil, vegetable oil, paraffin, polysiloxane, cyclopentasiloxane, dimethiconol, squalane, hemisqualane and mixtures thereof. In certain embodiments, the continuous hydrophobic phase may include at least a mixture of cyclopentasiloxane and dimethiconol, such as Cosmetic Fluid 1585-0H from Chemsil Silicones, Inc.

[0072] In one particular embodiment, the continuous hydrophobic phase of the formulations does not include any triglyceride.

[0073] In some embodiments, the continuous hydrophobic phase may include oleaginous ointment bases, absorption ointment bases, water/oil emulsion ointment bases, oil/water emulsion ointment bases, and water-miscible ointment bases such as white petrolatum, white ointment, hydrophilic petrolatum, anhydrous lanolin, Aquabase™, Aquaphor®, Polysorb®, cold cream type, hydrous lanolin, rose water ointment, Hydrocream™, Eucerin®, Nivea®, Dermabase™, Velvachol®, Unibase®, PEG ointment, and Polybase™.

[0074] In certain embodiments, the continuous hydrophobic phase may be serum/gel that includes cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone (ETHOCYN®), ubiquinone, various extracts, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera biennis* (evening primrose) oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer,

tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and corn oil.

[0075] ETHOCYN® is a bicyclooctane DHT competitive inhibitor/collagen suppressing compound, which could be topically applied with the formulation. Other collagen suppressing compounds could also or alternatively be incorporated into the formulation. In such embodiments, the formulations could be utilized to suppress keloid formation and hypertrophic scar formation by, e.g., daily application of such a formulation (e.g., for a finite number of days of, e.g., 7 to 28 days) to a surgical scar after surgery (e.g., at the site of incision).

[0076] In certain embodiments, the continuous hydrophobic phase does not include a fatty acid triglyceride. In some embodiments, the continuous hydrophobic phase includes from about 35%, 40%, 50%, 60% or 70% to about 70%, 80%, 90% or 95% of the total formulation.

[0077] In certain embodiments, a formulation comprises a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component. The continuous hydrophobic phase is a hydrophobic serum composed of cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone, ubiquinone, various extracts, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera Biennis* (evening primrose) oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and corn oil. The stabilizing component comprises TPGS and, optionally, at least one emulsifier having an HLB value of less than 10. The formulation comprises at least about 0.8 mg of the hydrophilic compound(s) per 1 g of the continuous hydrophobic phase.

[0078] In one embodiment, a topical formulation comprises or consists of a continuous hydrophobic phase, a hydrophilic phase, a stabilizing component, and at least about 0.1% *gig* of epigallocatechin gallate (EGCG) compound per the continuous hydrophobic phase. The stabilizing component comprises at least one polysorbate emulsifier having an HLB value of at least 10 and, optionally, at least one emulsifier having an HLB value of less than 10. The continuous hydrophobic phase is composed of cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone (ETHOCYN®), ubiquinone, various extracts, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera biennis* (evening primrose) oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and corn oil. The topical formulation may be stable at room temperature, without agitation, for at least one week.

[0079] In one embodiment, a topical formulation comprises a continuous hydrophobic phase, a hydrophilic phase, a stabilizing component, and at least about 0.1% (preferably at least about 1% *gig*) of epigallocatechin gallate (EGCG) compound per the continuous hydrophobic

phase. The stabilizing component comprises TPGS and, optionally, at least one emulsifier having an HLB value of less than 10. The continuous hydrophobic phase is composed of cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone (ETHOCYN®), ubiquinone, various extracts, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera Biennis* (evening primrose) oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and corn oil. The topical formulation may be stable at room temperature, without agitation, for at least one week.

[0080] In one embodiment, a topical formulation comprises or consists of a continuous hydrophobic phase comprising squalane, a hydrophilic phase, a stabilizing component, and at least about 1% *w/w* of epigallocatechin gallate (EGCG) compound per the continuous hydrophobic phase. The stabilizing component comprises at least one polysorbate emulsifier having an HLB value of at least 10, and at least one emulsifier having an HLB value of less than 10. The topical formulation may be in the form of nanoemulsion and stable at room temperature, without agitation, for at least one week.

[0081] In one embodiment, a topical formulation comprises or consists of a continuous hydrophobic phase, a hydrophilic phase comprising polyethylene glycol (PEG), a stabilizing component, and at least about 1% *w/w* of green tea extract per the continuous hydrophobic phase. The continuous hydrophobic phase comprises mineral, squalane, or a mixture thereof. The amount of hydrophilic phase in the formulation is at least about 1% *w/w* the hydrophilic phase per the continuous hydrophobic phase. The stabilizing component comprises at least one polysorbate emulsifier having an HLB value of at least 10, and at least one emulsifier having an HLB value of less than 10.

[0082] In certain embodiments, a formulation may comprises or consists of a continuous hydrophobic phase, a hydrophilic phase, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component comprising at least one polysorbate emulsifier having an HLB value of at least 10, and at least one emulsifier having an HLB value of less than 10. About 8% to about 30% by weight of the stabilizing component is polysorbate emulsifier(s) having an HLB value of at least 10. The formulation comprises no more than about 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10. The continuous hydrophobic phase may comprise mineral oil (e.g. DRAKEOL 35 from Penreco), vegetable oil, paraffin, squalene, hemisqualene or a mixture thereof. The hydrophilic phase may comprise water, polyethylene glycol, propylene glycol, or a mixture thereof. The weight ratio of the hydrophilic compound(s) to the hydrophilic phase may be from about 1:5 to about 1:10. The weight ratio of the continuous hydrophobic phase to the hydrophilic phase is at least 10:1. The weight ratio of the stabilizing

component to the continuous hydrophobic phase is from about 1:1 to about 1:10. The formulation may comprise at least about 10 mg of the hydrophilic compound(s) per 1 g of the continuous hydrophobic phase. [0070] In one embodiment, about 7.5% to about 12% by weight of the stabilizing component may be the polysorbate emulsifier(s) having an HLB value of at least 10.

[0083] In certain embodiments, a formulation comprises or consists of a continuous hydrophobic phase comprising mineral oil, a hydrophilic phase comprising polyethylene glycol, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component comprising at least one polysorbate emulsifier having an HLB value of at least 10, and at least one emulsifier having an HLB value of less than 10. About 10% by weight of the stabilizing component is the polysorbate emulsifier(s) having an HLB value of at least 10. The weight ratio of the hydrophilic compound(s) to the hydrophilic phase is about 1:10. The weight ratio of the hydrophilic phase to the continuous hydrophobic phase is about 1:10. The weight ratio of the stabilizing component to the continuous hydrophobic phase is about 1:1. The formulation comprises at least about 10 mg of the hydrophilic compound(s) per 1 g of the continuous hydrophobic phase.

[0084] In certain embodiments, a formulation comprises or consists of a continuous hydrophobic phase comprising squalane, a hydrophilic phase comprising propylene glycol, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component comprising at least one polysorbate emulsifier having an HLB value of at least 10, and at least one emulsifier having an HLB value of less than 10 and. About 8% to about 30% by weight of the stabilizing component is polysorbate emulsifier(s) having an HLB value of at least 10. The formulation comprises no more than about 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10. The weight ratio of the hydrophilic compound(s) to the hydrophilic phase is about 1:5. The weight ratio of the hydrophilic phase to the continuous hydrophobic phase is about 1:10. The weight ratio of the stabilizing component to the continuous hydrophobic phase is from about 1:4 to about 1:10. The formulation comprises at least about 20 mg of the hydrophilic compound(s) per 1 g of the continuous hydrophobic phase.

[0085] In certain embodiments, a topical formulation comprises or consists of a continuous squalane hydrophobic phase, a propylene glycol hydrophilic phase, an epigallocatechin gallate (EGCG) compound in an amount from about 1.0% to about 1.7% by weight based on total weight of the topical formulation, and a stabilizing component. The weight ratio of the continuous squalane hydrophobic phase to the propylene glycol hydrophilic phase is at least about 10:1. The stabilizing component comprises at least one polysorbate surfactant(s) having an HLB value of at least 10, and at least one fatty acid monoester of sorbitan. The polysorbate surfactant(s) comprises from about 8% to

about 30% by weight based on total weight of the stabilizing component, and no more than about 3.5% by weight based on total weight of the topical formulation.

[0086] In one embodiment, about 7.5% to about 12% by weight of the stabilizing component may be the polysorbate emulsifier(s) having an HLB value of at least 10.

[0087] In certain embodiments, a formulation comprises or consists of a continuous hydrophobic phase comprising mineral oil, a hydrophilic phase comprising polyethylene glycol, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component comprising at least one polysorbate emulsifier having an HLB value of at least 10, and at least one emulsifier having an HLB value of less than 10. About 10% by weight of the stabilizing component is the polysorbate emulsifier(s) having an HLB value of at least 10. The weight ratio of the hydrophilic compound(s) to the hydrophilic phase is about 1:10. The weight ratio of the hydrophilic phase to the continuous hydrophobic phase is about 1:10. The weight ratio of the stabilizing component to the continuous hydrophobic phase is about 1:1. The formulation comprises at least about 10 mg of the hydrophilic compound(s) per 1 g of the continuous hydrophobic phase.

[0088] In certain embodiments, a formulation comprises or consists of a continuous hydrophobic phase comprising squalane, a hydrophilic phase comprising propylene glycol, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component comprising at least one polysorbate emulsifier having an HLB value of at least 10, and at least one emulsifier having an HLB value of less than 10 and. About 8% to about 30% by weight of the stabilizing component is polysorbate emulsifier(s) having an HLB value of at least 10. The formulation comprises no more than about 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10. The weight ratio of the hydrophilic compound(s) to the hydrophilic phase is about 1:5. The weight ratio of the hydrophilic phase to the continuous hydrophobic phase is about 1:10. The weight ratio of the stabilizing component to the continuous hydrophobic phase is from about 1:4 to about 1:10. The formulation comprises at least about 20 mg of the hydrophilic compound(s) per 1 g of the continuous hydrophobic phase.

[0089] In certain embodiments, a topical formulation comprises or consists of a continuous squalane hydrophobic phase, a propylene glycol hydrophilic phase, an epigallocatechin gallate (EGCG) compound in an amount from about 1.0% to about 1.7% by weight based on total weight of the topical formulation, and a stabilizing component. The weight ratio of the continuous squalane hydrophobic phase to the propylene glycol hydrophilic phase is at least about 10:1. The stabilizing component comprises at least one polysorbate surfactant(s) having an HLB value of at least 10, and at least one fatty acid monoester of sorbitan. The polysorbate surfactant(s) comprises from about 8% to

about 30% by weight based on total weight of the stabilizing component, and no more than about 3.5% by weight based on total weight of the topical formulation.

