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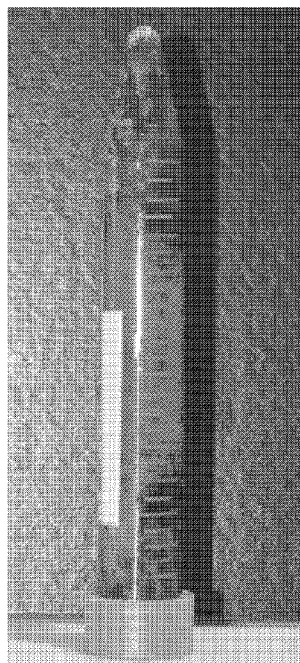


FIG 1

(57) Abstract: The invention relates to compositions comprising water-soluble complexes of α -cyclodextrin (alpha-cyclodextrin) and cannabinoids and/or complexes of α -cyclodextrin and cannabis-derived terpenes, methods of making these α -cyclodextrin complexes, and method of using the α -cyclodextrin complex-containing compositions. The invention also relates to food products comprising the α -cyclodextrin complex-containing compositions.



CANNABINOID-CONTAINING COMPOSITION

BACKGROUND

[0001] *Cannabis* contains more than 500 compounds, including at least 66 cannabinoids that are unique to *Cannabis* and at least 140 terpenes that are widespread throughout the plant kingdom. (Brenneisen, R., Chemistry and Analysis of Phytocannabinoids and Other Cannabis Constituents, in Forensic Science and Medicine: Marijuana and the Cannabinoids. Ed. El Sohly, MA. Humana Press Inc., Totowa, NJ. Chapter 2, pgs. 17-49. 2010.)

[0002] The term “phytocannabinoid” has been proposed to differentiate naturally-occurring cannabinoids from synthetically produced cannabinoids. Synthetically produced cannabinoids are cannabinoid compounds that are made synthetically in laboratories. Phytocannabinoids are all C₂₁ terpenophenolic compounds, of which tetrahydrocannabinol (THC) and cannabidiol (CBD) are perhaps the most studied and best understood for their therapeutic and recreational value. However, phytocannabinoids as a whole have become of interest for the treatment of various disorders and disease states, such as anxiety disorders, depression, cachexia, various forms of pain (*e.g.*, acute pain, chronic pain, neuropathic pain, trigeminal nerve pain, and pain associated with or accompanying migraine headaches and cancer).

[0003] The 140 terpenes that are present in *Cannabis* include monoterpenoids, sesquiterpenoids, diterpenoids, and triterpenoids. (Brenneisen, pgs. 17-49.) For the most part, these terpenes are hydrophobic and comprise short aliphatic branched chains or substituted monocyclic compounds. Terpenes present in *Cannabis* are responsible for the unpleasant turpentine or pine needle tastes and odors that are common to cannabis plant extracts.

[0004] Naturally-occurring cyclodextrins are cyclic polymers of glucose units that are formed by the enzymatic action of specific cyclodextrin glycosyltransferases (CGT) on partially-hydrolyzed corn starch. Depending on the CGT used, cyclic polymers of six, seven, or eight glucose units are produced, which are respectively named α -cyclodextrin, β -cyclodextrin, and γ -cyclodextrin. The size of the cyclodextrin molecule, and therefore the “pore” formed by the cyclodextrin molecule, is dictated by the number of glucose units in the polymer. Thus, α -cyclodextrin has the smallest pore, while γ -cyclodextrin has the largest. α -cyclodextrin is known to sequester small molecules (*e.g.*, fatty acids, nitrobenzene) (McGowan, M. et al., A peroxidase-coupled method for the colorimetric determination of serum triglycerides. Clin. Chem. 1983, 29, 538-542.), while β -cyclodextrin and γ -cyclodextrin sequester larger poly- and heterocyclic compounds (*e.g.*, cholesterol, THC or CBD).

[0005] Shoyama describes a method for the preparation of pure THC and β -cyclodextrin complexes and demonstrates that these complexes are stable. (Shoyama Y. et al., Preparation and stability of Δ^9 -

tetrahydrocannabinol- β -cyclodextrin inclusion complex, J. Nat. Prod. 1983, 46(5), 633-637.) Hazekamp assess the water solubility of pure THC in the presence of α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, and randomly methylated- β -cyclodextrins and states that only the randomly methylated- β -cyclodextrins increase the water solubility of THC. (Hazekamp, A. et al., Structure elucidation of the tetrahydrocannabinol complex with randomly methylated β -cyclodextrin, Eur. J. Pharm. Sci. 2006, 29, 340-347.) Mannila et al. describe the preparation of β -cyclodextrin complexes with CBD for the sublingual administration of CBD and the preparation of methylated-cyclodextrin complexes with CBD and THC. (U.S. Patent No. 7,592,328; Mannila J. et al., Precipitation complexation method produces cannabidiol/ β -cyclodextrin inclusion complex suitable for sublingual administration of cannabidiol, J. Pharm. Sci. 2007, 96(2), 312-319.) U.S. Patent No. 7,423,026 describes methylated β -cyclodextrin complexes with cannabinol, THC, and CBD. U.S. Patent No. 8,735,374 describes the preparation of an oral mucoadhesive dosage form of THC and γ -cyclodextrin and a mixture of THC and CBD with a mixture that includes both β - and γ -cyclodextrin.

[0006] U.S. Patent No. 2017/0224842 (“Czap”) describes γ -cyclodextrin complexes of cannabinoids from partially purified, low terpene containing, hemp oil. In order to release the guest cannabinoid molecule from the host cyclodextrin and to alleviate the concerns surrounding undigested cyclodextrins, Czap’s complexes are formulated with amylase-like enzymes that hydrolyze the cyclodextrin. Czap further discloses that a mixture of cyclodextrins may be used to sequentially form inclusion complexes with different size molecules. Czap’s formulation must be kept dry to prevent premature activation of the amylase-like enzymes. Thus Czap’s formulation is not feasible for use in beverages, food stuffs, and confections. Furthermore, hot beverages or a baking process will likely denature the amylase-like enzymes in Czap’s complexes.

[0007] WO 2017/180954 describes the emulsification of specific cannabinoids with a mixture of at least two emulsifiers, including a synthetic β -cyclodextrin. WO 2018/058235 describes the preparation of a complex using cannabis plant extract, β -cyclodextrin, and other ingredients (*e.g.*, release-modifying agents and excipients for use in a time-released tablet).

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0009] Fig. 1 depicts the results of adding an overly concentrated cannabis plant extract to a slurry of α -cyclodextrin in water.

[0010] Fig. 2 depicts a commercially-available cannabinoid-containing oil diluted with vegetable oil when first mixed with a slurry of α -cyclodextrin and water.

[0011] Fig. 3 depicts a commercially-available cannabinoid-containing oil diluted with vegetable oil mixed with a slurry of α -cyclodextrin in water after gentle mixing for several hours.

[0012] Fig. 4A and 4B depict a comparison between water with (Fig. 4A) or without (Fig. 4B) the addition of a dried cannabis plant extract composition comprising THC and α -cyclodextrin prepared as described herein. Fig. 4A depicts a graduated cylinder containing 100 mL water mixed with 863mg of a dried cannabis plant extract composition comprising 1mg THC and α -cyclodextrin (final concentration, 10mg/L THC). The concentration of THC in the aqueous mixture was 10 mg/L. Fig. 4B depicts a graduated cylinder containing 100 mL water without the addition of the THC/ α -cyclodextrin-containing cannabis plant extract.

[0013] Figure 5 depicts the results of pre-clinical studies to assess the sensory effects of a beverage containing cannabinoid/ α -cyclodextrin complexes prepared in accordance with this invention.

DESCRIPTION OF THE INVENTION

[0014] Described herein is method for preparing a composition comprising water soluble complexes of α -cyclodextrin and a cannabinoid by mixing one or more cannabinoids with an aqueous α -cyclodextrin-containing composition under conditions wherein the α -cyclodextrin forms complexes with the cannabinoids. The cannabinoids may be a phytocannabinoids, i.e., naturally-occurring cannabinoids, or a synthetically produced cannabinoids referred to hereinafter as “synthetic cannabinoids.” An embodiment of this invention is a method for preparing a cannabis plant-derived composition, by treating a cannabis plant extract with an aqueous α -cyclodextrin-containing composition under conditions wherein the α -cyclodextrin forms complexes with the cannabinoids and terpenes in the plant extract thereby producing the cannabis plant extract derived composition. Another embodiment of this invention is method for preparing a synthetic cannabinoid-derived composition comprising water soluble complexes of α -cyclodextrin and synthetic cannabinoids, by mixing a composition comprising synthetic cannabinoids with an aqueous α -cyclodextrin-containing composition under conditions wherein the α -cyclodextrin forms complexes with the synthetic cannabinoids thereby producing the synthetic cannabinoid-derived composition.

