BIPHASIC CANNABINOID DELIVERY

Field Of The Invention

The invention relates to compositions for delivery of a cannabinoid and related methods and uses. More particularly, the present invention relates to a cannabinoid biphasic lipid-vesicle composition and related methods and uses. The cannabinoid biphasic lipid-vesicle composition can be formulated into a variety of formats.

Background of the Invention

Cannabis sativa, commonly known as marijuana, and its major psychoactive ingredient, Δ^9-tetrahydrocannabinol (Δ^9-THC), and various other cannabis constituents, termed cannabinoids, have been widely studied. Herbal cannabis contains more than 400 chemicals and over 60 cannabinoids, including the tetrahydrocannabinols (THC), Δ^9-THC, ^{9}-THC Propyl Analogue (THC-V); Cannabidiol (CBD); Cannabidiol Propyl Analogue (CBD-V); Cannabinol (CBN), Cannabichromene (CBC); cannabinodiol (CBDL); cannabicyclol (CBL); Cannabichromene Propyl Analogue (CBC-V); cannabielsoin (CBE); cannabitriol (CBT) and Cannabigerol (CBG). Herbal cannabis also includes more than a dozen terpenoids and several flavonoids.

"Cannabinoid receptors" are cells in the brain and other organs that contain specific protein receptors which recognize THC and some other cannabinoids and trigger cell responses. Some of the cannabinoids do not bind to these cannabinoid receptors and exert their effects by other ways. CB1 receptors are found in high concentrations within the brain and spinal cord. They are also present in certain peripheral cells and tissues (some neurons, some endocrine glands, leukocytes, spleen, heart and parts of the reproductive, urinary and gastrointestinal tracts). CB2 receptors are expressed primarily by immune cells and tissues (leukocytes, spleen and tonsils).

Cannabinoids are lipophilic and potentially acid-labile compounds. Because of their hydrophobic nature, cannabinoids are poorly absorbed systemically from oral dosage forms because of the poor dissolution of cannabinoids in the aqueous environment of gastrointestinal tract. Because of their poor absorption and poor bioavailability, oral formulations are disadvantageous.

Topical compositions of cannabinoids are also known, as shown for example in U.S. 2012/0264818, U.S. 2013/0274321, U.S. 2016/094810, U.S. 9,095563 and U.S. 9,375,417. While the skin may be a desirable target, even lipophilic and low molecular weight compounds generally may only transfer in small amounts across the skin, resulting in difficulty in achieving therapeutic levels of drug in the bloodstream. Topical formulations provide better patient compliance versus injections or intravenous administration, however, depending on the formulation the release of the cannabinoid and thus effectiveness may vary.

Liposomal compositions to deliver interferon are described in US 6,656,499, WO 2015/0236000, WO 2015/023601, and WO 2008/119160. These compositions are generally intended for use in treating cervical displasia by intravaginal delivery.

It would be advantageous to develop a composition in which cannabinoids are delivered as needed to a desired area achieving a therapeutically effective dose to help minimize, reduce, prevent or ameliorate different types of cannabis-treatable conditions. As Δ^9-THC is prone to oxidation, prolonged contact with air results in the gradual oxidation of Δ^9-THC to cannabinol (CBN), it is also desired to provide a cannabinoid composition that retains efficacy and is less addictive if at all, compared to opioid pain treatment.

The present invention is directed toward overcoming one or more of the problems discussed above.

Summary of the Invention

Topical application of cannabinoids allows for a more controlled delivery rate. Delivery of a cannabinoid topically, such as through the skin allows for targeting specific sites and joints for treatment. An increase in the duration and/or effectiveness for delivery of the cannabinoid would improve clinical efficacy.

The invention presented herein demonstrates effects of delivery of a cannabinoid-containing biphasic lipid-vesicle composition. Topical delivery of the cannabinoid-containing composition may decrease pain in general, and pain associated with medical conditions without inducing abnormal behavior or other adverse effects. The compositions of the invention have use for the treatment of any type of pain inclusive of any type of paid associated with a wide variety of diseases/clinical conditions.

In an embodiment, the present invention includes a composition which contains a pharmaceutically effective amount of a cannabinoid for topical delivery of the cannabinoid to skin, mucous membrane, or eye of a user.

In an embodiment, the present invention comprises a composition which contains a pharmaceutically effective amount of a cannabinoid for topical delivery of the cannabinoid to skin, mucous membrane, or eye of a user.

In aspects, the composition is provided as suspended droplets of cannabinoid within at least one lipid bilayer.

In aspects, the composition is a biphasic lipid-vesicle composition comprising one or more cannabinoids. In aspects such composition can be formulated in a variety of formats including but not limited to: cream, lotion, liquid, gel, foam, drops, suppository, shampoo, soap bar, sprays and patch. The composition can be provided in a kit for use. The composition is so formulation to have desirable and in aspects, improved organoleptic properties for use.

The biphasic lipid-vesicle composition of the invention is a liposome-based technology designed to enable cannabinoid molecules to be delivered into the skin, mucosal membranes and the eye. The biphasic lipid-vesicle composition comprises phospholipid vesicles which are multilamellar structures with up to between about 15 and 20 layers separated by an oil-in-water microemulsion.

The cannabinoid is formulated as suspended droplets within an aqueous formation surrounded by one or more lipid bilayers (droplets contained in a core). The lipid bilayers each separated by compartments that can be aqueous or contain the suspended cannabinoid droplets. Thus each separate lipid bilayer compartment may be separated by solely an aqueous phase or an aqueous phase that contains the cannabinoid droplets. The cannabinoid droplets can be formulated with a surrounding surfactant if desired. Furthermore the cannabinoid droplets can consist of cannabinoid or comprise cannabinoid, meaning that a further agent may be incorporated into the droplet. The further agent may be a further therapeutic agent if desired. Optional stabilizers and/or optional anti-aggregants may be incorporated with the phase containing the cannabinoid droplets.

In one aspect, it is a biphasic lipid vesicle composition comprising a suspension of lipid-bilayer vesicles having entrapped therein, an oil-in-water emulsion, one or more cannabinoid

compounds, analogues, and/or cannabinoid agonists. The composition may optionally comprise an antioxidant and/or anti-aggregant. In aspects the antioxidant is provided in an amount between about 0.01 to about 0.5 weight percent and may be methionine, in aspects L-methionine. In aspects, the anti-aggregant is present in an amount of about 0.1 to about 5mg/kg, in aspects is a pharmaceutically acceptable salt of arginine L-arginine hydrochloride.

According to an aspect of the invention is a biphasic vesicle composition comprising: (a) a first phase comprising an oil-in-water emulsion which itself comprises oil, water, cannabinoid; and (b) a second phase comprising multilamellar lipid vesicles suspended in said first phase wherein said vesicles contain entrapped therein a composition comprising an oil-in-water emulsion which itself comprises oil, water, and cannabinoid, wherein each phase optionally comprises an amount sufficient of a stabilizer to stabilize the cannabinoid against oxidation, further wherein said composition comprises a therapeutically effective aggregate amount of said cannabinoid.

According to another aspect of the invention is a method for treating pain or pain symptoms in a patient, which method comprises administering to said patient a therapeutically effective amount of a biphasic vesicle composition comprising; a) a first phase comprising an oil-in-water emulsion which itself comprises oil in water, wherein a sufficient amount of oil is employed to form a composition suitable for topical application, and wherein the water comprises a cannabinoid, optional antioxidant and an optional anti-aggregant; and (b) a second phase comprising multilamellar lipid vesicles suspended in said first phase wherein said vesicles contain entrapped therein a composition comprising an oil-in-water emulsion wherein the water phase comprises cannabinoid, an optional antioxidant and an optional anti-aggregant, wherein the composition comprises a therapeutically effective amount of said cannabinoid, and wherein said optional anti-aggregant may preserve the cannabinoid in a form so as to enhance the shelf-life of said composition.

In another aspect, the invention is drawn to a method of treating pain in a subject by the transdermal administration of the cannabinoid biphasic lipid-vesicle composition to the subject.

In another aspect, the invention is drawn to a method of treating pain in a subject by the topical administration of the cannabinoid biphasic lipid-vesicle composition to the subject.

In another aspect, the invention is drawn to a method of treating pain in a subject by the mucosal administration of the cannabinoid biphasic lipid-vesicle composition to the subject.

In another aspect, the invention is drawn to a method of treating pain in a subject by the topical administration of the cannabinoid biphasic lipid-vesicle composition to an eye of the subject.

The compositions of the invention may comprise one or more cannabinoids. In some embodiments, the cannabinoid is a cannabinol, such as THC or CBN and analogues and mixtures thereof. In aspects, the cannabinoids or cannabinoid analogues are selected from the group consisting of cannabinol, cannabidiol, Δ^9-tetrahydrocannabinol, Δ^8-tetrahydrocannabinol, 11-hydroxy-tetrahydrocannabinol, 11-hydroxy-Δ^9-tetrahydrocannabinol, levonantradol, Δ^{11}-tetrahydrocannabinol, tetrahydrocannabivarin, dronabinol, amandamide, nabilone, a combination thereof, a natural or synthetic analogue thereof, and a natural or synthetic molecule with a basic cannabinoid structure. Mixtures of two or more cannabinoids may also be used; for example, CBD and THC may be used in a 1:1 ratio or any ratio as desired.

The invention has in aspects:

1. A biphasic vesicle composition comprising:

(a) a first phase comprising a first oil-in-water emulsion; and

(b) a second phase suspended in the first phase, the second phase comprising multilamellar lipid vesicles, the multilamellar lipid vesicles entrapping a second oil-in-water emulsion,

wherein at least one of the first and second oil-in-water emulsions comprises a therapeutically effective amount of a cannabis-derived compound.

2. The biphasic vesicle composition of claim 1, wherein the first and second oil-water-emulsions are the same or different.

3. The biphasic vesicle composition of claim 1 or 2, wherein the cannabis-derived compound is a cannabinoid.

4. The biphasic vesicle composition of claim 3, wherein the cannabis-derived compound is a cannabinoid selected from the group consisting of natural or synthetic cannabinoid, tetrahydrocannabinols (THC), Δ^9-THC, ^{9}-THC Propyl Analogue (THC-V); Cannabidiol (CBD); Cannabidiol Propyl Analogue (CBD-V); Cannabinol (CBN), Cannabichromene (CBC);

cannabinodiol (CBDL); cannabicyclol (CBL); Cannabichromene Propyl Analogue (CBC-V); cannabielsoin (CBE); cannabitriol (CBT), Cannabigerol (CBG), pharmaceutically acceptable salts of these cannabinoids, cannabinoid prodrugs, cannabinoid agonists, synthetic analogs thereof and combinations thereof.

5. The biphasic vesicle composition of claim 1 or 2, wherein the cannabis-derived compound is a cannabis extract.

6. The biphasic vesicle composition of any one of claims 1 to 5, further comprising an anti-oxidant.

6a. The biphasic vesicle composition of claim 6, wherein said anti-oxidance is methionine in at least one of the first and second oil-in-water emulsions.

7. The biphasic vesicle composition of any one of claims 1 to 6, wherein at least one of the first and second oil-in-water emulsion is comprised of oil droplets having a size of from about 0.1 μm to 1 μm.

8. The biphasic vesicle composition of any one of claims 1 to 7, wherein at least 30% of said cannabis-derived compound is entrapped within said vesicles.

9. The biphasic composition of any one of claims 1 to 8, wherein said multilamellar vesicles comprise from about 2 to about 4 weight percent cholesterol.

10. The biphasic composition of any one of claims 1 to 9 formulated as a cream, lotion, liquid, gel, foam, drops, suppository, shampoo, soap bar, spray or patch.

11. The biphasic composition of claim 10, provided as a kit, with optional instructions for use.

12. A method for the treatment of pain, comprising administering the composition of any one of claims 1 to 11 to a subject.

