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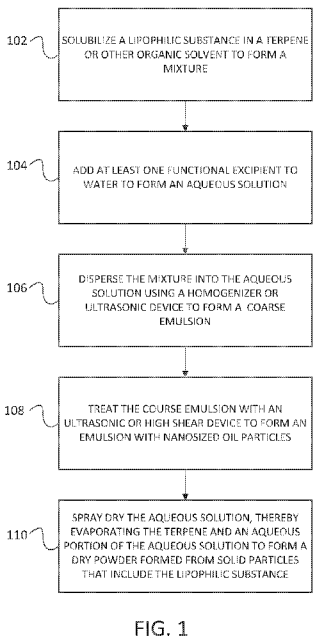


FIG. 1

(57) Abstract: A method of manufacturing a flowable and dispersible powder includes solubilizing a lipophilic substance in a terpene to form a mixture and treating the mixture to form a nanoemulsion dispersed in an aqueous solution. The aqueous solution includes at least one functional excipient. The nanoemulsion is then spray dried, thereby evaporating first the aqueous portion and then the terpene to form a dry powder formed from solid particles comprising the lipophilic substance.

WO 2017/127641 A1

ENCAPSULATION OF LIPOPHILIC INGREDIENTS IN DISPERSIBLE SPRAY DRIED POWDERS SUITABLE FOR INHALATION

BACKGROUND OF THE INVENTION

[0001] Due to their hydrophobic nature and low solubility in water, lipophilic active substances often exhibit poor bioavailability via the oral gastrointestinal (GI) delivery route. Furthermore, accurate and precise dosing is poor for drugs delivered via the GI system due to inherent variability caused by factors such as fasting state and first pass metabolism. As an alternative, pulmonary delivery using a dry powder inhaler (DPI) may be used. Traditional lactose-carrier (lactose blend) formulations for DPIs typically offer low drug loads, commonly less than 6 % (wt/wt), and low delivery efficiencies (DE), typically delivering < 30% of the drug to the lungs. Lactose blends are also highly flow rate dependent, showing significant variability with respect to aerodynamic performance. Once formulated, lactose blends rely on inter-particle forces to bind micronized drug to larger lactose carrier particles to maintain a uniform distribution of drug. This can present challenges during transportation and filling of powder into packages, which impart mechanical energy capable of redistributing or otherwise disturbing blend uniformity.

[0002] Engineered particles (e.g. spray dried) for DPIs offer significant improvements in drug payload, DE, good aerosol performance across a wide flow rates, and a lower risk for segregation of drug from excipients. However, lipophilic drug substances are challenging to encapsulate into dry, flowable, and dispersible powders that are compatible with dry powder inhalers. In addition, oils and fats exhibit poor dissolution and dispersion when incorporated into aqueous systems which are common in the preparation of annex solutions used to produce spray dried powders. This invention relates to new uses for terpenes as non-toxic, natural solubilizers for preparing vehicles (or annex solutions) which may then be spray dried to produce powders comprising various drugs, agricultural chemicals, cosmetics, and foods.

BRIEF SUMMARY OF THE INVENTION

[0003] The present disclosure generally relates to dry powder compositions and methods for administering and preparing such compositions. Embodiments are directed to dry powder compositions in which volatile terpenes are used as processing aids to create nanoemulsions containing lipophilic active substances, which may then be stabilized in dry powder form, and to methods for preparing and using such compounds. One group of such lipophilic active substance are extracts of cannabis, which are commercially available as sticky, resinous oils, or as high purity crystalline forms. The dry powder compositions may include any suitable lipophilic substance. For example, there may be an oil-in-water nanoemulsion composition that includes cannabinoids in the oil fraction that is spray dried to form a dry powder composition. The oil-in-water emulsion compositions may include a hydrophobic amino acid, e.g. leucine, a disaccharide, e.g. trehalose, and/or an oligosaccharide, e.g. inulin. Such dry powder compositions may be administered to a subject via pulmonary inhalation.

[0004] In one aspect, a method of manufacturing a flowable and dispersible powder is provided. The method may include solubilizing a lipophilic substance in a terpene to form a mixture and treating the mixture to form a nanoemulsion dispersed in an aqueous solution. The aqueous solution may include at least one functional excipient. The terpene fraction may include at least one functional excipient. The method may also include spraying drying the nanoemulsion, thereby evaporating at least a portion of the terpene and the majority of the water to form a suitable dry powder formed from solid particles that include the lipophilic substance.

[0005] In another aspect, a method of manufacturing a flowable and dispersible powder includes dissolving a lipophilic ingredient in an organic solvent to form a lipophilic phase and dissolving at least one of a surfactant or an emulsifier in the lipophilic phase. The method may also include dissolving one or more excipients into water to form an aqueous phase and chilling the aqueous phase to between about 1 °C and 10 °C. The method may further include dispersing the lipophilic phase into the chilled aqueous phase to form an emulsion that includes nanosized oil droplets. Alternatively, the emulsion may be prepared by heating the organic and aqueous phases to between 50 and 75 °C. The

method may include spray drying the emulsion to form a dry powder that includes one or more lipophilic ingredients.

[0006] In another aspect, a method of manufacturing a flowable and dispersible powder may include mixing an oil solution with a water solution to form an oil-in-water emulsion composition. The oil solution may include a cannabinoid. The method may also include spray drying the oil-in-water emulsion composition to form a dry powder composition.

[0007] In another aspect, a dry powder composition is provided. The dry powder composition may include a lipophilic component and one or more of a hydrophobic amino acid, a disaccharide, a oligosaccharide, a surfactant, an emulsifier, a stabilizing additive, or a bulking agent. The dry powder composition may have bulk density between 0.05 and 0.30 g/cm^3, tap density between 0.10 and 0.60 g/cm^3, and moisture content below about 10% w/w. The dry powder composition may also include between about 0.01% and 60 % w/w of the lipophilic component.

[0008] In another aspect, a method of aerosolizing a dry powder formulation is provided. The method may include providing a dry powder formulation that has a lipophilic component and one or more of a hydrophobic amino acid, a disaccharide, a oligosaccharide, a surfactant, an emulsifier, a stabilizing additive, or a bulking agent. The dry powder composition may include between about 0.01% and 50 % w/w of the lipophilic component. The method may also include introducing the dry powder formulation to an aerosolization device and introducing the dry powder formulation to a gas stream within the aerosolization device to disperse the dry powder formulation.

[0009] The features and advantages of the present invention will be apparent to those skilled in the art. While numerous changes may be made by those skilled in the art, such changes are within the spirit of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 is a flowchart depicting a process for manufacturing a flowable and dispersible powder according to embodiments.

[0011] FIG. 2 is a flowchart depicting a process for manufacturing a flowable and dispersible powder according to embodiments.

[0012] FIG. 3 is a flowchart depicting a process for manufacturing a flowable and dispersible powder according to embodiments.

[0013] FIG. 4 depicts a schematic of an annex solution that was prepared for spray drying according to embodiments.

[0014] FIG. 5 depicts a graph of a droplet size distribution after processing into a nanosized oil-in-water emulsion according to embodiments.

[0015] FIG. 6 is a plot of an optical particle size distribution of powders spray dried for pulmonary delivery according to embodiments.

[0016] FIG. 7 is a scanning electron microscopy image of spray dried particles containing cannabinoids according to embodiments.

[0017] FIG. 8 is a plot of an optical particle size distribution of powders spray dried for pulmonary delivery according to embodiments.

DETAILED DESCRIPTION OF THE INVENTION

[0018] Embodiments of the present invention relate to dry powder compositions for improved pulmonary, topical, enteral, or parenteral delivery of lipophilic substances, and to methods for the preparation and use of such compositions. More particularly, volatile terpenes are employed as processing aids to achieve dispersion of the lipophilic fraction(s) in a nanoemulsion which is stabilized and encapsulated in functional excipients using a spray drying method. Treatment with nano-sized units of lipophilic drug substances has shown enhanced bioavailability in vivo, as described in T. Yi, J. Wan, H. Xu, X. Yang. A new solid self-microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water soluble drugs. European

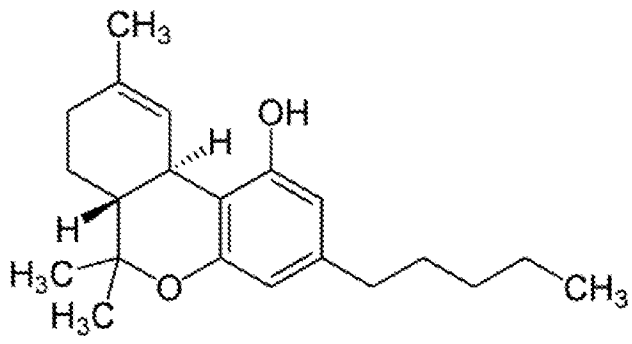
Journal of Pharmaceutics and Biopharmaceutics, Volume 70, Issue 2, October 2008, Pages 439–444 and in S. Gupta, R. Kesarla, A. Omri. Formulation Strategies to Improve the Bioavailability of Poorly Absorbed Drugs with Special Emphasis on Self-Emulsifying Systems. ISRN Pharmaceutics, Dec 2013, the entire contents of which are hereby incorporated by reference. The increase in surface area to volume with decreasing particle size results in greater potential for efficient transport and uptake in the human body. Such lipophilic dry powder compositions may be administered to a subject via pulmonary inhalation in an amount effective to treat and/or prevent a number of conditions, such as systemic and/or lung conditions.

[0019] An inhalable dry powder preparation for lipophilic drug substances offers advantages over oral GI delivery. For example, pulmonary delivery offers a high surface area with rapid absorption due to high vascularization and circumvention of the first pass effect, as described in Sung, J.C.; Pulliam, B.L.; Edwards, D.A. Nanoparticles for drug delivery to the lungs. Trends in Biotechnology. 2007, 25, 563–570, the entire contents of which is hereby incorporated by reference. Rapid drug absorption may be favorable in analgesic, antiemetic, and other medicaments. Further, powder compositions may be engineered such that a controlled fraction of the dose impacts the deep lung (fine particle fraction) while the remainder impacts mucosa in the upper airways. Such a delivery method results in rapid uptake via the lung followed by a slow, sustained release of drug via GI and transmucosal modes. By these means, pharmacokinetics of the product may be modulated.

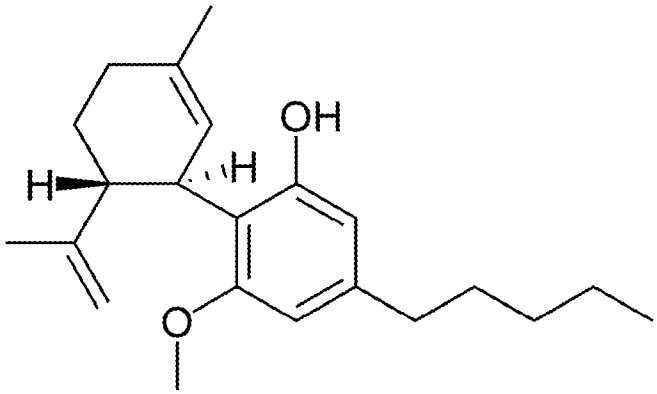
[0020] A formulation and a spray drying technique are used to stabilize lipophilic active ingredients in a dry powder having good flow properties and dispersibility. The lipophilic ingredients are solubilized and/or diluted in carrier terpene(s) and the combined mixture is treated to form a nanoemulsion dispersed in an aqueous solution. The aqueous fraction contains dissolved functional excipients which serve as bulking, encapsulation, stabilizing, and flow enhancement agents. During the spray drying process the aqueous and terpene carrier phases evaporate to form solid particles. The resulting powders exhibit excellent dispersibility into aerosol suitable for pulmonary delivery. Dissolution of powders into aqueous liquids produces a nano-sized dispersion of the oil phase. Such

methods have proven to be very efficient, stable, and exhibit excellent batch to batch consistency.

