emulsion system containing one or more different types of poorly water-soluble active and inactive compounds.

Notwithstanding the varied kinds of formulations that have been developed, their effectiveness and side effects have been less than desirable. There is a demand for better formulations to effectively deliver poorly water-soluble active and inactive chemical compounds to a human or an animal. There remains a need for improved formulations containing poorly water-soluble active and inactive chemical compounds. There exists a need for new aqueous based topical compositions containing poorly water-soluble active and inactive chemical compounds.

The approach described in this patent seeks to meet these needs by providing a novel aqueous based emulsion system without the substantial or complete presence of an oil phase. The emulsion system described herein can be used as a platform to formulate oil-free aqueous compositions containing poorly water-soluble active and inactive compounds, which can be beneficial to treat a variety of skin disorders and other types of diseases and ailments.

SUMMARY

Described herein is an aqueous emulsion system without the substantial or complete presence of an oil phase comprising the combination of:

(i) about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil, where n is 2 to about 1,000;

(iii) about 60% to about 92% by weight of water; and

(iv) about 0.05% to about 2.0 % by weight of a poorly water-soluble chemical compound that is dispersed in a substantially or completely oil-free emulsion.

The disclosure provides, in an aspect, a substantially or completely oil-free aqueous emulsion comprising:

(i) about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil, where n is 2 to about 1,000; optionally where n is about 30 to about 40;

(iii) about 60% to about 92% by weight of water; and

(iv) about 0.01% to about 2% by weight of a poorly water-soluble chemical compound dispersed in the aqueous emulsion;

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

The emulsion system can operate as a platform to deliver a poorly water-soluble chemical compound via a variety of ways, such as, orally, sublingually, topically, or via an infusion. It is particularly useful for topical cutaneous (skin) therapeutic applications.

In some examples, n is equal to about 30 to about 40 in the PEG chain of the polyethylene glycol derivative of castor oil. In certain examples, the polyethylene glycol derivative of castor oil is PEG 40 hydrogenated castor oil (PEG 40 HCO).

The oil-free aqueous composition can be a mini-, micro- or nano- emulsion. The nano-emulsions can have a d50 nano-particle size and a number weighted mean nano-particle size each of less than about 150 nm. Optimizing the loads of the ingredients in the composition can reduce or increase the particle size and droplet size. An exemplified example has a d50 nano-particle size and a number weighted mean nano-particle size of each less than about 50 nm.

The oil-free aqueous emulsion can be advantageously used for solubilizing poorly water-soluble active and inactive ingredients. In an example, the active ingredient can be a natural product, such as a

flavonoid (*e.g.,* flavanol) or a polyphenol. Exemplified below are oil-free aqueous emulsions containing one or more of the following different natural products - fisetin, *trans*-resveratrol, milk thistle extract comprising silymarin, quercetin (or dihydroquercetin), (-)-epigallocatechin-3-gallate (EGCG), salicylic acid, Centipeda minima, curcumin (or turmeric), rutin, diosmin, and imatinib or imatinib mesylate. These natural products have been the subject of many studies for potential uses, including the treatment and prevention of alopecia.

In one example, a hair growth composition was prepared comprising:

(i) about 2.5% to about 20% by weight of DEGEE;

(ii) about 5% to about 10% by weight of PEG 40 HCO;

(iii) about 60% to about 92% by weight of water; and

(iv) a poorly water-soluble active chemical compound comprising:

(a) about 0.075% to about 0.250% by weight of fisetin;

(b) about 0.075% to about 0.150% by weight of *trans*-resveratrol; and/or

(c) about 0.125% to about 0.250% by weight of a milk thistle extract comprising about 0.1% to about 0.2% by weight of silymarin.

The disclosure further includes methods of application that can be beneficial for treating a variety of skin disorders. The examples show various topical applications. Two exemplified skin disorders that can be effectively treated with the formulations described herein are alopecia and human papillomavirus (HPV) warts by topically applying a therapeutically effective amount of a formulation with the required active ingredient for a therapeutically effective amount of time to an affected area of the skin disorder in a human or animal in need thereof. The emulsion system can be used as a platform to create formulations with a variety of poorly water-soluble chemical compounds, including natural and synthetic, active and inactive compounds. The emulsions can be employed for applications other than topical (*e.g.*, ocular, mucosal, intravenous, intramuscular, and oral products. Depending on the active ingredient(s) that are selected, the emulsions can be used to treat a plethora of ailments (*e.g.*, psoriasis, cancer, inflammation, and pigmentary disorders, such as vitiligo and melasma) other than are exemplified herein.