[0090] In certain embodiments, a topical formulation comprises or consists of a continuous hydrophobic phase, a hydrophilic phase comprising propylene glycol, at least one hydrophilic compound substantially dissolved in the hydrophilic phase, and a stabilizing component comprising at least one polysorbate emulsifier having an HLB value of at least 10. The weight ratio of the hydrophilic compound(s) to the hydrophilic phase is about 1:5. The weight ratio of the hydrophilic phase to the continuous hydrophobic phase is about 1:240. The weight ratio of the stabilizing component to the continuous hydrophobic phase is about 1:1000. The topical formulation comprises at least about 0.8 mg of the hydrophilic compound(s) per 1 g of the continuous hydrophobic phase. The continuous hydrophobic phase comprises cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone (ETHOCYN®), ubiquinone, various extracts, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera Biennis* (evening primrose) oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and corn oil.

[0091] In certain embodiments, the formulation does not include a fatty acid triglyceride.

[0092] In some embodiments, the foregoing formulation(s) may further include a lower alkyl-substituted bicyclo[3.3.0]octan-3-one compound, such as 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (available under the trade name ETHOCYN® from BCS Business Consulting Services Pte Ltd of Singapore) or 6-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-3-one. Methods of manufacture, and uses of skin care compositions comprising a lower alkyl-substituted bicyclo[3.3.0]octan-3-one compound such as 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one ("ETHOCYN®") or 6-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (CYOCTOL™) are described in detail in U.S. Patents 4,689,349, 4,689,345, and 4,855,322 (the contents of each of which are incorporated herein in their entirety by this reference).

[0093] In some embodiments, the formulation(s) may further include an additional ingredient, a pharmaceutically and/or cosmetically acceptable additive, or both. As non-limiting examples, the formulations may further include at least one of the following: adjuvants, excipients, solubilizers, thickeners, gelling agents, fillers, colorants, lubricants, binders, moisturizing agents, preservatives, fragrances, electrolytes, adsorption enhancers, skin penetration enhancers, UV blocking materials; antioxidants, neutralizing agents, buffering agents, and viscosity enhancers (*e.g.*, bee's wax).

[0094] The formulations may be in various forms, *e.g.*, as a gel, ointment, or dermal adhesive patch.

[0095] The formulations may be prepared according to known methods for dispersing a

hydrophilic phase in a continuous hydrophobic phase.

[0096] In one embodiment, a hydrophilic compound is combined with a hydrophilic solvent to provide a solution of the hydrophilic compound. A selected stabilizing component is added to the solution of the hydrophilic compound. Upon combining with a hydrophobic carrier, a stabilized formulation is obtained that comprises a continuous hydrophobic phase and a dispersed phase in the form of reverse micelles that include a hydrophilic component.

[0097] In certain embodiments, the method of preparing a formulation comprises dissolving at least one hydrophilic compound in a hydrophilic phase to provide a solution of the hydrophilic compound(s), and combining the solution with a continuous hydrophobic phase to provide the formulation. The method further comprises adding a stabilizing component that include at least one polysorbate emulsifier having an HLB value of at least 10 and at least one emulsifier having an HLB of less than 10. About 8% to about 30% by weight of the stabilizing component is polysorbate emulsifier(s) having an HLB value of at least 10. The formulation comprises no more than about 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10.

[0098] In certain embodiments, the method of preparing a formulation may comprise dissolving at least one hydrophilic compound in a hydrophilic phase to provide a solution of at least one hydrophilic compound, and then adding a stabilizing component to the solution to produce a stabilizing component-containing solution of the hydrophilic compound(s). The method further comprises combining the stabilizing component-containing solution with a continuous hydrophobic phase to provide the formulation. The stabilizing component includes at least one polysorbate emulsifier having an HLB value of at least 10 and at least one emulsifier having an HLB of less than 10, wherein from about 8% to about 30% by weight of the stabilizing component is polysorbate emulsifier(s) having an HLB value of at least 10. The formulation comprises no more than about 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10.

[0099] Preferred formulations display enhanced shelf life, and tolerate a relatively wide range of temperatures and other conditions. Such formulations are stable at room temperature, without agitation, for at least one week. In certain embodiments, the formulations are stable for at least about 3 years.

[0100] In further embodiments, a topical formulation comprises a continuous hydrophobic phase, a hydrophilic phase, at least about 0.1% (preferably at least about 1%) by weight of green tea extract, *e.g.*, epigallocatechin gallate (EGCG) compound based upon total weight of the topical formulation, and a stabilizing component in an amount of at least about 15% by weight based upon total weight of the topical formulation. The continuous hydrophobic phase comprises mineral oil, squalane, or a mixture thereof. The stabilizing component comprises TPGS in an amount from about 8% to about 30% by weight, preferably from about

7.5% to about 12% by weight, based upon total weight of the stabilizing component, and at least one emulsifier having an HLB value of less than 10 (preferably about 3 to 8, and more preferably about 3 to 6). A weight ratio of the stabilizing component to the hydrophilic compound(s) is at least about 10:1.

[0101] In one particular embodiment, a topical formulation comprises a continuous squalane hydrophobic phase, a propylene glycol hydrophilic phase, an EGCG compound in an amount from about 1.0% to about 1.7% by weight based upon total weight of the topical formulation, and a stabilizing component in an amount of at least about 15% by weight based upon total weight of the formulation. The stabilizing component comprises TPGS in an amount from about 8% to about 30% by weight based upon total weight of the stabilizing component and at least one fatty acid monoester of sorbitan having an HLB value of less than 6. A weight ratio of the continuous squalane hydrophobic phase to the propylene glycol hydrophilic phase is about 10:1. A weight ratio of the continuous squalane hydrophobic phase to the stabilizing component is no more than about 5:1. A weight ratio of the stabilizing component to the EGCG compound is at least about 10:1.

[0102] In further particular embodiments, the formulations do not include triglyceride.

[0103] In some embodiments, the topical formulations further include ETHOCYN® (from BCS Business Consulting Services Pte Ltd of Singapore) or 6-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (CYOCTOL™). Methods of manufacture, and uses of skin care compositions comprising a lower alkyl-substituted ETHOCYN® or 6CYOCTOL™ are described in detail in U.S. Patents 4,689,349, 4,689,345, and 4,855,322 (the contents of each of which are incorporated herein in their entirety by this reference).

[0104] In some embodiments, the formulations further include an additional ingredient, a pharmaceutically and/or cosmetically acceptable additive, or both. As non-limiting examples, the formulations may further include at least one of the following: an adjuvant, an excipient, a solubilizer, a thickener, a gelling agent, a filler, a colorant, a lubricant, a binder, a moisturizing agent, a preservative, a fragrance, an adsorption enhancer, an UV blocking material; an antioxidant, a neutralizing agent, a buffering agent, and a viscosity enhancer (*e.g.*, bee's wax).

[0105] The formulations may be in various forms, *e.g.*, as a gel, ointment, or dermal adhesive patch.

[0106] The formulations may be prepared according to known methods for dispersing a hydrophilic phase in a continuous hydrophobic phase.

[0107] In some embodiments, the formulations may be prepared by dissolving at least one hydrophilic compound in a hydrophilic phase to provide a solution of the hydrophilic compound(s).

Then, TPGS may be added to the solution of the hydrophilic compound(s). Upon combining the solution with a mixture comprising a hydrophobic carrier and, optionally, at least one emulsifier having a HLB value of less than 10, a stabilized formulation may be obtained that comprise a continuous hydrophobic phase and a dispersed phase in the form of reverse micelles that include the hydrophilic component(s).

[0108] The formulations may have enhanced shelf stability or shelf life, and tolerate a wide range of temperatures and other conditions. The formulations may be stable at room temperature, without agitation, for at least one week. In certain embodiments, the formulations may be stable for at least about 3 years.

[0109] The formulations may be administered to a subject topically, such as in the form of ointments, drops or transdermal patches, as known in the pharmaceutical art or cosmetic art.

[0110] The formulations may be used to treat a condition (*e.g.*, to cure an abnormal condition, to prevent an undesirable condition, and/or to enhance a desirable condition) in a mammal, preferably human, in need thereof. The method of treating such a condition may involve topically administering the formulations to the subject in need of treatment. Accordingly, a method for treating a condition in a subject in need thereof comprises topically administering the formulation to the subject.

[0111] The formulations may be useful for delivering a hydrophilic compound to any animal, but preferably mammals. In embodiments, other uses are contemplated, for example application of a compound to an inanimate surface.

[0112] Also disclosed is a method for delivering a hydrophilic compound to a subject. The method comprises, for example, topically administering the formulation to the subject.

[0113] In certain embodiments, upon a topical application of the formulation to a skin, at least a portion of the hydrophilic compound contained in the reverse micelles may leave or disassociate from the reverse micelle and then transport through the skin. Thus, layer under the skin may benefit from the effect of the hydrophilic compound.

[0114] In certain but not all embodiments, upon a topical application of the formulation to a skin, at least a portion of the hydrophilic compound contained in the reverse micelles may transport through the skin and then leave or disassociate from the reverse micelle. Thus, a systemic delivery of the hydrophilic compound to the layer under skin may be achieved.

[0115] The disclosure is further described with the aid of the following illustrative Examples.

EXAMPLES

[0116] **EXAMPLE I: Formulations Comprising Hydrophilic EGCG Compound in a**

Continuous Hydrophobic Phase With or Without TPGS Emulsifier

[0116] The hydrophilic epigallocatechin gallate (EGCG, (catechins (tea extract) Sunphenon™ EGCg from Taiyo Green Power Co., Ltd of Wuxi Jiangsu, China – distributed as Stauber Item# 24845 by Stauber of California)) compound was extracted from green tea. Propylene glycol (PG) was used as the hydrophilic solvent. Squalane (OleaClear™ Olive Squalane from Tri-K Industries of Northvale, NJ, US) and mineral oil hydrophobic solvents were tested as the continuous hydrophobic phase. TPGS emulsifier was obtained from Eastman Chemical Company. Sorbitan monooleate surfactant having an HLB value of 4.3 (SPAN™ 80 surfactant from Croda Inc.) was used as the emulsifier having an HLB value of less than 10.