[0021] Lipophilic ingredients, such as cannabinoid extracts, are commonly available as sticky, viscous concentrates which present processing challenges for discretization into more desirable nano-sized particles. Dissolving these challenging drug substances in solvents reduces surface tension and enables their break up into nano-sized droplets via high shear mechanisms such as ultrasonics or microfluidizers. The inclusion of surfactant in the oil phase stabilizes nano-sized droplets in an emulsion by acting as a barrier against droplet coalescence, thereby enhancing emulsion stability. Formulating with excipients having low aqueous solubility (e.g. leucine), the nano-sized sticky oil phase is encapsulated within a shell which precipitates first during the drying event. This entrapment produces particles having surface characteristics which are dominated by the encapsulating excipient. Use of leucine as an encapsulating excipient has been shown to impart excellent flowability and dispersibility to powders. Cannabinoids are a class of compounds derived from Cannabis plants. At least 113 cannabinoids have been identified in the plant, as described in O. Aizpurua-Olaizola, U. Soydaner, E. Öztürk, et al. Evolution of the Cannabinoid and Terpene Content during the Growth of Cannabis sativa Plants from Different Chemotypes. J. Nat. Prod., 2016, 79 (2), pp 324–331, the entire contents of which is hereby incorporated by reference. The two primary cannabinoids contained in Cannabis are Δ9-tetrahydrocannabinol (THC):



and cannabidiol (CBD):



[0022] Commonly used recreationally, cannabinoids are being used and studied for use in a number of medical conditions including, but not limited to, epilepsy, refractory epilepsy, fragile X syndrome, osteoarthritis, anxiety, chronic pain. Other medical uses may include the treatment of sleep disorders including insomnia, fibromyalgia, spinal injury, phantom limbs, migraines and/or other headaches, cramps, sleep apnea, cancer, muscular dystrophy, HIV/AIDS, glaucoma, hypertension, fatigue, asthma, ALS, lack of appetite, anorexia, cachexia, gastrointestinal disorders, nausea, diabetes, Crohn's, anxiety, ADD/ADHD, stress, bipolar disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), depression, Tourette's, seizures (including Dravet Syndrome), multiple sclerosis, Alzheimer's, Parkinson's, spasticity, osteoporosis, inflammation, arthritis, sexual performance and libido enhancement, and/or symptoms thereof.

[0023] While largely discussed in relation to cannabinoid compositions, it will be appreciated that compositions containing other lipophilic drug substances may be manufactured and/or administered using the methods described herein. Examples of other lipophilic/low solubility drug substances include, but are not limited to, those shown in Table 1 below.

Table 1. Lipophilic/low solubility drug substances

Drug	Solubility (ug/ml)	Class
Alpha tocopherol	0.007	tocopherol
Amphotericin B	82	aminoglycoside
Atorvastatin	0.5	statin

Azithromycin	514	azalide (macrolide antibiotic)
Beclomethasone	2.1	glucocorticoid
Budesonide	46	glucocorticoid
Caspofungin	367	echinocandin
Ciprofloxacin	1350	fluoroquinoline
Clemastine	0.4	antihistamine
Clofazimine	1.5	leprostatic
Cyclosporine	5	immunosuppressant
Dihydroergotamine	229	ergot alkaloid
Dronabinol	2.6	cannabinoid
Dutasteride	0.9	5alpha reductase inhibitors
Erithromycin	459	macrolide antibiotic
Felodipine	7.1	calcium channel blocker
Fentanyl	24	opiate
Flecainide	32	sodium channel blocker
Fluticasone furoate	43.4	glucocorticoid
Fluticasone proprionate	11.4	glucocorticoid
Furosemide	118	loop diuretic
Glycopyrronium	0.95	LAMA
Indacaterol	8	LABA
Itraconazole	9.6	triazole
Loxapine	103	tricyclic antipsychotic
Mometasone	5.2	glucocorticoid
Nimodipine	12	calcium channel blocker
Tacrolimus	4	macrolide immunosuppressant
Tretinoin	4.8	retinoid
Vilanterol	11.8	LABA

[0024] In one embodiment, a composition of the present disclosure is a dry powder that includes cannabinoids. As used herein, the term cannabinoids includes natural derivatives of cannabis or hemp plant, or synthesized analogues. As used herein, the term "dry" means that the composition has a moisture content such that micron-size particles are readily dispersible in an inhalation device to form an aerosol, while larger particles exhibit good flow properties. In some embodiments, this moisture content may be below about 10% by weight water, below about 7% by weight water, below about 5% by weight water or below about 3% by weight water. Furthermore, as used herein, the term "inhalation powder" means a composition that includes finely dispersed solid particles that are capable of being readily dispersed in an inhalation device and

subsequently inhaled by a subject so that the particles reach the lungs to permit penetration into the upper and lower airways. Thus, the powder is said to be "respirable." In some embodiments, a dry powder composition of the present disclosure may have a tap density greater than about 0.1 g/cm^3, greater than about 0.20 g/cm^3 or greater than about 0.4 g/cm^3 and mass median aerodynamic diameter (MMAD) between 1 and 4 μm. While cannabinoids may be predominately used in the descriptions contained in this disclosure, it should be understood that the present disclosure may be practiced with any other substantially lipophilic active and low solubility drug substances (such as those disclosed in Table 1 above), and derivatives and analogues thereof, among other things, to treat various respiratory and systemic conditions.

[0025] In certain specific embodiments, a dry powder composition of the present disclosure comprises cannabinoids present in an amount of between about 1% and 30%, in some cases between about 4% and 15%, and still in other cases about 12% by weight of the composition, the powder having a tap density between about 0.1 g/cm^3 and 0.3 g/cm^3. The dry powder compositions may further include leucine in an amount of between about 10% and 90%, trehalose or inulin of between about 1% and 60%, and surfactant of between about 0.1% and 10% by weight of the composition. In some cases, the dry powder compositions may further include leucine in an amount of between about 40% and 70%, trehalose or inulin of between about 20% and 50%, surfactant of between about 0.1% and 5% by weight of the composition. In still other cases, the dry powder compositions may further include leucine in an amount of about 60%, trehalose or inulin in the amount of about 20%, surfactant in the amount of about 1.5% by weight of the composition. In some embodiments, particles of a dry powder composition may have an average particle size of less than or equal to about 10 micrometers (μm) in diameter as defined by the MMAD. In some embodiments, at least 95% of the particles have a MMAD of less than about 10 μm. In some embodiments, the diameter may be less than or equal to about 7 μm. In other embodiments, the diameter may be less than or equal to about 5 μm. In certain specific embodiments, the diameter may be between about 0.5 μm and about 5 μm in diameter, particularly between about 1 μm to about 3 μm. Dry powder compositions of the present disclosure that include particles having an average particle

size of less than or equal to about 5 μm in diameter may be particularly useful for delivery via an oral inhalation device. In the case of cannabinoids, advantages of pulmonary delivery via DPI approach include rapid absorption similar to smoking or vaporizing but without the health risks associated with these traditional forms of inhaled delivery. Additional advantages include DE's greater than 60% and high dose precision. Aerodynamic properties of a number of powder batches according to the present invention are shown in Tables 2 and 3 below.

Table 2. Mean values (n=3) for physical and aerodynamic properties (Anderson Cascade Impactor and Plastiape RS01 inhaler) of select powder batches containing oily extracts [GSD – geometric standard deviation; FPF – fine particle fraction (powder mass recovered on plates 2 to 7 + powder mass recovered on filter) / (mass emitted from capsule – residual powder mass on inhaler)]

Batch Id	Oil Extract (% wt/wt)	Bulk Density (g/mm^3)	Tap Density (g/mm^3)	D_{50} (um)	MMAD (um)	GSD	ED (%)	FPF (%)	DE (%)
P20150828-2	6.4	0.12	x	2.1	3.4	1.5	82	82	67
P20150828-3	6.4	0.13	x	1.9	2.9	1.8	78	93	72
P20170105-1	7.5	0.12	x	2.2	2.8	1.6	90	95	85
P20170105-2	6.6	0.20	x	2.0	3.3	1.6	86	85	73
P20161222-7	7.4	0.12	x	2.2	2.7	1.8	88	88	78
P20160611-1	12.0	0.06	0.11	1.9	2.4	1.9	95	85	81
P20160611-3	12.3	0.06	0.12	2.2	2.3	2.1	97	93	90
P20160611-7	18.4	0.09	0.16	2.6	3.5	2.0	99	64	64

Table 3. Mean values (n=3) for aerodynamic properties (Anderson Cascade Impactor and Plastiape RS01 inhaler) of batch P20161222-7 tested at two standard flow rates.

Flow Rate (lpm)	MMAD (um)	GSD	ED (%)	FPF (%)	DE (%)
28.3	3.43	1.45	82	82	67
60	2.92	1.77	78	93	72

[0026] In other embodiments, a dry powder composition of the present disclosure may comprise particles having an average particle size of greater than or equal to about 10 μm in diameter as defined by MMAD (measured using cascade impaction). In some embodiments, at least 95% of the particles have a MMAD of greater than about 10 μm. In certain specific embodiments, the particle size may be between about 10 μm and about 50 μm in diameter, particularly about 20 μm to about 40 μm. Dry powder compositions of the present disclosure that include particles having an average particle size of greater than or equal to about 10 μm in diameter may be particularly useful for nasal delivery or for oral solid dosage forms, or as preparations intended to enhance stability of the active component.

[0027] In other embodiments, a dry powder composition may include particles having a broader range, having approximately 90% of the particles between 1 to about 12 μm. This range of particle sizes may be useful for simultaneous delivery of actives to the lungs and upper airways via an oral inhalation device. For example, the finer particles impact the deep lung while the larger particles impact mucosa in the upper airways, resulting in rapid uptake via the lung followed by a slow, sustained release of drug via GI and transmucosal modes. Specifically, a control of size fractions present in a bimodal and/or broad monomodal distribution would allow for control over pharmacokinetic profile. Active lipophilic substances delivered to the lungs would be more rapidly absorbed into the bloodstream, while the fraction deposited on the upper airways would be absorbed more slowly, similar to the absorption of oral solid dosages. This could prospectively result in a fast-acting drug (short Tmax) with sustained drug activity (long half-life).

[0028] In some embodiments, the particles may be hollow. In some embodiments, the particles may be porous, having a sponge-like appearance. In some embodiments, the particles may have a spheroidal shape distribution, which may be relatively uniform. In other embodiments the particles are corrugated, appearing as wrinkled raisins. In cannabinoid embodiments, the potency as measured by select cannabinoid concentration is effectively unchanged when compared to the unformulated drug (i.e. within 10% of the unformulated drug).

[0029] Administration of an effective amount of a cannabinoid composition, including tetrahydrocannabinol (THC), tetrahydrocannabinolic acid (THCa), cannabidiol (CBD), cannabidiolic acid (CBDa), cannabinol (CBN), cannabichromene (CBC), cannabigerol (CBG) and others, of the present disclosure may be particularly useful in treating conditions including, but not limited to, pain, cancer, HIV, seizures, spasticity, multiple sclerosis, muscular dystrophy, Parkinson's, Tourette syndrome, Huntington's disease, Alzheimer's, glaucoma, anxiety, anorexia, cachexia, PTSD, OCD, inflammation, insomnia, arthritis, lupus, neurodegenerative diseases, and sexual performance disorders.

[0030] When heated during smoking or vaping, cannabinoid acids such as THCa and CBDa decarboxylate to form THC and CBD. Due to the relatively low temperatures employed in the spray drying process (i.e. < 80 °C), production of powders containing cannabinoid acids (e.g. THCa, CBDa) of interest would be feasible.

[0031] In cannabinoid embodiments, suitable forms of lipophilic drug substances include oils, resins, and crystals which may be used to formulate dry powder products. These drug substances may be produced by any number of commercially available methods including solvent (e.g. butane, propane, hexane) and supercritical extraction (e.g. CO_2). The resultant drug substances may be comprised of 40-99.9 % cannabinoids. Synthetic cannabinoids, such as the THC MARINOL® (dronabinol), may also be included.

[0032] In some embodiments, in addition to lipophilic drugs, a composition of the present disclosure may further include one or more additives. One example of a suitable additive is a hydrophobic amino acid. Such hydrophobic amino acids may include, but

are not limited to, tryptophan, tyrosine, leucine, dileucine, trileucine and phenylalanine. In some embodiments, it may be desirable to include a hydrophobic amino acid in a lipophilic composition so as to improve the physical stability and/or dispersibility of the composition, to improve the chemical stability of cannabinoids and/or to alter the taste of the composition by masking the bitter taste of cannabinoids, and/or to alter the rate the composition is absorbed into the systemic circulation from the lung (e.g., increase or slow the rate of absorption). While not wishing to be bound to any particular theory, it is currently believed that the hydrophobic amino acid additive remains on the surface of the particles and protects them from moisture and light, thereby increasing the stability of the formulation.

[0033] Another suitable additive may be a cellulose based polymer and/or a polymeric agent used to modify surface properties. Such polymeric agents may include, but are not limited to, hyaluronic acid, polyethyleneglycol, hydroxypropylmethylcellulose (HPMC) and methylcellulose (MC). In some lipophilic dry powder embodiments, it may be desirable to include cellulose based polymers to improve the physical stability, powder handling, and/or dispersibility of the composition, to improve the chemical stability, and/or to alter the rate the composition is absorbed into the systemic circulation from the lung (e.g., increase or slow the rate). While not wishing to be bound to any particular theory, it is currently believed that the cellulose based polymer additive remains on the surface of the particles and protects them from moisture and light, thereby increasing the stability of the formulation.