[0015] Also described herein is a cannabis plant extract-derived composition comprising complexes of α -cyclodextrin and at least one cannabinoid, or complexes of α -cyclodextrin and at least one terpene, or both complexes of α -cyclodextrin and at least one cannabinoid and complexes of α -cyclodextrin and at least one terpene. The cannabinoids may be, e.g., THC, CBD, cannabitol, or mixtures thereof.

[0016] Also described herein is a composition comprising complexes of α -cyclodextrin and at least one synthetic cannabinoid. Synthetic cannabinoids are well known in the art and include, e.g., 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-[(1 R, 3 S)-3-hydroxycyclohexyl]-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-[(1 R, 3 S)-3-hydroxycyclohexyl]-phenol (cannabicyclohexanol; CP-47,497 C8 homologue) and other CBD analogs (see e.g., Morales et al. *Frontiers in Pharmacology* 28 June 2017 Vol 8, Article 422 p. 1-18). Synthetic cannabinoids also include the FDA approved compounds dronabinol, a synthetic delta-9-tetrahydrocannabinol (THC), and nabilone, which has a chemical structure similar to THC and is synthetically derived.

[0017] The compositions of this invention, e.g., the cannabis plant extract-derived composition and synthetic cannabinoid-derived compositions comprising complexes of α -cyclodextrin and cannabinoids and/or complexes of α -cyclodextrin and terpenes, exhibit reduced or no odor and/or taste associated with cannabinoids or terpenes, as compared to the starting material, e.g. a cannabis plant extract or synthetic cannabinoid. Moreover, the compositions of this invention achieve the effects associated with administration of cannabinoids, e.g., reduction in symptoms of pain or anxiety, or an increase in feelings of well-being, more rapidly than achieved with the starting material, e.g., the untreated cannabis plant extract or synthetic cannabinoid. These effects are also prolonged as compared to the effects achieved with the untreated material. Without wishing to be bound by theory it is contemplated that the α -cyclodextrin and cannabinoids complexes are amphiphilic complexes, having a hydrophilic or polar end and a hydrophobic or nonpolar end, that are absorbed quickly through mucosal membranes such that the cannabinoids are absorbed into the blood stream of the subject more quickly as compared to the uncomplexed cannabinoids. The compositions of this invention comprising the complexes of complexes of α -cyclodextrin and cannabinoids, and/or complexes of α -cyclodextrin and terpenes may be in the form of, e.g., a powder, an aqueous solution, an aqueous slurry, or an aqueous suspension. The powder, aqueous solution, uniform aqueous slurry and uniform aqueous suspension offer the added benefit of controlled and consistent dosing of the cannabinoids contained therein.

[0018] It has been discovered that α -cyclodextrin renders phytocannabinoids and terpenes in cannabis plant extracts, and synthetic cannabinoids having aliphatic chains long enough to complex with α -cyclodextrin, soluble in aqueous medium. Without wishing to be bound by theory, it is contemplated that the terpenes form complexes with the α -cyclodextrin and the aliphatic chains of cannabinoids are long enough to form a complex with α -cyclodextrin. Thus, α -cyclodextrin eliminates the terpene taste and odor characteristic of cannabis plant extracts, e.g., cannabis oil or cannabis tar,

and renders the cannabinoids and terpenes in the compositions of this invention soluble in an aqueous medium.

[0019] The cannabis plant that serves as the source of the plant extract from which the inventive compositions are derived may be, e.g., a *Cannabis sativa*, *Cannabis indica* or *Cannabis ruderalis*, hemp, and strains and hybrid varieties, including crossbred varieties, of such cannabis plants. In an embodiment the cannabis plant is not hemp, e.g., a cannabis plant having a THC content of less than or equal to 0.2% or less than or equal to 0.3% of the dried flowering portion of the plant. In some embodiments the extract is from a cannabis plants having a THC content of the dried flowering portion of the plant of less than or equal to 0.3%. In some embodiments the cannabis plant is marijuana. In some embodiments the extract is from a cannabis plants having a THC content of the dried flowering portion of the plant of greater than 0.3%. In embodiments of this invention the extract is prepared from a cannabis plant having greater than 0.3% to about 30% and in some embodiments the THC content of the dried flowering portion of the plant is about 5% to about 30% or about 5% to about 20% of the dried flowering portion of the plant.

[0020] In addition to the commercially available cannabis plant extracts comprising cannabinoids that are suitable for use in the methods of this invention, those of skill in the art recognize that there are a variety of extraction methods, e.g., solvent extraction, and CO₂ extraction, known in the art for producing a cannabis plant extract comprising cannabinoids, or an extract comprising cannabinoids and terpenes, that are suitable for use in the methods of this invention. Some of the known methods produce cannabis plant extracts containing high levels of THC, in some instances as high as 80%, 90% or more (see e.g., Romano and Hazekamp *Cannabinoids* 2013:1(1):1-11, U.S. Patent No. 8895078, and WO 00/25127, incorporated herein by reference in their entirety). In some embodiments the cannabis plant extract is treated to increase the ratio of cannabinoids to terpenes, e.g. by reducing the amount of terpenes and/or increasing the concentration of cannabinoids. For example, the cannabis plant extract may be subjected to purification techniques known in the art, such as distillation, chromatography, or crystallization to obtain a composition high in cannabinoid content with a reduced level of terpenes. A benefit of using an unpurified cannabis plant extract to produce the composition of this invention is that the resulting composition contains a broad spectrum, if not all, of the medicinally beneficial cannabinoids of the starting cannabis plant extract.

[0021] One embodiment of the invention is a method for making a cannabis plant-derived composition comprising α -cyclodextrin and a compound selected from cannabinoids, terpenes, or mixtures thereof, the method comprising the steps of: (a) combining a cannabis plant extract comprising at least one cannabinoid and/or at least one terpene with an aqueous α -cyclodextrin-containing composition, e.g., an aqueous α -cyclodextrin solution, an aqueous α -cyclodextrin slurry, or an aqueous α -cyclodextrin suspension; and (b) mixing the cannabis plant extract and the aqueous α -

cyclodextrin composition for a sufficient time to form a complex between the α -cyclodextrin and the cannabinoid(s) and/or terpene(s), thereby producing an aqueous mixture comprising complexes of α -cyclodextrin and a compound selected from cannabinoids, terpenes, and/or mixtures thereof. The method may further comprise the step of (c) drying the mixture from step (b), thereby producing a cannabis plant extract-derived composition comprising complexes of α -cyclodextrin and at least one cannabinoid, or complexes of α -cyclodextrin and at least one terpene, or mixtures of complexes of α -cyclodextrin and at least one cannabinoid and complexes of α -cyclodextrin and at least one terpene, in the form of an odorless and/or tasteless water-soluble powder. Suitable methods for drying the mixture include evaporating the mixture in dishes or pans, evaporating under reduced pressure and/or ambient temperatures and/or moderately elevated temperatures (*e.g.*, temperatures ranging from 40-150 °C), evaporating in a rotary evaporator, freeze drying or lyophilization, spray drying, or by any other drying method known to a person of skill in the art. This method may also be applied to a synthetic cannabinoid containing composition rather than a cannabis plant extract to produce a synthetic cannabinoid-derived composition comprising complexes of α -cyclodextrin and one or more synthetic cannabinoids.

[0022] The cannabis plant extract or synthetic cannabinoids and the aqueous α -cyclodextrin-containing composition are mixed together for a length of time sufficient to form complexes between the α -cyclodextrin and the cannabinoid(s) and/or terpene(s), *e.g.*, at least 5 minutes, at least 15 minutes, at least 30 minutes, at least 45 minutes, at least 1 hour, at least 3 hours, at least 6 hours, or at least 12 hours. The cannabis plant extract or synthetic cannabinoids and the aqueous α -cyclodextrin containing composition are mixed together under conditions wherein an emulsion is not formed. In one embodiment, the synthetic cannabinoid-derived composition of this invention comprising complexes of α -cyclodextrin and the synthetic cannabinoids is not an emulsion.

[0023] Suitable aqueous α -cyclodextrin-containing compositions for mixing with the cannabis plant extract or synthetic cannabinoids in the methods described herein comprise at least 15% w/v α -cyclodextrin. Preferable α -cyclodextrin slurries or suspensions comprise at least 20% w/v α -cyclodextrin. Preferable α -cyclodextrin slurries or suspensions comprise at least 25% w/v α -cyclodextrin. Suitable aqueous α -cyclodextrin slurries or suspensions comprise an amount of α -cyclodextrin that exceeds the solubility of α -cyclodextrin in the solution such that non-solubilized α -cyclodextrin is present in the slurry or suspension. In an embodiment of this invention the aqueous α -cyclodextrin compositions for mixing with the cannabis plant extract or synthetic cannabinoids comprises about 15% w/v to about 40% w/v α -cyclodextrin, about 20% w/v to about 35% w/v α -cyclodextrin or about 20% to about 30% w/v α -cyclodextrin.