[0117] The EGCG compound was dissolved in propylene glycol (PG) hydrophilic solvent to produce a solution (*i.e.*, hydrophilic phase) having a weight ratio of EGCG compound to PG solvent of about 1:5. The solution of EGCG was mixed with a predetermined amount of TPGS emulsifier, and then combined with a mixture of the selected hydrophobic solvent and sorbitan monooleate surfactant at a weight ratio of the hydrophilic solvent PG to the hydrophobic solvent of about 1:10.

[0118] To test the effect of the stabilizing component on the stability of the formulation, the formulations having various combinations and amounts of the stabilizing component were prepared as shown in **TABLE 1**. The formulations were tested for stability at room temperature.

[0119] As shown in **TABLE 1**, **Formulations A1, B1, C1, D1 and E1** were not stable when the stabilizing component in the formulations did not include any TPGS emulsifier, regardless the amounts of sorbitan monooleate. Thus, the formulations required TPGS emulsifier to enhance their shelf stabilities, and sorbitan monooleate surfactant (HLB value of 4.3) alone was not sufficient. The formulations using squalane hydrophobic solvent showed similar stability as those using mineral oil as a hydrophobic solvent. The stability of the formulations decreased as the weight ratio of the stabilizing component to the EGCG compound reduced. **Formulations E2, E3, and EX** showed that the weight ratio of the stabilizing component to the EGCG compound of at least about 10:1 was required for an enhanced stability of the formulations.

TABLE 1

Compound	Formulation (each component in mg unit)									
	AI	A2	A3	AX	BI	B2	B3	BX		
EGCG	100	100	100	100	100	100	100	100		
Propylene Glycol	500	500	500	500	500	500	500	500		
TPGS Emulsifier	0	1000	500	500	0	800	400	400		
Sorbitan Monooleate	5000	4000	4500	4500	4000	3200	3600	3600		
Squalane	5000	5000	5000	—	5000	5000	5000	—		
Mineral Oil	—	—	—	5000	—	—	—	5000		
% TPGS (%wt in Stabilizing Component)	0%	20%	10%	10%	0%	20%	10%	10%		
% Stabilizing Component (%wt in Formulation)	47%	47%	47%	47%	42%	42%	42%	42%		
% EGCG (%wt in Formulation)	0.94%	0.94%	0.94%	0.94%	1.04%	1.04%	1.04%	1.04%		
Weight Ratio of Hydrophobic Solvent: Stabilizing Component	1:1	1:1	1:1	1:1	1.25:1	1.25:1	1.25:1	1.25:1		
Weight Ratio of Stabilizing Component : EGCG	50:1	50:1	50:1	50:1	40:1	40:1	40:1	40:1		
Stability	Phase Separated	Good	Good	Good	Phase Separated	Good	Good	Good		

TABLE 1 (Con't)

Compound	Formulation (each component in mg unit)									
	C1	C2	C3	ex	D1	D2	D3	DX		
EGCG	100	100	100	100	100	100	100	100		
Propylene Glycol	500	500	500	500	500	500	500	500		
TPGS Emulsifier	0	600	300	300	0	400	200	200		
Sorbitan Monooleate	3000	2400	2700	2700		2000	1800	1800		
Squalane	5000	5000	5000	—		5000	5000	—		
Mineral Oil	—	—	—	5000	—	—	—	5000		
% TPGS (%wt in Stabilizing Component)	0%	20%	10%	10%	0%	20%	10%	10%		
% Stabilizing Component (%wt in Formulation)	26%	26%	26%	26%	15%	15%	15%	15%		
% EGCG (%wt in Formulation)	1.32%	1.32%	1.32%	1.32%	1.52%	1.52%	1.52%	1.52%		
Weight Ratio of Hydrophobic Solvent: Stabilizing Component	1.67:1	1.67:1	1.67:1	1.67:1	2.5:1	2.5:1	2.5:1	2.5:1		
Weight Ratio of Stabilizing Component : EGCG	30:1	30:1	30:1	30:1	20:1	20:1	20:1	20:1		
Stability	Phase Separated	Good	Good	Good	Phase Separated	Good	Good	Good		Good

TABLE 1 (Con't)

Compound	Formulation (each component in mg unit)				
	E1	E2	E3	EX	F
EGCG	100	100	100	100	83.33
Propylene Glycol	500	500	500	500	416.67
TPGS Emulsifier	0	200	100	100	100
Sorbitan Monooleate	1000	800	900	900	900
Squalane	5000	5000	5000	—	5000
Mineral Oil	—	—	—	5000	—
% TPGS (%wt in Stabilizing Component)	0%	20%	10%	10%	10%
% Stabilizing Component (%wt in Formulation)	15%	15%	15%	15%	15%
% EGCG (%wt in Formulation)	1.32%	1.32%	1.32%	1.32%	1.28%
Weight Ratio of Hydrophobic Solvent: Stabilizing Component	5:1	5:1	5:1	5:1	5:1
Weight Ratio of Stabilizing Component : EGCG	10:1	10:1	10:1	10:1	12:1
Stability	Phase Separated	Fair	Fair	Fair	

[0120] EXAMPLE 2: Formulation F Comprising Hydrophilic EGCG Compound in a Hydrophobic Squalane Solvent with a Stabilizing Component Comprising TPGS and Sorbitan Monooleate Emulsifiers

[0088] About 4 g of a hydrophilic EGCG compound was dissolved in about 20 g of a propylene glycol hydrophilic solvent, and the mixture was heated to about 60°C to provide a solution (*i.e.*, hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the propylene glycol hydrophilic solvent of about 1:5. To about 500 mg of the solution, about 100 mg of TPGS emulsifier was added. The resulting solution was then combined with a mixture composed of 5000 g squalane hydrophobic solvent and 900 mg of sorbitan monooleate surfactant (SPAN™ 80 surfactant, HLB value of 4.3) and stirred vigorously to provide **Formulation F of TABLE 1**. **Formulation F** showed good stability at room temperature for at least one week without agitation. See **TABLE 1**, *supra*.

[0121] EXAMPLE 3: Formulations Comprising Hydrophilic EGCG Compound in a Hydrophobic Squalane Solvent Using Different Stabilizing Components

[0122] The EGCG compound was dissolved in propylene glycol (PG) hydrophilic solvent to produce a solution (*i.e.*, hydrophilic phase) having a weight ratio of EGCG compound to PG solvent of about 1:5. The solution of EGCG was mixed with a predetermined amount of TPGS emulsifier, and then combined with a mixture composed of squalane hydrophobic solvent and sorbitan monooleate surfactant at a weight ratio of the hydrophilic solvent PG to the hydrophobic squalane solvent of about 1:10. To test the effect of the stabilizing component on the stability of the formulation, the formulations having various combinations and amounts of the stabilizing component were prepared as shown in **TABLE 2**. The formulations were tested for stability at room temperature.

[0123] As shown in **TABLE 2**, when squalane was used as the continuous phase for the formulation of EGCG hydrophilic compound, the stability of the formulation was achieved by using a stabilizing component composed of both TPGS emulsifier and an emulsifier having an HLB value less than 10 (*e.g.*, sorbitan monooleate, HLB value of 4.3). The formulations were not stable when the amounts of the stabilizing component failed below 15% by weight-based upon total weight of the formulations. Furthermore, the stability of the formulations decreased as the weight ratio of the stabilizing component to the EGCG compound reduced to below 10:1.

TABLE 2

Compound	Formulation (each component in mg unit)											
	I	II	III	IV	v	VI	VII	VIII	IX	x	XI	XII
EGCG	100	100	100	100	100	100	100	100	100	100	100	100
Propylene glycol	500	500	500	500	500	500	500	500	500	500	500	500
TPGS Emulsifier	200	200	200	200	200	200	100	100	100	100	100	100
Sorbitan Monoolea	500	600	700	800	900	1000	500	600	700	800	900	1000
Squalane	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000
TPGS (%wt in Stabilizing	29%	25%	22%	20%	18%	17%	17%	14%	13%	11%	10%	9%
Stabilizing Component (%wt in Form.)	11%	13%	14%	15%	16%	18%	10%	11%	13%	14%	15%	16%
EGCG (%wt in Form.)	1.59%	1.56%	1.54%	1.52%	1.49%	1.47%	1.61%	1.59%	1.56%	1.54%	1.52%	1.49%
Weight Ratio of Hydrophobic Solvent: Stabilizing	7.14:1	6.25:1	5.56:1	5:1	4.55:1	4.17:1	8.33:1	7.14:1	6.25:1	5.56:1	5:1	4.55:1
Weight Ratio of Stabilizing	7:1	8:1	9:1	10:1	11:1	12:1	6:1	7:1	8:1	9:1	10:1	11:1

Stability I	Phase Separate d I	Phase Separate d	Phase Separate d	Fair	Good	Good	Good
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[0124] EXAMPLE 4: Formulation Comprising Hydrophilic EGCG Compound in a Hydrophobic Squalane Solvent

[0125] About 4 grams of the hydrophilic EGCG compound was mixed with about 20 grams of propylene glycol (hydrophilic solvent). The mixture was heated to about 60°C until the hydrophilic EGCG compound was fully dissolved in the hydrophilic solvent to provide a EGCG solution (*i.e.*, hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the hydrophilic solvent of about 1:5.

[0126] To a stainless steel mortar and pestle, about 5 grams of squalane (or, alternatively, an equal amount of medicinal liquid paraffin) was added and heated to about 60°. Then, about 0.9 grams of sorbitan monooleate surfactant having an HLB value of 4.3 (SPAN™ 80 surfactant from Croda Inc.) was added and mixed well with the squalane. About 500 mg of the EGCG solution (*i.e.*, hydrophilic phase) and about 100 mg of TPGS emulsifier were then added to the stainless steel mortar and pestle, and the mixture in the stainless steel mortar and pestle was mixed immediately. Then, the resulting mixture was allowed to cool down to room temperature under continued mixing to provide a formulation comprising about 1.3% by weight of the hydrophilic EGCG compound based on total weight of the formulation. After that, a portion of the formulation was transferred from the stainless steel mortar and pestle to a clear vial for a stability study. The formulation was a clear liquid having a light orange-beige color without opalescence or haze. The formulation showed an improved stability.

[0127] EXAMPLE 5: Formulation Comprising Hydrophilic EGCG Compound in Anhydrous Hydrophobic Serum

[0128] An anhydrous hydrophobic serum was prepared composed of cyclopentasiloxane, squalane (OleaClear™ Olive Squalane from Tri-K Industries of Northvale, NJ, US), dimethiconol, ethoxyheptyl bicyclooctanone (ETHOCYN®), ubiquinone, various extracts, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera Biennis* (evening primrose) oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and corn oil.