[0034] Another example of a suitable additive is a carbohydrate bulking agent. Such carbohydrate bulking agents may include, but are not limited to, lactose, mannitol, trehalose, raffinose, and maltodextrins. In some embodiments, it may be desirable to include a carbohydrate bulking agent in a composition of the present disclosure so as to improve the physical stability of the composition. Furthermore, in some embodiments, the carbohydrate bulking agent may also improve the chemical stability of cannabinoids or lipophilic substances.

[0035] Another suitable additive is a volatile terpene. Such terpenes may include, but are not limited to, d-limonene, other grades of limonene, and beta-myrcene. Naturally

occurring and refined cannabinoid substances may contain over 100 terpenes, as described in Turner C. E., M. A. Elsohly and E. G. Boeren, 1980. Constituents of Cannabis sativa L. XVII. A review of the natural constituents. Journal of Natural Products 43 (2): 169-234 and in R. Brenneisen, M.A ElSohly. Marijuana and the Cannabinoids, Chapter 2, p. 28, the entire contents of which are hereby incorporated by reference. In some embodiments, it may be desirable to include additional terpenes to aid in the processing of viscous lipophilic active substances into nanometer sized droplets dispersed in an aqueous phase prior to powder production via spray drying. The active lipophilic substance is dissolved into the terpene and then sequentially processed into nano/micrometer scale oil in water emulsions using homogenizers (e.g. Ultra-Turrax, IKA) or ultrasonic methods (e.g. Sonifier, Branson). Further refinement into nanometer scale (D_{50} of 0.1 to 0.5 μm) oil-in-water emulsions is accomplished using ultrasonic (e.g. Sonifier, Branson) and/or high shear (e.g. M110Y, Microfluidics) equipment operated according to common practiced methods. In some embodiments, it may be desirable to incorporate surfactant(s) into the active oil/terpene mixture to stabilize emulsion droplet size during processing. While not wishing to be bound to any particular theory, it is currently believed that, like water, the terpenes are largely fugitive during the spray drying process and that residual added terpenes used for processing are minimal in the dried powder compositions. It will be apparent to experts in the field that the use of other fugitive or volatile elements is not restricted to terpenes and that other volatiles may be contemplated.

[0036] Surfactants and/or emulsifiers may be used to stabilize the active/solvent phase as an oil in water emulsion having nanometer sized droplets. Examples of stabilizing additives include non-ionic detergents, nonionic block copolymers, ionic surfactants, phospholipids (including DSPC), citrates (including sodium citrate and dylauryl citrate), polysorbates, sorbitan laurate, polyglyceryl-4 laurate, and cyclic oligosaccharides (e.g. alphadextrin and beta-cyclodextrin). Other additives known to those of ordinary skill in the art may also be included.

[0037] Generally, additives suitable for use in the compositions of the present disclosure may be included in an amount of about 99% or less by weight of the dry

powder composition, 90% or less by weight of the composition, or 75% or less by weight of the composition. In other embodiments, additives suitable for use in the compositions of the present disclosure may be included in an amount of from about 75% to about 99% by weight of the composition. In other embodiments, additives suitable for use in the compositions of the present disclosure may be included in an amount of from about 10% to about 20% by weight of the composition.

[0038] The compositions of the present disclosure may further include pharmaceutically acceptable auxiliary substances or adjuvants, including, without limitation, pH adjusting and buffering agents and/or tonicity adjusting agents, such as, for example, citrate, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, etc. Similarly, the compositions of the present disclosure may contain pharmaceutically or nutritionally acceptable carriers and excipients including microspheres, microcapsules, nanoparticles or the like.

[0039] In certain embodiments, the dry powder composition may be reconstituted and the resulting reconstituted powder may have a pH greater than 3.0, preferably greater than 3.5 and most preferably greater than 4.0. Reconstitution may be done by introducing a solvent, such as water or an acidic compound, to the dry powder composition to form the reconstituted formulation. This formulation may be usable with liquid aerosolizers, nebulizers, injectables (e.g. parenteral, intradermal, subcutaneous, intramuscular, intraosseous, intraperitoneal, intravenous) oral liquid dosage forms (e.g. syrup, oral suspension, oral solution, oral drop, oral emulsion, mixture, linctuse, elixir), and/or other administration techniques.

[0040] An inhalation powder composition of the present disclosure may be delivered to a subject by any means so long as the solid particles of the dry powder composition are capable of being inhaled by a subject so that the particles reach the lungs to permit penetration into the upper and lower airways. In certain embodiments, a dry powder composition of the present disclosure may be delivered to a subject by placing the dry powder within a suitable dosage receptacle in a sufficient amount. Suitable dosage receptacles include those used in reservoir devices (e.g., devices that contain more than one dose in which the device itself meters the dose) or factory- metered dose devices

(e.g., devices in which each dose is contained in either a single unit or multiple units). In one example, a suitable reservoir device may have a dosage receptacle that fits within a suitable inhalation device to allow for the aerosolization of the dry powder composition by dispersion into a gas stream to form an aerosol and then delivering the aerosol so produced from a mouthpiece attached for subsequent inhalation by a subject in need of treatment. Such a dosage receptacle includes any container enclosing the composition known in the art such hydroxypropyl methyl cellulose or polymer capsules with a removable portion or body that can be cut or pierced that allows dispersal of the dry powder composition (e.g., via a gas stream directed into the container and via centrifugal force). Such containers are exemplified by those shown in U.S. Pat. No. 4,227,522, U.S. Pat. No. 4,192,309, and U.S. Pat. No. 4,105,027, the entire contents of which are hereby incorporated by reference.

[0041] Suitable containers also include those used in conjunction with Plastiape's RS series of inhalers, GlaxoSmithKline's Ventolin Rotahaler brand powder inhaler and/or Fisons' Spinhaler brand powder inhaler. Another suitable unit-dose container which provides a superior moisture barrier is formed from an aluminum foil plastic laminate. The powder composition is filled by weight or by volume into the depression in the formable foil and hermetically sealed with a covering foil-plastic laminate. Such a container for use with a powder inhalation device is described in U.S. Pat. No. 4,778,054 and is used with GlaxoSmithKline's Diskhaler (U.S. Pat. Nos. 4,627,432; 4,811,731; and 5,035,237), the entire contents of which are hereby incorporated by reference. Another such container and powder inhalation device including a vibrating mechanism is described in U.S. Pat. No. 9,132,246, the entire contents of which are hereby incorporated by reference. Yet another suitable delivery system would be a single use disposable device where the dry powder is pre-packaged within the device. In other embodiments, a dry powder composition of the present disclosure may be delivered to a subject via a tracheal tube.

[0042] In some embodiments, compositions of the present disclosure may be prepared by spray drying an oil-in-water emulsion containing cannabinoids or other lipophilic ingredients and pharmaceutically acceptable carrier(s) under conditions sufficient to

provide a respirable dry powder composition. In some embodiments, the dry powder composition is substantially amorphous.

[0043] Dry powder formulations are often prepared by spray drying. Spray drying of the formulations is carried out, for example, as described in the "Spray Drying Handbook", 5th ed., K. Masters, John Wiley & Sons, Inc., NY, N.Y. (1991) and in Platz, R. et al., U.S. Pat. No. 6,592,904, the entire contents of which are hereby incorporated by reference. Generally speaking, spray drying is a process in which a mixture, suspension, or hybrid of soluble and insoluble ingredients and excipients is atomized via a nozzle to form fine droplets which are introduced into and mixed with a hot gas or other fluid stream. For the atomization process, methods such as rotary atomization, pressure atomization and two-fluid atomization can be used. Examples of suitable devices are disclosed in U.S. Pat. No. 6,372,258, the entire contents of which are hereby incorporated by reference. The mixture prepared for spray drying, or annex solution, may be an emulsion, a solution, suspension, slurry, or the like, but care must be taken such that its constituents uniformly distributed and, ultimately, the powdered composition. Preferably the aqueous mixture is a solution. In some embodiments, the aqueous mixture may have a solids content of at least 1% by weight water. In other embodiments, the aqueous mixture may have a solids content of at least 2% by weight water. In other embodiments, the aqueous mixture may have a solids content of at least 4% by weight water. The solvents, water, and terpenes, evaporate from the droplets producing a dry powder containing the lipophilic ingredient and any excipients. The powder is pneumatically conveyed via ducts from the drying chamber to a collection system where it is separated from the drying gas stream. Suitable powder collection systems include bag house type filters, cyclones, and electrostatic separators.

[0044] In some embodiments, the spray drying is done under conditions that result in a substantially amorphous powder of homogeneous constitution having a particle size that is respirable, has a low moisture content, and has characteristics that allow for ready aerosolization. In some embodiments, the particle size of the resulting powder is such that more than about 95% of the mass is in particles having a diameter of about 10 μm or less. Powder production by spray drying may be scaled-up from lab to pilot-scale batch

sizes. The process can produce up to kilogram quantities of powder per day at high yield (> 80%) and with no loss in purity and little to no loss in potency (<5%).

[0045] By increasing the percentage of solids in the annex solution (nanoemulsion), other dry powder cannabinoid compositions suitable for oral delivery forms, incorporation into edibles, or for long term storage at room temperature, can be produced at high yields (85-99%) by spray drying, or more preferably by granulation. Such powders exhibit excellent chemical stability and good flow properties. The optical particle size distribution for such powders is in the 5-100 μm range. Ingredients suitable for producing a 100 g batch of such a powder may include, for example, leucine (8 g), trehalose (70 g), d-limonene (48 g), DSPC (3.5 g), citrate (0.5 g) supercritically extracted cannabis oil containing 30 % CBD (or another lipophilic substance) (18 g), and water (400 g).

[0046] In some embodiments, dry powder compositions may be prepared by other processes such as lyophilization and jet milling as disclosed in WO 91/16038, the entire disclosure of which is hereby incorporated by reference. A number of formulation and processing strategies may be useful to improve, among other things, the storage and stability properties of the dry powder cannabinoid compositions of the present disclosure. In certain embodiments, the cannabinoids used may be chosen to be of a higher purity. In other embodiments, steps may be taken to avoid oxidation of cannabinoids. For example, processing and packaging of the composition may be performed under argon or nitrogen. Similarly, in some embodiments the processing and packaging may be performed to minimize exposure to direct light. Such steps may reduce light-mediated degradation of cannabinoids. In some embodiments, steps such as post spray drying treatment in a vacuum oven may be taken to reduce the amount of moisture or residual terpenes in the composition. Such steps may be useful to avoid hydrolysis, deamidation, and/or oxidation of cannabinoids or other lipophilic actives. As mentioned above, a carbohydrate bulking agent or encapsulation additives may be added to the composition, which also may improve chemical stability.

[0047] Furthermore, while the dry powder lipophilic drug substance compositions of the present disclosure have many advantageous properties in certain embodiments. One

particularly advantageous property is that the compositions may have a pharmacokinetic profile that is favorable for treatments where rapid uptake and rapid onset of effect is desirable and/or where a prolonged high concentration of drug in the lung or bloodstream is preferable. Advantages in the in vivo pharmacokinetic profiles of cannabinoids, e.g. CBD, THC, CBN, as described in the examples given in this invention, whereby referring to a specific cannabinoid, may be assumed to be similarly advantageous for other cannabinoids.

[0048] For example, in certain cannabinoid embodiments, therapeutic value (plasma concentrations of between approximately 10 and 200 ng/mL) is achieved within 4 to 8 minutes after administration via inhalation. The maximum concentration of THC-COOH (Tmax) may be less than or equal to about 30 minutes, less than or equal to about one hour, or less than or equal to about six hours. In some embodiments, median Tmax may be between about three minutes and three hours. Similarly, in certain embodiments, the median amount of time necessary for blood plasma levels of a subject to decrease to one half of the total maximum concentration of THC-COOH ($T_{1/2}$) may be greater than two hours. In some embodiments, $T_{1/2}$ may be about three hours.

[0049] In certain embodiments, upon administration of a dry powder THC composition to a subject, the mean maximum blood plasma concentration of THC-COOH (Cmax) may be within the range of about 50% to about 150% of about n x 70 ng/mL, wherein n represents a factor to be multiplied and may be a value from 0.01 to 10 and when n =1, the dose is 1 mg.

[0050] In one particular embodiment, a dry powder composition having THC present in an amount of about 1mg may provide a mean maximum blood plasma concentration of THC-COOH within the range of about 50% to about 150% of about 70 ng/mL as measured following a single pulmonary administration. As would be recognized by one of skill in the art, for dry powder compositions containing lower or higher concentrations of THC than 1 mg, the above ranges may be adjusted directly proportionally by the dose. Accordingly, in certain embodiments the present disclosure also provides compositions where the THC or other cannabinoid is present in the dry powder composition in an amount of about n x 1 mg. The dry powder composition provides a mean maximum

blood plasma concentration of THC-COOH (Cmax) within the range of about 50% to about 150% of about n x 70 ng/mL. The maximum blood plasma concentration of THC-COOH is measured following a single pulmonary administration of the dry powder composition where n represents a factor to be multiplied and may be a value from 0.01 to 10.