[0024] It is recognized that the amount of α -cyclodextrin to be mixed with the cannabis plant extract or synthetic cannabinoids to complex with the cannabinoids and terpenes may be varied depending on

the characteristics of the starting material, e.g., its viscosity, its solids content, its cannabinoid content, or its terpene content, and the desired characteristics of the composition produced by the methods described herein, e.g., a solution, a powder, or a slurry. In an embodiment of the invention the ratio of α -cyclodextrin to the cannabis plant extract is at least about 70:1 weight/weight (w/w), at least about 80:1 w/w, at least about 85:1 w/w, at least about 95:1 w/w or at least about 100:1 w/w, at least about 120:1 and ranges there between.

[0025] In one embodiment of the invention, the aqueous α -cyclodextrin-containing composition, e.g., a solution, slurry, or suspension, is combined with the cannabis plant extract or synthetic cannabinoids in an amount and mixed for a time and at a temperature such that at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 100% of the cannabinoids are complexed with the α -cyclodextrin.

[0026] In one embodiment of the invention, the aqueous α -cyclodextrin-containing composition, e.g., a solution, slurry, or suspension, is combined with the cannabis plant extract in an amount such that at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 100% of the terpenes are complexed with the α -cyclodextrin.

[0027] In one embodiment of the invention, the aqueous α -cyclodextrin-containing composition, e.g., solution, slurry, or suspension, is combined with the cannabis plant extract or synthetic cannabinoids in an amount such that at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 100% of the cannabinoids and terpenes are complexed with the α -cyclodextrin.

[0028] In an embodiment of this invention, to achieve the cannabis plant extract-derived composition or synthetic cannabinoid-derived composition of this invention having essentially no odor or taste typically associated with a cannabinoid, the ratio of α -cyclodextrin to cannabinoids in the extract or synthetic cannabinoid is greater than about 70:1 w/w, greater than 85:1 w/w, greater than 90:1 w/w, greater than 95:1 w/w, greater than about 100:1 w/w and greater than about 120:1 w/w and ranges there between.

[0029] U.S. Patent No. 2017/0224842 (Czap) describes mixing cyclodextrin with cannabinoids from partially purified, low terpene containing, hemp oil. Unlike the Czap formulations, which are formulated with amylase-like enzymes that hydrolyze the cyclodextrins, the cannabis plant extract-derived compositions and synthetic cannabinoid-derived composition of this invention, do not require an amylase-like enzyme to be effective and achieve their desired results. Thus an aspect of this invention is a cannabis plant extract-derived compositions or synthetic cannabinoid-derived composition comprising complexes of α -cyclodextrin and a compound selected from cannabinoids, terpenes, or mixtures thereof, wherein the compositions do not comprise an amylase or an amylase-

like enzyme, e.g., a cyclodextrinase, maltogenic amylase, or neopullulanase, that is formulated so that the cyclodextrin-degrading activity of the enzyme is activated on delivery of the composition to a subject.

[0030] In one embodiment, the plant extract-derived compositions of this invention comprise α -cyclodextrin complexes comprising THC, CBD, cannabinol, or mixtures thereof. In an embodiment of the invention, the cannabinoids in complex with α -cyclodextrin are selected from the group consisting of THC, CBD, cannabinol, and mixtures thereof.

[0031] Preferably the cannabis plant extract and synthetic cannabinoids (or compositions comprising synthetic cannabinoids) have a consistency that facilitates its mixing with the aqueous α -cyclodextrin-containing composition. For example, the cannabis plant extract and synthetic cannabinoids may have the consistency of a free flowing oil. Thus, in an embodiment of this invention, the cannabis plant extract or synthetic cannabinoid is mixed with a solvent to facilitate its mixing with an aqueous α -cyclodextrin-containing composition. The solvent may be for example water, an oil, or an alcohol. The amount of solvent added to the cannabis plant extract or synthetic cannabinoid is sufficient such that the cannabis plant extract or synthetic cannabinoid is free flowing. The amount of solvent added to the cannabis plant extract or synthetic cannabinoid may be up to 95% v/v of the total volume of the solvent and cannabis plant extract mixture. The amount of solvent added to the cannabis plant extract or synthetic cannabinoid is preferably up to 75% v/v. The amount of solvent added to the cannabis plant extract or synthetic cannabinoid is more preferably up to 50% v/v. The extract or synthetic cannabinoid may be mixed with the solvent before or after, preferably before, combining the extract or synthetic cannabinoid with an aqueous α -cyclodextrin-containing composition. Preferably the solvent is mixed with the extract or synthetic cannabinoid before combining the extract or synthetic cannabinoid with the aqueous cyclodextrin-containing composition and then mixing the cannabis plant extract or synthetic cannabinoid and the aqueous cyclodextrin-containing composition for a sufficient time to form complexes between the α -cyclodextrin and the cannabinoid(s) and/or terpene(s). The aqueous α -cyclodextrin-containing composition for use in the method may be an aqueous α -cyclodextrin-containing solution, slurry, or suspension.

[0032] Suitable oils for mixing with the cannabis plant extract or synthetic cannabinoid include non-toxic oils, such as edible oils, macerated oils, essential oils, and pharmaceutically acceptable oils. Examples of suitable edible oils include coconut oil, corn oil, olive oil, palm oil, cottonseed oil, peanut oil, rapeseed oil, safflower oil, sunflower oil, sesame oil, soybean oil, almond oil, pumpkin or squash seed oil, Brazil nut oil cashew oil, hazelnut oil, macadamia nut oil, pecan oil, pine nut oil, pistachio oil, walnut oil, citrus oils, carob oil, cocoa butter, shea butter, hemp oil, flaxseed oil, grapeseed oil, other seed oils. Examples of suitable macerated oils include arnica oil, calendula oil, carrot oil, chickweed oil, comfrey oil, galangal oil, horse chestnut oil, linden blossom oil, marigold

oil, meadowsweet oil, mullein oil, sea weed oil, and St. John's Wort oil. Examples of suitable essential oils include bergamot oil, camphor oil, peppermint oil, cannabis flower essential oil, cardamom seed oil, cinnamon oil, citronella oil, coffee oil, eucalyptus oil, garlic oil, fennel seed oil, fenugreek oil, ginger oil, henna oil, jasmine oil, rose oil, rosehip oil, lavender oil, ylang-ylang oil, wintergreen oil, turmeric oil, thyme oil. Examples of pharmaceutically acceptable oils include ethyl butyrate, ethyl caprylate, ethyl oleate, triglycerides, and soybean oil.

[0033] Suitable alcohols for mixing with the cannabis plant extract or synthetic cannabinoid include alcohols that are suitable for food and/or natural products and/or pharmaceutical production. Examples of suitable alcohols are ethanol and isopropanol. The amount of alcohol added to the cannabis plant extract or synthetic cannabinoid is sufficient to make the cannabis plant extract or synthetic cannabinoid free flowing. The amount of alcohol added to the cannabis plant extract or synthetic cannabinoid may be up to 95% v/v, 90% v/v, 85% v/v, 80% v/v, 75% v/v, 70% v/v, 65% v/v, 60% v/v, 55% v/v, 50% v/v, or 45% v/v of the total volume of the alcohol and cannabis plant extract mixture. The cannabis plant extract or synthetic cannabinoid may be mixed with the alcohol before or after combining the extract or synthetic cannabinoid with an aqueous α -cyclodextrin-containing composition. Preferably the alcohol is mixed with the extract or synthetic cannabinoid before mixing the extract or synthetic cannabinoid with the aqueous α -cyclodextrin-containing composition, e.g., an aqueous solution, slurry, or suspension. The cannabis plant extract or synthetic cannabinoid may be mixed with an alcohol in a 1:15 w/v, 1:10 w/v, 1:5 w/v, 1:2 w/v ratio of extract to alcohol, and ranges there between.