13. The composition of any one of claims 1 to 9, formulated as eye drops.

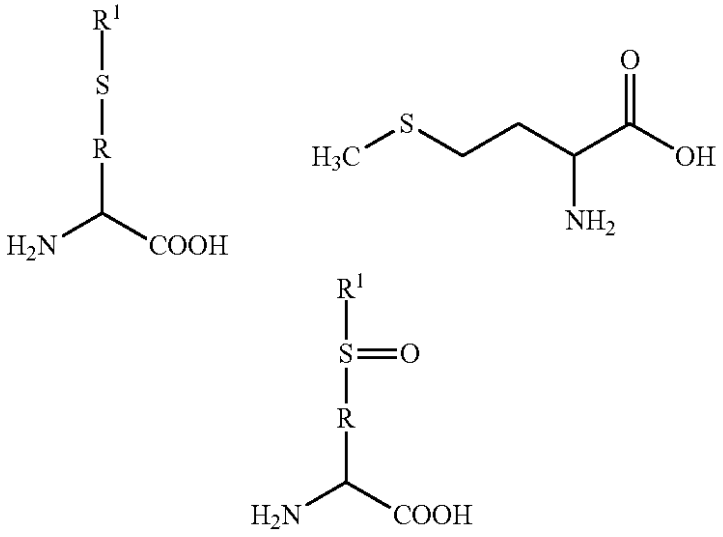
14. The composition of claim 13, further comprising salicylic acid, oxyacetic acid, salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, fenamic acid derivatives, coxibs, sulphonanilides and mixtures thereof.

15. The composition of claim 14, further comprising an antibiotic selected from the group consisting of chloramphenicol, fusidic acid, fluoroquinolones, aminoglycoside, polymycin B sulfate and mixtures thereof.

20 A biphasic vesicle composition comprising:

(a) a first phase comprising an oil-in-water emulsion which itself comprises oil, water, cannabinoid and methionine; and

(b) a second phase comprising multilamellar lipid vesicles suspended in said first phase wherein said vesicles contain entrapped therein a composition comprising an oil-in-water emulsion which itself comprises oil, water, cannabinoid and methionine, wherein each phase comprises an amount sufficient of methionine to stabilize said cannabinoid against oxidation, wherein said methionine is the amino acid methionine of the chemical structure:



further wherein said composition comprises a therapeutically effective aggregate amount of said cannabinoid.

21. The biphasic vesicle composition of claim 20, wherein said oil-in-water emulsion is comprised of oil droplets having a size of from about 0.1 μm to 1 μm.

22. The biphasic vesicle composition of claim 20, wherein said methionine is present in a concentration of from 0.01 to 0.5 weight percent.

23. The biphasic vesicle composition of claim 20, wherein at least 30% of said cannabinoid and said methionine is entrapped within said vesicles as part of said oil-in-water emulsion.

24. The biphasic vesicle composition of claim 21, wherein at least 30% of said cannabinoid and said methionine is entrapped within said vesicles as part of said oil-in-water emulsion.

25. The biphasic vesicle composition of claim 22, wherein at least 30% of said cannabinoid and said methionine is entrapped within said vesicles as part of said oil-in-water emulsion.

26. The biphasic composition of claim 20, wherein said multilamellar vesicle comprises from about 2 to about 4 weight percent cholesterol.

27. The biphasic composition of claim 20, wherein said methionine used in each phase is L-methionine.

30. A method for treating pain in a patient, which method comprises administering to said, patient a therapeutically effective amount of a biphasic vesicle composition comprising; a) a first phase comprising an oil-in-water emulsion which itself comprises oil in water, wherein a sufficient amount of oil is employed to form a composition suitable for topical application, and wherein the water comprises cannabinoid , an antioxidant and an anti-aggregant; and (b) a second phase comprising multilamellar lipid vesicles suspended in said first phase wherein said vesicles contain entrapped therein a composition comprising an oil-in-water emulsion wherein the water phase comprises cannabinoid , an antioxidant and an anti-aggregant, wherein the composition comprises a therapeutically effective amount of said cannabinoid.

31. The method of claim 30, wherein the antioxidant is selected from the group consisting of L-methionine, D-methionine and racemic mixtures thereof.

32. The method of claim 31, wherein the antioxidant is L-methionine and is present in an amount of from 0.1 to 5 mg/g.

33. The method of claim 31, wherein the anti-aggregant is a pharmaceutically acceptable salt of arginine.

34. The method of claim 33, wherein the pharmaceutically acceptable salt of arginine is L-arginine hydrochloride.

35. The method of claim 34, wherein the L-arginine hydrochloride is present in an amount of 0.1 to 5 mg/g.

100. A method of delivering a cannabinoid to the bloodstream of a person comprising the steps of:

A. Providing said composition of any one of claims 1 to 9;

B. Providing a backing layer selected from the group consisting of a patch, strip, bandage and covering for holding said composition;

C. Placing an effective amount of said composition onto said backing layer; and,

D. Attaching said backing layer to the skin of said person so that said transdermal preparation is in contact with said skin.

101. The method of claim 100 comprising the additional steps of:

providing an adhesive mixture containing an effective amount of said composition; and,

carrying out step C by applying said adhesive mixture onto said backing layer.

102. The method of claim 100 comprising the additional step of providing a reservoir means to said backing layer for holding said transdermal preparation.

103. The method of claim 102 wherein said reservoir means is any one or combination of a member of the group consisting of a cavity, matrix material, adhesive layer and film.

104. The method of claim 1 wherein after step D, maintaining said composition in contact with said skin for an effective period of time.

105. A cannabis transdermal delivery structure comprising:

a backing layer selected from the group consisting of a patch, strip, bandage or covering;

said backing layer having the composition of any one of claim 1 to 9.

106. The structure of claim 105 wherein said backing layer includes a reservoir means for holding said composition.

107. The structure of claim 105 wherein said reservoir means is any one or combination of a member of the group consisting of a cavity, matrix material, adhesive layer and film.

108. The structure of claim 105 wherein said matrix material is selected from the group consisting of an open pore material, open weave fabric and a membrane.

109. The transdermal structure of claim 105 wherein said reservoir means comprises a convex portion of said backing layer.

110. The structure of claim 105 wherein a secondary layer is attached to said backing layer, said secondary layer having an opening which forms a retention cavity with said backing layer for holding said composition.

111. A structure for administering cannabis to skin, comprising:

at least one layer of backing material suitable for attachment to said skin; and,

the composition of any one of claims 1 to 9.

112. The structure of claim 111, wherein said backing material is any one or combination of a member selected from the group consisting of fabric, plastic, metal foil, rubber, resin film and membrane.

113. The structure of claim 112 wherein said structure further comprises a reservoir means that includes a rate control means for regulating the flow of said composition to said skin.

These and other objects and features of the invention will be more fully appreciated when the following detailed description of the invention is read in conjunction with the accompanying drawings.

Brief Description of the Drawings:

Figure 1 is a scanned image, magnified 440x of vesicles made for use as a topical lotion.

Figure 2A is a scanned image of multilamellar liposomes prepared using an "anhydrous plastic proliposome-gel" (`melt` or `fusion`) method.

Figure 2B is a scanned image of multilamellar liposomes, the same composition as in 2A, but prepared by a solvent evaporation method.

Figure 3 is a schematic sectional view of a biphasic multilamellar lipid vesicle (MLV) with a central aqueous emulsion core.

Figure 4 is an enlarged portion of the MLV of FIG. 3.

Description of the Invention

Unless otherwise explained, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only, and is not intended to be limiting.

In understanding the scope of the present application, the articles “a”, “an”, “the”, and “said” are intended to mean that there are one or more of the elements.

Additionally, the term "comprising" and its derivatives, as used herein, are intended to be open ended terms that specify the presence of the stated features, elements, components, groups, integers, and/or steps, but do not exclude the presence of other unstated features, elements, components, groups, integers and/or steps. The foregoing also applies to words having similar meanings such as the terms, "including", "having" and their derivatives.

It will be understood that any aspects described as “comprising” certain components may also “consist of” or “consist essentially of,” wherein “consisting of” has a closed-ended or restrictive meaning and “consisting essentially of” means including the components specified but excluding other components except for materials present as impurities, unavoidable materials present as a result of processes used to provide the components, and components added for a purpose other than achieving the technical effect of the invention. For example, a composition defined using the phrase “consisting essentially of” encompasses any known pharmaceutically acceptable additive, excipient, diluent, carrier, and the like. Typically, a composition consisting essentially of a set of components will comprise less than 5% by weight, typically less than 3% by weight, more typically less than 1% by weight of non-specified components.

It will be understood that any component defined herein as being included may be explicitly excluded from the claimed invention by way of proviso or negative limitation. In aspects, the composition does not comprise an interferon. In addition, all ranges given herein include the end of the ranges and also any intermediate range points, whether explicitly stated or not.

Terms of degree such as "substantially", "about" and "approximately" as used herein mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms may refer to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ± 20% or ± 10%, more typically ± 5%, even more typically ± 1%, and still more typically ± 0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

Compositions of the present invention contain one or more cannabinoids. By “cannabinoids” is meant a class of diverse chemical compounds that act on cannabinoid

receptors on cells that affect neurotransmitter release in the brain. The cannabis plant produces an estimated 80+ cannabinoids, each of which has unique pharmacologic effects. Δ^9-tetrahydrocannabinol (Δ^9-THC), is the primary psychoactive compound of cannabis. Cannabis refers to various strains of plants *Cannabis sativa* or *Cannabis indica*. Generally, cannabinoids are collected from the female plant. Thus "cannabinoid" is included herein, tetrahydrocannabinols (THC), Δ^9-THC, ^{9}-THC Propyl Analogue (THC-V); Cannabidiol (CBD); Cannabidiol Propyl Analogue (CBD-V); Cannabinol (CBN), Cannabichromene (CBC); cannabinodiol (CBDL); cannabicyclol (CBL); Cannabichromene Propyl Analogue (CBC-V); cannabielsoin (CBE); cannabitriol (CBT), Cannabigerol (CBG), pharmaceutically acceptable salts of these cannabinoids, cannabinoid prodrugs, cannabinoid agonists, synthetic analogs thereof and any combination of the aforementioned. Cannabinoids to use in the present invention also include the carboxylic acid forms of cannabinoids, or the cannabinoid acids. When the cannabinoid acids are desired for use, the present invention avoids the use of steps such as heat and/or drying which can result in decarboxylation of the alkaloids (i.e., carboxylic acid forms) to minimize or prevent decarboxylation.

Cannabinoids to use in the present invention include any of the cannabinoids as discussed above. In one embodiment, the cannabinoid to use in the composition is CBN, CBDα, CBD, THC, THCα, or mixtures of CBD (or CBDα) and THC (or THCα). Mixtures of CBD or CBDα and THC or THCα can be, for example, 1:1 w/w or any other mixture. Various ratios of the above-described cannabinoids can be used for the topical applications described herein. The ratios can be adjusted based on pharmacological effects required. Ratios of enriched/purified cannabinoids for the cannabinoid products of the invention can be adjusted, such as, for example, 1:1 w/w CBD:THC. Ratios include but are not limited to 0.1:1, 0.2:1, 0.3:1, 0.4:1, 0.5:1, 0.6:1, 0.7:1, 0.8:1, 0.9:1, 1:1, 1:1.2, 1:1.5, 1:1.3, 1:1.5, 1:1.7, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8 or 1:10 (all ratios given are w/w). These ratios can be for CBD:THC or THC:CBD.

"Cannabinoid," as used herein, is further meant to include compounds which interact with the cannabinoid receptor and various cannabinoid mimetics, such as certain tetrahydropyran analogs (e.g., Δ9-tetrahydrocannabinol, Δ8-tetrahydrocannabinol, 6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol, 3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one, (−)-(3S,4S)-7-hydroxy-Δ6-tetrahydrocannabinol-1,1-

dimethylhept-yl, (+)-(3S,4S)-7-hydroxy-Δ6-tetrahydrocannabinol-1,1-dimethylh-eptyl,11-hydroxy-Δ9-tetrahydrocannabinol, and Δ8-tetrahydrocannabinol-11-oic acid)); certain piperidine analogs (e.g., (−)-(6S,6aR,9R,10aR)-5,6,6a,7,8,9,10,10a-octahydro-6-methyl-1-3-[(R)-1-methyl-4-phenylbutoxy]-1,9-phenanthridinediol 1-acetate)), certain aminoalkylindole analogs (e.g., (R)-(+)-[2,3-dihydro-5-methyl-3-(−4-morpholinylmethyl)-pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone), certain open pyran ring analogs (e.g., 2-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenedi-ol and 4-(1,1-dimethylheptyl)-2,3′-dihydroxy-6′alpha-(3-hydroxypropyl)-1′,-2′,3′,4′,5′,6′-hexahydrobiphen-yl), as well as their pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors.

"Δ9-THC," as used herein, is meant to refer to Δ9-tetrahydrocannabinol as well as to its pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors. Δ9-tetrahydrocannabinol is marketed under the generic name "dronabinol."

"Cannabinol," as used herein, is meant to refer to 6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol as well as to pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors of 6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol.