[0051] In some embodiments, the dry powder cannabinoid compositions of the present disclosure may provide average delivery efficiencies (DEs) (ED*FPF) between 40 % and 90 %. In other embodiments, the dry powder cannabinoid compositions of the present disclosure may provide average delivery efficiencies between 70 % and 90 %. Delivery efficiency is the emitted dose (ED) (%) (i.e., the amount of the dry powder that exits the inhaler as a percentage of the initial amount of the dry powder present in the capsule) multiplied by the fine particle fraction (%) (i.e., respirable amount or the amount of the dry powder having a MMAD of 5.8 μm or less as a percentage of the emitted dose). In other words, ED is equivalent to (powder mass packaged in capsule – residual powder mass in capsule after actuation – residual powder mass on inhaler) / (powder mass packaged in capsule).

[0052] In some embodiments, the dry powder cannabinoid compositions of the present disclosure may provide a bioavailability of 40% or more. Bioavailability is herein defined fraction of a packaged dose of drug that reaches the systemic circulation by either pulmonary, mucosal, or gastrointestinal absorption.

[0053] Compositions of the present disclosure may be administered to a subject via pulmonary administration in an amount effective to achieve the desired cannabinoid concentration in the blood. Administration of an effective amount of a composition of the present disclosure may be useful in pharmaceutical, medicinal, and recreational cannabis applications.

[0054] As will be recognized by one of ordinary skill in the art, the effective amount needed to treat a particular condition or disease state will depend on the individual, the condition, length of treatment, the regularity of treatment, the type of cannabinoid(s) used, and other factors, but can be readily determined by one of ordinary skill. The

patient can achieve a desired dosage by inhaling or otherwise administering an appropriate amount of the composition.

[0055] **FIG. 1** depicts a flowchart of a process 100 for manufacturing a flowable and dispersible powder. At block 102, the process 100 may include solubilizing a lipophilic substance in a terpene or other organic solvent to form a mixture. The lipophilic substance may include a cannabinoid, budesonide, ciclesonide, cyclosporine, fluticasone, formoterol, mometasone furoate, mycophenolate, rapamycin, salmeterol, tacrolimus, tiotropium, vilanterol trifenatate, and/or derivatives or analogues thereof. Possible cannabinoids include, without limitation, tetrahydrocannabinol (THC), tetrahydrocannabinolic acid (THCa), cannabidiol (CBD), cannabidiolic acid (CBDa), cannabinol (CBN), cannabichromene (CBC), and/or cannabigerol (CBG). At least one functional excipient may be added to water to form an aqueous solution at block 104. The mixture may be dispersed into the aqueous solution using a homogenizer or ultrasonic device at block 106 to form a coarse emulsion. The coarse emulsion may then mixture may then be treated with an ultrasonic or high shear device at block 108 to help form the emulsion with nano-sized oil particles. The terpene may help the lipophilic substance form nano-sized oil droplets in the emulsion. The terpene may include d-limonene, other limonenes, beta-myrcene, and/or other terpenes. In some embodiments, the aqueous solution may include at least one functional excipient. Functional excipients may include, for example, hydrophobic amino acid, a disaccharide, an oligosaccharide, a surfactant, an emulsifier, a stabilizing additive, and/or a bulking agent. The nanoemulsion may be spray dried at block 110, thereby evaporating at least a portion of the terpene and substantially all of the water to form a dry powder formed from solid particles that include the lipophilic substance. As used herein, substantially all may mean that at least 93% of the water is evaporated, in some cases at least 96% of the water is evaporated, and in other cases at least 98% of the water is evaporated. Such dry powder may be administered using a dry powder inhaler and/or be reconstituted for use in other administration techniques.

[0056] In some embodiments, the dry powder composition may have a moisture content below about 10% by weight water, with a preferred range between 1 and 6%.

The dry powder composition may include between about 0.1% and 30% by weight of cannabinoid component. The dry powder composition may have a tap density between about 0.1 g/cm and 0.4 g/cm. In some embodiments, the dry powder composition may include a hydrophobic amino acid, a disaccharide, a oligosaccharide, a surfactant, an emulsifier, a stabilizing additive, and/or a bulking agent. The hydrophobic amino acid may include tryptophan, tyrosine, leucine, dileucine, trileucine, and/or phenylalanine. Surface modifying and flow enhancing agents may include hyaluronic acid, polyethyleneglycol, hydroxypropylmethylcellulose (HPMC) , and/or methylcellulose (MC). In other embodiments, the bulking agent may include lactose, mannitol, trehalose, raffinose, and/or maltodextrins. In some embodiments, the stabilizing additive includes a non-ionic detergent, a nonionic block copolymer, an ionic surfactant, phospholipids, citrates, polysorbates, sorbitan laurate, polyglyceryl-4 laurate, and/or cyclic oligosaccharisdes.

[0057] **FIG. 2** shows a flowchart of a process 200 of manufacturing a flowable and dispersible powder. Process 200 may be similar to process 100, and may include similar steps and include similar chemical components. At block 202, process 200 may include dissolving a lipophilic ingredient in an organic solvent to form a lipophilic phase. The lipophilic ingredient may include one or more of a cannabinoid (which may be a naturally derived cannabinoid a synthetically derived cannabinoid, and/or a combination thereof), budesonide, ciclesonide, cyclosporine, fluticasone, formoterol, mometasone furoate, mycophenolate, rapamycin, salmeterol, tacrolimus, tiotropium, vilanterol trifenatate, and/or derivatives or analogues thereof. The lipophilic ingredient may also, or alternatively, include an extract of hops, an extract of sage (Salvia officinalis/lavandulaefolia), rosmarinic acid, a polyphenolic compound, caffeic acid, and/or nicotine. In some embodiments, the lipophilic ingredient includes at least two of the above substances. In some embodiments, each of the lipophilic substances is encapsulated in a unique domain, while in other embodiments, the multiple lipophilic substances are encapsulated in domains as a mixture. Improved delivery efficiency of combination therapeutics may be possible with the approach presented herein. It may also present a new pathway to repurpose existing drugs or offer new processing options

to address past formulation problems. Optionally, formulating combination products in this manner could enable multiple drugs (dual, triple, and so on) to be processed in separate lipophilic fractions which may limit or prevent degradation due to chemical incompatibility. In cases where lipophilic and hydrophilic combinations are desired, the respective fractions may be formulated and spray dried to produce a single particle of the combination drugs. Still in other cases an insoluble or sparingly soluble micronized drug could be introduced to the lipophilic fraction to segregate it from chemically incompatible active or inactive components. Examples of combination products (two or more APIs) include Combivent Respimat® (albuterol + ipratropium), Advair Diskus® (fluticasone + salmeterol), Symbicort HFA® (budesonide + formoterol), Utibron™ Neohaler® (indacaterol + glycopyrronium), and Flutiform® (fluticasone propionate + formoterol fumarate). The organic solvent may include a terpene, such as d-limonene, other limonenes, and/or beta-myrcene. Other organic solvents may include an alcohol such as ethanol or methanol. In some embodiments, the lipophilic ingredient is combined with the organic solvent in a ratio of less than 1.0 by weight.

[0058] At block 204, at least one of a surfactant or an emulsifier is dissolved in the lipophilic phase. Emulsifiers may include non-ionic detergents, nonionic block copolymers, ionic surfactants, and/or combinations thereof. Other emulsifiers may include phospholipids, polysorbates, sorbitan laurate, polyglyceryl-4 laurate, dylauryl citrate, and/or combinations thereof. In some embodiments, the emulsifier may include a cyclic oligosaccharide, such as an alphadextrin and/or beta-cyclodextrin. At block 206, one or more excipients are dissolved into water to form an aqueous phase. Stability of the nanoemulsion may be enhanced by adjustments to pH by the introduction excipients such as citrate or sodium citrate. The lipophilic phase is dispersed into theaqueous phase at block 208 to form an emulsion that includes nano-sized oil droplets. This dispersing may include the use of ultrasonic homogenization and/or high pressure/high shear homogenization. In some embodiments, the emulsion may be formed in a continuous, inline manner such that emulsifiers are not required. Such an emulsion may be rapidly fed into a spray dryer. The nanosized droplets have a droplet size d_{50} between about 20

nm and 1 μm, a droplet size d_{50} between about 20 and 500 nm, or a droplet size d_{50} between about 50 and 300 nm.

[0059] The emulsion may include a matrix forming excipient. Matrix forming excipients may include an oligosaccharide, such as inulin. In some embodiments, the matrix forming excipients include a saccharide and/or a polysaccharide. The emulsion may further include an encapsulating excipient, such as an amino acid like leucine.

[0060] The emulsion may be spray dried to form a dry powder that includes the lipophilic ingredient at block 210. The emulsion may also be sonified with an ultrasonic horn operating in pulse mode. Droplets formed during the spray drying may be atomized using a multi-fluid atomizer and at least one fluid utilized by the multi-fluid atomizer may be a compressed gas. In some embodiments, the dry powder includes between about 0.01% and 50% w/w of the lipophilic ingredient.

[0061] **FIG. 3** depicts a flowchart of a process 300 of manufacturing a flowable and dispersible powder, similar to processes 100 and 200 described above. Process 300 may include mixing an oil solution with a water solution (or other solvent) to form an oil-in-water emulsion composition at block 302. The oil solution may include a cannabinoid or other lipophilic ingredient. The oil-in-water emulsion composition may include at least one of a hydrophobic amino acid, a disaccharide, and/or a oligosaccharide. The oil-in-water emulsion composition may be spray dried to form a dry powder composition at block 304. This dry powder composition may be administered, such as by pulmonary inhalation, in the treatment of a number of systemic and/or lung conditions.

[0062] To facilitate a better understanding of the present invention, the following examples of certain aspects of some embodiments are given. In no way should the following examples be read to limit, or define, the entire scope of the invention. Additionally, the processes for manufacture and administration of the dry powder compositions described herein may include additional steps, have steps omitted, and/or steps combined.

EXAMPLE 1

[0063] An annex solution (feedstock) for spray drying into dry powder was prepared in two portions: a lipophilic phase preparation and an aqueous phase preparation. The preparation of the lipophilic phase involved dissolving a lipophilic active ingredient (hops oil extract) into an organic solvent (d-limonene) followed by dissolving a surfactant (emulsifier) into the lipophilic/solvent mixture. The aqueous phase preparation involved selecting excipients (e.g. amino acids, carbohydrates, disaccharides, oligosaccharides, cellulose) and dissolving these excipients into water at or near 20 °C, or at higher temperatures depending on excipient solubility.

[0064] The lipophilic phase preparation was dispersed into the aqueous phase preparation to form an emulsion 400 that includes nanosized oil droplets 402 distributed within aqueous phase preparation 404 as shown in **FIG. 4**. The majority of oil droplets 402 ranged between about 0.01 nm and 0.3 nm. The particle size distribution for the oil droplets 402 as determined by Malvern Mastersizer 3000 with HydroMV is shown in **FIG. 5**. The particle size distribution included the following values: D_{10} (um) = 0.103; D_{50} (um) = 0.205; and D_{90} (um) = 0.453. The emulsion containing nano-particles was formed using common practices such as ultrasonic and/or high pressure homogenizer techniques. The resultant annex solution was spray dried into dry powder which had D_{10} (um) = 1.0; D_{50} (um) = 2.2; and D_{90} (um) = 4.1. Capsules filled with powder (10 mg target) were aerosol tested (ACI at 28.3 lpm) with the RS01 inhaler were found to have MMAD (um) = 3.3, FPF =85%, and DE = 73%.

[0065] "Active substances" or "active ingredient" as described herein includes a lipophilic agent, drug, compound, composition of matter or mixture thereof which provides some pharmacological, nutraceutical, or nutritional action.

EXAMPLE 2

[0066] As in Example 1, an annex solution (feedstock) for spray drying into dry powder was prepared in two portions: a lipophilic phase preparation and an aqueous phase preparation. The preparation of the lipophilic phase involved dissolving a lipophilic active ingredient into an organic solvent followed by adding a surfactant (emulsifier) into the lipophilic/solvent mixture. The aqueous phase preparation involved

selecting excipients (e.g. amino acids, carbohydrates, disaccharides, oligosaccharides, cellulose, acids) and dissolving these excipients into water at or near 20 °C, or at higher temperatures depending on excipient solubility.