[0034] The effects of the consistency and/or viscosity of the plant extract in the methods of this invention are shown in Figures 1-3. As shown in Fig. 1, adding an overly concentrated tar-like cannabinoid-containing extract to an α -cyclodextrin slurry results in the tar-like material not being suspended in the α -cyclodextrin slurry. Instead, the tar-like material congeals into clumps of material that stick to the walls of the container (e.g., a tube). The clumps of material remain unchanged even after extensive mixing. In contrast, Fig. 2 shows a tube containing a commercially-available cannabinoid-containing oil diluted with vegetable oil when it is first mixed with an aqueous α -cyclodextrin containing slurry. As can be seen, undissolved α -cyclodextrin rests at the bottom of the tube while the middle portion of the tube contains an aqueous layer comprising both dissolved α -cyclodextrin and suspended undissolved α -cyclodextrin. The cannabinoid-containing oil appears to be distributed between the undissolved α -cyclodextrin layer and the top of the aqueous layer. Gentle mixing is used in order to avoid the formation of froth, as seen at the top of the container, and to avoid the formation of an emulsion. After gently mixing the tube for several hours the α -cyclodextrin/oil slurry mixture appears homogeneous and has a uniform off-white color (Fig. 3). Due to the gentle mixing, an emulsion is not formed and there is no froth at the top of the container. The aqueous

mixture in the container is ready for using as a slurry in an edible product, *e.g.*, a cupcake, and/or for drying, *e.g.*, into a powder.

[0035] An embodiment of this invention is a cannabis plant extract-derived composition or synthetic cannabinoid-derived composition comprising complexes of cannabinoids and α -cyclodextrin that are water soluble. Fig 4A depicts a graduated cylinder containing a mixture of 100 mL water and 863 mg of a dried cannabis plant extract-derived composition of this invention comprising 1mg THC in complexes with α -cyclodextrin and Fig 4B depicts a graduated cylinder with just 100 ml water. The mixture in Fig. 4A and the water in Fig. 4B are indistinguishable. The cannabis plant extract composition combined with water depicted in Fig. 4A was prepared from cannabis plant distillate.

[0036] An aspect of this invention is a cannabis plant extract-derived composition comprising water soluble complexes of α -cyclodextrin and terpenes; α -cyclodextrin and THC; α -cyclodextrin and CBD, or α -cyclodextrin and cannabiniol, or mixtures of such complexes. Another aspect of the invention is a cannabis plant extract-derived composition comprising complexes selected from the group consisting of α -cyclodextrin and terpenes, α -cyclodextrin and THC, α -cyclodextrin and CBD, α -cyclodextrin and cannabiniol, and mixtures of such complexes that are water soluble. An aspect of this invention is a synthetic cannabinoid-derived composition comprising water soluble complexes of α -cyclodextrin and one or more synthetic cannabinoids.

[0037] In one embodiment of the invention, the cannabis plant-derived composition or synthetic cannabinoid-derived composition of this invention is an aqueous solution, an aqueous slurry, or an aqueous suspension comprising complexes of α -cyclodextrin and cannabinoid(s) and/or complexes of α -cyclodextrin and terpene(s) or mixtures of such complexes.

[0038] In one embodiment of the invention, the cannabis plant-derived composition or synthetic cannabinoid-derived composition of this invention is a water-soluble powder comprising complexes of α -cyclodextrin and cannabinoid(s) and/or complexes of α -cyclodextrin and terpene(s) or mixtures of such complexes.

[0039] An embodiment of the invention is a liquid comprising the cannabis plant extract-derived composition or synthetic cannabinoid-derived composition described herein comprising complexes of α -cyclodextrin and cannabinoid(s) and/or complexes of α -cyclodextrin and terpene(s) or mixtures of such complexes. The liquid may be, *e.g.*, water, a tea, a coffee, a juice, a carbonated beverage, or an alcoholic beverage.

[0040] Another aspect of the invention is a food product comprising a cannabis plant extract-derived composition or synthetic cannabinoid-derived composition of this invention such that the food comprises complexes of α -cyclodextrin and at least one cannabinoid and/or complexes of α -

cyclodextrin and at least one terpene, or mixtures of such complexes. In one embodiment, the food product of the invention may comprise a sweetening agent, a coloring agent and/or a flavoring agent known in the art.

[0041] In one embodiment, the food product is a farinaceous food product or a confection. Examples of a farinaceous food product include, *e.g.*, cake, muffin, brownie, cookie, cracker, doughnut, or biscuit. Examples of a confection include *e.g.*, caramel, chocolate, nougat, chewing gum, toffee, lozenge, fondant, halvah, jelly, gelatin, candies, *e.g.*, gummies (*e.g.*, gummy bears), suckers or lollipops, licorice, marshmallow, taffy, or marzipan.

[0042] In another embodiment, the food product is a non-farinaceous food product. Examples of a non-farinaceous food product include *e.g.*, a dairy product, a meat product, a fruit product, or a vegetable product. Preferred examples of a non-farinaceous food product include beverages, such as tea, herbal tea, coffee, juice, bottled water, a carbonated beverage, or an alcoholic beverage.

[0043] While cannabis plant-derived compositions and synthetic cannabinoid-derived compositions of this invention can be added to the food products in any amount, it is understood that a preferred amount would be such that the organoleptic properties between the food product with or without the cannabis plant-derived compositions or synthetic cannabinoid-derived compositions are not significantly different.

[0044] The cannabis plant extract-derived composition or synthetic cannabinoid-derived composition of this invention may be mixed with an edible oil, *e.g.*, include coconut oil, corn oil, olive oil, palm oil, cottonseed oil, peanut oil, rapeseed oil, safflower oil, sunflower oil, sesame oil, soybean oil, almond oil, pumpkin or squash seed oil, Brazil nut oil cashew oil, hazelnut oil, macadamia nut oil, pecan oil, pine nut oil, pistachio oil, walnut oil, citrus oils, carob oil, cocoa butter, shea butter, hemp oil, flaxseed oil, grapeseed oil, other seed oils.

[0045] Another aspect of this invention is a method for increasing the content of THC and/or CBD and/or synthetic cannabinoid in a food product by adding the cannabis plant-derived composition or synthetic cannabinoid-derived composition of this invention to a food product in an amount sufficient to increase the THC and/or CBD and/or synthetic cannabinoid content of the food product.

[0046] The cannabis plant-derived composition or synthetic cannabinoid-derived composition of this invention may be added to the food product at any stage of its preparation. For example, a cannabis plant extract-derived composition or synthetic cannabinoid-derived composition described herein may be mixed with the food product's ingredients so that it is distributed throughout the food product and the product may then be cooked, or the composition may be mixed or added to the final food product. In some instances a cannabis plant extract-derived composition and synthetic cannabinoid-derived

composition of this invention may be applied to the surface of the food product, *e.g.*, as a glaze, icing, or coating, or the composition may be simply sprinkled on or mixed with the food product, *e.g.*, stirred into a beverage, *e.g.*, a tea, cocoa, coffee, juice, smoothie, or alcoholic beverage.

[0047] Another embodiment of the invention is a topical formulation comprising a cannabis plant extract-derived composition of this invention. An embodiment of this invention a topical formulation comprising a synthetic cannabinoid-derived compositions of this invention. The topical formulation may be, for example, a lotion, an oil, a topical gel, a spray, an ointment, or a cream comprising the cannabis plant extract-derived composition or synthetic cannabinoid-derived composition of this invention comprising complexes of α -cyclodextrin and at least one cannabinoid or complexes of α -cyclodextrin and at least one terpene, or comprising mixtures of such complexes. The topical formulation may include a compound which enhances absorption or penetration of the α -cyclodextrin complexes through the skin. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, dimethylsulfoxide, polyethylene glycol and propylene glycol. The cannabis plant extract-derived composition or synthetic cannabinoid-derived composition of this invention may be added to the topical formulation at any stage of its preparation, *e.g.*, the cannabis plant extract-derived composition or synthetic cannabinoid-derived composition may be mixed with the topical formulation's ingredients and then mixed together or the cannabis plant extract-derived composition or synthetic cannabinoid-derived composition may be mixed or added to the final topical formulation. The cannabis plant extract-derived composition or synthetic cannabinoid-derived composition of this invention may be mixed with an oil suitable for topical application, *e.g.*, an essential oil, *e.g.*, bergamot oil, camphor oil, peppermint oil, cannabis flower essential oil, cardamom seed oil, cinnamon oil, citronella oil, coffee oil, eucalyptus oil, garlic oil, fennel seed oil, fenugreek oil, ginger oil, henna oil, jasmine oil, rose oil, rosehip oil, lavender oil, ylang-ylang oil, wintergreen oil, turmeric oil, thyme oil.