[0129] The hydrophilic epigallocatechin gallate (EGCG) compound is readily commercially available (e.g., "catechins" (tea extract) Sunphenon™ EGCg from Taiyo Green Power Co., Ltd of Wuxi Jiangsu, China – distributed as Stauber Item# 24845 by Stauber of California, US).

[0130] Various formulations comprising the hydrophilic EGCG compound in the anhydrous hydrophobic serum at different concentrations were prepared using Methods 1, 2, or 3. The resulting formulations were tested for stability at room temperature.

[0131] Method 1: Direct dispersion of hydrophilic EGCG compound into the anhydrous hydrophobic serum

[0132] Hydrophilic EGCG compound from green tea extract was mixed directly with the anhydrous hydrophobic serum at various concentrations with or without colloidal silicon dioxide: 0.1%, 0.2%, 0.5%, and 10% by weight of EGCG compound per total weight of the formulation.

[0133] The produced formulations at all tested EGCG concentrations were stable at room temperature without agitation for only a few hours, and then precipitation and/or creaming of the formulations were observed.

[0134] Method 2: Dispersion of a hydrophilic solution of hydrophilic EGCG compound into the anhydrous hydrophobic serum without using any stabilizing component [00100] The hydrophilic EGCG compound was dissolved in a macrogol polyethylene glycol (PEG 800) hydrophilic solvent to produce a solution (*i.e.*, hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the PEG 800 hydrophilic solvent of about 1:10. The hydrophilic phase was then mixed with the anhydrous hydrophobic serum at various concentrations to provide the formulations containing about 50 to 1000 mL of the PEG 800 hydrophilic phase per 5 mL of the anhydrous hydrophobic serum.

[0135] The tests showed that up to about 10% *g/g* of the hydrophilic EGCG compound per the anhydrous hydrophobic serum could be produced without losing integrity of the anhydrous hydrophobic serum. However, such formulations had poor stability and phase separated within one day at room temperature without agitation.

[0136] Method 3: Dispersion of a hydrophilic solution of hydrophilic EGCG compound into the anhydrous hydrophobic serum using a stabilizing component

[0137] About 4 g of a hydrophilic EGCG compound was dissolved in about 20 g of a propylene glycol hydrophilic solvent, and the mixture was heated to about 60°C to provide a solution (*i.e.*, hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the propylene glycol hydrophilic solvent of about 1:5. To about 500 mg of the solution, about 100 mg of polysorbate 80 surfactant having an HLB value of 15 (PEG-20 sorbitan monooleate, TWEEN® 80 from Croda Inc.) was added. Then, the hydrophobic serum was gradually added while the mixture was stirred vigorously until the total weight of the mixture/formulation was 100 g.

[0138] The resulting formulation had a weight ratio of the hydrophilic phase to the continuous hydrophobic phase is about 1:240, and a weight ratio of the stabilizing component to the continuous hydrophobic phase is about 1:1000. The formulation was composed of about 0.8 mg of the active EGCG compound per 1 g of the hydrophobic serum. The formulation showed excellent stability for up to 3 weeks at room temperature without agitation.

[0139]— —Therefore by using a stabilizing component, the stable formulation composed of about 0.8 mg of the active EGCG compound per 1 g of the hydrophobic serum was achieved.

[0140] EXAMPLE 6: Formulation Comprising Hydrophilic EGCG Compound in a Hydrophobic Mineral Oil Solvent

[0141] The hydrophilic EGCG compound was dissolved in a macrogol polyethylene glycol PEG 800 (hydrophilic solvent) to produce a solution (*i.e.*, hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the hydrophilic solvent of about 1:10. Then, the hydrophilic phase was mixed with mineral oil (hydrophobic solvent) to provide a formulation having a weight ratio of the hydrophilic solvent (macrogol PEG 800) to the mineral oil of about 1:10.

[0142] To test the effect of the stabilizing component on the stability of the formulation, the hydrophilic phase was mixed with mineral oil using different combinations and amounts of the stabilizing component. Polysorbate 80 surfactant having an HLB value of 15 (PEG-20 sorbitan monooleate, TWEEN® 80 surfactant), and sorbitan monooleate surfactant having an HLB value of 4.3 (SPAN™ 80 surfactant) were studied as the stabilizing component.

[0143] Various combinations of polysorbate 80 and sorbitan monooleate emulsifiers were tested as the stabilizing component for the formulation of active EGCG compound, and at various weight amount ratios in relation to the hydrophobic mineral oil, as shown in TABLE 3.

TABLE 3

Compound	Formulation (each component in mg unit)						
	A	B	c	D	F	H	I
EGCG <i>hydrophilic cpd</i>	50	50	50	50	50	50	50

PEG800 <i>Hydrophilic solvent</i>	500	500	500	500	500	500	500
Mineral Oil <i>Hydrophobic solvent</i>	5000	5000	5000	5000	5000	5000	5000
Polysorbate <i>High HLB emulsifier</i>	0	500	500	500	500	0	0
Sorbitan Monooleate <i>Low HLB emulsifier</i>	0	0	500	1000	4500	2000	1000
Stability	Phase Separated	Phase Separated	Phase Separated	Phase Separated	Good	Phase Separated	Phase Separated

[0144] As shown in TABLE 3, the formulation A which did not include a stabilizing component showed poor stability (*i.e.*, phase separation). The formulation B, which used only polysorbate emulsifier also showed poor stability. Likewise, the formulations H and I, each of which used only the low HLB surfactant, showed poor stability.

[0145] The most enhanced stability was observed in the formulation F, which included both polysorbate 80 (HLB value of 15) and sorbitan monooleate (HLB value of 4.3) emulsifiers as the stabilizing component. Formulation F had a weight ratio of the stabilizing component to the mineral oil of about 1:1, and about 10% weight of the stabilizing component was polysorbate 80.

[0146] Therefore, when mineral oil was used as the continuous phase for the formulation of EGCG hydrophilic compound, the stability of the formulation was achieved by using a stabilizing component composed of both polysorbate emulsifier having an HLB value of at least 10 (*e.g.*, polysorbate 80, HLB value of 15) and an emulsifier having an HLB value less than 10 (*e.g.*, sorbitan monooleate, HLB value of 4.3). The formulation had a weight ratio of the hydrophilic EGCG compound to the hydrophilic solvent (macrogol PEG 800) of about 1:10, a weight ratio of the hydrophilic solvent (macrogol PEG 800) to the mineral oil (hydrophobic solvent) of about 1:10, a weight ratio of the stabilizing component to the mineral oil of about 1:1, and about 10% weight of the stabilizing component was the polysorbate emulsifier having an HLB value of at least 10 (*e.g.*, polysorbate 80, HLB value of 15).

[0147] EXAMPLE 7: Formulations Comprising Hydrophilic EGCG Compound in a Hydrophobic Squalane Solvent Using Different Stabilizing Components

[0148] The hydrophilic EGCG compound was dissolved in propylene glycol (hydrophilic solvent) a solution (*i.e.*, hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the hydrophilic solvent of about 1:5. Then, the hydrophilic phase was mixed with squalane (hydrophobic solvent) to provide a formulation having a weight ratio of the hydrophilic solvent (propylene glycol) to the squalane solvent of about 1:10.

[0149] To test the effect of the stabilizing component on the stability of the formulation, the hydrophilic phase was mixed with the squalane solvent using different combinations and amounts of the stabilizing components. Polysorbate 80 surfactant having an HLB value of 15 (PEG-20 sorbitan monooleate, TWEEN® 80 from Croda Inc.), and sorbitan monooleate surfactant having an HLB value of 4.3 (SPAN™ 80 surfactant from Croda Inc.) were studied as the stabilizing component

[0150] Various combinations of polysorbate 80 and sorbitan monooleate emulsifiers were tested as the stabilizing component for the formulation of active EGCG compound, and at various weight amount ratios in relation to the hydrophobic squalane solvent, as shown in TABLE 4.

[0151] As shown in TABLE 4, when squalane was used as the continuous phase for the formulation of EGCG hydrophilic compound, the stability of the formulation was achieved by using a stabilizing component composed of both polysorbate emulsifier having an HLB value of at least 10 (*e.g.*, polysorbate 80, HLB value of 15) and an emulsifier having an HLB value less than 10 (*e.g.*, sorbitan monooleate, HLB value of 4.3).

TABLE 4

Compound	Formulation éach component in mg unit											
	I	II	III	IV	V	VI	VII	VII	IX	X	XI	XII
EGCG <i>Active Compound</i>	100	100	100	100	100	100	100	100	100	100	100	100
Propylene glycol <i>Hydrophilic solvent</i>	500	500	500	500	500	500	500	500	500	500	500	500
Squalane <i>Hydrophobic solvent</i>	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000
Polysorbate ⁸⁰ <i>High HLB emulsifier</i>	200	200	200	200	200	200	100	100	100	100	100	100
Sorbitan Monooleate <i>Low HLB emulsifier</i>	500	600	700	800	900	1000	500	600	700	800	900	1000
Stability	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good

[0152] EXAMPLE 8: Formulation Comprising Hydrophilic EGCG Compound in a Hydrophobic Squalane Solvent

[0153] About 4 grams of the hydrophilic EGCG compound was mixed with about 20 grams of propylene glycol (hydrophilic solvent). The mixture was heated to about 60°C until the hydrophilic EGCG compound was fully dissolved in the hydrophilic solvent to provide a EGCG solution (*i.e.*, hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the hydrophilic solvent of about 1:5.

[0154] To a stainless steel mortar and pestle, about 5 grams of squalane (or, alternatively, an equal amount of medicinal liquid paraffin) was added and heated to about 60°

C. Then, about 2.7 grams of sorbitan monooleate surfactant having an HLB value of 4.3 (SPAN™ 80 surfactant from Croda Inc.) was added and mixed well with the squalane.

[0155] About 500 mg of the EGCG solution (*i.e.*, hydrophilic phase) and about 300 mg of polysorbate 80 surfactant having an HLB value of 15 (PEG-20 sorbitan monooleate, TWEEN® 80 from Croda Inc.) were then added to the stainless steel mortar and pestle, and the mixture in the stainless steel mortar and pestle was mixed immediately. Then, the resulting mixture was allowed to cool down to room temperature under continued mixing to provide a formulation comprising about 1% by weight of the hydrophilic EGCG compound based on total weight of the formulation. After that, a portion of the formulation was transferred from the stainless steel mortar and pestle to a clear vial for a stability study. The formulation was a clear liquid having a light orange-beige color without opalescence or haze. The formulation showed an improved stability.