[0067] The aqueous and lipophilic preparations were heated to between about 60 °C and 70 °C. The lipophilic phase preparation was then dispersed into the aqueous phase preparation to form an emulsion 400 that includes nanosized oil droplets 402 distributed within aqueous phase preparation 404. The majority of oil droplets 402 ranged between about 0.01 nm and 0.3 nm. The droplet size distribution as measured by Malvern Mastersizer 3000 with HydroMV included the following values: D_{10} (um) = 0.2; D_{50} (um) = 0.3; and D_{90} (um) = 0.5. The emulsion containing nano-particles was formed using common practices such as ultrasonic and/or high pressure homogenizer techniques. The resultant annex solution was spray dried into a dry powder (7.5 % oil extract content) which had D_{10} (um) = 0.8; D_{50} (um) = 2.0; and D_{90} (um) = 4.0. Capsules filled with powder (10 mg target) were aerosol tested (ACI at 28.3 lpm) with the RS01 inhaler had MMAD(um) = 2.5, FPF = 95 %, and DE = 89 %.

[0068] "Active substances" or "active ingredient" as described herein includes a lipophilic agent, drug, compound, composition of matter or mixture thereof which provides some pharmacological, nutraceutical, or nutritional action.

EXAMPLE 3

[0069] Dry powder cannabinoid compositions suitable for pulmonary delivery were produced using a spray dryer at high yield (80-90%) and at 5 g batch sizes. These powders exhibited very good aerosol performance when actuated via the RS01 inhaler (Plastiape, Italy) as evidenced by mean DE of 68% and fine FPF of 83% as determined by Anderson Cascade Impactor (ACI). Particle size distribution for two batches of spray dried powder is depicted in **FIG. 6**. The particle size distribution included the following values for the first batch: D_{10} (um) = 0.9; D_{50} (um) = 2.1; and D_{90} (um) = 4.6. The particle size distribution included the following values for the second batch: D_{10} (um) = 0.8; D_{50} (um) = 1.9; and D_{90} (um) = 4.1. Particle size distribution was very consistent

across the two batches. A scanning electron micrograph showing particle appearance is shown in **FIG. 7**.

[0070] Ingredients for producing a dry powder composition having approximately 6.4 % by weight cannabinoid active ingredient include leucine (2.9 g), inulin (1.0 g), HPMC (0.15 g), d-limonene (1.1 g), Plantamulse ™ (0.4 g), supercritically extracted cannabis oil containing 90 % THC (0.3 g), and water. The emulsion (annex solution) was prepared in accordance with the process of Example 1.

[0071] A Production Minor (GEA Group, DE) with custom high efficiency cyclone was used to generate and collect the powder. The equilibrium drying condition was established using de-ionized water. When stable operation was achieved, the nozzle input was switched to annex (feedstock) solution. The solution was fed to the dryer until it was depleted and then the nozzle was switched back to water for approximately 5 minutes to clear the system. The collector containing dry powder was exchanged for a clean collector and the dryer was then shut down. The filled collector was rapidly capped on removal to minimize exposure to room humidity. The filled collector was transferred into a low humidity glove box purged with clean dry air or nitrogen where the powder was transferable into other vessels for storage or into capsules and/or other unit dose packets.

EXAMPLE 4

[0072] A carbohydrate bulking agent was included in an oil extract-leucine formulation. The addition of trehalose as a carbohydrate bulking agent can improve the chemical stability of dry-powder cannabinoid compositions of the present disclosure. Additionally, trehalose and DSPC were inserted in the powder formulation based on their inclusion in DPI products approved by the FDA, e.g TOBI® Podhaler™ (Novartis, AG).

[0073] Dry powder oil extract compositions suitable for pulmonary delivery were produced using a Mobile Minor (GEA Group, DE) spray dryer. Capsules filled with these powders (10 mg target) had an MMAD of 2.3 μm and exhibited excellent aerosol performance when actuated via the RS01 inhaler (Plastiape, Italy) as evidenced by FPF of 93 % and DE of 90 %. The particle size distribution for the spray dried powder is

depicted in **FIG. 8**. The particle size distribution included the following values: D_{10} (um) =1.1; D_{50} (um) =2.2; and D_{90} (um) =4.2.

[0074] Ingredients for producing a dry powder composition having approximately 12 % by weight active ingredient include leucine (80 %), trehalose (6.5 %), DSPC (1.5 %), and supercritically extracted oil (12 %). Water and d-limonene were used as solvents. The emulsion (annex solution) was prepared in accordance with the process of Example 1.

EXAMPLE 5

[0075] A carbohydrate bulking agent was included in a cannabinoid-leucine formulation. The addition of trehalose as a carbohydrate bulking agent can improve the chemical stability of dry-powder cannabinoid compositions of the present disclosure. Additionally, trehalose has been incorporated in powder for pulmonary administration products approved by the FDA, e.g TOBI® Podhaler™ (Novartis, AG).

[0076] Dry powder cannabinoid compositions suitable for pulmonary delivery were produced using a Mobile Minor (GEA Group, DE) spray dryer. These powders exhibited very good aerosol performance when actuated via the RS01 inhaler (Plastiape, Italy) as evidenced by mean DE of 68% and fine FPF of 83% as determined by Anderson Cascade Impactor (ACI operated at 28.3 lpm). The particle size distribution for the spray dried powder is depicted in **FIG. 9**. The particle size distribution included the following values: D_{10} (um) =0.5; D_{50} (um) =2.7; and D_{90} (um) =6.0.

[0077] Ingredients for producing a dry powder composition having approximately 5 % by weight cannabinoid active ingredient include leucine (47 %), trehalose (47 %), DSPC (1 %), and supercritically extracted cannabis crystals containing 99 % CBD (5 %). Water and d-limonene were used as solvents. The emulsion (annex solution) was prepared in accordance with the process of Example 1.

WHAT IS CLAIMED IS:

1. A method of manufacturing a flowable and dispersible powder, the method comprising:

solubilizing a lipophilic substance in a terpene to form a mixture;

adding at least one functional excipient to water to form an aqueous solution;

dispersing the mixture into the aqueous solution using one or both of a homogenizer or an ultrasonic device to form a coarse emulsion;

treating the coarse emulsion with one or both of the ultrasonic device or a high shear device to form a nanoemulsion; and

spraying drying the nanoemulsion, thereby evaporating at least a portion of the terpene and substantially all of the water to form a dry powder formed from solid particles comprising the lipophilic substance.

2. The method of manufacturing a flowable and dispersible powder of claim 1, wherein:

the dry powder has a mass median aerosol diameter (MMAD) between 1.5 and 3.5 um, and a fine particle fraction (FPF) and delivery efficiency (DE) greater than 60 %.

3. The method of manufacturing a flowable and dispersible powder of any of claims 1 and 2, wherein:

the dry powder has a moisture content below about 10% by weight water.

4. The method of manufacturing a flowable and dispersible powder of any of claims 1-3, wherein:

the dry powder has a tap density between about 0.1 g/cm^3 and 0.3 g/cm^3.

5. The method of manufacturing a flowable and dispersible powder of any of claims 1-4, wherein:

the lipophilic substance comprises one or more of a cannabinoid, alpha tocopherol, amphotericin B, atorvastatin, azithromycin, beclomethasone, budesonide, caspofungin, ciprofloxacin, clemastine, clofazimine, cyclosporine, dihydroergotamine, dronabinol, dutasteride, erythromycin, felodipine, fentanyl, flecainide, fluticasone furoate, fluticasone propionate, furosemide, glycopyrronium, indacaterol, itraconazole, loxapine, mometasone, nimodipine, tacrolimus, tretinoin, vilanterol, or derivatives or analogues thereof.

6. The method of manufacturing a flowable and dispersible powder of any of claims 1-5, wherein:

the lipophilic substance is dissolved in the aqueous phase and the utility of the lipophilic phase is to impart favorable aerosol characteristics.

7. The method of manufacturing a flowable and dispersible powder of any of claims 1-6, wherein:

the lipophilic substance comprises nicotine.

8. The method of manufacturing a flowable and dispersible powder of any of claims 1-7, wherein:

a plurality of emulsions containing separate drug substances are combined with the aqueous solution and once spray dried, produce combination products.

9. The method of manufacturing a flowable and dispersible powder of any of claims 1-8, wherein:

separate drug substances are contained within the aqueous solution and the mixture and once spray dried, produce combination products.

10. The method of manufacturing a flowable and dispersible powder of any of claims 1-9, wherein:

a plurality of emulsions containing separate drug substances are combined with the aqueous solution and once spray dried, produce combination products.

11. The method of manufacturing a flowable and dispersible powder of any of claims 1-10, wherein:

a plurality of emulsions containing separate drug substances are combined with the aqueous solution and once spray dried, produce combination products.

12. The method of manufacturing a flowable and dispersible powder of any of claims 1-11, wherein:

the dry powder comprises between about 1% and 20% by weight of a cannabinoid.

13. The method of manufacturing a flowable and dispersible powder of claim 12, wherein:

the cannabinoid comprises at least one of tetrahydrocannabinol (THC), tetrahydrocannabinolic acid (THCa), cannabidiol (CBD), cannabidiolic acid (CBDa), cannabinol (CBN), cannabichromene (CBC), or cannabigerol (CBG).

14. The method of manufacturing a flowable and dispersible powder of any of claims 1-13, wherein:

the dry powder further comprises one or more of a hydrophobic amino acid, a disaccharide, a oligosaccharide, a surfactant, an emulsifier, a stabilizing additive, or a bulking agent.

15. The method of manufacturing a flowable and dispersible powder of claim 14, wherein:

the hydrophobic amino acid comprises one or more of tryptophan, tyrosine, leucine, trileucine, or phenylalanine.

16. The method of manufacturing a flowable and dispersible powder of claim 14, wherein:

the stabilizing additive comprises one or more of a non-ionic detergent, a nonionic block copolymer, an ionic surfactant, phospholipids, citrates, sorbitan laurate, polyglyceryl-4 laurate, or cyclic oligosaccharisdes.

17. The method of manufacturing a flowable and dispersible powder of any of claims 1-16, wherein:

the dry powder contains one or more of hydroxypropylmethylcellulose (HPMC) or methylcellulose (MC).

18. The method of manufacturing a flowable and dispersible powder of any of claims 1-17, wherein:

the dry powder comprises one or more of lactose, mannitol, trehalose, raffinose, or maltodextrins.

19. The method of manufacturing a flowable and dispersible powder of any of claims 1-18, wherein:

the terpene comprises one or more of d-limonene, other limonenes, or beta-myrcene.

20. A method of manufacturing a flowable and dispersible powder, the method comprising:

dissolving a lipophilic ingredient in an organic solvent to form a lipophilic phase;

dissolving at least one of a surfactant or an emulsifier in the lipophilic phase;

dissolving one or more excipients into water to form an aqueous phase;

dispersing the lipophilic phase into the aqueous phase to form an emulsion comprising nanosized oil droplets; and

spray drying the emulsion to form a dry powder comprising the lipophilic ingredient.

21. The method of manufacturing a flowable and dispersible powder of claim 20, wherein:

dispersing the lipophilic phase comprises one or more of ultrasonic homogenization or high pressure homogenization.

22. The method of manufacturing a flowable and dispersible powder of any of claims 20 and 21, wherein:

the organic solvent comprises a terpene.

23. The method of manufacturing a flowable and dispersible powder of any of claims 20-22, further comprising:

during spray drying:

maintaining the emulsion between about 1 °C and 10 °C; and

sonifying the emulsion with an ultrasonic horn operating in pulse mode.

24. The method of manufacturing a flowable and dispersible powder of any of claims 20-23, wherein:

the lipophilic ingredient is combined with the organic solvent in a ratio of less than 1.0 by weight.

25. The method of manufacturing a flowable and dispersible powder of any of claims 20-24, wherein:

the organic solvent comprises d-limonene or other limonenes.

26. The method of manufacturing a flowable and dispersible powder of any of claims 20-25, wherein:

the organic solvent comprises beta-myrcene.

27. The method of manufacturing a flowable and dispersible powder of any of claims 20-26, wherein:

the organic solvent comprises an alcohol.

28. The method of manufacturing a flowable and dispersible powder of any of claims 20-27, wherein:

the organic solvent comprises one or more of ethanol, or methanol.

29. The method of manufacturing a flowable and dispersible powder of any of claims 20-28, wherein:

the lipophilic ingredient comprises a naturally derived cannabinoid substance, a synthetically cannabinoid, or a combination thereof.

30. The method of manufacturing a flowable and dispersible powder of any of claims 20-29, wherein:

the lipophilic ingredient comprises one or more of a cannabinoid, alpha tocopherol, amphotericin B, atorvastatin, azithromycin, beclomethasone, budesonide, caspofungin, ciprofloxacin, clemastine, clofazimine, cyclosporine, dihydroergotamine, dronabinol, dutasteride, erythromycin, felodipine, fentanyl, flecainide, fluticasone furoate, fluticasone propionate, furosemide, glycopyrronium, indacaterol, itraconazole, loxapine, mometasone, nimodipine, tacrolimus, tretinoin, vilanterol, or derivatives or analogues thereof.