[0048] In one embodiment, the topical formulation of this invention comprises complexes of α -cyclodextrin and cannabinoids, *e.g.*, α -cyclodextrin and THC, α -cyclodextrin and CBD, α -cyclodextrin and cannabinal, or α -cyclodextrin and one or more synthetic cannabinoids, or mixtures thereof. In one embodiment, the topical formulation comprises complexes selected from the group consisting of THC- α -cyclodextrin complexes, CBD- α -cyclodextrin complexes, or cannabinal- α -cyclodextrin complexes, and mixtures thereof. In one embodiment, the topical formulation comprises complexes of α -cyclodextrin in complex with one or more of 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-[(1 R, 3 S)-3-hydroxycyclohexyl]-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-[(1 R, 3 S)-3-hydroxycyclohexyl]-phenol (cannabicyclohexanol; CP-47,497 C8 homologue) and other CBD analogs (see *e.g.*, Morales et al.

Frontiers in Pharmacology 28 June 2017 Vol 8, Article 422 p. 1-18 incorporated herein by reference in its entirety), dronabinol, or nabilone. In one embodiment, the topical formulation comprises complexes of α -cyclodextrin in complex with one or more synthetic cannabinoids selected from the group consisting of 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-[(1 R, 3 S)-3-hydroxycyclohexyl]-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-[(1 R, 3 S)-3-hydroxycyclohexyl]-phenol (cannabicyclohexanol; CP-47,497 C8 homologue), dronabinol, and nabilone.

[0049] An aspect of the invention is a method of alleviating pain in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a cannabis plant-derived composition or synthetic cannabinoid-derived composition of the invention described herein, comprising complexes of α -cyclodextrin and at least one cannabinoid (*e.g.*, THC, CBD, and/or cannabitol or a synthetic cannabinoid). The cannabis plant-derived composition administered may also comprise complexes α -cyclodextrin and at least one terpene. A therapeutically effective amount of the cannabis plant-derived composition or the synthetic cannabinoid-derived composition in this embodiment is an amount sufficient to alleviate pain in the subject in need thereof. The subject in need thereof is a subject, *e.g.* a human, horse, cow sheep, goat, dog, cat, rat or mouse, suffering from pain.

[0050] An aspect of the invention is a method of alleviating anxiety in a subject in need thereof, comprising administering a therapeutically effective amount of a cannabis plant-derived composition or synthetic cannabinoid-derived composition of the invention described herein comprising complexes of α -cyclodextrin and at least one terpene and/or α -cyclodextrin and at least one cannabinoid (*e.g.*, THC, CBD, and/or cannabitol, or synthetic cannabinoid) to the subject. A therapeutically effective amount of the composition of this invention is an amount sufficient to alleviate anxiety in the subject in need thereof. The subject in need thereof is a subject, *e.g.* a human, horse, cow sheep, goat, dog, cat, rat or mouse, suffering from anxiety.

[0051] An aspect of the invention is a method of increasing feelings of well-being and relaxation in a subject comprising administering a sufficient amount of a cannabis plant-derived composition or synthetic cannabinoid-derived composition of the invention comprising complexes of α -cyclodextrin and at least one terpene and/or α -cyclodextrin and at least one cannabinoid (*e.g.*, THC, CBD, and/or cannabitol, or synthetic cannabinoid) to the subject. A sufficient amount of the compositions of this invention is an amount sufficient to increase feelings of well-being and relaxation in the subject.

[0052] Another aspect of the invention is a method of treating a subject, *e.g.* a human, a non-human primate, a horse, cow sheep, goat, dog, cat, rat or mouse, having a disorder having symptoms that are

alleviated by treatment with a cannabinoid. The method comprises administering a therapeutically effective amount of a cannabis plant-derived composition or synthetic cannabinoid-derived composition of the invention comprising complexes of α -cyclodextrin and at least one terpene and/or α -cyclodextrin and at least one cannabinoid (*e.g.*, THC, CBD, and/or cannabitol and/or a synthetic cannabinoid) to the subject having the disorder. In an aspect of the invention, the composition of this invention administered to the subject comprises complexes of α -cyclodextrin and cannabinoids (*e.g.*, THC, CBD, cannabitol, and synthetic cannabinoids). Examples of disorders that can be treated with the compositions described herein include trigeminal neuralgia, agitation, Alzheimer's dementia, anxiety disorders, jet lag, depression, anorexia, Attention Deficit Disorder (ADD) with or without hyperactivity, Autism Spectrum Disorder (ASD), cachexia, cancer, chronic cluster headaches, Crohn's disease, convulsions, epilepsy, gastrointestinal tract distress (*e.g.*, heartburn indigestion, stomach ache), glaucoma, HIV/AIDS, Huntington's disease, inflammation (chronic or acute), inflammatory bowel disease, irritable bowel syndrome (IBS) with or without diarrhea or constipation, migraine headaches whether hormone mediated or not, muscle spasms, nausea, neurodegenerative diseases including Lou Gehrig's disease, all forms of pain (*e.g.*, acute, chronic, neuropathic, trigeminal nerve pain, pain associated with or accompanying migraine headaches and cancer), Parkinson's disease and Parkinsonian-type symptoms, spinal-cord injuries, postmenstrual syndrome (PMS), Post-Traumatic Stress Disorder (PTSD), seasonal affective disorder (SAD), seizures, seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, sleep disorders such as insomnia, spasticity from multiple sclerosis, ulcerative colitis, and vomiting. An embodiment of this invention is a method for treating a subject, *e.g.* a human, having cancer, chronic cluster headaches, Crohn's disease, convulsions, epilepsy, glaucoma, migraine headaches whether hormone mediated or not, nausea, or trigeminal nerve pain by administering to the subject a therapeutically effective amount of a cannabis plant extract-derived composition or synthetic cannabinoid-derived composition of this invention.

[0053] Treatment of a disorder as described herein refers to reducing or eliminating one or more symptoms of the disorder. A therapeutically effective amount of a composition of this invention as described herein for treating a disorder is an amount sufficient to reduce or eliminate one or more symptoms of the disorder. For example, if a subject has a disorder that is associated with pain, a therapeutically effective amount is an amount sufficient to reduce or eliminate the pain. For example, if the disorder is an anxiety disorder a therapeutically effective amount is an amount sufficient to reduce or eliminate anxiety.

[0054] A therapeutically effective amount of a cannabis plant-derived composition or synthetic cannabinoid-derived composition of the invention described herein, comprising complexes of α -cyclodextrin and at least one cannabinoid (*e.g.*, THC, CBD, and/or cannabitol or a synthetic cannabinoid) administered to a subject, *e.g.* a subject having anxiety, pain or another disorder having

symptoms that are alleviated by treatment with a cannabinoid, may be administered to the subject in any suitable form, e.g., a tablet, capsule, pill, elixir, wafer, beverage or a food product.

[0055] The compositions of this invention may be administered to the subject by any suitable method, e.g., orally (swallowed), sublingually (under the tongue), transdermally, transmucosally, intranasally, topically, or rectally, in an amount suitable to achieve the desired effects.

[0056] It has been found that the cannabinoids and/or terpenes complexed with α -cyclodextrin in the compositions of this invention are absorbed more rapidly through the mucosal membranes of a subject than are cannabinoids and/or terpenes that are not complexed with α -cyclodextrin. Moreover, the effects of the cannabinoids in the α -cyclodextrin complexes in the cannabis plant extract-derived compositions and synthetic cannabinoid-derived compositions of this invention are prolonged as compared to the effects of the cannabinoids in the untreated cannabis plant extracts or synthetic cannabinoids. Without wishing to be bound by theory, it is contemplated that the α -cyclodextrin and cannabinoid complexes are amphiphilic and are thereby absorbed more readily through a mucosal membrane. It is also contemplated that at least a portion of the complexes are delivered to the subject's stomach and intestines where the cannabinoids are released thereby prolonging their effect on the subject. An embodiment of this invention is a composition comprising cannabinoids formulated to enhance absorption of the cannabinoids through mucosal membranes of a subject, and/or to prolong the effect of the cannabinoids on the subject, wherein the cannabinoids are in the form of complexes with α -cyclodextrin.

[0057] An embodiment of this invention is a method for enhancing the absorption of cannabinoids and/or terpenes in a cannabis plant extract or absorption of synthetic cannabinoids through mucosal membrane of a subject by mixing the cannabis plant extract and synthetic cannabinoids with an aqueous α -cyclodextrin-containing composition under conditions suitable to form complexes of α -cyclodextrin and the cannabinoids and/or terpenes, or both. The resulting composition comprising the complexes may be administered to the subject or the complexes in the mixture may then be collected, e.g., by filtering the mixture, or drying the mixture, and then administered to the subject.