"Cannabidiol," as used herein, is meant to refer to 2-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenedi-ol as well as to pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors of 2-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenedi-ol.

"Nabilone," as used herein, is meant to refer to 3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9-H-dibenzo[b,d]pyran-9-one as well as to pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors of 3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one.

"Levonantradol," as used herein, is meant to refer to (−)-(6S,6aR,9R,10aR)-5,6,6a,7,8,9,10,10a-octahydro-6-methyl-3-[(R)-1-meth-yl-4-phenylbutoxy]-1,9-phenanthridinediol 1-acetate, as well as to pharmaceutically acceptable salts, solvates, metabolites (e.g.,

cutaneous metabolites), and metabolic precursors of (−)-(6S,6aR,9R, OaR)-5,6,6a,7,8,9,10,10a-octahydro-6-methyl-3-[(R)-1-methyl-4-phenylbuto-xy]-1,9-phenanthridinediol 1-acetate. (−)-(6S,6aR,9R,10aR)-5,6,6a,7,8,9,10,10a-octahydro-6-methyl-3-[(R)-1-methyl-4-phenylbuto-xy]-described in U.S. Pat. Nos. 4,206,225, 4,232,018, and 4,260,764, which are hereby incorporated by reference; in U.S. Pat. No. 4,235,913 which is hereby incorporated by reference; in U.S. Pat. No. 4,243,674 which is hereby incorporated by reference; and in U.S. Pat. Nos. 4,263,438, 4,270,005, and 4,283,569, which are hereby incorporated by reference.

"(−)-HU-210," as used herein, is meant to refer to (−)-(3S,4S)-7-hydroxy-Δ6-tetrahydrocannabinol-1,1-dimethylhept-yl as well as to pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors of (−)-(3S,4S)-7-hydroxy-Δ6-tetrahydrocannabinol-1,1-dimethylhept-yl. (−)-(3S,4S)-7-hydroxy-Δ6-tetrahydro-cannabinol-1,1-dimethylheptyl is particularly useful in pain control, and its preparation is described in U.S. Pat. Nos. 4,876,276 and 5,521,215, which are hereby incorporated by reference.

"(+)-HU-210," as used herein, is meant to refer to (+)-(3S,4S)-7-hydroxy-Δ6-tetrahydrocannabinol-1,1-dimethylhept-yl as well as to pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors of (+)-(3S,4S)-7-hydroxy-Δ6-tetrahydrocannabinol-1,1-dimethylhept-yl. (+)-(3S,4S)-7-hydroxy-Δ9-tetra-hydrocannabinol-1,1-dimethylh-eptyl is sometimes referred to as HU-211 and/or dexanabinol; it is an antagonist of the N-methyl-D-aspartate receptor; and is described in U.S. Pat. Nos. 4,876,276 and 5,521,215, which are hereby incorporated by reference.

"11-hydroxy-Δ^9-THC," as used herein is meant to refer to 11-hydroxy-Δ^9-tetrahydrocannabinol as well as to its pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors. 11-hydroxy-Δ^9-tetrahyd-rocannabinol is a more hydrophilic, psychoactive metabolite of Δ^9-tetrahydrocannabinol, and its laboratory synthesis is described in Siegel et al., *J. Org. Chem.,* 54:5428 (1989), which is hereby incorporated by reference.

"Δ^8-THC-11-oic acid," as used herein, is meant to refer to Δ^8-tetrahydrocannabinol-11-oic acid, as well as to its pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors. Δ^8-tetrahydrocannabino-1-11-oic acid is a naturally

occurring derivative of 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (which is a minor component of *Cannabis* sativa). A8-tetrahydrocannabinol-11-oic acid can also be produced synthetically as set forth in U.S. Pat. No. 6,162,829, which is hereby incorporated by reference. Δ^8-tetrahydrocannabin-ol-11-oic acid is more hydrophilic than 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-diben-zo[b,d]pyran-1-ol, and it has analgesic activity.

"CP 55,940," as used herein, refers to 4-(1,1-dimethylheptyl)-2,3′-dihydroxy-6′alpha-(3-hydroxypropyl)-1′, 2′,3′,4′,5′,6′-hexahydrobiphenyl, as well as to its pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors. 4-(1,1-dimethylheptyl)-2,3′-dihydroxy-6′alpha-(3-hydroxypropyl)-1′,2′,3′,4′,5′,6′-hexahydro-biphenyl is sometimes referred to as (−)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxyprop-yl)cyclohexanol, and has been described in U.S. Pat. No. 4,371,720 and U.S. Pat. No. 4,663,474 which are hereby incorporated by reference.

"R(+)-WIN 55,212-2," as used herein, refers to (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)-pyrrolo[1,2,3-de]-1-,4-benzoxazin-6-yl]-1-naphthalenyl-methanone, as well as to its pharmaceutically acceptable salts, solvates, metabolites (e.g., cutaneous metabolites), and metabolic precursors. (R)-(+)-[2,3-dihydro-5-methyl-3-(-4-morpholinylmethyl)-pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenyl-1-methanone (in its mesylate form).

"Metabolic precursors" of cannabinoids, as used herein, are meant to include prodrugs and other materials that are metabolized in the subject's body (e.g., cutaneously or systemically or both) to a cannabinoid or an active cannabinoid mimetic. Suitable metabolic precursors include those that are less lipophilic (i.e., more water soluble) relative to the cannabinoid into which they are metabolized. Examples of such metabolic precursors include those described in, for example, U.S. Pat. No. 5,847,128 which is hereby incorporated by reference.

Specific cannabis preparations currently under evaluation in clinical trials are contemplated for use herein and include, for example,

- Dronabinol (Marinol®)
- Vaporized Cannabis
- Vaporized Cannabis 3.7% THC/5.6% CBD
- Nabilone

- Cannabis | Device: Volcano® Medic Vapourizer
- Avidekel oil | Drug: Enriched Avidekel oil by MedReleaf Markham ON
    - Avidekel cannabis oil 6-to-1 ratio of CBD to THC or
      enriched Avidekel cannabis oil 20-to-1 ratio of CBD to THC
- nabiximols high dose (21.6 mg THC + 20 mg CBD), nabiximols low dose (10.8 mg THC + 10 mg CBD),
- Sativex (nabiximols)
- THC 7.2% | THC 3.0%
- Cannabinoids - 99% pure cannabinoids mix
- OWC MGC cream
- TIL-TC150 Cannabis product from Nanaimo BC
- Active delta-9-THC
- Active inhaled delta-9-THC
- Very Low Dose THC
- CanniMed 1:20
- Delta-9-tetrahydrocannabinol | Cannabidiol
- Tetrahydrocannabinol
- Cannabidiol (Epidiolex)
- Dronabinol Cap 5 milligrams (MG) | Dronabinol Cap 10 milligrams (MG)
- PTL 201: Cannabidiol/tetrahydrocannabinol - PhytoTech Therapeutics
- 50 mg of cannabidiol per chewing gum in case of the CanChew
- PPP001 (Tetra BioPharma) 505(b)(2) pathway and combination product + pipe product for cancer related pain

An "effective amount" as used herein, means an amount which provides a therapeutic or prophylactic benefit.

The term “therapeutically effective amount” or “therapeutically and/or prophylactically effective amount” as used herein refers to an amount of a cannabinoid that is sufficient to elicit the required or desired therapeutic and/or prophylactic response. Typically the “therapeutically effective amount” or “therapeutically and/or prophylactically effective amount” of cannabinoid

is sufficient to alleviate one or more symptoms associated with pain and/or one or more symptoms associated with a cannabis- or cannabinoid-treatable condition. For example, while pain is provided herein as a specific exemplary treatable condition/symptom, the compositions described herein may find use in treating any condition in which cannabis or a cannabis extract is useful. For example, cannabinoids, natural or synthetic, are typically agonists at cannabinoid receptors and many diseases or conditions or symptoms of such diseases or conditions can be alleviated at least in part by the administration of cannabinoid receptor agonists. Other compounds within cannabis, in the form of an extract or purified compound or mixture of compounds, may also find use in the compositions described herein.

Diseases and conditions are that of pain and conditions that include pain as symptom. Such diseases and conditions include but are not limited to the following: pain (including but not limited to acute pain; chronic pain; neuropathic pain and cancer pain), immunomodulation (such as increasing a positive immune response or decreasing a negative immune response, or inducing tolerance to an immunogenic agent), neurodegenerative disease (including but not limited to Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; Huntington's disease; multiple sclerosis; frontotemporal dementia; prion disease; Lewy body dementia; progressive supranuclear palsy; vascular dementia; normal pressure hydrocephalus; traumatic spinal cord injury; HIV dementia; alcohol induced neurotoxicity; Down's syndrome; epilepsy or any other related neurological or psychiatric neurodegenerative disease), ischemic disease (including but not limited to stroke; cardiac ischemia; coronary artery disease; thromboembolism; myocardial infarction or any other ischemic related disease), brain injury or damage (including but not limited to traumatic brain injury including: diffuse axonal injury; concussion; contusion; whiplash or any other traumatic head or brain injury), acquired brain injury (including but not limited to stroke; anoxic brain injury; hypoxic brain injury or any other acquired brain injury), age related inflammatory or autoimmune disease, cachexia (including related conditions such as AIDS wasting disease, weight loss associated with cancer, chronic obstructive pulmonary disease or infectious diseases such as tuberculosis), nausea and vomiting, glaucoma, movement disorders, rheumatoid arthritis, asthma, allergy, psoriasis, Crohn's disease, systemic lupus erythematosus, diabetes, cancer, osteoporosis, renal ischemia and nephritis.

In particular aspects, the compositions described herein may find use, for example, as an analgesic for treatment of arthralgia, neuralgia, inflammation, for inducing appetite, is treatment of sleep apnea, hypertension, inhibiting growth of cancerous cells, among many other medical treatments and therapies, including restoring the human body to health, regulating homeostasis, treating pain, inhibiting growth of cancerous cells, inducing appetite, assisting mood and sleep disorders, treating digestive disorders and other disorders and diseases.

In other particular aspects, the compositions described herein may find use, for example, in treating one or more of:

- Cancer Patients During Chemotherapy Treatment
- Sickle Cell Disease
- Chronic Pain
- Low Back Pain
- Neuropathic Pain
- Cannabis Dependence
- Teratozoospermia
- Schizophrenia | Dual Diagnosis | Psychotic Disorder | Cannabis Use Disorder
- Osteoarthritis, Knee
- Lung Cancer
- COPD | Insomnia
- Epilepsy
- Chronic Obstructive Pulmonary Disease (COPD) | Breathlessness | Exercise Intolerance
- Neck Pain
- Spasticity | Dystonia
- Posttraumatic Stress Disorder
- Marijuana Abuse | Sleep Initiation and Maintenance Disorders
- Attention-deficit/Hyperactivity Disorder
- Pain, Postoperative | Postoperative Nausea and Vomiting | Anxiety
- Multiple Sclerosis
- Autistic Disorder

- Intra Ocular Pressure
- Obsessive-Compulsive Disorder
- Brain Tumor | Spinal Tumor
- Esophageal Diseases
- Stiffness of Shoulder, Not Elsewhere Classified
- Ulcerative Colitis | Crohn's Disease | Colon Cancer
- Cancer Cachexia | Atypical Anorexia Nervosa
- Parkinson's Disease
- Schizophrenia
- Acute-graft-versus-host Disease
- Non-Small Cell Lung Cancer | Anorexia | Cachexia | Weight Loss
- Amphetamine Addiction
- Substance Use Disorder | Cocaine Dependence | Withdrawal From Addictive Substance; Detoxification
- Psychosis
- Alzheimer Disease | Agitation | Weight Loss | Pain | Oxidative Stress
- Tourette Syndrome
- Nausea | Vomiting | Familial Dysautonomia

A therapeutically and/or prophylactically effective amount of a drug for a subject is dependent inter alia on the body weight of the subject as well as other factors known to a person of ordinary skill in the art. A “subject” herein to which a therapeutic agent or composition thereof can be administered includes mammals such as a human subject of either sex and of any age.

The term “pharmaceutically acceptable” means that the compound or combination of compounds is compatible with the remaining ingredients of the formulation for pharmaceutical use, and that it is generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "pharmaceutically acceptable carrier" includes, but is not limited to solvents, dispersion media, coatings, antibacterial agents, antifungal agents, isotonic and/or absorption delaying agents and the like. The use of pharmaceutically acceptable carriers is well known.