[0156] EXAMPLE 9: Formulation Comprising Hydrophilic EGCG Compound in a Hydrophobic Squalane Solvent

[0157] About 1 gram of sunphenon EGCG was mixed with about 6 grams of propylene glycol (hydrophilic solvent). The mixture was heated to about 60°C until all solids were fully dissolved in the hydrophilic solvent to provide a EGCG solution (*i.e.* hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the hydrophilic solvent of about 1:6.

[0158] To this mixture, about 3 grams of TPGS were added. The resulting mixture was then mixed until it yielded a clear solution.

[0159] About 75 grams of squalane and about 15 grams of SPAN 80 were then combined in a main container and then mixed until they yielded a clear solution. The hydrophilic phase containing EGCG, propylene glycol, and TPGS was then added to the squalane-SPAN 80 mixture. The resulting mixture was then mixed until it yielded a clear solution. The formulation showed an improved stability. In certain embodiments, the ingredients may be mixed in the following percentages in the formulation: PROPYLENE GLYCOL 6.220, SUNPHENON EGCG (TAIYO) 1.240, TPGS – TOCOPHEROSAN (ISOLAN) 2.990, SQUALANE 74.630, and SPAN 80 (CRODA) 14.920.

[0160] EXAMPLE 10: Formulation Comprising Hydrophilic EGCG Compound in a Hydrophobic Drakeol 35 Solvent

[0161] About 1 gram of sunphenon EGCG was mixed with about 9 grams of propylene glycol (hydrophilic solvent). The mixture was heated to about 60°C until all solids were fully dissolved in the hydrophilic solvent to provide a EGCG solution (i.e. hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the hydrophilic solvent of about 1:9.

[0162] To this mixture, about 4 grams of tocopherosan were added. The resulting mixture was then mixed until it yielded a clear solution.

[0163] About 110 grams of Drakeol 35 and about 21 grams of SPAN 80 were then combined in a main container and then mixed until they yielded a clear solution. The hydrophilic phase containing EGCG, propylene glycol, and tocopherosan was then added to the Drakeol 35-SPAN 80 mixture. The resulting mixture was then mixed until it yielded a clear solution. The formulation showed an improved stability. In certain embodiments, the ingredients may be mixed in the following percentages in the formulation: PROPYLENE GLYCOL 6.220, SUNPHENON EGCG (TAIYO) 0.691, TOCOPHEROSAN (ISOCHEM) 2.990, DRAKEOL 35 (PENRECO), and SPAN 80 (CRODA) 14.920.

[0164] EXAMPLE 11: Formulation Comprising Hydrophilic EGCG Compound in a Hydrophobic FINSOLV TN (c12-15 Alkyl Benzoate) Solvent

[0165] About 1 gram of sunphenon EGCG was mixed with about 9 grams of propylene glycol (hydrophilic solvent). The mixture was heated to about 60°C until all solids were fully dissolved in the hydrophilic solvent to provide a EGCG solution (i.e. hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the hydrophilic solvent of about 1:9.

[0166] To this mixture, about 4 grams of tocopherosan were added. The resulting mixture was then mixed until it yielded a clear solution.

[0167] About 110 grams of FINSOLV TN and about 21 grams of SPAN 80 were then combined in a main container and then mixed until they yielded a clear solution. The hydrophilic phase containing EGCG, propylene glycol, and tocopherosan was then added to the FINSOLV TN-SPAN 80 mixture. The resulting mixture was then mixed until it yielded a clear solution. The formulation showed an improved stability. In certain embodiments, the ingredients may be mixed in the following percentages in the formulation: PROPYLENE GLYCOL 6.220, SUNPHENON EGCG (TAIYO) 0.691, TOCOPHEROSAN (ISOCHEM) 2.990, FINSOLV TN (INNOSPEC) 75.179, and SPAN 80 (CRODA) 14.920.

[0168] EXAMPLE 12: Formulation Comprising Hydrophilic EGCG Compound in a Hydrophobic Hemisqualane Solvent

[0169] About 1 gram of sunphenon EGCG was mixed with about 9 grams of propylene glycol (hydrophilic solvent). The mixture was heated to about 60°C until all solids were fully dissolved in the hydrophilic solvent to provide a EGCG solution (i.e. hydrophilic phase) having a weight ratio of the hydrophilic EGCG compound to the hydrophilic solvent of about 1:9.

[0170] To this mixture, about 4 grams of tocopherosan were added. The resulting mixture was then mixed until it yielded a clear solution.

[0171] About 110 grams of hemisqualane and about 21 grams of SPAN 80 were then combined

in a main container and then mixed until they yielded a clear solution. The hydrophilic phase containing EGCG, propylene glycol, and tocopherosan was then added to the hemisqualane-SPAN 80 mixture. The resulting mixture was then mixed until it yielded a clear solution. The formulation showed an improved stability. In certain embodiments, the ingredients may be mixed in the following percentages in the formulation: PROPYLENE GLYCOL 6.220, SUNPHENON EGCG (TAIYO) 0.691, TOCOPHEROSAN (ISOCHEM) 2.990, HEMISQUALANE 75.179, and SPAN 80 (CRODA) 14.920.

[0172] EXAMPLE 13: Formulation Comprising Hydrophilic Centellin CG Compound in a Hydrophobic Squalane Solvent

[0173] About 1 gram of Centellin CG was mixed with about 19 grams of propylene glycol (hydrophilic solvent). The mixture was heated to about 60°C until all solids were fully dissolved in the hydrophilic solvent to provide a Centellin CG solution (i.e. hydrophilic phase) having a weight ratio of the hydrophilic Centellin CG compound to the hydrophilic solvent of about 1:19.

[0174] To this mixture, about 9 grams of tocopherosan were added. The resulting mixture was then mixed until it yielded a clear solution.

[0175] About 230 grams of squalane and about 45 grams of SPAN 80 were then combined in a main container and then mixed until they yielded a clear solution. The hydrophilic phase containing Centellin CG, propylene glycol, and tocopherosan was then added to the squalane-SPAN 80 mixture. The resulting mixture was then mixed until it yielded a clear solution. The formulation showed an improved stability. In certain embodiments, the ingredients may be mixed in the following percentages in the formulation: PROPYLENE GLYCOL 6.220, CENTELLIN CG (SABINSA) 0.330, TOCOPHEROSAN (ISOCHEM) 2.990, SQUALANE 75.410, and SPAN 80 (CRODA) 14.920.

[0176] EXAMPLE 14: Formulation Comprising Hydrophilic Guarana Dry Extract Compound in a Hydrophobic Hemisqualane Solvent

[0177] About 1 gram of guarana dry extract was mixed with about 9 grams of propylene glycol (hydrophilic solvent). The mixture was heated to about 60°C until all solids were fully dissolved in the hydrophilic solvent to provide a Centellin CG solution (i.e. hydrophilic phase) having a weight ratio of the hydrophilic Centellin CG compound to the hydrophilic solvent of about 1:9.

[0178] To this mixture, about 4 grams of tocopherosan were added. The resulting mixture was then mixed until it yielded a clear solution.

[0179] About 110 grams of hemisqualane and about 22 grams of SPAN 80 were then combined in a main container and then mixed until they yielded a clear solution. The hydrophilic phase containing guarana dry extract, propylene glycol, and tocopherosan was then added to the hemisqualane-SPAN 80 mixture. The resulting mixture was then mixed until it yielded a clear solution. The formulation showed an improved stability. In certain embodiments, the ingredients may be mixed in the following percentages in the formulation: PROPYLENE GLYCOL 6.220, GUARANA DRY EXTRACT (IDENA) .690, TOCOPHEROSAN (ISOCHEM) 2.940,

HEMISQUALANE (NEOSSANCE) 75.150, and SPAN 80 (CRODA) 15.000.

[0180] In certain embodiments, hydrophobic phase ingredients that did not form successful nanoemulsion formulations (generally began cloudy and separated into two phases, primarily within 24 hours) when substituted into the above examples include tocopheryl linoleate, olive oil, safflower oil, isopropyl palmitate, cetyl octanoate, octyl stearate, dimethicone, cyclopentasiloxane, and ethylhexyl benzoate.

[0181] In embodiments, hydrophobic phase ingredients that did form clear formulations were hydrocarbons (Squalene, Mineral Oil, C13-15 Alkane) and C12-15 Alkyl Benzoate. In certain embodiments, hydrogenated polydecene, isododecane, isohexdecane, isoeicosane, and/or isoparaffins may substitute for squalane, mineral oil, C13-14 alkane, and/or C12-15 alkyl benzoate as hydrophobic phase ingredients in Examples 1-14 and yield mixtures with similarly improved stability.

Embodiments of formulations include a hydrophilic phase, which includes a humectant

[0182] Various modifications to the implementations described in this disclosure may be made, and the generic principles defined herein may be applied to other implementations without departing from the spirit or scope of this disclosure. Thus, the scope of the disclosure is not intended to be limited to the implementations shown herein, but are to be accorded the widest scope consistent with this disclosure, the principles and the novel features disclosed herein.

[0183] Certain features that are described in this specification in the context of separate embodiments also can be implemented in combination in a single embodiment. Conversely, various features that are described in the context of a single embodiment also can be implemented in multiple embodiments separately or in any suitable subcombination. Moreover, although features may be described above as acting in certain combinations and even initially claimed as such, one or more features from a claimed combination can in some cases be excised from the combination, and the claimed combination may be directed to a subcombination or variation of a subcombination.

WHAT IS CLAIMED IS:

1. A formulation comprising: a continuous hydrophobic phase; a hydrophilic phase dispersed throughout said continuous hydrophobic phase; a stabilizing component comprising:
 - from 8% to 30% by weight D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) based upon total weight of the stabilizing component, and
 - from 70% to 92% by weight at least one emulsifier having an HLB value of less than 10; anda hydrophilic component comprising a compound that is normally insoluble in said continuous hydrophobic phase at room temperature absent an emulsifying agent, wherein the hydrophilic component is substantially dissolved in the hydrophilic phase utilizing reverse micelles comprising the TPGS and the emulsifier, and wherein the weight ratio of the stabilizing component to the hydrophilic component is at least 10:1.
2. The formulation of claim 1, wherein the hydrophilic component is present therein in an amount of at least 0.1% by weight based upon total weight of the formulation.
3. The formulation of claim 1, wherein the stabilizing component is present in an amount of at least 15% by weight based upon total weight of the formulation.
4. The formulation of claim 1, wherein the weight ratio of the continuous hydrophobic phase to the stabilizing component is no more than 5:1.
5. The formulation of claim 1, wherein the TPGS is present in an amount of from 8% to 30% by weight based upon total weight of the stabilizing component, and the at least emulsifier has an HLB value of 3 to 8.
6. The formulation of claim 1, wherein the emulsifier comprises a fatty acid monoester of sorbitan.
7. The formulation of claim 1, wherein the emulsifier comprises sorbitan monooleate.
8. The formulation of claim 1, wherein the hydrophilic component includes an

ingredient selected from the group consisting of green tea extract, grape seed extract, fruit extract, centellin asiatica extract, guarana extract (*paullina cupana* seed extract) and polyphenol(s).