EXAMPLES

Example 1 - Tasteless, Odorless Cannabis Powder

[0058] A high CBD-containing cannabis viscous oil was diluted 1:15 (w/v) with either ethyl or isopropyl alcohol and gently mixed using a tube rocking apparatus, for up to 3 hours to make the viscous oil less viscous. An α -cyclodextrin slurry was prepared by adding 900 mg of α -cyclodextrin to 10 mL of a 10% (w/v) aqueous α -cyclodextrin solution. 600 μ L of the above-mentioned alcohol diluted cannabis viscous oils was added to the aqueous α -cyclodextrin slurry to form suspensions. The suspensions were shaken vigorously by hand for 30 seconds and then gently mixed at ambient

temperature for at least 1 hour or until all visible signs of the deep green diluted viscous oil disappear. The suspensions were shaken vigorously by hand for a few seconds and then poured into an evaporating dish. The suspensions were dried at ambient temperatures for at least 48 hours or at 90-120 °C for 1-3 hours, scraped into a mortar, and ground to a fine greenish-tinged off-white powder. The powder was odorless, tasteless, and water soluble. Recovery based upon the quantity of solids in the initial mix of oil and α -cyclodextrin slurry was near 100%.

Example 2 – Tasteless, Odorless Cannabis Powder

[0059] A commercially-available cannabinoid oil [Tweed <https://www.tweed.com>] that had been diluted with vegetable oil by the supplier to contain 5.16 mg/mL THC and 4.77 mg/mL CBD was made into an off-white tasteless and odorless powder as follows. 600 mg of α -cyclodextrin was suspended in 7 mL of 10% (w/v) α -cyclodextrin in water. To this α -cyclodextrin suspension, 420 μ L of the commercially available cannabinoid oil was added and briefly shaken by hand. The suspension was then mixed gently overnight or until all signs of the oil disappeared and the suspension appeared homogenous. The homogenous suspension was transferred to an evaporating dish and dried at ambient temperature for 48-72 hours. The dried material was transferred to a mortar and ground to an off-white waxy powder. At least a portion of this material was not soluble in cold water and formed small oil droplets in hot water. However, this material was tasteless and odorless. Analysis of the commercially available cannabinoid oil demonstrated that 2.0 mg of CBD and 2.17 mg of THC were added to the α -cyclodextrin suspension. Analysis of the off-white waxy powder generated by the method demonstrated 0.12% (w/w) THC and 0.13% (w/w) CBD. Recovery based upon total solids was near 100%.

Example 3 – Tasteless, Odorless Cannabis Suspension for Baking

[0060] 3.0 mL of a commercially-available cannabis oil (Spectrum Cannabis, <https://spectrumcannabis.com>) containing 25 mg/mL THC was added to 45 mL of water containing 9.5 g α -cyclodextrin powder to make a suspension. The suspension was shaken vigorously by hand for one minute and then gently rocked for 3 hours. The resulting slurry was then added to a commercially available cupcake mix (e.g., Betty Crocker Vanilla Butter Cream) as a direct substitute for the same amount of water required by the manufacturer's cupcake recipe. As instructed by the cupcake recipe, the batter was divided into 12 equal portions and baked as indicated by the cupcake recipe. The olfactory and organoleptic properties of the resulting cupcakes were indiscernible from those of cupcakes prepared according to the unaltered cupcake recipe.

Example 4 – Tasteless, Odorless, High CBD-Containing Beverage

[0061] High CBD cannabis containing viscous oil (50.9 mg CBD/100 mg oil) was diluted 1:15 (w/v) with isopropyl alcohol with gentle rocking until the oil was totally dissolved. The diluted oil (1.6 mL) was added to 10% (w/v) α -cyclodextrin aqueous solution (40 mL) containing additional solid α -

cyclodextrin (8 g). The suspension was briefly mixed vigorously by hand before being rocked gently for 3-4 hours. The resulting homogeneous-appearing slurry was poured into a drying dish, and the solvents in the slurry were evaporated over several hours at approximately 110 °C. Off-white crystalline material was recovered, and the yield (based on the measured amount of cannabinoid in the diluted oil) based on total mass of solids was 97%. The off-white crystalline material was transferred to a mortar and ground to a fine off-white powder. Analysis of the powder indicated that the powder contained 0.46% (w/w) CBD. The off-white powder (1.3 g of powder, the equivalent of 6 mg CBD) was dissolved in water (500 mL). The resulting solution was filtered through filter paper to remove traces of green material, believed to be vegetable matter. Although the resulting solution had a slight opalescence, the solution was transparent and tasteless. A volunteer suffering from chronic trigeminal nerve facial pain consumed approximately one-third of the CBD-containing solution. The volunteer reported pain relief within 10-15 minutes and reported that the relief lasted for over 4 hours after consuming the CBD-containing solution.

Example 5 – Tasteless, Odorless, High THC-Containing Iced Tea Beverage

[0062] The procedure used to make a high THC iced tea beverage was similar to the procedure used in Example 4. A THC-containing powder was prepared from a high THC-containing distillate as set forth in Example 4 and a sufficient amount of the powder was mixed with an iced tea beverage such that the resulting iced tea beverage contained 2.5 mg THC in 341 ml. Eight volunteers, two suffering from anxiety (group 1), three suffering from headaches (group 2) and three having neither headaches of anxiety (group 3), consumed 341 ml of the iced tea beverage and reported rapid onset of the desired effects, i.e., reduction of anxiety (group 1), reduction of headache (group 2) and an enhanced relaxation, happiness, and heightened sensory perception (groups 1, 2 and 3) that persisted for more than 2.5 hours.

[0063] None of the eight volunteers reported detecting any cannabis and/or terpene taste or odor typically associated with cannabis extract in the iced tea beverage. The volunteers reported that they only detected the flavor and odor of the tea in the iced tea beverage.

Example 6 –Preparing Tasteless, Odorless Cannabis Powder from a Cannabis Oil

[0064] High CBD containing cannabis extract with the consistency of a tar was diluted 1:15 (w/v), with isopropyl alcohol and gently mixed by rocking the tube on a rocking apparatus for up to 3 hours to make the tar less viscous. An α -cyclodextrin slurry was prepared by adding 12g of α -cyclodextrin to 40 mL of water followed by vigorous shaking by hand for 2 minutes. 1.6 mL of the above-mentioned alcohol diluted cannabis tar was added to the aqueous α -cyclodextrin slurry to form a suspension. This suspension was shaken vigorously by hand for 30 seconds and then gently mixed for at least 1 hour or until all visible signs of the deep green diluted tar disappear. The suspension was shaken vigorously by hand for a few seconds and then poured into an evaporating dish. The

suspension was dried at ambient temperature for at least 48 hours, scraped into a mortar, and ground to a fine off-white powder. The yield, based upon solids added, was near 100%.

Example 7 – Tasteless, Odorless, Water-Soluble THC-Containing Cannabis Powder

[0065] A commercially available THC distillate (300 mg) (<https://www.thconcentrates.ca>) was diluted with isopropyl alcohol (4.2 mL). The diluted distillate (1.6 mL) was added to 40 mL of water containing 10 g of α -cyclodextrin. The resulting suspension was shaken vigorously by hand in order to evenly distribute the diluted distillate throughout the suspension. The suspension was then rocked gently for 3 hours before being transferred to a drying dish. The suspension was dried at ambient temperature for at least 48 hours to yield a powder containing 11.6 mg THC per 1 g powder.

Example 8 – Tasteless, Odorless, THC Water Beverage

[0066] The powder of Example 7(435 mg) was dissolved in 500ml water. Brief mixing produced a tasteless, odorless THC-containing water beverage containing 5 mg THC.

Example 9 – Tasteless, Odorless, THC-Containing Tea Beverage

[0067] The powder of Example 7(174 mg) was added to a tea cup containing one tea bag of commercially available herbal tea (Stress Buster, www.tealish.com). The powder dissolved completely upon addition of boiling water (250 mL). After steeping the tea bag for 5 minutes, an herbal tea beverage containing 2 mg THC was produced.

[0068] THC-containing cannabis powders were prepared by mixing various ratios of THC distillate, commercially available from, e.g., <https://www.thconcentrates.ca>, and α -cyclodextrin. The THC distillate (300 mg) was diluted with isopropyl alcohol (4.2 mL) and then added to an α -cyclodextrin aqueous solution to generate suspensions having a ratio of α -cyclodextrin to THC distillate of 70:1, 87:1, 105:1 and 122:1. The resulting suspensions were shaken vigorously by hand in order to evenly distribute the diluted distillate throughout the suspensions. The suspensions were then rocked gently for 3 hours before being transferred to a drying dish. The suspensions were dried at ambient temperature for 48-72 hours or at 90-120 °C for 1-3 hours. Sufficient amounts of each resulting powder were added to water to produce solutions having a THC concentration of 10mg/L. The solutions were then tasted by volunteers. The results are presented in Table 1. Table 1 recites the ratios of α -cyclodextrin (α -CD) to THC distillate and the taste characteristics of THC-containing solutions. All the solutions showed opalescence that decreased as the percent α -cyclodextrin increased and the ratio of α -cyclodextrin to distillate increased.