The cannabinoid amount, in terms of weight percent, in the composition is generally between about 0.01% and about 5% of the composition, between about 0.05% and about 4%, between about 0.1% and about 3.5%, between about 0.2% and about 3%, between about 0.4% and about 2%, or between about 0.6% and about 1.5%. In one embodiment, the amount is between about 0.8% and 1.2%, or about 1%. Alternatively, the cannabinoid amount can be about 0.01%, about 0.05%, about 0.1%, about 0.2%, about 0.4%, about 0.6%, about 0.8%, about 0.9%, about 1%, about 1.1%, about 1.2%, about 1.4%, about 1.6%, about 1.8%, about 2%, about 3%, about 4%, about 5%, about 6%, about 8%, about 10%, about 15%, or about 20%. The remaining ingredients are adjusted to maintain the desired weight percent of the desired cannabinoid. As discussed above, in one embodiment, the composition provides an individual dose of about 10 mg of cannabinoid.

In some embodiments individual doses of the compositions of the present invention contain from about 0.1 to about 100 milligrams (mg) of cannabinoid, from about 0.5 to about 50 mg, from about 1 to about 40 mg, from about 2 to about 20 mg, from about 5 mg to about 15 mg, or about 0.1 mg., 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 8 mg, 10 mg, 12 mg, 14 mg, 16 mg, 18 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg or more per dose.

For transdermal delivery of the composition of the invention involves contacting the composition comprising one or more cannabinoids with the subject's skin under conditions effective for at least one of the provided cannabinoids to penetrate the skin and enter the bloodstream. The compositions of the present invention allow for significant transdermal delivery across the skin. A number of methods known in the art can be used to assess delivery across the skin. In one method, delivery may be assessed by measurement of the remaining cannabinoid in the composition after use. After the composition was present on the skin of a patient for at least 12 hours, for example, at least 0.1% of the cannabinoid can be delivered across the skin, at least 0.5% of the cannabinoid can be delivered across the skin, at least 1% of the cannabinoid can be delivered across the skin, at least 2% of the cannabinoid can be delivered across the skin, at least 3% of the cannabinoid can be delivered across the skin, at least 4% of the

cannabinoid can be delivered across the skin, at least 5% of the cannabinoid can be delivered across the skin, at least 6% of the cannabinoid can be delivered across the skin, at least 7% of the cannabinoid can be delivered across the skin, at least 8% of the cannabinoid can be delivered across the skin, at least 9% of the cannabinoid can be delivered across the skin, at least 10% of the cannabinoid can be delivered across the skin, at least 11% of the cannabinoid can be delivered across the skin, at least 12% of the cannabinoid can be delivered across the skin, at least 14% of the cannabinoid can be delivered across the skin, at least 16% of the cannabinoid can be delivered across the skin, at least 18% of the cannabinoid can be delivered across the skin, at least 20% of the cannabinoid can be delivered across the skin, at least 25% of the cannabinoid can be delivered across the skin, at least 30% of the cannabinoid can be delivered across the skin, at least 35% of the cannabinoid can be delivered across the skin, at least 40% of the cannabinoid can be delivered across the skin, at least 45% of the cannabinoid can be delivered across the skin, at least 50% of the cannabinoid can be delivered across the skin, at least 55% of the cannabinoid can be delivered across the skin, at least 60% of the cannabinoid can be delivered across the skin, at least 65% of the cannabinoid can be delivered across the skin, at least 70% of the cannabinoid can be delivered across the skin, at least 75% of the cannabinoid can be delivered across the skin, at least 80% of the cannabinoid can be delivered across the skin, at least 85% of the cannabinoid can be delivered across the skin, at least 90% of the cannabinoid, at least 90% of the cannabinoid can be delivered across the skin, and at least 95% of the cannabinoid can be delivered across the skin.

The cannabinoid or mixture thereof is provided in the first and/or second phase of the biphasic vesicle composition. Optional opioids can be combined with the cannabinoids in the first and/or second phase of the biphasic vesicle composition or as an adjunct to the compositions of the invention. Opioids are often used for acute pain, such as short-term pain after surgery. Some examples of opioids include but are not limited to: morphine, fentanyl, oxycodone and codeine. Other components may also be included in the compositions described herein, as will be understood. For example, in one particular aspect, the compositions described herein may be similar to those described in US 6,656,499, WO 2015/0236000, WO 2015/023601, or WO 2008/119160 (each of which is incorporated herein by reference in its entirety) and further comprising a cannabis-derived compound or comprising a cannabis-derived compound instead of

interferon. Thus, in particular aspects, the compositions described herein may include both a cannabis-derived compound and an interferon, or they may explicitly exclude an interferon.

In aspects, the compositions described herein may act additively or synergistically with other conventional anti-pain treatments, whether administered concurrently or consecutively in any order and/or whether administered topically or by any other known method.

In aspects, the compositions described herein may be formulated with a non-steroidal anti-inflammatory drug (NSAID) such as salicylic acid and oxyacetic acid. Other examples of NSAID that can be used include salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, fenamic acid derivatives, coxibs, sulphonanilides, etc. In some preferred embodiments, the NSAID can be acetylsalicylic acid or Bendazac. This may be particularly useful in the treatment of eye pain when the composition is formulated as an eye drop.

By format, it is meant that the cannabinoid biphasic lipid-vesicle compositions of the invention can be provided as an ointment, cream, suspension, liquid, lotion, paste, gel, spray, foam, oil, semi-solid (i.e. suppository), bar (soap bar), shampoo and combinations thereof. Any of these formats as suitable can be incorporated, for example, into a patch for transdermal administration or into a suppository for transmucosal administration.

The invention relates to a lipid-bilayer or liposome or lipid vesicle composition for use in delivering a cannabinoid by topical application meaning the provision of a local effect, where the composition is applied directly where its action is desired. The term *topical* may be defined as application to a localized area of the body or to the surface of a body part, without necessarily involving a targeted effect of the substance, resulting in a systemic effect. Examples of topical administration/use includes, for example, transdermal, transmucosal delivery (e.g., by intravaginal administration, rectal, or intranasal) and ocular. In aspects, there are also localized benefits from topical administration. For example, topically administered cannabinoids may find use in alleviating pain and other conditions originating near the surface of the skin. Transdermal includes application to any skin portion of the body.

In one embodiment, compositions described herein are suitable for transdermal administration. Transdermally administrable compositions are adapted for administration in and/or around the abdomen, back, chest, legs, arms, scalp or other suitable skin surface and may include formulations in which the cannabinoid biphasic lipid-vesicle composition is administered

in patches, ointments, creams, suspensions, liquids, lotions, pastes, gels, sprays, foams, soaps, shampoos or oils.

In an further embodiments, the composition of the invention is formulated to be applied to the eye as a drop, in this type of embodiment the composition can be a liquid, liquid suspension or gel that is not overly viscous. Furthermore, as an eye drop the composition of the invention may additionally comprise a lubricant (e.g., glycerin, polysorbate, hypromellose, hydroxyethyl cellulose, carboxymethylcellulose, etc.), a redness reliever (e.g., naphazoline hydrochloride, tetrahydrozoline, etc.), an astringent (e.g., zinc sulfate, etc.) or various inactive ingredients (e.g., borate buffer, silver sulphate preservative, benzalkonium chloride, boric acid, chlorobutanol, edentate disodium, menthol, sodium borate, calcium chloride, magnesium chloride, potassium chloride, sodium chloride, sodium lactate, a pH adjuster (e.g., hydrochloric acid, sodium hydroxide, etc.), a buffer, etc.). Antibiotics such as chloramphenicol, fusidic acid, fluoroquinolones, aminoglycoside and polymycin B sulfate may also be incorporated into the composition of the invention or used concurrently therewith.

After transdermal application of the composition, essentially no limitations exist as to the length of time that the composition can remain in contact with the user's skin. Since the amount of cannabis in the composition will decrease as it is absorbed into the user's skin, the composition can be removed when the amount of cannabinoid remaining in the composition decreases to an amount that is no longer effective to the user. It is to be understood that the amount of cannabinoid initially carried in the composition will affect the length of time the composition will be effective once the composition is applied to the user's skin. For example, in an aspect of the invention, the composition contains a cannabinoid in the amount of about 10 milligrams. In such an aspect, the composition may be removed after approximately 12 hours, and after that time replaced with a new dose of the composition for continued absorption of cannabinoid into the user's skin to provide therapeutic levels of the cannabinoid to the user. However, the composition may optionally be left on longer than, or removed sooner than, the length of time that is necessary or recommended for complete diffusion of the cannabinoid into the user's skin. As mentioned above, the composition of the present invention placed on the skin is capable of delivering cannabis through the stratum corneum layer of the epidermis and through the dermis into the microvasculature.

"Alleviate" as used herein, is meant to include complete elimination as well as any clinically or quantitatively measurable reduction in the subject's symptoms and/or discomfort.

By pain as used herein is meant both acute and chronic. For example acute pain usually comes on suddenly and is caused by something specific. It is sharp in quality. Acute pain usually does not last longer than six months. It goes away when there is no longer an underlying cause for the pain. Causes of acute pain include: surgery, broken bones, dental work, burns, cuts, strains, sprains, pain due to intercourse and the like. Chronic pain is pain that is ongoing and usually lasts longer than six months. This type of pain can continue even after the injury or illness that caused it has healed or gone away. Pain signals remain active in the nervous system for weeks, months, or years. Some people suffer chronic pain even when there is no past injury or apparent body damage. Chronic pain is linked to conditions including but not limited to: headache, arthritis, cancer, nerve pain, back pain, fibromyalgia, bursitis, carpal tunnel syndrome, gout, and other muscular and joint aches and pains.

Neuropathic pain is generated by pathology in the peripheral or central nervous system. A large number of disorders can give rise to neuropathic pain. This may range from nerves being cut (trauma or surgery) or damaged by viruses, ischemic and metabolic injury or complex genetic disorders to name a few. Neuropathic pain may arise from local damage to neural tissues as well as tissues remote to initial trauma and may also arise as a result of chronic inflammatory disease. Pharmacological management is one of the most used pain treatment options but results are poor with many patients obtaining inadequate relief with currently available agents. There is therefore a need for new agents for treatment of neuropathic pain. Neuropathic pain may affect any part of the body including the eye for which there are no adequate treatments at present.

The composition of the invention has use to help prevent or relieve pain associated with the eyes associated with at least one of the following eye disorders: (a) cataracts; (b) diabetic retinopathy; (c) glaucoma; (d) macular degeneration; (e) dry eye syndrome (e.g., irritated eyes, sandy or gritty sensation, red eyes, burning sensation, poor visual acuity, poor tear quality, decreased tear break up time, poor schrimer test performance, increased eye sensitivity to wind and heat, etc.); (f) proptosis (e.g., dryness, eye pain, eye redness, etc.); (g) keratoconus; (h) pterygium/pinguecula (e.g., distorted vision, blurred vision, decreased visual acuity,

inflammation, irregular astigmatism, etc.); (i) ocular allergy (e.g., eye irritation, blurred vision, decreased visual acuity, etc.; or any other eye disorders and signs or symptoms.

Pain associated with uveitis, an intraocular inflammation within the eye from the uvea (iris, ciliary body and choroid) to the sclera, retina and optic nerve is also encompassed within the scope of the present invention. It involves either infectious or non-infectious conditions, which can be localized within the eye or associated with systemic inflammatory and autoimmune diseases, including reactive arthritis and multiple sclerosis. The most common form of uveitis, anterior uveitis, with inflammation of the iris and ciliary body, is additionally associated with considerable pain and photophobia (Jabs, Nussenblatt et al. 2005; Lee and Dick 2012). Untreated uveitis can lead to permanent loss of vision. Severe uveitis is treated aggressively to mitigate the damage caused by inflammation.

Anterior uveitis (iritis) is associated with inflammation of iris and anterior tissues and this leads to pain and light sensitivity with pupillary changes in response to light. Anterior uveitis pain is typically resolved when the inflammation is treated so is not classed as neuropathic pain. Generally uveitis represents hyperactivation of the body's immune system; a form of local sepsis. Inflammatory conditions are represented by activation, recruitment, and migration of immune cells, release of proinflammatory cytokines, swelling, oedema and/or tissue damage. In posterior uveitis, this can also include gliosis, and activation of resident immune cells (microglia). In some retinal inflammatory diseases, cell proliferation with subsequent fibrosis and retinal detachment is present (i.e. proliferative vitreoretinopathy).