9. The formulation of claim 1, wherein the hydrophilic component includes a compound selected from the group consisting of epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin (EC), epicatechin gallate (ECG), asiaticoside, madecassoside, asiatic acid, madecassic acid, caffeine, and catechin(s).

10. The formulation of claim 1, wherein the hydrophilic component includes a compound selected from the group consisting of hydrolyzed pepper fruit extract (*Piper nigrum*), hydrolyzed soy protein, peppermint extract (*Mentha piperita*), lotus (*Nelumbo nucifera*), coriander (*Coriandrum sativum*), *Verbena officinalis* extract, and *Helianthus annuus* (sunflower) seed extract.

11. The formulation of claim 1, wherein the hydrophilic component includes an ingredient selected from the group consisting of *Saccharomyces cerevisiae* extract, *Withania somnifera* root extract, butylene glycol and hydrolyzed *Coriandrum sativum* fruit extract and *Citrus aurantium dulcis* (orange) fruit extract, *Helianthus annuus* (sunflower) seed extract, *Taraxacum officinale* (dandelion) extract, hydrolyzed *Viola tricolor* extract, *Pyrus malus* (apple) fruit extract, hydrolyzed *Celosia cristata* extract and hydrolyzed *Prunella vulgaris* extract, hydrolyzed *Citrus aurantium dulcis* fruit extract, hydrolyzed *Candida saitoana* extract, *Lindera strychnifolia* root extract, *Triticum vulgare* (wheat germ) extract, *Secale cereale* (rye) seed extract, hydrolyzed sesame extract, *Tropaeolum majus* flower extract, *Spiraea ulmaria* extract, hydrolyzed sweet almond protein, *Salix Alba* (willow) leaf extract, *Mentha piperita* (peppermint) extract, *Triticum vulgare* (wheat) germ extract, butylene glycol and *Butyrospermum parlatii* (shea butter) seedcake extract, hydrolyzed lupine protein octenylsuccinate, hydrolyzed *Cucurbita pepo* (pumpkin) seedcake, hydrolyzed *Opuntia ficus indica* flower extract, *Medicago sativa* (alfalfa) seed extract and hydrolyzed lupine protein, *Lentinus edodes* extract, hydrolyzed *Ceratonia siliqua* seed extract, *Gossypium hirsutum* (cotton) extract, *Helianthus annuus* (sunflower) seed extract, *Jasminum officinale* (jasmine) flower extract, hydrolyzed *Manihot esculenta* tuber extract, butylene glycol and *Iris florentina* root extract, hydrolyzed wheat protein, hydrolyzed *Myrtus communis* leaf extract, butylene glycol and *Boerhavia diffusa* root extract, *Cynara scolymus* (artichoke) leaf extract, yeast extract, hydrolyzed rice protein, *Nasturtium officinale* extract, *Avena sativa* (oat) kernel extract, *Tropaeolum majus* flower/leaf/stem extract, *Lens esculenta* (lentil) seed extract (including oligosaccharides thereof), *Cyperus esculentus* tuber extract, *Prunus amygdalus dulcis* (sweet almond) seed extract, hydrolyzed soy fiber, *Pichia anomala* extract, butylene glycol and *Nelumbo nucifera* leaf extract, yeast extract, butylene glycol and *Artemisia abrotanum* extract, hydrolyzed soy flour, *Castanea sativa* (chestnut) seed extract,

propylene glycol and *Citrus aurantium amara* (bitter orange) flower extract, hydrolyzed pepper fruit extract, hydrolyzed soy protein, butylene glycol and *Spiraea ulmaria* extract, hydrolyzed linseed extract, butylene glycol and *Peumus boldus* leaf extract, red algae (*Kappaphycus alvarezii*) galactans, *Pichia anomala* (including biopeptides thereof) extract, sulfated galactans of *Hypnea musciformis*, *Glycine soja* hydrolyzed soy protein, *Oryza sativa* extract, *Cyperus esculentus* tuber extract, *Piper nigrum* hydrolyzed pepper fruit extract, *Verbena officinalis* extract, butylene glycol and *Peumus boldus* leaf extract, butylene glycol and *Peumus boldus* leaf extract, seed extract, hydrolyzed *Cicer* seed extract, *Triticum Vulgare* (wheat) germ extract, hydrolyzed pea, butylene glycol and *Silybum Marianum* extract, hydrolyzed lupine protein, *Kappaphycus alvarezii* (red algae) extract, *Triticum vulgare* (wheat) protein, yeast extract, *Cichorium intybus* (chicory) root extract, *Prunus persica* (peach) leaf extract, *Verbena officinalis* extract, *Medicago sativa* (alfalfa) extract, *Paeonia albiflora* root extract, *Palmaria palmata* extract, hydrolyzed millet, butylene glycol and triethanolamine and *Punica granatum* extract, glycerin and *Prunus amygdalus dulcis* (sweet almond) extract, hydrolyzed sweet almond seedcake, butylene glycol and *Fumaria officinalis* extract, butylene glycol and *Camelliasinensis* leaf extract, and soytrimonium chloride.

12. The formulation of claim 1, wherein the hydrophilic component includes a compound selected from the group consisting of a peptide, an amino acid, a polynucleotide, and a hydrophilic drug.

13. The formulation of claim 1, wherein the hydrophilic phase includes at least one solvent selected from the group consisting of water, ethanol, dimethyl sulfoxide, propylene glycol, and polyethylene glycol.

14. The formulation of claim 1, wherein the continuous hydrophobic phase comprises a solvent selected from the group consisting of mineral oil, vegetable oil, paraffin, polysiloxane, cyclopentasiloxane, dimethiconol, squalane, C12-15 alkyl benzoate (such as Finsolv TN), C13-15 alkane (such as hemisqualane) and mixtures thereof.

15. The formulation of claim 1, wherein

the hydrophilic component comprises a green tea extract, centella asiatica extract, and/or guarana extract in an amount of at least 0.1% by weight based upon total weight of the formulation; and

the stabilizing component is present in an amount of at least 15% by weight based upon total weight of the formulation, the stabilizing component consisting of

from 8% to 30% by weight TPGS based upon total weight of the

stabilizing component and

from 70% to 92% by weight emulsifier(s) having an HLB value of 3 to 8 based upon total weight of the stabilizing component,

wherein a weight ratio of the stabilizing component to the green tea extract is at least

10:1.

16. The formulation of claim 1, further comprising at least one of the following an adjuvant, an excipient, a solubilizer, a thickener, a gelling agent, a filler, a colorant, a lubricant, a moisturizing agent, a preservative, a fragrance, an adsorption enhancer, an UV blocking material; an antioxidant, a neutralizing agent, a buffering agent, and/or a viscosity enhancer.

17. A method of preparing the formulation of claim 1, the method comprising: dissolving the hydrophilic component in the hydrophilic phase to provide a solution of the hydrophilic component;

adding TPGS emulsifier to the solution of hydrophilic component; and then

mixing with a mixture comprising the continuous hydrophobic phase and the emulsifier(s) having an HLB value of less than 10 so as to provide the formulation.

18. A method for treating a subject in need, the method comprising:

topically administering the formulation of claim 1 to the subject so as to apply the compound that is normally insoluble in the continuous hydrophobic phase.

19. A topical formulation comprising:

a continuous hydrophobic phase consisting of squalane, mineral oil, C12-15 alkyl benzoate (such as Finsolv TN), C13-15 alkane (such as hemisqualane) and/or a mixture thereof;

a propylene glycol hydrophilic phase dispersed throughout said continuous hydrophobic phase;

an epigallocatechin gallate (EGCG) compound in an amount from 1.0% to 1.7% by weight based upon total weight of the topical formulation; and

a stabilizing component in an amount of at least 15% by weight based upon total weight of the topical formulation, the stabilizing component comprising TPGS in an amount of from 8% to 30% by weight based upon total weight of the stabilizing component and at least one fatty acid monoester of sorbitan having an HLB value of less than 6,

wherein the weight ratio of the continuous hydrophobic phase to the stabilizing component is no more than 5:1, and the weight ratio of the stabilizing component to the EGCG compound is at least 10:1.

20. A topical formulation comprising:

a continuous hydrophobic phase comprising cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone, ubiquinone, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera biennis* oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and com oil;

a hydrophilic phase; and

a hydrophilic component substantially dissolved in the hydrophilic phase utilizing a stabilizing component comprising D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS),

wherein the topical formulation comprises 0.8 mg of the hydrophilic component per 1 g of the continuous hydrophobic phase.

21. The formulation of claim 1, wherein, at room temperature, the formulation exists as a nanoemulsion with the hydrophilic component dispersed throughout the formulation, but, upon application to a subject's skin, with the concomitant temperature change caused thereby, the nanoemulsion disrupts and the formulation directly deposits the hydrophilic component onto the subject's skin.

22. The formulation of claim 1, wherein the hydrophilic component includes a collagen suppressing compound.

23. The formulation of claim 22, wherein the collagen suppressing compound is a bicyclooctanone.

24. A method of suppressing keloid formation in a subject undergoing surgery, the method comprising:

utilizing the formulation of claim 22 to suppress keloid formation in the subject.

25. The method according to claim 24, wherein the formulation is applied to an incision site for a finite number of days after surgery.

26. A formulation comprising:

a continuous hydrophobic phase,

and a hydrophilic phase

comprising: 39

a stabilizing component comprising:

from 8% to 30% by weight of a first, polysorbate, emulsifier having a hydrophilic-lipophilic balance ("HLB") value of at least 10, and

from 70% to 92% by weight of a second emulsifier having an HLB value of less than 10; and

a hydrophilic component normally insoluble in said continuous hydrophobic phase at room temperature absent emulsifier,

wherein the hydrophilic component is substantially dissolved in the continuous hydrophilic phase of the formulation utilizing reverse micelles comprising said first and second emulsifiers, and

wherein the formulation comprises no more than 4% by weight of the first emulsifier.