Table 1

% α -CD	α -CD : Isopropanol	α -CD : THC Distillate	Solution Characteristics
20	0.20	70:1	Slight “off” taste, like stale water, with a thin and sparse layer on top of water
25	0.16	87:1	No taste, small film on surface of water
30	0.13	105:1	No taste, all solid material dissolved
35	0.11	122:1	No taste, all solid material dissolved

[0069] The following Table 2 provides examples of cannabis plant extract-derived compositions prepared from different cannabis plant extracts, i.e., a tar, a distillate or an oil according to methods of the invention. “% Starting Material” in Table 2 refers to the approximate % mass (tar) or volume (distillate or oil) of the original tar, distillate, or oil mixed with an aqueous α -cyclodextrin composition. “% α -CD” is the % of α -cyclodextrin by weight in the aqueous cyclodextrin-containing composition mixed with the cannabis plant extract. “End Product” means the cannabis plant extract-derived composition produced by treating the plant extract with the aqueous α -cyclodextrin composition as described herein and dried to a powder form or not dried such that the end-product is in the form of a slurry.

Table 2

	Starting Material	End Product	% α -CD	% Starting Material
1	Tar	Powder	30	0.3
2	Distillate	Powder	25	0.3
3	Commercial Oil	Slurry	21	6.7

Example 10 – A Preparation of Water-Soluble, Odourless and Tasteless Cannabinoid Powder - 50gm Scale

[0070] Cannabinoid distillate/tar (500mg¹) were dissolved in 7mL of either ethanol or isopropyl alcohol. A slurry of alpha-cyclodextrin (α -CD) in water was prepared by mixing 167mL of water to 50g² of α -CD. Because all the α -CD did not dissolve in the water, the slurry was kept suspended with gentle mixing. The 7mL of the diluted cannabinoid distillate/tar was added to the aqueous slurry of α -CD and gently mixed for 2-6 hr to form a particulate suspension. The suspension was transferred, with as little water or alcohol as possible, to a dryer³ and dried for sufficient time to remove all or essentially all the water or alcohol. The dried material was transferred to a mill or mortar and ground to a fine powder.

[0071] The cannabinoid content of the starting diluted material and final dried product was evaluated using a HPLC/UV. The percent recovery was determined by comparing the amount of cannabinoids in the starting diluted material and the final product. In particular, the quantity of cannabinoid (THC or CBD) in the alcohol diluted starting material, from several different sources, was compared to the amount of cannabinoid found in the final powder (see Table 3). Stated accuracy of test results $\pm 10\%$ and that two measurements were required to calculate recovery. “Expected Level” was calculated based on measured level in the alcohol diluted starting material. Testing was performed by an independent third-party licensed laboratory. As stated elsewhere recoveries are 100% within the margin of error.

Table 3

Starting Material/Solvent	Expected Level of Cannabinoid in Final Product (mg/g)	Level of Cannabinoid Found in Final Product (mg/g)	Recovery (%)
High CBD Tar/Ethanol	7.3	6.8	93
High THC Distillate/Isopropanol	6.0	5.5	91
High CBD Tar/Isopropanol	5.2	5.5	107

Example 11 – Pre-Clinical Sensation Testing

¹ The final product should be about 5-5.5mg/g cannabinoid, adjust the amount of starting material accordingly.

² Assuming food grade and six waters of hydration.

³ A domestic food dehydrator set at 60°C works very well. Avoid elevated temperatures in excess of 100°C and/or significantly reduced pressures as the desired volatiles may be lost.

[0072] Preclinical studies with human volunteers were conducted to assess the sensory effects, i.e., pain relief, euphoria, increased feelings of well-being and relaxation, of a cannabinoid/ α -cyclodextrin-containing composition prepared as described herein.

[0073] Thirty-four volunteers drank a beverage containing the THC/ α -cyclodextrin-containing composition of this invention. Depending on the volunteers' level of experience with cannabinoids, they drank an amount of the beverage to provide 2.5, 5, 10 or 15mg of THC. It is apparent that the onset of effects is very rapid suggesting absorption through the oral mucosa whereas the peak effects are achieved at about 90-120 minutes post ingestion and prolonged effects of three or more hours suggest that further absorption through the gastrointestinal tract. See Figure 5.

Example 11 – pH Effects

[0074] All samples were prepared with a cyclodextrin mixture to contain approximately 10mg cannabinoid per litre of tap water.

[0075] Samples of cannabis tar having high THC or high levels of CBD, and THC distillates were dissolved in water and then adjusted to various pH values with citric acid and sodium carbonate powders except for the Company C THC distillate, which was adjusted to various pH values with citric acid and sodium bicarbonate powders. Visually there was no obvious difference in the appearance of the samples over the range of studied pH's. See Table 4

	Tar - High THC	Tar – High CBD	Company L THC Distillate	Company C THC Distillate
pH Range	2.69 – 8.82	2.80 – 9.90	2.82 – 9.90	2.64 – 7.80

[0076] The foregoing description and examples have been set forth merely to illustrate the invention and are not meant to be limiting. Since modifications of the described embodiments incorporating the spirit and the substance of the invention may occur to persons skilled in the art, the invention should be construed broadly to include all variations within the scope of the claims and equivalents thereof.

Claims:

1. A method for making a composition comprising complexes of α -cyclodextrin and one or more cannabinoids, one or more terpenes, or mixtures of such complexes, the method comprising the steps of:

(a) combining a first composition comprising at least one cannabinoid and/or at least one terpene or mixtures of such cannabinoids and terpenes with an aqueous α -cyclodextrin-containing composition; and

(b) mixing the first composition and the aqueous α -cyclodextrin-containing composition for a sufficient time to form complexes between the α -cyclodextrin and at least one cannabinoid and/or at least one terpene.

2. The method of claim 1, further comprising the step of:

(c) drying the mixture from step (b).

3. The method of claim 1, wherein the first composition is a cannabis plant extract comprising one or more phytocannabinoids or a composition comprising one or more synthetically produced cannabinoid ("synthetic cannabinoid").

4. The method of claim 3, wherein the phytocannabinoid is THC, CBD, cannabinal, or mixtures thereof and wherein the synthetic cannabinoid is 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-butyl-3-(1-naphthoyl)indole (JWH-073), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-[(1 R, 3 S)-3-hydroxycyclohexyl]-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-[(1 R, 3 S)-3-hydroxycyclohexyl]-phenol (cannabicyclohexanol; CP-47,497 C8 homologue) dronabinol, nabilone, or mixtures thereof.

5. The method of claim 1, wherein the aqueous α -cyclodextrin-containing composition is an aqueous solution, an aqueous slurry, or an aqueous suspension.

6. The method of claim 1, wherein the α -cyclodextrin solution comprises about 15% w/v to about 40% w/v α -cyclodextrin.

7. The method of claim 2, wherein the mixture is dried by evaporating the mixture in dishes or pans at ambient or moderately elevated temperatures, under reduced pressure, or in a rotary evaporator, by freeze drying or lyophilization, or by spray drying.

8. A method for complexing a compound in a Cannabis plant extract with α -cyclodextrin comprising the steps of:
- (a) combining a Cannabis plant extract with an aqueous α -cyclodextrin-containing composition to produce a mixture,
 - (b) mixing the mixture from step (a) for sufficient time to form a composition comprising complexes of α -cyclodextrin with the compound,
- wherein the compound is a cannabinoid, a terpene, and/or mixtures thereof.
9. The method of claim 8, wherein the compound is a cannabinoid selected from the group consisting of cannabiol, THC, and CBD.
10. A food product comprising a composition comprising complexes of one or more cannabinoids and α -cyclodextrin produced by the method of claim 1.
11. The food product of claim 10, wherein the food product is a farinaceous food product, a non-farinaceous food product, or a confection.
12. The food product of claim 11, wherein
- the food product is a farinaceous food product selected from the group consisting of cake, muffin, brownie, cookie, cracker, doughnut, and biscuit or,
 - the food product is a confection selected from the group consisting of caramel, chocolate, nougat, lozenge, chewing gum, toffee, fondant, halvah, jelly, gelatin, gummies, suckers, lollipops, licorice, marshmallow, taffy, or marzipan, or
 - the food product is a beverage selected from the group consisting of a water, tea, a coffee, a juice, a carbonated beverage, an alcoholic beverage, or a smoothie.
13. A topical formulation comprising a composition comprising complexes of α -cyclodextrin and cannabinoids, complexes of α -cyclodextrin and terpenes, or mixtures of such produced by the method of claim 1.
14. The topical formulation of claim 13, wherein the topical formulation is a lotion, a cream, or an oil.
15. A composition comprising complexes of α -cyclodextrin and a phytocannabinoid, complexes of α -cyclodextrin and a synthetically produced cannabinoid, complexes of α -cyclodextrin

and terpenes, or mixtures of two or more of such complexes, formulated such that the complexes are water soluble.