Corneal neuropathic hyperalgesia involves a dysfunctional corneal pain system and is associated with significant discomfort and persistent heightened sensitivity of the cornea (peripheral sensitization) in the absence of overt trauma or noxious stimuli (reviewed in Belmonte et al., 2004; Rosenthal & Borsook, 2012; Rosenthal et al., 2009). Ongoing excitation of corneal nerves, following corneal damage or irritation, results in the release of neuropeptides and inflammatory mediators that augment the inflammatory reaction (neurogenic inflammation) leading to hyperalgesia. Corneal hypersensitivity, neuroinflammation, pain and photophobia are reported in patients following refractive surgery and chemical/toxic exposure, including repetitive use of benzalkonium chloride-preserved eye drops. Corneal neuropathic pain is also a central pathogenic feature of eye disorders that are collectively referred to as dry eye, and

include non-infectious immunological causes such as Sjogren syndrome and systemic lupus as well as infections with Herpes Zoster (reviewed in Rosenthal & Borsook, 2012; Yawn et al., 2013).

In aspects, the cannabinoid biphasic vesicle composition described herein comprises a) a first phase comprising an oil-in-water emulsion which itself comprises oil in water, wherein a sufficient amount of oil is employed to form a composition suitable for topical application, and wherein the water comprises a cannabinoid, an optional antioxidant and an optional anti-aggregant; and (b) a second phase comprising multilamellar lipid vesicles suspended in said first phase wherein said vesicles contain entrapped therein a composition comprising an oil-in-water emulsion wherein the water phase comprises cannabinoid, an optional antioxidant and an optional anti-aggregant, wherein the composition comprises a therapeutically effective amount of said cannabinoid, and wherein said anti-aggregant preserves the cannabinoid so as to enhance the shelf-life of the composition. The composition surprisingly provides for the loading of at least one cannabinoid in a manner that is stable and is released when topically applied in a manner to help alleviate pain and pain associated with a variety of conditions as described herein. In aspects the composition comprises THC and CBD, whether together in one of the phases of the vesicle or separately in different phases of the vesicle. One of skill in the art would appreciate that the vesicles can comprise more than two phases and each can be loaded with a desired cannabinoid such as THC and CBD in desired ratios.

The composition described herein is, in aspects, safe and effective and may find particular advantages for use. For example, the compositions described herein may bypass many of the euphoric activities of THC and enable more effective transdermal delivery of cannabinoids into the dermis.

It can in aspects be used in a variety of formats and also applied to a patch (to form a cannabis transdermal delivery structure) that is constructed to have a backing layer selected from the group consisting of a patch, strip, bandage or covering, for example, the backing layer comprising the composition of the invention and optional other skin permeation enhancer(s) or other components. One of skill in the art would recognize that the composition described herein can be incorporated into a variety of patch formats such as for example but not limited to those

disclosed in U.S. 6,113,940, U.S. 6,328,992 and U.S. 9,375,417 each of which are incorporated herein by reference in their entirety.

The cannabinoid biphasic lipid-vesicle composition of the invention can be provided as a kit with instructions for use depending on the format of the composition.

The cannabinoid biphasic lipid-vesicle composition of the invention may be effective for the treatment of all types of pain whether acute or chronic or as a result of injury, surgery, or disease state. The cannabinoid biphasic lipid-vesicle composition of the invention can be applied topically to any part of the body inclusive of orifices and to the eye as drops for example.

Unless otherwise indicated, all numbers used herein to express quantities, dimensions, and so forth used should be understood as being modified in all instances by the term "about." In this application, the use of the singular includes the plural unless specifically stated otherwise, and use of the terms "and" and "or" means "and/or" unless otherwise indicated. Moreover, the use of the term "including," as well as other forms, such as "includes" and "included," should be considered non-exclusive. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one unit, unless specifically stated otherwise.

While various aspects and features of certain embodiments have been summarized above, the following detailed description illustrates a few embodiments in further detail to enable one of skill in the art to practice such embodiments. The described examples are provided for illustrative purposes and are not intended to limit the scope of the invention.

Examples

The following examples are provided for illustrative purposes only and are not intended to limit the scope of the invention.

A. Formation of an Anhydrous Plastic Proliposome Gel

A liposome-forming component and other necessary excipients are melted with a pharmaceutically acceptable hydrophilic solvent, such as propylene glycol.

The expression "liposome-forming component" designates the substance or substances used as major component of the lipid bilayers. Typical liposome-forming components include glycolipids, lecithins, phospholipids, ceramides or mixtures thereof which are used as a primary

ingredient in the formation of the lipid bilayer. However, other natural and synthetic compounds having the required amphipatic character can be incorporated with the phospholipid, glycolipid or ceramide, replacing some of these expensive materials, provided that the essential character of the lipid bilayers is not adversely affected. The choice of the appropriate materials is within the knowledge of the person skilled in the art. Examples include phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, cardiolipin, phosphatidic acid and the cerebrosides, ether lipids and phytanols.

The liposomal formulations of the present invention preferably contain saturated and/or unsaturated phospholipids, more preferably phosphatidylcholine, lysophosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, glycolipids and ceramides. The phospholipids are preferably in combination with a penetration enhancing agent such as monolauroyllysine, dipalmitoyllysine or methyl salicylate to achieve predominantly transdermal delivery potential.

A "fatty substance" can be used to enhance the strength of the lipid bilayers. Examples of useful fatty substances include steroids such as cholesterol, coprostanol, cholestanol and cholestane and long chain fatty acids (C_{16} to C_{22}), especially saturated ones such as stearic acid. In addition to enhancing strength of the lipid bilayer, acids impart a negative charge. Saturated or unsaturated acids can be used. Other fatty substances that can be used include C_{16} to C_{22} fatty amines, fatty acylated proteins, fatty acylated peptides, fatty acylated PEG and derivatives. These fatty substances are incorporated with the abovementioned liposome-forming components and improve physical stability and appearance of the product.

The hydrophilic solvent is used as a plasticizer of the liposome-forming component and an aid to prepare a uniform melt. Examples of hydrophilic solvents include but are not restricted to propylene glycol, glycerol, polyethylene glycol having a molecular weight ranging between 300 and 8000, ethanol, and mixtures thereof. The resulting melt can be described as being an anhydrous plastic proliposome gel. This anhydrous plastic proliposome gel contains all the lipid phase ingredients and can be prepared and stored in advance in large quantities. It is a semisolid material with a homogenous consistency.

B. Formation of the Multilamellar Lipid Vesicles

Hydrophilic ingredients such as penetration enhancers, preservatives and the like, are prepared separately as an aqueous solution, which forms the continuous phase of an emulsion.

This is added to the lipid phase melt, previously heated to the appropriate melting temperature that can range from 40°C to 80°C, and vigorously mixed by any given technique which allows the achievement of the desired product size. Examples of mixing techniques include vortexing or propeller mixing. At this stage, it is also possible to incorporate (dissolve) solid biologically active agents that will be entrapped within the lipid bilayers.

This procedure is suitable for the preparation of various amounts of topical liposomal product. If vortex mixing is used as the agitation, up to about 20 g of the product can be prepared. If a laboratory scale propeller mixer is used, up to about 2 kg to 10 kg of the product can be made. This formulation procedure can also be adapted for large scale manufacturing. Hence, the propeller mixing technique can be directly scaled up by geometrically increasing the size of the vessel and the diameter of the propeller mixer. However, as the vessel size increases, the preferred set up would be a combination mixer, i.e. a high intensity mixer with propeller mixer and a scraped surface agitator. The aqueous phase can either be pumped from tank A to tank B containing the anhydrous plastic proliposome gel or the aqueous phase can be mixed with the emulsion prior to adding to Tank B at the required temperature and mixed. This procedure is suitable for the production of any topical liposomal product on a large scale.

Liposomal compositions can be prepared with the multilamellar lipid vesicles of the present invention by using appropriate pharmaceutical additives. For example, it might be required to add viscosity increasing agents to the final liposome preparation. The addition of other pharmaceutically acceptable compounds is within the purview of the person skilled in the art.

C. Characteristics of the Final Multi-lamellar Lipid Vesicle Product

A schematic representation of a multi-lamellar lipid vesicle prepared in accordance with the process described above is shown at FIG. 3. The multi-lamellar lipid vesicle, generally designated by reference numeral 2, is made of a series of spaced apart lipid bilayers 4, 6 and 8 which define a series of peripheral aqueous solution compartments 3 and 5. The smallest lipid bilayer 7 defines in its center a central core compartment 9. Although only six lipid bilayers are shown, it should be appreciated that the figure is simplified and schematic and in fact many more than six lipid bilayers are present.

FIG. 4 is an enlargement of the vesicle of FIG. 3 showing in more detail the central core compartment and parts of some of the lipid bilayers. The central core compartment 9 is occupied by an aqueous emulsion composed of water 10 as continuous phase and lipophilic droplets or fine solid particles 11 as dispersed phase that contain the cannabinoid. The lipophilic cannabinoid droplets or fine solid particles are surrounded by a layer of surfactant molecules 12, the hydrophilic portions 13 of each surfactant molecule extending into the aqueous phase and the hydrophobic portions being at the surface of the oil droplets.

Surrounding the core compartment is the innermost lipid bilayer 15. The lipid bilayer is composed of two layers of lipid molecules 16. Each lipid molecule 16 in a layer is oriented substantially parallel to adjacent lipid bilayers, and two layers that form a bilayer have the polar ends 17 of their molecules exposed to the aqueous phase and the non-polar ends 18 adjacent to each other. Between the innermost lipid bilayer 15 and the next innermost lipid bilayer 19 is a peripheral compartment 20 that is filled either with water or with the aqueous emulsion containing cannabinoid. As shown, surfactant surrounded lipophilic droplets or particles 11 containing cannabinoid can be present in the peripheral compartment 20.

Surrounding the peripheral compartment 20 is the next innermost lipid bilayer 19, which is in turn surrounded by a further peripheral compartment and a further lipid bilayer.

It will be appreciated that the biologically active ingredient, cannabinoid, optional stabilizers, optional anti-aggregant such as arginine and an optional water soluble antioxidant (e.g., methionine), as well as any other desired components (other active therapeutic agent), will be present in the water of the aqueous emulsion in the central core compartment 9 and in the peripheral compartments 20. Other inactive ingredients that are lipophilic, such as consistency enhancers or uptake enhancers, can be present in the dispersed phase of the emulsion in the central compartment 9 and in the peripheral compartments 20. They can also be present in the interior of the lipid bilayers as shown at 21. The biologically active ingredient can constitute the lipophilic droplets 21, or the biologically active ingredient can be dissolved in a lipophilic solvent that forms droplets 21. Thus, the invention permits the topical application of biologically active ingredients that are water-soluble or water-insoluble.

In various aspects of the invention, an anti-aggregant, such as arginine, may be present in the intra-vesicular and extra-vesicular spaces of the multilamellar vesicles.

The term "stability" refers to the physical, chemical, and/or conformational stability of formulations of cannabinoid of the invention (including maintenance of biological potency). Instability of a protein formulation may be caused by chemical degradation or aggregation of the protein molecules to form higher order polymers, deglycosylation, modification of glycosylation, oxidation or any other structural modification that reduces at least one biological activity of the compositions of the invention.

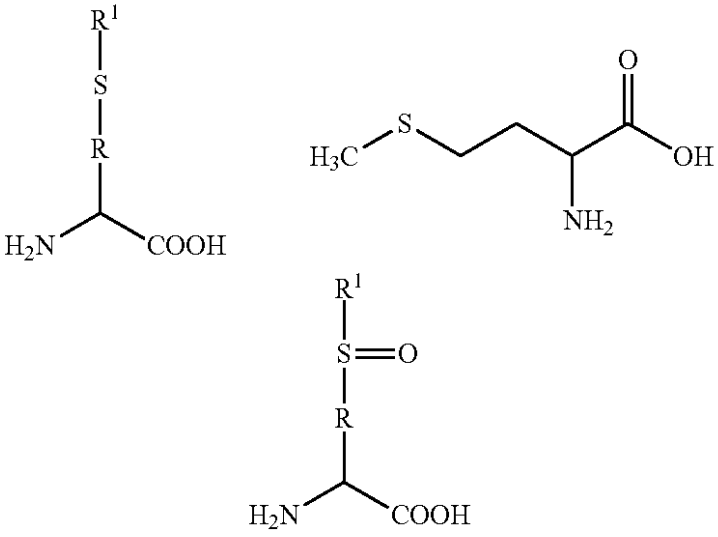
A "stable" or "stabilized" composition is one wherein the degree of degradation, modification, aggregation, loss of biological activity and the like, of proteins therein is acceptably controlled, and does not increase unacceptably with time. Typically, the composition retains at least or about 60%, more typically at least at or about 70%, most typically at least at or about 80% of the labeled cannabinoid activity over a period of 24 months. The stabilized cannabinoid compositions of the invention preferably have a shelf-life of at least about 18 months, more preferably at least 20 months, still more preferably at least about 22 months and most preferably at least about 24 months when stored under refrigerated conditions (2°C-8°C).