27. The formulation of claim 26, wherein the first emulsifier has an HLB value of 12 to 17.

28. The formulation of claim 26, wherein the second emulsifier has an HLB value of 3 to 9.

29. The formulation of claim 26, wherein the stabilizing component comprises at least sorbitan monooleate emulsifier.

30. The formulation of claim 26, wherein the hydrophilic component includes an ingredient selected from the group consisting of green tea extract, grape seed extract, fruit extract, and polyphenol compounds.

31. The formulation of claim 26, wherein the hydrophilic component includes a compound selected from the group consisting of epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin (EC), epicatechin gallate (ECG), and catechin.

32. The formulation of claim 26, wherein the hydrophilic component includes an ingredient selected from the group consisting of hydrolyzed pepper fruit extract (*Piper nigrum*), hydrolyzed soy protein, peppermint extract (*Mentha piperita*), lotus (*Nelumbo nucifera*), coriander (*Coriandrum sativum*), *Verbena officinalis* extract, and *Helianthus annuus* (sunflower) seed extract.

33. The formulation of claim 26, wherein the hydrophilic component includes an ingredient selected from the group consisting of *Saccharomyces cerevisiae* extract, *Withania somnifera* root extract, butylene glycol and hydrolyzed *Coriandrum sativum* fruit extract and *Citrus aurantium dulcis* (orange) fruit extract, ⁴⁰*Helianthus annuus* (sunflower) seed extract, *Taraxacum officinale* (dandelion) extract, hydrolyzed *Viola tricolor* extract, *Pyrus malus* (apple)

fruit extract, hydrolyzed *Celosia cristata* extract and hydrolyzed *Prunella vulgaris* extract, hydrolyzed *Citrus aurantium dulcis* fruit extract, hydrolyzed *Candida saitoana* extract, *Lindera strychnifolia* root extract, *Triticum vulgare* (wheat germ) extract, *Secale cereale* (rye) seed extract, hydrolyzed sesame extract, *Tropaeolum majus* flower extract, *Spiraea ulmaria* extract, hydrolyzed sweet almond protein, *Salix Alba* (willow) leaf extract, *Mentha piperita* (peppermint) extract, *Triticum vulgare* (wheat) germ extract, butylene glycol and *Butyrospermum parkii* (shea butter) seedcake extract, hydrolyzed lupine protein octenylsuccinate, hydrolyzed *Cucurbita pepo* (pumpkin) seedcake, hydrolyzed *Opuntia ficus indica* flower extract, *Medicago sativa* (alfalfa) seed extract and hydrolyzed lupine protein, *Lentinus edodes* extract, hydrolyzed *Ceratonia siliqua* seed extract, *Gossypium hirsutum* (cotton) extract, *Helianthus annuus* (sunflower) seed extract, *Jasminum officinale* (jasmine) flower extract, hydrolyzed *Manihot esculenta* tuber extract, butylene glycol and *Iris florentina* root extract, hydrolyzed wheat protein, hydrolyzed *Myrtus communis* leaf extract, butylene glycol and *Boerhavia diffusa* root extract, *Cynara scolymus* (artichoke) leaf extract, yeast extract, hydrolyzed rice protein, *Nasturtium officinale* extract, *Avena sativa* (oat) kernel extract, *Tropaeolum majus* flower/leaf/stem extract, *Lens esculenta* (lentil) seed extract (including oligosaccharides thereof), *Cyperus esculentus* tuber extract, *Prunus amygdalus dulcis* (sweet almond) seed extract, hydrolyzed soy fiber, *Pichia anomala* extract, butylene glycol and *Nelumbo nucifera* leaf extract, yeast extract, butylene glycol and *Artemisia abrotanum* extract, hydrolyzed soy flour, *Castanea saliva* (chestnut) seed extract, propylene glycol and *Citrus aurantium amara* (bitter orange) flower extract, hydrolyzed pepper fruit extract, hydrolyzed soy protein, butylene glycol and *Spiraea ulmaria* extract, hydrolyzed linseed extract, butylene glycol and *Peumus boldus* leaf extract, red algae (*Kappaphycus alvarezii*) galactans, *Pichia anomala* (including biopeptides thereof) extract, sulfated galactans of *Hypnea musciformis*, *Glycine soja* hydrolyzed soy protein, *Oryza sativa* extract, *Cyperus esculentus* tuber extract, *Piper nigrum* hydrolyzed pepper fruit extract, *Verbena officinalis* extract, butylene glycol and *Peumus boldus* leaf extract, butylene glycol and *Peumus boldus* leaf extract, seed extract, hydrolyzed *Cicer* seed extract, *Triticum Vulgare* (wheat) germ extract, hydrolyzed pea, butylene glycol and *Silybum Marianum* extract, hydrolyzed lupine protein, *Kappaphycus alvarezii* (red algae) extract, *Triticum vulgare* (wheat) protein, yeast extract, *Cichorium intybus* (chicory) root extract, *Prunus persica* (peach) leaf extract, *Verbena officinalis* extract, *Medicago sativa* (alfalfa) extract, *Paeonia albiflora* root extract, *Palmaria palmata* extract, hydrolyzed millet, butylene glycol and triethanolamine and *Punica granatum* extract, glycerin and *Prunus amygdalus dulcis* (sweet almond) extract, hydrolyzed sweet almond seedcake, butylene glycol and *Fumaria officinalis* extract, butylene glycol and *Camellia sinensis* leaf extract, and soy trimonium chloride.

34. The formulation of claim 26, wherein the hydrophilic component includes a

compound selected from the group consisting of a peptide, a nucleic acid, an amino acid, and a hydrophilic drug or biologically active agent.

35. The formulation of claim 26, wherein the formulation comprises at least 0.1% (w/w) of the hydrophilic component.

36. The formulation of claim 26, wherein the hydrophilic phase includes at least one solvent selected from the group consisting of water, ethanol, dimethyl sulfoxide (DMSO), propylene glycol, and polyethylene glycol (PEG).

37. The formulation of claim 26, wherein the hydrophilic phase comprises a solvent selected from the group consisting of mineral oil, vegetable oil, paraffin, polysiloxane, cyclopentasiloxane, dimethiconol, squalene, and a mixture of any thereof.

38. The formulation of claim 26, wherein the continuous hydrophobic phase consists of cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone, ubiquinone, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera biennis* oil, tocopherol linoleateoleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, capryliccapric triglyceride, dimethicone, and corn oil.

39. The formulation of claim 26, wherein the hydrophilic component consists of epigallocatechin gallate (EGCG).

40. The formulation of claim 26, wherein

The continuous hydrophobic phase comprises mineral oil, squalene, or a mixture thereof, and

The hydrophilic phase comprises

propylene glycol, polyethylene glycol, or a mixture thereof, in an amount of at least 1% *g/g* the hydrophilic phase per the continuous hydrophobic phase; and

at least 0.1% *g/g* of the epigallocatechin gallate (EGCG) compound per the continuous hydrophobic base.

41. The formulation of claim 26, wherein:

a weight ratio of the hydrophilic component to the hydrophilic phase is from 1:5 to 1:10,

a weight ratio of the continuous hydrophobic phase to the hydrophilic phase is at least 10:1;

a weight ratio of the stabilizing component to the continuous hydrophobic phase is from 1:1 to 1:10, and

the formulation comprises at least 10 mg of the hydrophilic component per 1 g of the continuous hydrophobic phase.

42. The formulation of claim 26, wherein the formulation does not include a fatty acid glyceride.

42

43. The formulation of claim 26, further comprising an adjuvant, an excipient, a solubilizer,

a thickener, a colorant, a lubricant, a moisturizing agent, a preservative, fragrance, an adsorption enhancer, a UV blocking or protective material, and/or an antioxidant.

44. The method of preparing the formulation of claim 26, the method comprising:

dissolving the at least one hydrophilic component in a hydrophilic phase to provide a solution of at least one hydrophilic component;

adding a stabilizing component composed of the first emulsifier and the second emulsifier; and

combining the solution with a hydrophobic phase to provide the formulation.

45. A method of preparing the formulation of claim 26, the method comprising:

dissolving the at least one hydrophilic component in the hydrophilic phase to provide a solution of the hydrophilic component;

adding a stabilizing component to the solution to produce a stabilizing component-containing solution of at least one hydrophilic component, wherein the stabilizing component includes the first emulsifier and the second emulsifier; and

combining the stabilizing component-containing solution with a continuous hydrophobic phase to provide the formulation.

46. A method for treating a subject with a condition amenable to treatment with a hydrophilic compound, the method comprising

Topically administering the formulation of claim 26 containing such hydrophilic compound to the subject.

47. A formulation consisting of:

a continuous squalene hydrophobic phase;

a propylene glycol hydrophilic phase;

an epigallocatechin gallate (EGCG) compound in an amount from 1.0% to 1.7% by weight based on total weight of the formulation; and

a stabilizing component comprising at least one polysorbate emulsifier having an HLB value of at least 10 and at least one fatty acid monoester of sorbitan emulsifier having an HLB value of less than 10, wherein from 8% to 30% by weight of the stabilizing component is the polysorbate emulsifier(s) having an HLB value of at least 10,

wherein the weight ratio of the continuous squalene hydrophobic phase to the propylene glycol hydrophilic phase is at least 10:1,

wherein the formulation comprises ⁴³no more than 4% by weight of the polysorbate emulsifier(s) having an HLB value of at least 10.

48. A topical formulation comprising:

a continuous hydrophobic phase composed of cyclopentasiloxane, squalane, dimethiconol, ethoxyheptyl bicyclooctanone, ubiquinone, tetrahexyldecyl ascorbate, safflower seed oil, *Oenothera Biennis* oil, tocopherol linoleate/oleate, octyldodecyl citrate crosspolymer, tocopherol acetate, polydecene, caprylic/capric triglyceride, dimethicone, and corn oil,

a hydrophilic phase comprising propylene glycol;

at least one hydrophilic component substantially dissolved in the hydrophilic phase; and

a stabilizing component comprising at least one polysorbate emulsifier having an HLB value of at least 10,

wherein the topical formulation comprises 0.8 mg of the hydrophilic component per 1 g of the continuous hydrophobic phase.

49. The formulation of claim 48, wherein the hydrophilic component further comprises an epigallocatechin gallate compound.

50. The formulation of claim 48, wherein the stabilizing component comprises at least one polysorbate emulsifier having an HLB value of 12 to 17.

51. The formulation of claim 26, wherein the hydrophilic phase includes a collagen suppressing compound.

52. The formulation of claim 51, wherein the collagen suppressmg compound is a bicyclooctanone.

53. A method of suppressing keloid formation in a subject undergoing surgery, the method comprising:

utilizing the formulation of claim 51 to suppress keloid formation in the subject.