31. The method of manufacturing a flowable and dispersible powder of any of claims 20-30, wherein:

the lipophilic ingredient comprises at least two substances selected from budesonide, ciclesonide, cyclosporine, fluticasone, formoterol, mometasone furoate, mycophenolate, rapamycin, salmeterol, tacrolimus, taxol, tiotropium, or vilanterol trifenatate; and

each of the at least two substances is encapsulated in a unique domain.

32. The method of manufacturing a flowable and dispersible powder of any of claims 20-30, wherein:

the lipophilic ingredient comprises at least two substances selected from budesonide, ciclesonide, cyclosporine, fluticasone, formoterol, mometasone furoate, mycophenolate, rapamycin, salmeterol, tacrolimus, taxol, tiotropium, or vilanterol trifenatate; and

the at least two substances are encapsulated in domains as a mixture.

33. The method of manufacturing a flowable and dispersible powder of any of claims 20-32, wherein:

the lipophilic ingredient comprises one or more of an extract of hops, an extract of sage (Salvia officinalis/lavandulaefolia), rosmarinic acid, a polyphenolic compound, or caffeic acid.

34. The method of manufacturing a flowable and dispersible powder of any of claims 20-33, wherein:

the dry powder comprises between about 0.01% and 50 % w/w of the lipophilic ingredient.

35. The method of manufacturing a flowable and dispersible powder of any of claims 20-34, wherein:

the emulsifier comprises one or more of non-ionic detergents, nonionic block copolymers, ionic surfactants, or combinations thereof.

36. The method of manufacturing a flowable and dispersible powder of any of claims 20-35, wherein:

the emulsifier comprises one or more of phospholipid, a citrate, sodium citrate, sorbitan laurate, polyglyceryl-4 laurate, dylauryl citrate, or combinations thereof.

37. The method of manufacturing a flowable and dispersible powder of any of claims 20-36, wherein:

the emulsifier comprises a cyclic oligosaccharide.

38. The method of manufacturing a flowable and dispersible powder of claim 37, wherein:

the cyclic oligosaccharide comprises one or more of an alphadextrin or beta-cyclodextrin.

39. The method of manufacturing a flowable and dispersible powder of any of claims 20-38, wherein:

the emulsion comprises a matrix forming excipient.

40. The method of manufacturing a flowable and dispersible powder of claim 39 wherein:

the matrix forming excipient comprises an oligosaccharide.

41. The method of manufacturing a flowable and dispersible powder of claim 40, wherein:

the oligosaccharide comprises inulin.

42. The method of manufacturing a flowable and dispersible powder of claim 39, wherein:

the matrix forming excipient comprises one or both of a saccharide or a polysaccharide.

43. The method of manufacturing a flowable and dispersible powder of claim 42, wherein:

the polysaccharide comprises trehalose.

44. The method of manufacturing a flowable and dispersible powder of any of claims 20-43, wherein:

the emulsion comprises an encapsulating excipient.

45. The method of manufacturing a flowable and dispersible powder of claim 44, wherein:

the encapsulating excipient comprises an amino acid.

46. The method of manufacturing a flowable and dispersible powder of claim 45, wherein:

the amino acid comprises leucine.

47. The method of manufacturing a flowable and dispersible powder of any of claims 20-46, wherein:

the emulsion is formed using one or both of an ultrasonic or high shear technique.

48. The method of manufacturing a flowable and dispersible powder of any of claims 20-46, wherein:

the emulsion is formed in a continuous, inline method such that emulsifiers are not required and the emulsion is rapidly fed into a spray dryer.

49. The method of manufacturing a flowable and dispersible powder of any of claims 20-48, wherein:

the nanosized oil droplets have a droplet size d_{50} between about 20 nm and 1 μm.

50. The method of manufacturing a flowable and dispersible powder of any of claims 20-48, wherein:

the nanosized oil droplets have a droplet size d_{50} between about 20 and 500 nm.

51. The method of manufacturing a flowable and dispersible powder of any of claims 20-48, wherein:

the nanosized oil droplets have a droplet size d_{50} between about 50 and 300 nm.

52. The method of manufacturing a flowable and dispersible powder of any of claims 20-51, wherein:

droplets formed during the spray drying are atomized using a multi-fluid atomizer; and

at least one fluid utilized by the multi-fluid atomizer is a compressed gas.

53. A method of manufacturing a flowable and dispersible powder, the method comprising:

mixing an oil solution with a water solution to form an oil-in-water emulsion composition, the oil solution comprising a cannabinoid;

spray drying the oil-in-water emulsion composition to form a dry powder composition.

54. The method of manufacturing a flowable and dispersible powder of claim 53, wherein:

the oil-in-water emulsion composition comprises at least one of a hydrophobic amino acid, a disaccharide, or a oligosaccharide.

55. A dry powder composition, comprising:

a lipophilic component; and

one or more of a hydrophobic amino acid, a disaccharide, a oligosaccharide, a surfactant, an emulsifier, a stabilizing additive, or a bulking agent, wherein:

the dry powder composition has a tap density greater than about 0.2 g/cm;

the dry powder composition has a moisture content below about 10% by weight water

the dry powder composition comprises between about 0.01% and 50 % w/w of the lipophilic component.

56. A method of aerosolizing a dry powder formulation, the method comprising:

providing a dry powder formulation comprising:

a lipophilic component; and

one or more of a hydrophobic amino acid, a disaccharide, a oligosaccharide, a surfactant, an emulsifier, a stabilizing additive, or a bulking agent, wherein the dry powder composition comprises between about 0.01% and 50 % w/w of the lipophilic component;

introducing the dry powder formulation to an aerosolization device; and

introducing the dry powder formulation to a gas stream within the aerosolization device to disperse the dry powder formulation.

57. The method of aerosolizing a dry powder formulation of claim 56, wherein:

the dry powder composition has a tap density greater than about 0.2 g/cm; and

the dry powder composition has a moisture content below about 10% by weight water.

58. The method of aerosolizing a dry powder formulation of any of claims 56 and 57, wherein:

the lipophilic component comprises one or more of a cannabinoid, alpha tocopherol, amphotericin B, atorvastatin, azithromycin, beclomethasone, budesonide, caspofungin, ciprofloxacin, clemastine, clofazimine, cyclosporine, dihydroergotamine, dronabinol, dutasteride, erythromycin, felodipine, fentanyl, flecainide, fluticasone furoate, fluticasone propionate, furosemide, glycopyrronium, indacaterol, itraconazole, loxapine, mometasone, nimodipine, tacrolimus, tretinoin, vilanterol, or derivatives or analogues thereof.

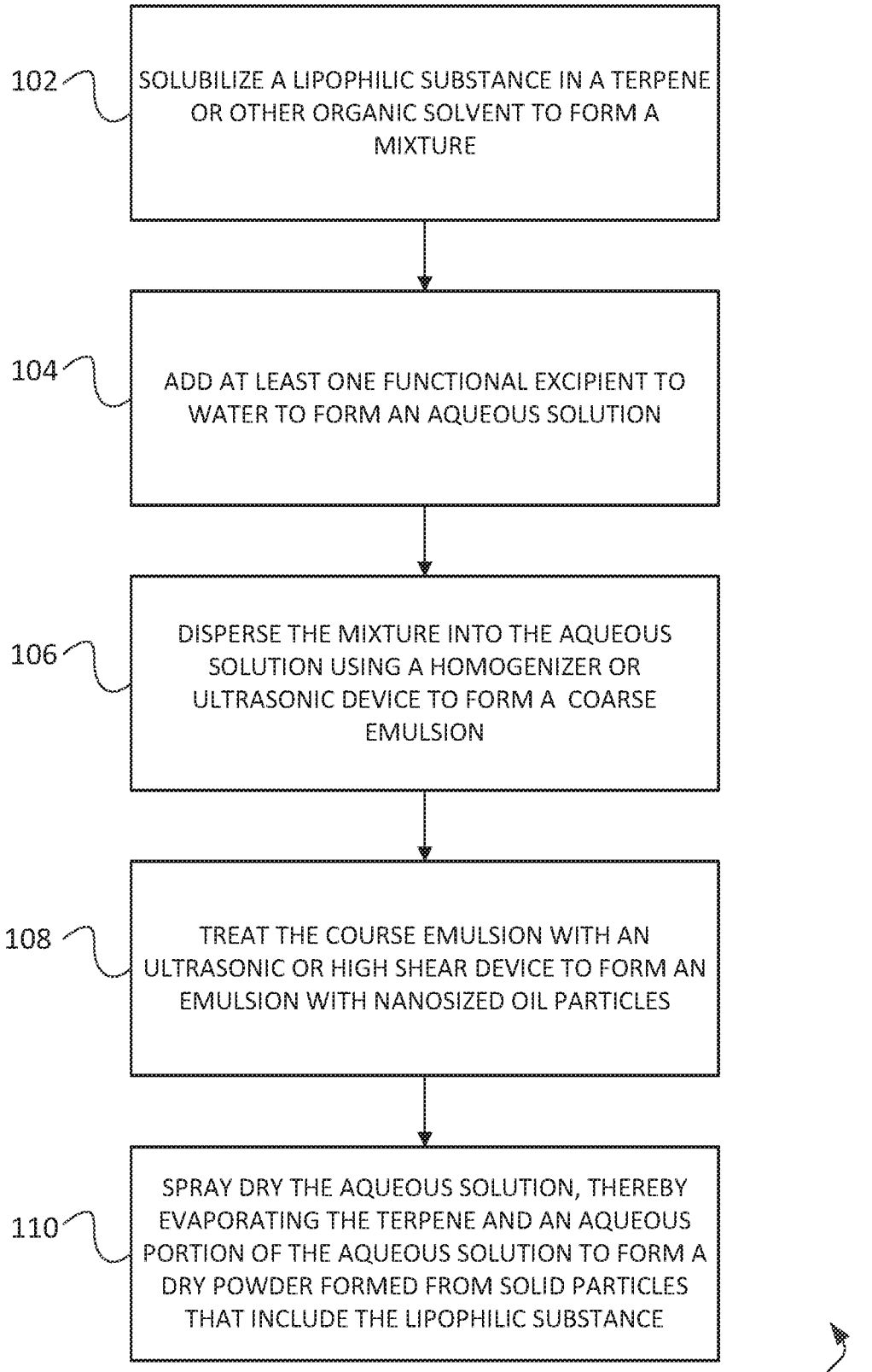

102
SOLUBILIZE A LIPOPHILIC SUBSTANCE IN A TERPENE OR OTHER ORGANIC SOLVENT TO FORM A MIXTURE
104
ADD AT LEAST ONE FUNCTIONAL EXCIPIENT TO WATER TO FORM AN AQUEOUS SOLUTION
106
DISPERSE THE MIXTURE INTO THE AQUEOUS SOLUTION USING A HOMOGENIZER OR ULTRASONIC DEVICE TO FORM A COARSE EMULSION
108
TREAT THE COURSE EMULSION WITH AN ULTRASONIC OR HIGH SHEAR DEVICE TO FORM AN EMULSION WITH NANOSIZED OIL PARTICLES
110
SPRAY DRY THE AQUEOUS SOLUTION, THEREBY EVAPORATING THE TERPENE AND AN AQUEOUS PORTION OF THE AQUEOUS SOLUTION TO FORM A DRY POWDER FORMED FROM SOLID PARTICLES THAT INCLUDE THE LIPOPHILIC SUBSTANCE
100