In exemplary embodiments, a sufficient amount of an antioxidant, for example methionine, is employed to stabilize the cannabinoid present in the intra-vesicular space in the central core compartment 9 as well as in the peripheral compartments 20 to provide oxidative stability to the cannabinoid in the intra-vesicular space. Additionally, the antioxidant employed in this manner also serves to provides oxidative stability to the cannabinoid retained in the extra-vesicular space. In various aspects, one or more antioxidants may be included in the formulations according to the invention, and in certain aspects a combination of two or more antioxidants is employed.

In particular embodiments, the antioxidant employed is L-methionine, although it is also contemplated that D-methionine can be used, or alternatively a racemic mixture of both. Thus, any stereoisomer (i.e., L, D or DL isomer) of methionine may be used in the compositions of the invention. Preferably, the L-stereoisomer is used. Analogues of methionine may also be used, the term "methionine analogue" referring to a derivative of the naturally occurring methionine, for instance, methionine derivatives with alpha and/or beta-amino substituted groups. In exemplary embodiments, the amount of methionine used in the composition preferably ranges from about 0.01 to about 5 weight percent based on the total weight of the composition. More preferably, the

amount of methionine ranges from about 0.01 to about 0.5 weight percent based on the total weight of the composition.

The composition may further comprise at least one additional antioxidant to further stabilize cannabinoid in the biphasic lipid vesicles. Additional antioxidants include, but are not limited to, ascorbic acid and its salts, ascorbyl palmitate, ascorbyl stearate, N-acetylcysteine, benzyl isothiocyanate, caffeic acid, sodium metabisulfate, benzyl alcohol and tocopherols, including alpha-tocopherol and its salts. Further examples of antioxidants that may be used include:



where R is C_1 to C_6 alkylene and R^1 is C_1 to C_6 alkyl. Additionally, substitution of alpha-amino acids with their beta-amino acid analogues and/or homologs can also be used as antioxidants.

Further, the term "anti-aggregant" as used herein refers to any biocompatible compound that inhibits and/or reduces the aggregation of cannabinoids, e.g., formation of aggregates of cannabinoid. The process of aggregation (e.g., cannabinoid aggregation) can be influenced by a variety of factors, such as but not limited to physicochemical stresses, including heat, pressure, pH, agitation, shear forces, freeze-thawing, dehydration, heavy metals, oxygen, phenolic compounds, silicon oil, denaturants and the like.

The term "guanidine" as used herein includes guanidine and derivatives thereof (e.g., in which the hydrogen atom attached to the amidino nitrogen (dbd.NH) is replaced by substituted or

unsubstituted carboxyl groups, substituted or unsubstituted amino groups, substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, and substituted or unsubstituted heteroaryl groups). In preferred embodiments, the anti-aggregants include compounds that contain a guanidine group, for example, guanidinoacetic acid, substituted or unsubstituted guanidinobenzoic acid, guanidine carbaniedine, guanidine acetate, guanidine amine, guanidine carbonate, guanidine nitrate, guanidine hydrochloride, arginine, arginine analogues and the like. Arginine that has been derivatized at the carboxy or alpha-amino groups is also contemplated. In a preferred embodiment, L-arginine hydrochloride is used as an anti-aggregant.

A pharmaceutically acceptable salt of arginine may impart enhanced shelf-life to the composition by reducing the formation of aggregates. The arginine employed is preferably a pharmaceutically acceptable salt of L-arginine although it is contemplated that D-arginine can also be used, as can a racemic mixture of both. Suitable pharmaceutical salts include, by way of example only, well known organic and inorganic salts such as hydrochloride salts, hydrobromide salts, C_1 to C_6 carboxylic acid salts such as acetate, proprionate, succinate, oxalate, benzoate salts. A particularly preferred salt is the hydrochloride salt of L-arginine as this allows arginine to incorporate into the aqueous solution of cannabinoid. The amount of pharmaceutically acceptable salt of arginine used in the composition preferably ranges from about 0.01 to about 5 weight percent based on the total weight of the composition. More preferably, the amount of the pharmaceutically acceptable salt of arginine ranges from about 0.1 to about 0.5 weight percent based on the total weight of the composition.

Without being limited to any theory, it is believed that the arginine allows the cannabinoid to remain a form that inhibits the formation of aggregates in the composition thereby extending the shelf-life of the composition.

In particular embodiments, compounds containing a guanidine group, such as arginine, are suitable anti-aggregating stabilizing agents for cannabinoid. The term "salts" herein refers to both salts of carboxyl groups and to acid addition salts of amino groups of the stabilizing agents described above or analogs thereof. In some aspects, the arginine employed is a pharmaceutically acceptable salt of L-arginine, although it is contemplated that D-arginine can also be used, or alternatively a racemic mixture of both. In other embodiments, suitable pharmaceutical salts

include, by way of example only, well known organic and inorganic salts such as hydrochloride salts, hydrobromide salts, C_1 to C_6 carboxylic acid salts such as acetate, proprionate, succinate, oxalate, or benzoate salts. A particularly preferred salt is the hydrochloride salt of L-arginine. The amount of pharmaceutically acceptable salt of arginine used in the composition preferably ranges from about 0.01 to about 5 weight percent based on the total weight of the composition. More preferably, the amount of the pharmaceutically acceptable salt of arginine ranges from about 0.01 to about 0.5 weight percent based on the total weight of the composition.

The composition, containing the pharmaceutically acceptable salt of arginine is preferably, formed under conditions in which at least about 30 weight percent, and preferably between about 40 and 70 weight percent of these aqueous components is present in liposome entrapped form, as opposed to being carried in the extra-vesicular bulk phase of the composition. These levels of entrapment can be achieved by various known strategies, e.g., forming the liposomes by a reverse-phase evaporation method and/or encapsulating the aqueous phase material at a high concentration of liposome-forming lipids, thus minimizing the amount of bulk aqueous phase.

FIG. 1 is an image, magnified 440x, of cannabinoid vesicles made for use as a topical lotion. This product displayed the consistency of a lotion or semi-solid cream. This embodiment shows multi-lamellar structures with uniform size distribution. These have displayed physical stability for extended periods of time of more than one year.

In order to demonstrate the difference in properties observed in the liposome population produced in accordance with a preferred method, are comparative tests between two liposome compositions prepared from the same ingredients but using in one case the solvent evaporation method and in the other case the preferred anhydrous plastic proliposome gel method. FIG. 2A is a scanned image of the liposome population prepared using the anhydrous proliposome gel (`melt` or `fusion`) method and FIG. 2B is a scanned image of the liposome population prepared using the solvent evaporation method. As can be seen, the liposome population obtained using the anhydrous plastic proliposome gel method has a liposome size distribution which is substantially more uniform than that obtained using the solvent evaporation method. Also, minimal amounts of aggregated or fused liposomes are formed when using the anhydrous plastic

proliposome gel method, whereas large aggregates can be observed in the liposome population obtained using the solvent evaporation method.

In some embodiments of the invention, the lipophilic substance is an oil or solid/semisolid lipophilic consistency enhancer which can be encapsulated into liposomes. As solid or semisolid lipophilic consistency enhancers there are mentioned fatty alcohols, waxes, fatty alcohol fatty acid esters, glyceride esters, white petrolatum and mixtures thereof. Examples of oils which have successfully been encapsulated into liposomes include pentaerythritol tetracaprylate/caprate, pentaerythritol tetraisostearate, cetearyl octanoate and canola oil, jojoba oil, peanut oil, rice bran oil, cottonseed oil, sunflower oil, corn oil, walnut oil, avocado oil, peru balsam, clove oil and eugenol and mixtures thereof. Plant extracts based on oil have also been successfully incorporated into liposomes. Solid/semi solid lipophilic consistency enhancer ingredients can be selected from waxes, fatty alcohols, fatty acid esters, glyceryl stearate, petrolatum or combinations thereof. Specific examples of preferred consistency enhancers include beeswax, glyceryl tribehenate, glyceryl stearate, stearyl heptanoate, stearyl palmitate, cetyl alcohol, stearyl alcohol, myristyl myristate, behenyl erucate and cetyl palmitate and mixtures thereof.

The viscosity of a composition of vesicles in accordance with the invention and containing a consistency enhancer is greater than the viscosity of corresponding vesicles that do not include a consistency enhancer but are otherwise identical. By varying the amount of consistency enhancer it is possible to achieve virtually any required viscosity, from a relatively mobile liquid, to a "lotion", to "creamy" to "thick cream" to “semi-solid”. The amounts of consistency enhancer required to achieve a particular viscosity of the composition can be determined by routine experiment.

The surfactant used to coat the oil droplet or the solid/semisolid lipophilic consistency enhancer ingredients is important for the successful encapsulation of a lipophilic core into multilamellar lipid vesicles. About 30 different types of surfactants were screened and primary cationic emulsifiers were found to give the most acceptable results. The most preferred surfactant is benzalkonium chloride or other cationic surfactants such as benzethonium chloride, cetylpyridinium chloride, cetrimide. Nonionic or amphoteric surfactants can also be used, such as naturally derived emulsifiers: PEG-60 almond glycerides, avocado oil diethanolamine,

ethoxylated jojoba oil (PEG-40 Jojoba acid and PEG-40 Jojoba alcohol); polyoxyethylene derivatives: polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (20) sorbitan monostearate; lanolin derivatives: polychol 20 (Laneth 20), polychol 40 (laneth 40); neutral phosphate esters: PPG-cetyl ether phosphate, DEA oleth-3 phosphate. It is also possible to use anionic surfactants such as acylglutamates: TEA-cocoyl glutamate, sodium lauroyl glutamate, sodium hydrogenated tallow glutamate and sodium cocoyl glutamate. It is desirable that the surfactant has a high critical micellar concentration (CMC).

In a particular aspect, the composition described herein is a delivery system for a cannabinoid comprising surfactant in admixture with a cannabinoid in a topical formulation, wherein, the delivery system, when in contact with the skin or mucosal membrane, releases the cannabinoid in a therapeutically-effective amount to provide a localized or systemic effect for treatment of pain or pain- associated condition.

When preparing the lipophilic cannabinoid-in-water emulsion, the hydrophilic ingredients and surfactants are all incorporated in water. Once the water phase of the emulsion has been prepared, the oil and/or solid/semisolid lipophilic ingredients are added to the water in a homogenizer for a period of time ranging from 5 to 30 minutes to obtain relatively small droplet size. In aspects droplet size ranges from 0.1 μm to 1 μm, in further aspects below about 0.5 μm. The lipid phase melt (anhydrous plastic proliposome gel) is then heated and the lipophilic cannabinoid-in-water emulsion is added and vigorously mixed by either vortexing or propeller mixing depending on the product size.

The composition/formulation procedure described above can be easily adopted for large scale manufacturing. The propeller mixing approach can be directly scaled up by geometrically increasing the size of the vessel and the diameter of the propeller mixer. However, as the vessel size increases, a preferred set up might be a combination mixer such as a high intensity mixer with propeller mixer and a scraped surface agitator. In a large scale operation, the lipophilic substance (called the oil phase)-in-water emulsion can be pumped from a first tank into a second tank containing the anhydrous plastic pro-liposome gel at the required temperature and mixed.

With the multi-lamellar lipid vesicle of the present invention, oil droplets containing solubilized cannabinoid or marijuana plant extracts can be delivered through liposome encapsulation. Furthermore, the possibility of multi-compartment encapsulation provides

cannabinoid release over extended periods of time. Also, encapsulation of lipophilic solid/semisolid consistency enhancers into the central lipophilic core compartment provides enhanced viscosity to the final liposome composition. In this case, the addition of viscosity-increasing agents in the final liposome preparation can be avoided.

Overall, the preparation of multi-lamellar lipid vesicles with a central emulsion core component provides a physically stable, uniform liposome composition. The composition has a viscosity that is suitable for topical administration and can be easily manufactured on a large scale.