The disclosure provides, in another aspect, a cosmetic method to promote hair growth in a human or animal in need thereof, the method comprising topically applying a therapeutically effective amount of a substantially or completely oil-free aqueous emulsion for a therapeutically effective time to the skin of the human or animal, wherein the aqueous emulsion comprises:

(i) about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil, where n is 2 to about 1,000; optionally where n is about 30 to about 40;

(iii) about 60% to about 92% by weight of water; and

(iv) about 0.01% to about 2% by weight of a poorly water-soluble chemical compound dispersed in the aqueous emulsion; and

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

The disclosure provides, in another aspect, a substantially or completely oil-free aqueous emulsion for use in promoting hair growth, or treating a skin disorder or a varicose vein, in a human or animal in need thereof, wherein the aqueous emulsion is to be topically applied to the skin of the human or animal, wherein the aqueous emulsion comprises:

(i) about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil, where n is 2 to about 1,000; optionally where n is about 30 to about 40;

(iii) about 60% to about 92% by weight of water; and

(iv) about 0.01% to about 2% by weight of a poorly water-soluble chemical compound dispersed in the aqueous emulsion;

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

The disclosure provides, in another aspect, use of a substantially or completely oil-free aqueous emulsion in the manufacture of a medicament for promoting hair growth or treating a skin disorder or a varicose vein in a human or animal in need thereof, wherein the medicament is to be topically applied to the skin of the human or animal, wherein the aqueous emulsion comprises:

(i) about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil, where n is 2 to about 1,000; optionally where n is about 30 to about 40;

(iii) about 60% to about 92% by weight of water; and

(iv) about 0.01% to about 2% by weight of a poorly water-soluble chemical compound dispersed in the aqueous emulsion; and

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

The disclosure further includes a method of formulating an oil-free aqueous emulsion.

The disclosure provides, in another aspect, a method of making a substantially or completely oil-free aqueous emulsion, the steps comprising:

(i) dissolving about 0.05% to about 2% by weight of a poorly water-soluble chemical compound in about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) diluting the mixture of step (i) with about 60% to about 92% by weight of water; and

(iii) adding about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil to the mixture of step (ii), where n is 2 to about 1,000; optionally where n is about 30 to about 40;

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

The foregoing and other objects and features of the disclosure will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures. Further embodiments, forms, features, aspects, benefits, objects, and advantages of the invention shall become apparent from the detailed description and figures provided herewith.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the specification and are included to further demonstrate certain embodiments or various aspects of the invention. In some instances, embodiments of the invention can be best understood by referring to the accompanying drawings in combination with the detailed description presented herein. The description and accompanying drawings may highlight a certain specific example, or a certain aspect of the invention. However, one skilled in the art will understand that portions of

What is claimed is:

1. A substantially or completely oil-free aqueous emulsion comprising:

(i) about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil, where n is 2 to about 1,000; optionally where n is about 30 to about 40;

(iii) about 60% to about 92% by weight of water; and

(iv) about 0.01% to about 2% by weight of a poorly water-soluble chemical compound dispersed in the aqueous emulsion;

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

2. The aqueous emulsion of Claim 1, wherein the chemical compound comprises a natural product.

3. The aqueous emulsion of Claim 1, wherein the chemical compound comprises fisetin, *trans*-resveratrol, a milk thistle extract comprising silymarin, quercetin, dihydroquercetin, curcumin, turmeric, (-)-epigallocatechin-3-gallate (EGCG), rutin, salicylic acid, diosmin, imatinib, imatinib mesylate, and/or an extract of Centipeda minima; wherein, optionally, the chemical compound comprises:

(i) fisetin, *trans*-resveratrol, and/or a milk thistle extract comprising silymarin;

(ii) EGCG and/or quercetin or dihydroquercetin;

(iii) salicylic acid; or

(iii) rutin, *trans*-resveratrol, and/or diosmin.

4. The aqueous emulsion of any one of Claims 1 to 3, wherein the PEG derivative of castor oil comprises PEG 40 hydrogenated castor oil (PEG 40 HCO).

5. The aqueous emulsion of Claim 1, comprising:

(i) about 2.5% to about 20% by weight of DEGEE; and

(ii) about 5% to about 10% by weight of the PEG derivative of castor oil.

6. The aqueous emulsion of Claim 1, wherein the chemical compound comprises fisetin, *trans*-resveratrol, and/or a milk thistle extract comprising silymarin, in the following proportions:

(i) about 0.075% to about 0.25% by weight of fisetin;

(ii) about 0.075% to about 0.15% by weight of *trans*-resveratrol; and/or

(iii) about 0.125% to about 0.25% by weight of the milk thistle extract comprising about 0.1% to about 0.2% by weight of silymarin.