FIG. 1

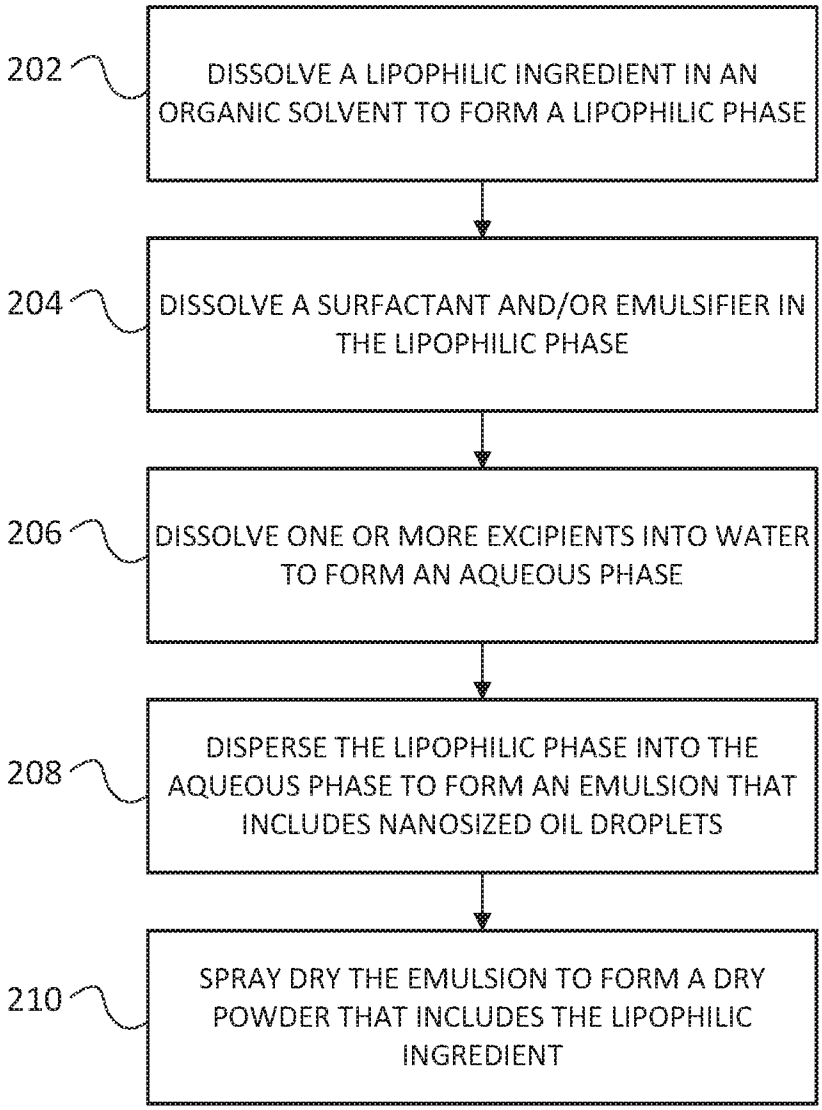

202
DISSOLVE A LIPOPHILIC INGREDIENT IN AN ORGANIC SOLVENT TO FORM A LIPOPHILIC PHASE
204
DISSOLVE A SURFACTANT AND/OR EMULSIFIER IN THE LIPOPHILIC PHASE
206
DISSOLVE ONE OR MORE EXCIPIENTS INTO WATER TO FORM AN AQUEOUS PHASE
208
DISPERSE THE LIPOPHILIC PHASE INTO THE AQUEOUS PHASE TO FORM AN EMULSION THAT INCLUDES NANOSIZED OIL DROPLETS
210
SPRAY DRY THE EMULSION TO FORM A DRY POWDER THAT INCLUDES THE LIPOPHILIC INGREDIENT

FIG. 2

200

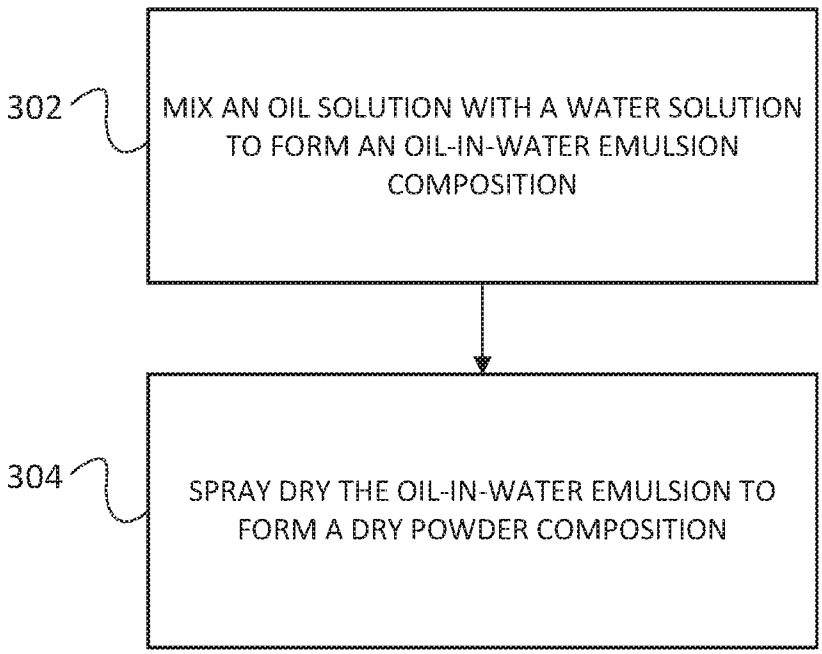

302
MIX AN OIL SOLUTION WITH A WATER SOLUTION TO FORM AN OIL-IN-WATER EMULSION COMPOSITION
304
SPRAY DRY THE OIL-IN-WATER EMULSION TO FORM A DRY POWDER COMPOSITION

FIG. 3

300

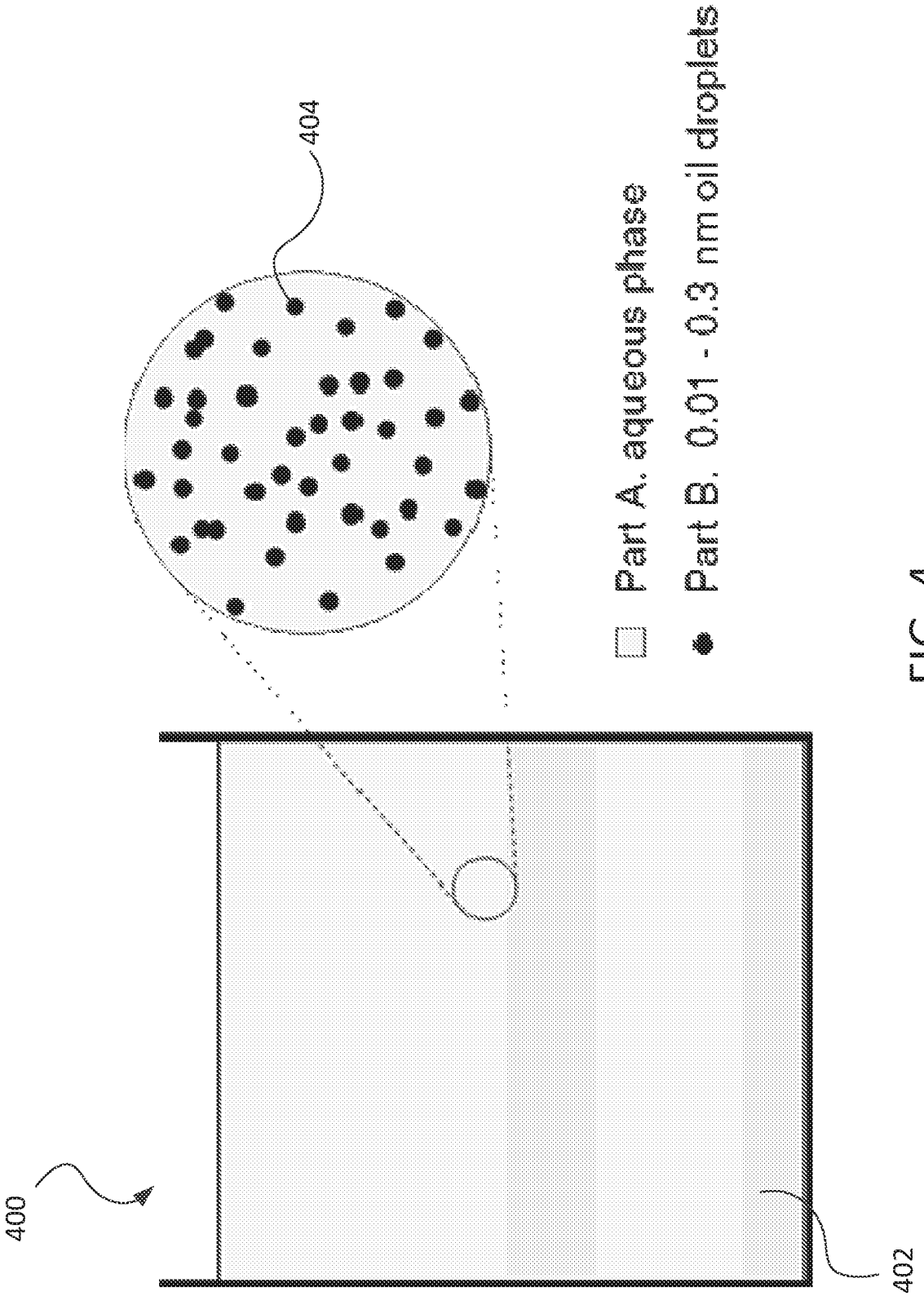
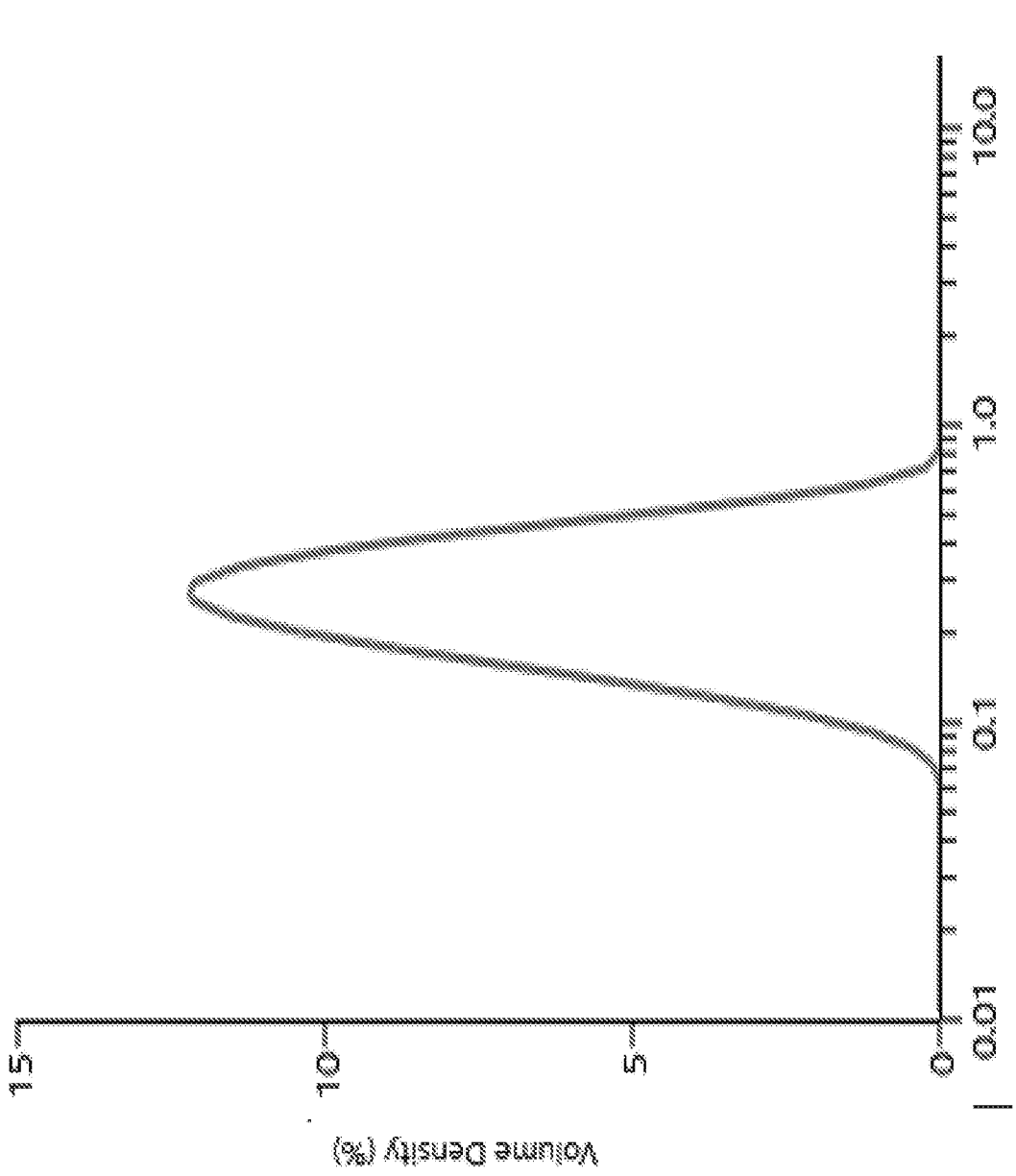
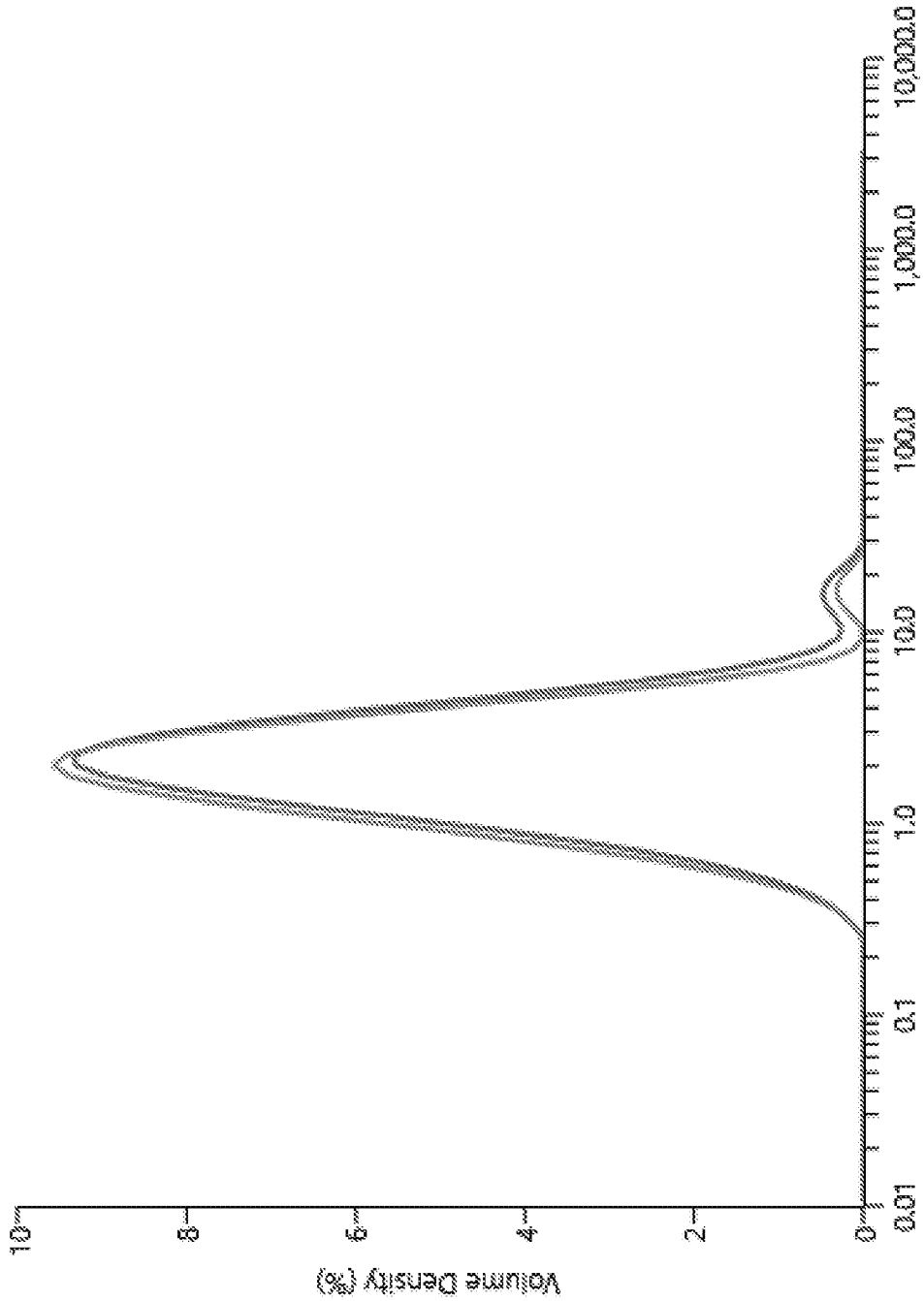