Without being limited to any theory, it is believed that the biphasic nature of this composition provides for both topical treatment of the mucosal layer as well as penetration of the vesicles into the mucosal layer and endocytosis to gain access to the intracellular space. Binary treatment of the mucosal layer is achieved by the biphasic nature of the composition which allows the extra-vesicular emulsion to target the topical mucosal layer while the vesicles can penetrate into the lipophilic mucosa and promote endocytosis which will result in vesicle rupture.

In addition, the biphasic nature of the composition and the oil-in-water emulsion used permits one of skill in the art to provide for a cream or lotion with a viscosity such will be retained at the point of application for a sufficient period of time to allow therapeutic release of the cannabinoid.

D. Exemplary Cannabinoid-Cream Formulations for Topical Use

Table 1 gives the components for a comparative composition lacking an anti-aggregating stabilizing agent such as arginine in a lipid-bilayer composition where the amount of each component is expressed in units of mg/g final composition, and given in both ranges and exemplary quantities (parentheses). The resulting composition is referred to in the studies below as "Formulation A", and is formed as detailed below.

Component	Quantity mg/g	
Active		
Cannabinoid	0.01-1 to 5	(0.808)
Excipients and protective agents		

Component	Quantity mg/g	
Benzalkonium Chloride 50% Solution	1-10	(2)
Butylated Hydroxytoluene	0.1-0.5	(0.102)
Cetyl Alcohol	2-40	(20.514)
Cholesterol	2-40	(20)
Edetate Disodium Dihydrate	0.1-0.5	(0.103)
Glycerol Monostearate 40-55, Type 1	5-50	(30.771)
Glycine	0.1-5	(1)
L-Methionine	0.1-5	(1.126)
Methylparaben	0.1-5	(1.538)
Olive Oil, Super Refined	10-70	(51.285)
PEG-40 Castor Oil, Hydrogenated	10-70	(51.285)
Sodium phosphate, Dibasic, Heptahydrate	1-2	(1.670)
Sodium phosphate, Monobasic, anhydrous	0.25-1	(0.480)
Phospholipon 90H	60-200	(100)
Propylene Glycol	30-100	(69.95)
Propylparaben	0.1-1	(0.513)
Purified Water	Q.S. to 1000	(646.846)

Table 2 gives the components in one exemplary lipid-bilayer composition formed in accordance with the invention, where the amount of each component is expressed in units of mg/g as both ranges and exemplary quantities. The resulting composition is referred to as "Formulation B."

TABLE 2

Excipients	Range (mg/g)	Exemplary quantity (mg/g)
PEG-40 Castor Oil, Hydrogenated, USP/NF	10-70	51.285
Benzalkonium chloride 50% solution, NF	1-10	2.00
Methylparaben, NF	0.1-5	1.538
Propylparaben, NF	0.1-1	0.513
L-methionine, USP	0.1-5	1.126
Edetate Sodium, dihydrate, USP	0.1-0.5	0.103
Phosphate buffer (composed of Sodium phosphate dibasic heptahydrate USP and Sodium phosphate Monobasic USP, anhydrous)	1-70	51.285
Purified water, USP	Q.S. to 1000	596.72
Olive oil, Super refined, NF	10-70	51.285
Glycerol monostearate 40-55, Type 1, EP	5-50	30.771
Cetyl alcohol, NF	2-40	20.514
Lipid Antioxidant, NF	0.1-0.5	0.102
Phospholipon 90H	60-200	100.00
Cholesterol, NF	2-40	20.00
Propylene glycol, USP	30-100	69.95
Glycine, USP	0.1-5	1.0
L-arginine hydrochloride, USP	0.1-5	1.0

TABLE 2

Excipients	Range (mg/g)	Exemplary quantity (mg/g)
Nitrogen, NF	0 to Q.S.	n/a
Cannabinoid	0.01-1 to5	2 MIU/g

Description of the Manufacturing Process for the Formulation.

Step 1. Preparation of Oil-in-Water Submicron Emulsion (System A):

Olive oil, glycerol monostearate 40-55 Type I, cetyl alcohol and butylated hydroxy toluene are melted together at 75°C+/-5°C. The aqueous component of the emulsion including purified water, PEG-40 castor oil hydrogenated, benzalkonium chloride 50% solution, methylparaben, propylparaben, L-methionine, edetate disodium dihydrate, and phosphates are heated together in a stainless steel vessel at 75°C+5°C while stirring until the ingredients are dissolved. The oil component (75°C+/-5°C) is then added to the aqueous component (75°C+/-5°C) gradually, while mixing to form a coarse emulsion. Coarse emulsion is then homogenized by processing through a Microfluidizer until a homogeneous emulsion is formed. This submicron emulsion is cooled down to 8°C-12°C.

Step 2: Preparation of the Lipid Phase:

The Lipid Phase is prepared by melting Phospholipon 90H, cholesterol and butylated hydroxy toluene with propylene glycol in a mixer by heating to about 80-90°C. while mixing at a slow speed. The mixing and heating of the Lipid Phase ingredients is continued until a clear melt is formed which is then cooled to about 60°C.

Step 3: Preparation of the Aqueous Phase:

The required quantity of cannibinoid is added and mixed gently with a mixture of L-methionine, glycine, L-arginine hydrochloride and purified water.

Step 4: Product Formulation:

The Aqueous Phase containing cannabinoid (from Step 3) is added to the System A (from Step 1) in a stainless steel jacketed mixing tank. This mixture is maintained between 8°C-12°C. while the mixture is mixed slowly and purged with nitrogen gas. The cooled mixture of System A-Aqueous Phase is rapidly added to the Lipid Phase which is being mixed at high speed in the mixer. Mixing proceeds for 10-15 minutes while the temperature of the mixture is maintained about 57-60°C. The bulk product thus formed is slowly mixed and cooled to 19°C-25°C in a mixer. The product is transferred from the mixer into a stainless steel storage vessel and purged with nitrogen gas. The bulk product is filled into 5 g polypropylene tubes or polypropylene pre-fill applicators. The tubes or applicators are purged with nitrogen and then the required amount of the product is filled into the tubes or pre-fill applicators, which are thermally sealed in case of tubes whereas prefilled applicators are capped. The filled tubes or pre-filled applicators of Cannabinoid Cream drug product are stored at 5°C+/-3°C.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All technical and patent publications cited herein are incorporated herein by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Although the invention has been described with respect to particular embodiments, it will be apparent to those skilled in the art that various changes and modifications can be made without departing from the invention.

Claims

1. A biphasic vesicle composition comprising:

(a) a first phase comprising a first oil-in-water emulsion; and

(b) a second phase suspended in the first phase, the second phase comprising multilamellar lipid vesicles, the multilamellar lipid vesicles entrapping a second oil-in-water emulsion,

wherein at least one of the first and second oil-in-water emulsions comprises a therapeutically effective amount of a cannabis-derived compound.

2. The biphasic vesicle composition of claim 1, wherein the first and second oil-water-emulsions are the same or different.

3. The biphasic vesicle composition of claim 1 or 2, wherein the cannabis-derived compound is a cannabinoid.

4. The biphasic vesicle composition of claim 3, wherein the cannabis-derived compound is a cannabinoid selected from the group consisting of natural or synthetic cannabinoid, tetrahydrocannabinols (THC), Δ^9-THC, ^{9}-THC Propyl Analogue (THC-V); Cannabidiol (CBD); Cannabidiol Propyl Analogue (CBD-V); Cannabinol (CBN), Cannabichromene (CBC); cannabinodiol (CBDL); cannabicyclol (CBL); Cannabichromene Propyl Analogue (CBC-V); cannabielsoin (CBE); cannabitriol (CBT), Cannabigerol (CBG), pharmaceutically acceptable salts of these cannabinoids, cannabinoid prodrugs, cannabinoid agonists, synthetic analogs thereof and combinations thereof.

5. The biphasic vesicle composition of claim 1 or 2, wherein the cannabis-derived compound is a cannabis extract.

6. The biphasic vesicle composition of any one of claims 1 to 5, further comprising an anti-oxidant.

6a. The biphasic vesicle composition of claim 6, wherein said anti-oxidance is methionine in at least one of the first and second oil-in-water emulsions.

7. The biphasic vesicle composition of any one of claims 1 to 6, wherein at least one of the first and second oil-in-water emulsion is comprised of oil droplets having a size of from about 0.1 μm to 1 μm.

8. The biphasic vesicle composition of any one of claims 1 to 7, wherein at least 30% of said cannabis-derived compound is entrapped within said vesicles.

9. The biphasic composition of any one of claims 1 to 8, wherein said multilamellar vesicles comprise from about 2 to about 4 weight percent cholesterol.

10. The biphasic composition of any one of claims 1 to 9 formulated as a cream, lotion, liquid, gel, foam, drops, suppository, shampoo, soap bar, spray or patch.

11. The biphasic composition of claim 10, provided as a kit, with optional instructions for use.

12. A method for the treatment of pain, comprising administering the composition of any one of claims 1 to 11 to a subject.

13. The composition of any one of claims 1 to 9, formulated as eye drops.

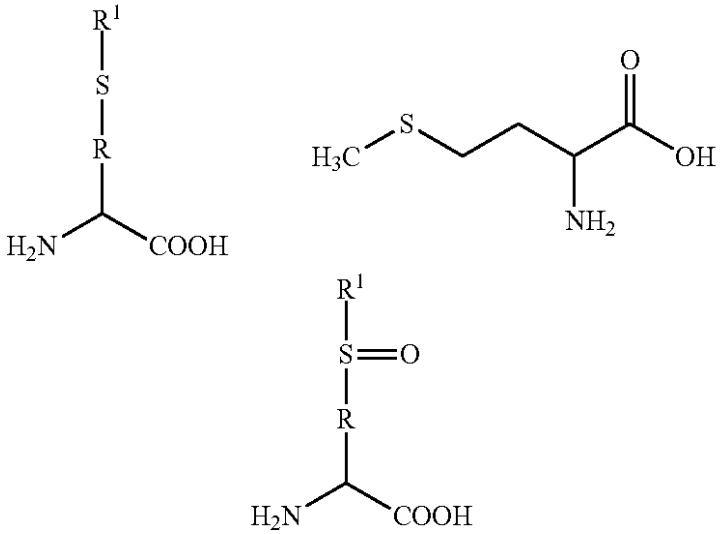
14. The composition of claim 13, further comprising salicylic acid, oxyacetic acid, salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, fenamic acid derivatives, coxibs, sulphonanilides and mixtures thereof.

15. The composition of claim 14, further comprising an antibiotic selected from the group consisting of chloramphenicol, fusidic acid, fluoroquinolones, aminoglycoside, polymycin B sulfate and mixtures thereof.

20 A biphasic vesicle composition comprising:

(a) a first phase comprising an oil-in-water emulsion which itself comprises oil, water, cannabinoid and methionine; and

(b) a second phase comprising multilamellar lipid vesicles suspended in said first phase wherein said vesicles contain entrapped therein a composition comprising an oil-in-water emulsion which itself comprises oil, water, cannabinoid and methionine, wherein each phase comprises an amount sufficient of methionine to stabilize said cannabinoid against oxidation, wherein said methionine is the amino acid methionine of the chemical structure:



further wherein said composition comprises a therapeutically effective aggregate amount of said cannabinoid.

21. The biphasic vesicle composition of claim 20, wherein said oil-in-water emulsion is comprised of oil droplets having a size of from about 0.1 μm to 1 μm.

22. The biphasic vesicle composition of claim 20, wherein said methionine is present in a concentration of from 0.01 to 0.5 weight percent.

23. The biphasic vesicle composition of claim 20, wherein at least 30% of said cannabinoid and said methionine is entrapped within said vesicles as part of said oil-in-water emulsion.

24. The biphasic vesicle composition of claim 21, wherein at least 30% of said cannabinoid and said methionine is entrapped within said vesicles as part of said oil-in-water emulsion.

25. The biphasic vesicle composition of claim 22, wherein at least 30% of said cannabinoid and said methionine is entrapped within said vesicles as part of said oil-in-water emulsion.

26. The biphasic composition of claim 20, wherein said multilamellar vesicle comprises from about 2 to about 4 weight percent cholesterol.