7. The aqueous emulsion of Claim 1, wherein the chemical compound comprises about 0.05% to about 0.1% of quercetin or dihydroquercetin; or wherein the chemical compound comprises:

(i) about 0.03% to about 0.1% of curcumin or turmeric; and/or

(ii) about 1% to about 2% of (-)-epigallocatechin-3-gallate (EGCG); or wherein the chemical compound comprises about 0.1% to about 1% of salicylic acid; or wherein the chemical compound comprises:

(i) about 0.25% to about 0.75% of rutin; and/or

(ii) about 0.075% to about 0.15% by weight of *trans*-resveratrol.

8. The aqueous emulsion of any one of Claims 1 to 7, comprising nano-particles having a d50 particle size and a number weighted mean particle size each of less than about 150 nm.

9. The aqueous emulsion of any one of Claims 1 to 8, wherein the aqueous emulsion is formulated to be administered to a human or animal in need of the aqueous emulsion topically, ocularly, mucosally, intravenously, intramuscularly, or orally, wherein, optionally, the aqueous emulsion is formulated for topical administration.

10. A cosmetic method to promote hair growth in a human or animal in need thereof, the method comprising topically applying a therapeutically effective amount of a substantially or completely oil-free aqueous emulsion for a therapeutically effective time to the skin of the human or animal, wherein the aqueous emulsion comprises:

(i) about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil, where n is 2 to about 1,000; optionally where n is about 30 to about 40;

(iii) about 60% to about 92% by weight of water; and

(iv) about 0.01% to about 2% by weight of a poorly water-soluble chemical compound dispersed in the aqueous emulsion; and

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

11. A substantially or completely oil-free aqueous emulsion for use in promoting hair growth, or treating a skin disorder or a varicose vein, in a human or animal in need thereof, wherein the aqueous emulsion is to be topically applied to the skin of the human or animal, wherein the aqueous emulsion comprises:

(i) about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil, where n is 2 to about 1,000; optionally where n is about 30 to about 40;

(iii) about 60% to about 92% by weight of water; and

(iv) about 0.01% to about 2% by weight of a poorly water-soluble chemical compound dispersed in the aqueous emulsion;

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

12. Use of a substantially or completely oil-free aqueous emulsion in the manufacture of a medicament for promoting hair growth or treating a skin disorder or a varicose vein in a human or animal in need thereof, wherein the medicament is to be topically applied to the skin of the human or animal, wherein the aqueous emulsion comprises:

(i) about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil, where n is 2 to about 1,000; optionally where n is about 30 to about 40;

(iii) about 60% to about 92% by weight of water; and

(iv) about 0.01% to about 2% by weight of a poorly water-soluble chemical compound dispersed in the aqueous emulsion; and

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

13. The cosmetic method of Claim 10, the aqueous emulsion for use of Claim 11 or the use of Claim12, wherein the chemical compound comprises fisetin, *trans*-resveratrol, a milk thistle extract comprising silymarin, quercetin, dihydroquercetin, curcumin, turmeric, (-)-epigallocatechin-3-gallate (EGCG), rutin, salicylic acid, diosmin, imatinib, imatinib mesylate, and/or an extract of Centipeda minima.

14. The cosmetic method, the aqueous emulsion for use or the use of Claim 13, wherein the chemical compound comprises:

(i) fisetin, *trans*-resveratrol, and/or a milk thistle extract comprising silymarin;

(ii) EGCG and/or quercetin or dihydroquercetin;

(iii) salicylic acid; or

(iii) rutin, *trans*-resveratrol and/or diosmin.

15. A method of making a substantially or completely oil-free aqueous emulsion, the steps comprising:

(i) dissolving about 0.05% to about 2% by weight of a poorly water-soluble chemical compound in about 2.5% to about 50% by weight of diethylene glycol monoethyl ether (DEGEE);

(ii) diluting the mixture of step (i) with about 60% to about 92% by weight of water; and

(iii) adding about 5% to about 20% by weight of a polyethylene glycol (PEG: $H(OCH_2CH_2)_nOH$) derivative of castor oil to the mixture of step (ii), where n is 2 to about 1,000; optionally where n is about 30 to about 40;

wherein the aqueous emulsion is substantially or completely devoid of an oil phase.

16. The method of Claim 15, wherein the chemical compound comprises fisetin, *trans*-resveratrol, a milk thistle extract comprising silymarin, quercetin, dihydroquercetin, curcumin, turmeric, (-)-epigallocatechin-3-gallate (EGCG), rutin, salicylic acid, diosmin, imatinib, imatinib mesylate, and/or an extract of *Centipeda minima*.