FIG. 4



Sample Name	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)
F20170104-1_MFIC 14K 2x	0.144	0.268	0.505

FIG. 5



Sample Name	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)
P20150628-2	0.872	2.05	4.64
P20150628-3	0.817	1.90	4.06

FIG. 6

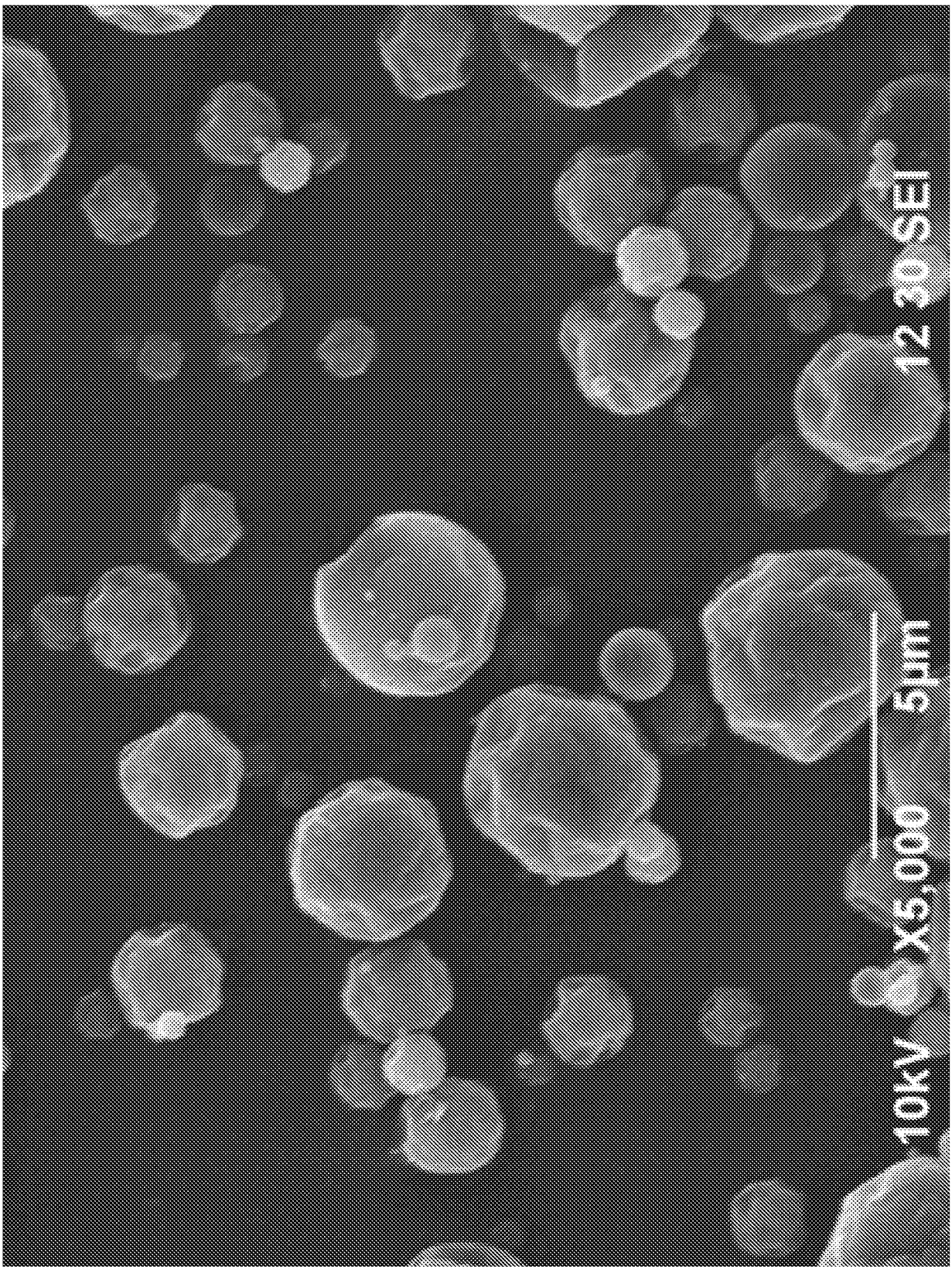
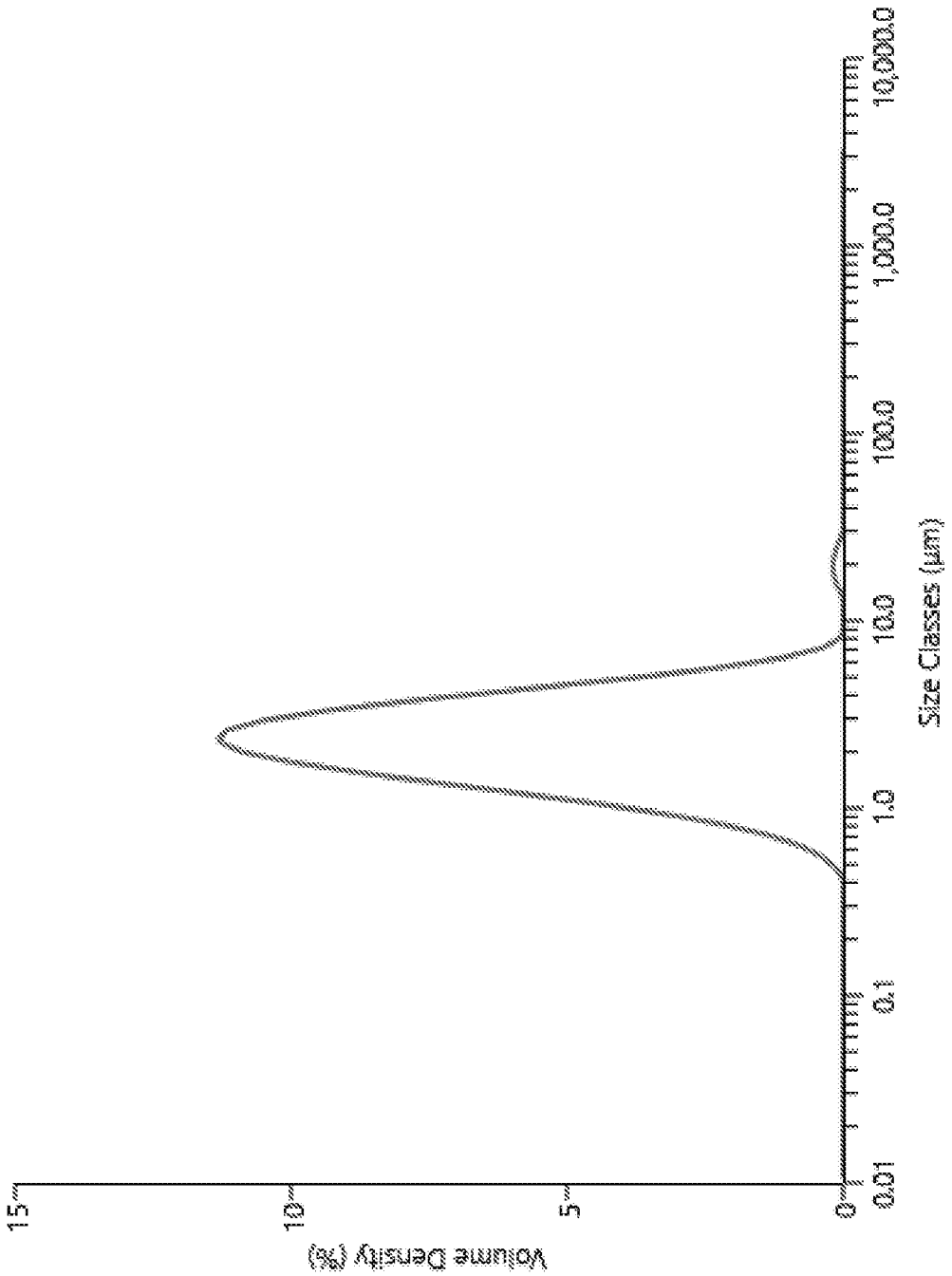


FIG. 7



Sample Name	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)
P20160611-3	1.11	2.24	4.24

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/14279

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 9/14, 9/107, 31/352, 47/06; C08G 8/30 (2017.01)
CPC - A61K 9/14, 9/145, 31/352; 47/06; C08G 8/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2013/0102591 A1 (SALZMAN, AL et al.) 25 April 2013; paragraphs [0028], [0084], [0088], [0096]-[0097], [0108]-[0112]	20 1-2, 3/1-2, 21, 22/20-21, 53-57, 58/56-57
Y	(JAFARI, SM et al.) Nano-Emulsion Production by Sonication and Microfluidization – A Comparison. International Journal of Food Properties. 2006. vol. 9, no. 3. pages 475-485; abstract	1-2, 3/1-2, 21, 22/20-21
Y	US 7,097,827 B2 (PLATZ, RM et al.) 29 August 2006; column 4, lines 62-67; column 5, lines 10-20 and 26-43; column 6, lines 19-24 and 59-64; column 7, lines 5-10; column 9, lines 2-5; claims 1, 5	2, 3/1-2, 54-57, 58/56-57
Y	US 6,383,513 B1 (WATTS, PJ et al.) 7 May 2002; column 1, lines 64-66; column 6, lines 14-25	53-54, 58/56-57

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 March 2017 (04.03.2017)	30 MAR 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/14279

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-19 and 23-52
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.