27. The biphasic composition of claim 20, wherein said methionine used in each phase is L-methionine.

30. A method for treating pain in a patient, which method comprises administering to said, patient a therapeutically effective amount of a biphasic vesicle composition comprising; a) a first phase comprising an oil-in-water emulsion which itself comprises oil in water, wherein a sufficient amount of oil is employed to form a composition suitable for topical application, and wherein the water comprises cannabinoid , an antioxidant and an anti-aggregant; and (b) a second phase comprising multilamellar lipid vesicles suspended in said first phase wherein said vesicles contain entrapped therein a composition comprising an oil-in-water emulsion wherein the water phase comprises cannabinoid , an antioxidant and an anti-aggregant, wherein the composition comprises a therapeutically effective amount of said cannabinoid.

31. The method of claim 30, wherein the antioxidant is selected from the group consisting of L-methionine, D-methionine and racemic mixtures thereof.

32. The method of claim 31, wherein the antioxidant is L-methionine and is present in an amount of from 0.1 to 5 mg/g.

33. The method of claim 31, wherein the anti-aggregant is a pharmaceutically acceptable salt of arginine.

34. The method of claim 33, wherein the pharmaceutically acceptable salt of arginine is L-arginine hydrochloride.

35. The method of claim 34, wherein the L-arginine hydrochloride is present in an amount of 0.1 to 5 mg/g.

100. A method of delivering a cannabinoid to the bloodstream of a person comprising the steps of:

A. Providing said composition of any one of claims 1 to 9;

B. Providing a backing layer selected from the group consisting of a patch, strip, bandage and covering for holding said composition;

C. Placing an effective amount of said composition onto said backing layer; and,

D. Attaching said backing layer to the skin of said person so that said transdermal preparation is in contact with said skin.

101. The method of claim 100 comprising the additional steps of:

providing an adhesive mixture containing an effective amount of said composition; and,

carrying out step C by applying said adhesive mixture onto said backing layer.

102. The method of claim 100 comprising the additional step of providing a reservoir means to said backing layer for holding said transdermal preparation.

103. The method of claim 102 wherein said reservoir means is any one or combination of a member of the group consisting of a cavity, matrix material, adhesive layer and film.

104. The method of claim 1 wherein after step D, maintaining said composition in contact with said skin for an effective period of time.

105. A cannabis transdermal delivery structure comprising:
a backing layer selected from the group consisting of a patch, strip, bandage or covering;
said backing layer having the composition of any one of claim 1 to 9.

106. The structure of claim 105 wherein said backing layer includes a reservoir means for holding said composition.

107. The structure of claim 105 wherein said reservoir means is any one or combination of a member of the group consisting of a cavity, matrix material, adhesive layer and film.

108. The structure of claim 105 wherein said matrix material is selected from the group consisting of an open pore material, open weave fabric and a membrane.

109. The transdermal structure of claim 105 wherein said reservoir means comprises a convex portion of said backing layer.

110. The structure of claim 105 wherein a secondary layer is attached to said backing layer, said secondary layer having an opening which forms a retention cavity with said backing layer for holding said composition.

111. A structure for administering cannabis to skin, comprising:
at least one layer of backing material suitable for attachment to said skin; and,
the composition of any one of claims 1 to 9.

112. The structure of claim 111, wherein said backing material is any one or combination of a member selected from the group consisting of fabric, plastic, metal foil, rubber, resin film and membrane.

113. The structure of claim 112 wherein said structure further comprises a reservoir means that includes a rate control means for regulating the flow of said composition to said skin.

Abstract

A biphasic vesicle composition comprises: (a) a first phase comprising a first oil-in-water emulsion; and (b) a second phase suspended in the first phase, the second phase comprising multilamellar lipid vesicles, the multilamellar lipid vesicles entrapping a second oil-in-water emulsion, wherein at least one of the first and second oil-in-water emulsions comprises a therapeutically effective amount of a cannabis-derived compound.

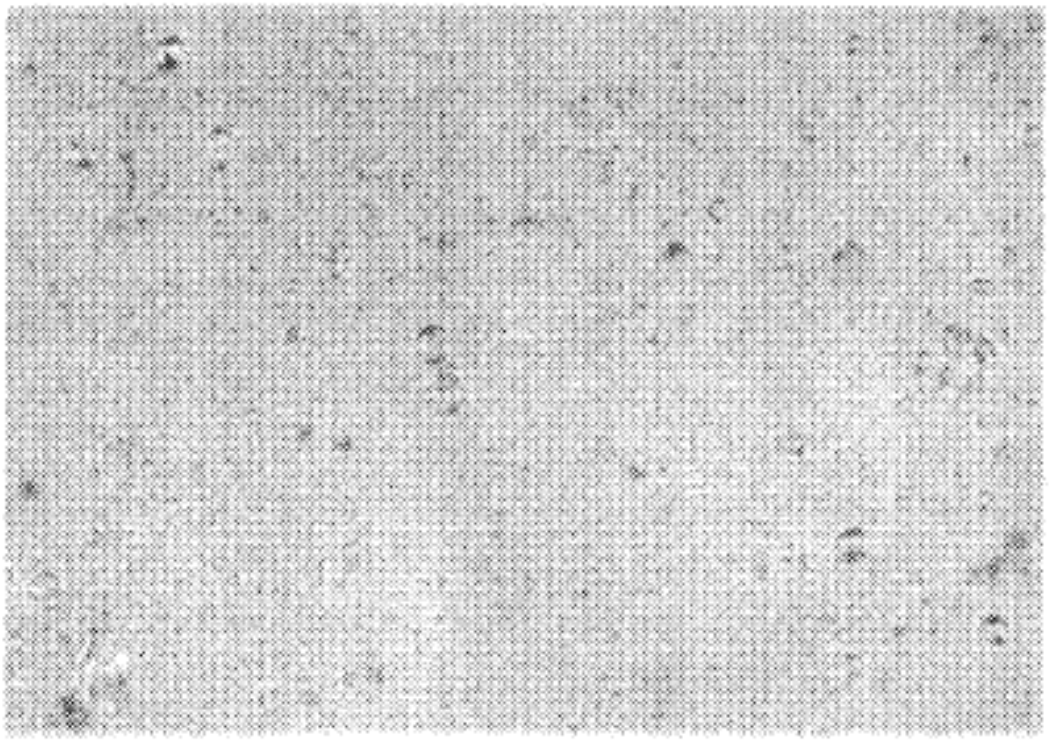


FIG. 1

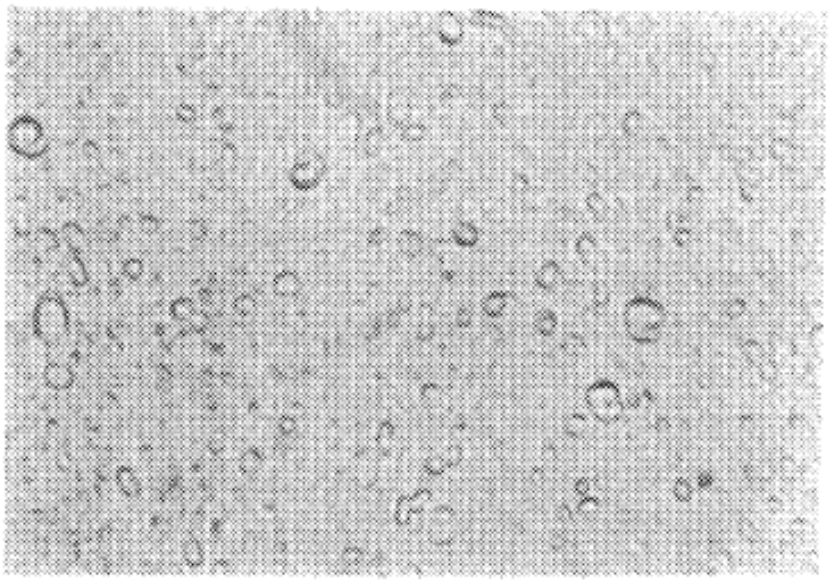


FIG. 2A

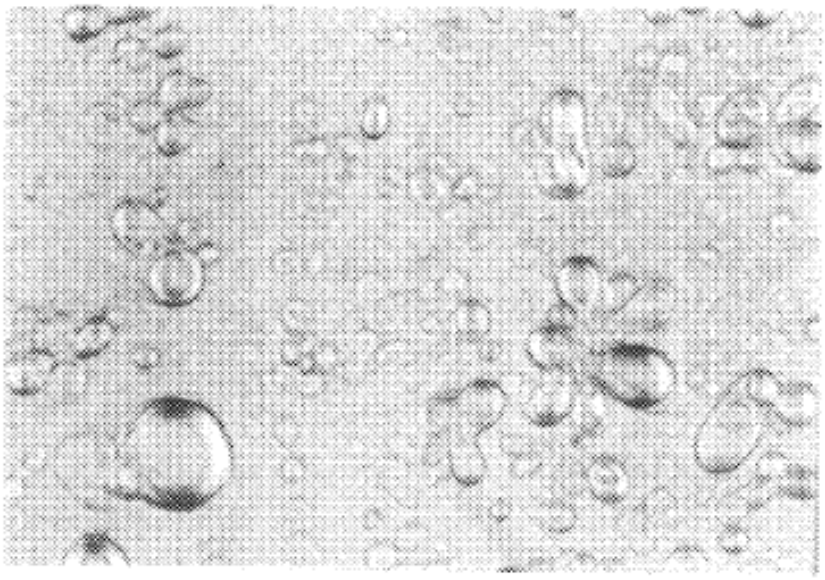


FIG. 2B

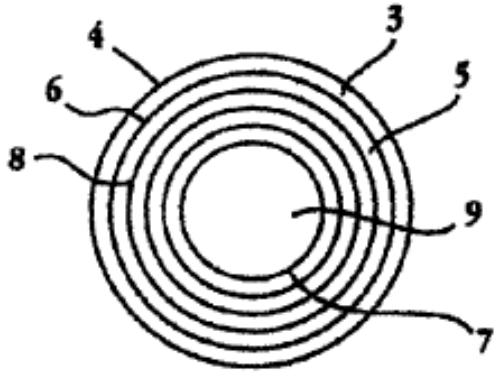


Fig. 3

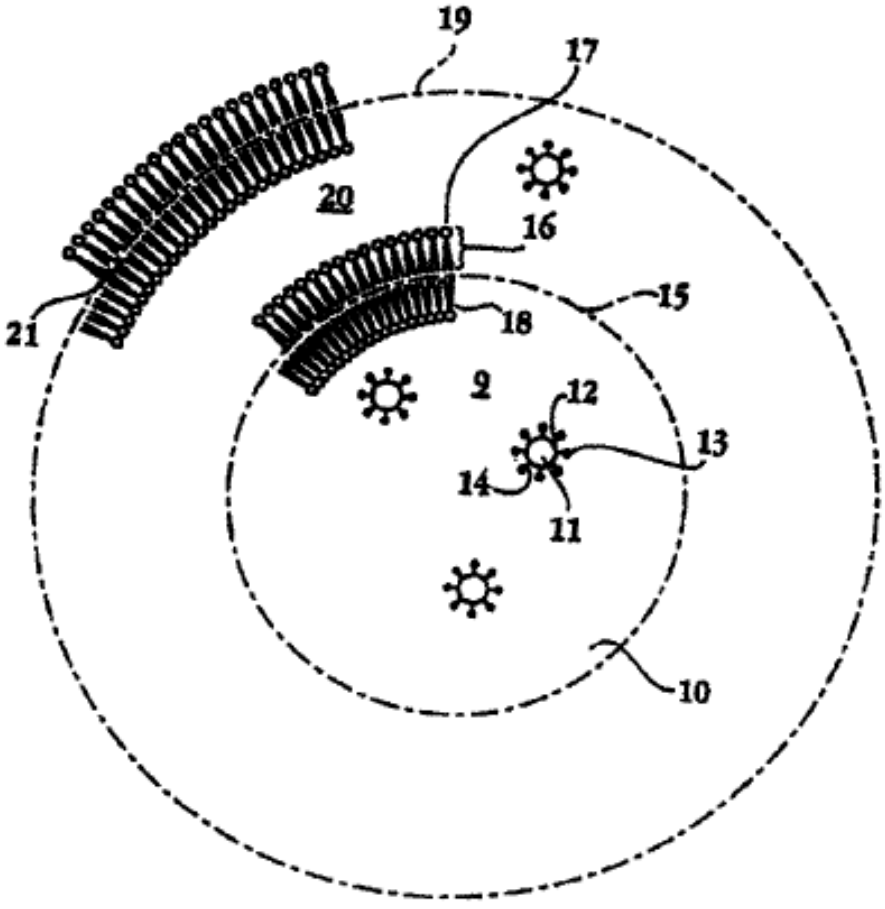


Fig. 4