54. The method according to claim 53, wherein the formulation is applied to an incision site for a finite number of days after surgery.

1/3

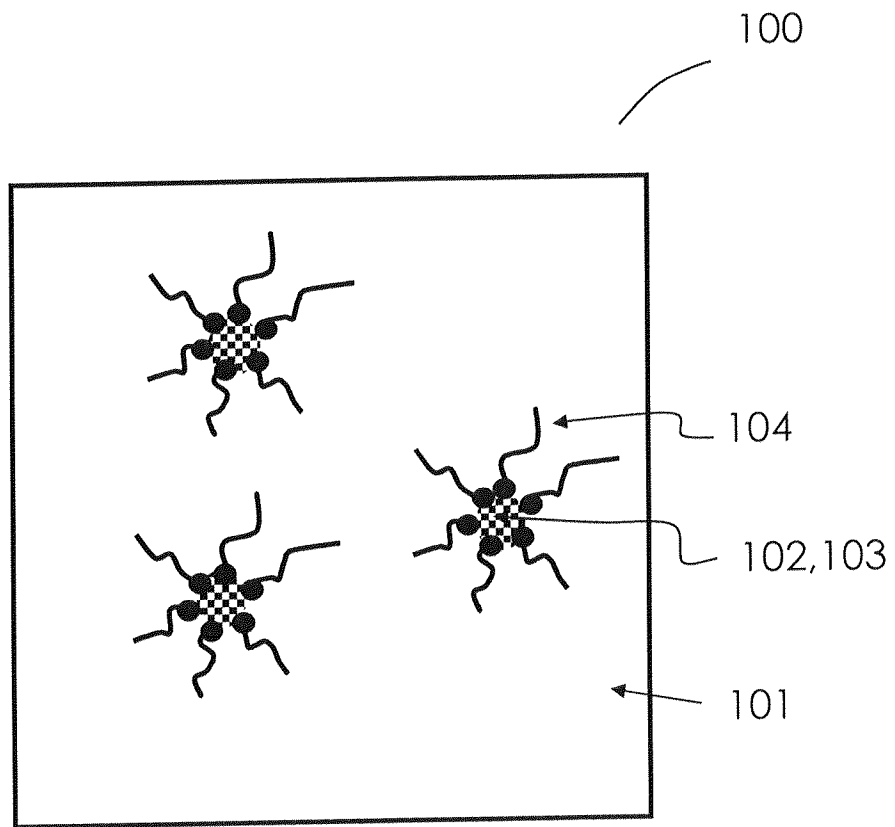


FIG. 1

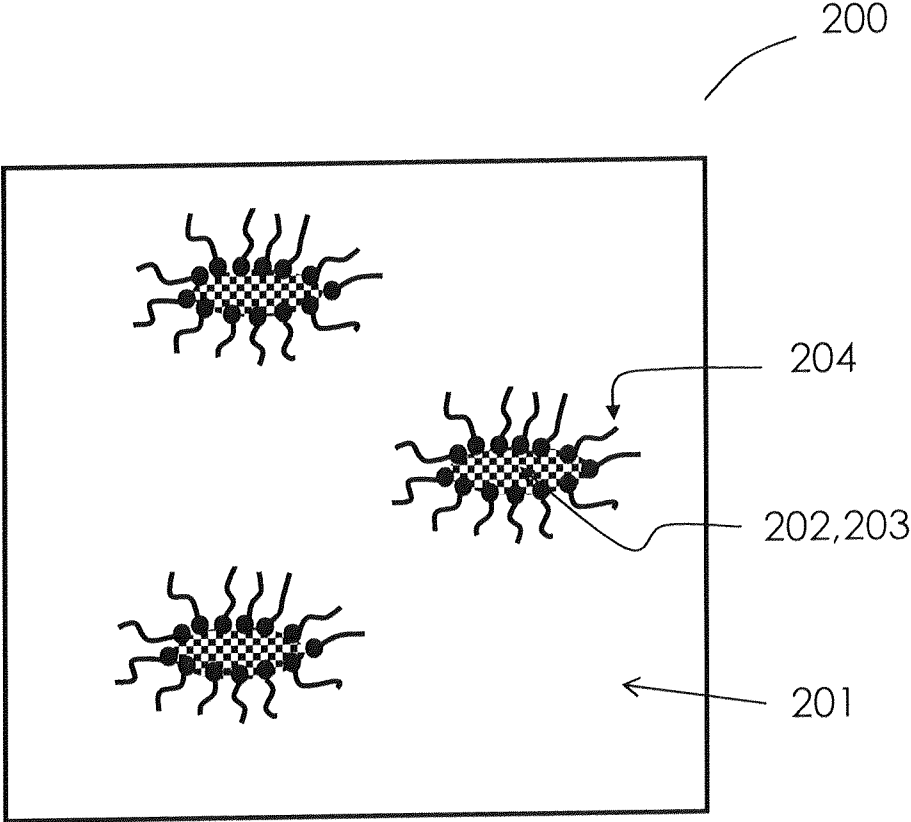


FIG. 2

3/3

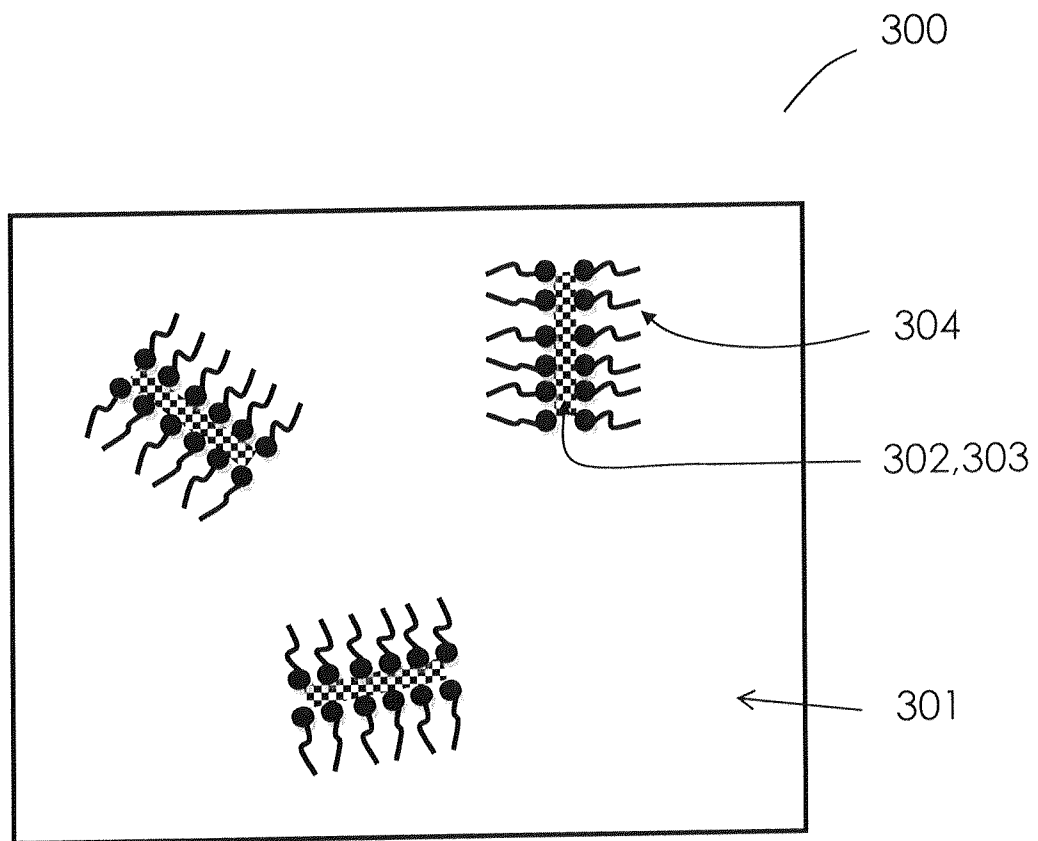


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/14600

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 17/02; A61P 17/18; A61K 31/353; A61K 36/82 (2016.01)

CPC - A61K 2800/522; A61K 8/678; A61Q 19/00; A61K 31/353; A61K 36/82

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)

IPC(8): A61P 17/02; A61P 17/18; A61K 31/353; A61K 36/82 (2016.01)

CPC: A61K 2800/522; A61K 8/678; A61Q 19/00; A61K 31/353; A61K 36/82

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/59; 424/729; 549/399 (key word limited; see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, Google Scholar

Search terms used: topical formulation/composition/lotion/cream, keloid, treat, hydrophobic/squalene, hydrophilic/propylene glycol, epigallocatechin gallate, polyphenol, green tea extract, TPGS, sorbitan monooleate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0274176 A1 (JOHNSON et al.) 06 November 2008 (06.11.2008); para [0017], [0021], [0023], [0026], [0035]-[0036], [0039], [0041], [0045], [0049]-[0051], [0062], [0069], [0080]-[0081], [0118], [0138]-[0140], [0142]	1-18, 20-47, 51-54
Y	US 2009/0297665 A1 (BROMLEY) 03 December 2009 (03.12.2009); para [0016], [0020], [0024], [0033], [0036]-[0037], [0041], [0066]-[0067], [0081], [0176], [0191], [0194], [0227], [0294]-[0298], [0385]	1-19, 21-54
Y	US 2013/0045196 A1 (SHI et al.) 21 February 2013 (21.02.2013); para [0003], [0006], [0017], [0044], [0106]-[0110], [0117]	19-20, 40, 47
Y	US 2007/0160550 A1 (CHARLES NEE NEWSHAM et al.) 12 July 2007 (12.07.2007); para [0004], [0018], [0022], [0030], [0034], [0040]	8-9, 19, 30-31, 39-40, 47-50
Y	US 2014/0301958 A1 (BOJANOWSKI et al.) 09 October 2014 (09.10.2014); para [0042], [0052]	10-11, 32-33
Y	US 2005/0208138 A1 (YANG et al.) 22 September 2005 (22.09.2005); para [0169], [0258]	15
Y	US 2012/0251596 A1 (FRATTER) 04 October 2012 (04.10.2012); para [0009]-[0010]	21
Y	US 4,855,322 A (KASHA et al.) 08 August 1989 (08.08.1989); col 2 ln 15-23, 60-67; col 3 ln 12-13, 65-67; col 35 ln 18-21; col 36 ln 10-19; col 40 ln 3-11	2-25, 51-54

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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"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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 March 2016 (14.03.2016)

Date of mailing of the international search report

11 APR 2016

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

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