16. The composition of claim 15, wherein the composition is an aqueous solution, an aqueous slurry, an aqueous suspension, or a water-soluble powder.

17. A food product comprising a composition of claim 15.

18. A method for increasing the THC and/or CBD and/or synthetic cannabinoid content of a food product comprising adding the composition of claim 15 to the food product.

19. A method of treating a subject having a disorder, comprising administering a therapeutically effective amount of the composition comprising complexes of α -cyclodextrin and one or more cannabinoids of claim 15 to the subject having the disorder.

20. The method of claim 19, wherein the disorder is agitation, Alzheimer's dementia, anxiety disorders, jet lag, depression, anorexia, Attention Deficit Hyperactivity Disorder (ADHD) with or without hyperactivity, Autism Spectrum Disorder (ASD), cachexia, cancer, chronic cluster headaches, Crohn's disease, convulsions, epilepsy, gastrointestinal tract distress (*i.e.*, heartburn indigestion, stomach ache, etc.), glaucoma, HIV/AIDS, Huntington's disease, inflammation (chronic or acute), inflammatory bowel disease (IBS), irritable bowel syndrome (IBS) with or without diarrhea or constipation, migraine headaches whether hormone mediated or not, muscle spasms, nausea, neurodegenerative diseases including Lou Gehrig's disease, all forms of pain (*i.e.*, acute chronic, neuropathic, trigeminal nerve pain, and pain associated with or accompanying migraine headaches and cancer), Parkinson's disease and Parkinsonian-type symptoms, spinal-cord injuries, postmenstrual syndrome (PMS), Post-Traumatic Stress Disorder (PTSD), seasonal affective disorder (SAD), seizures, seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, sleep disorders such as insomnia, spasticity from multiple sclerosis, ulcerative colitis (UC), or vomiting.

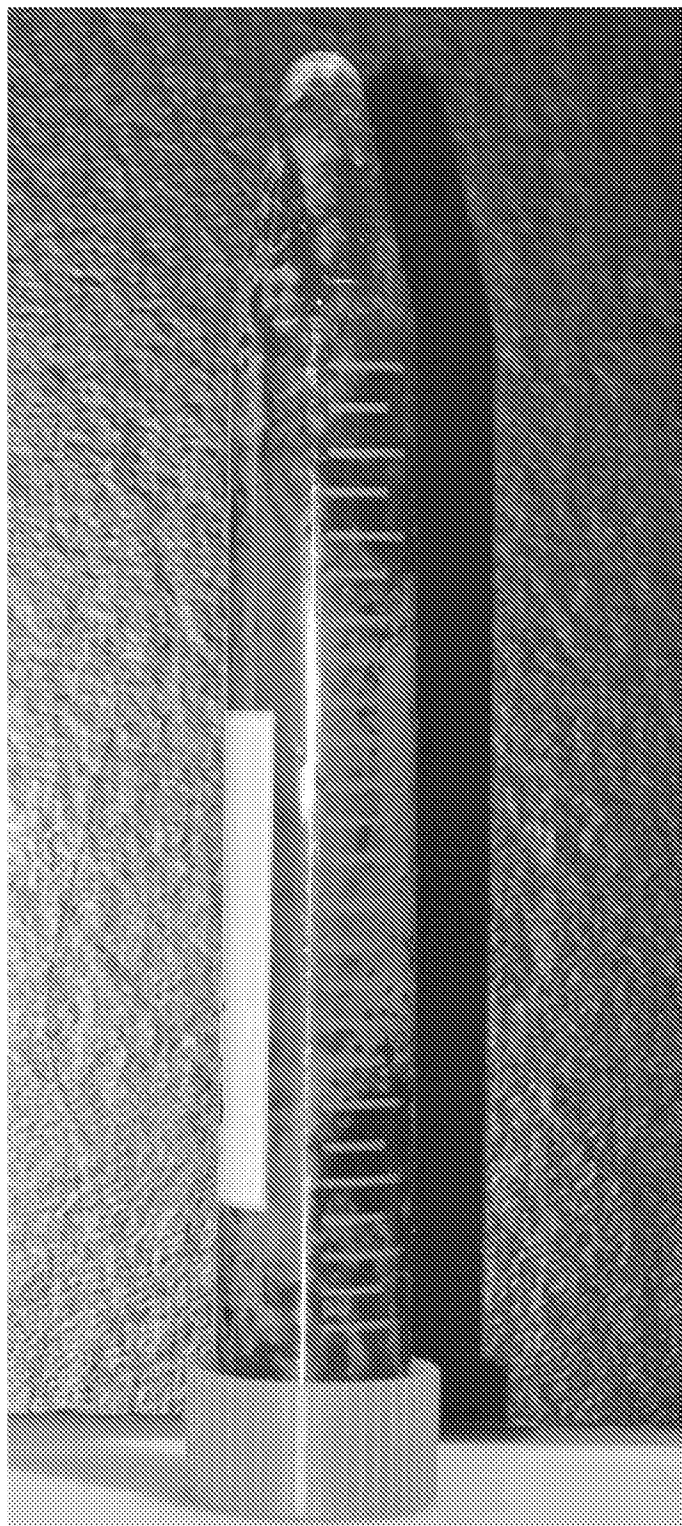


FIG 1

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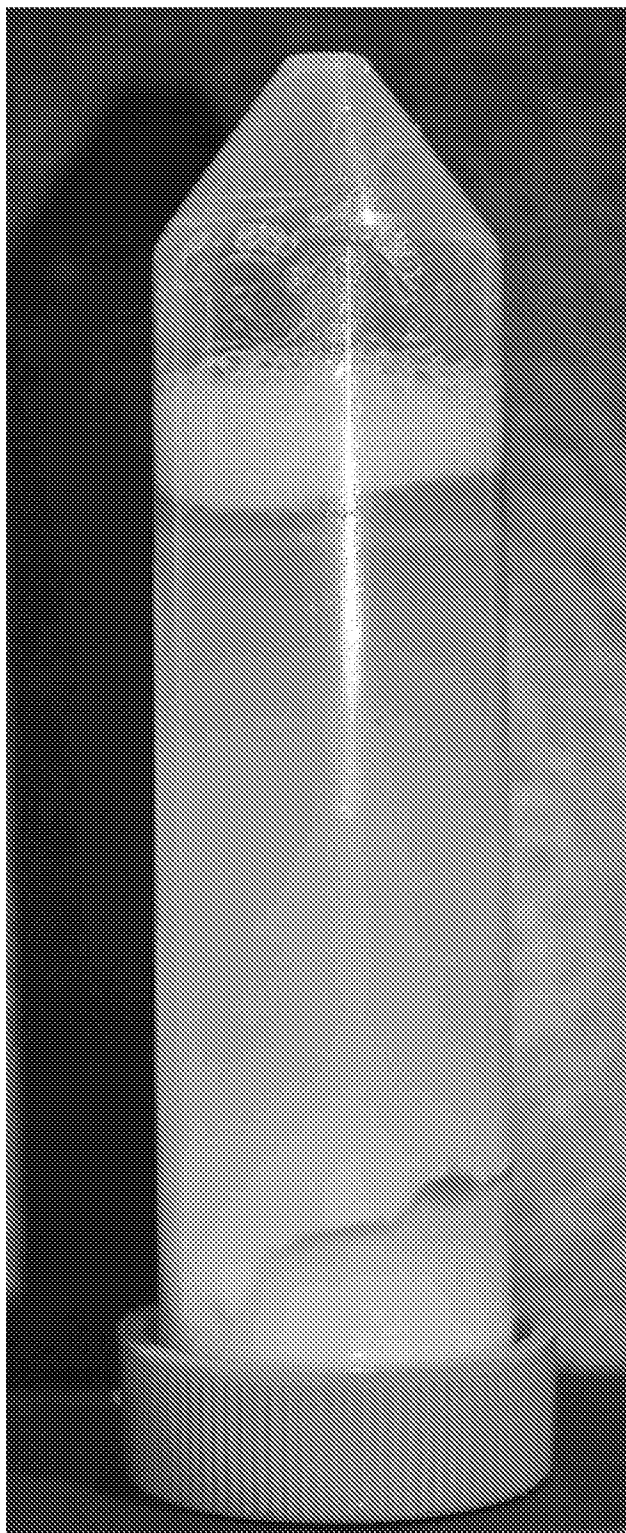


FIG 2

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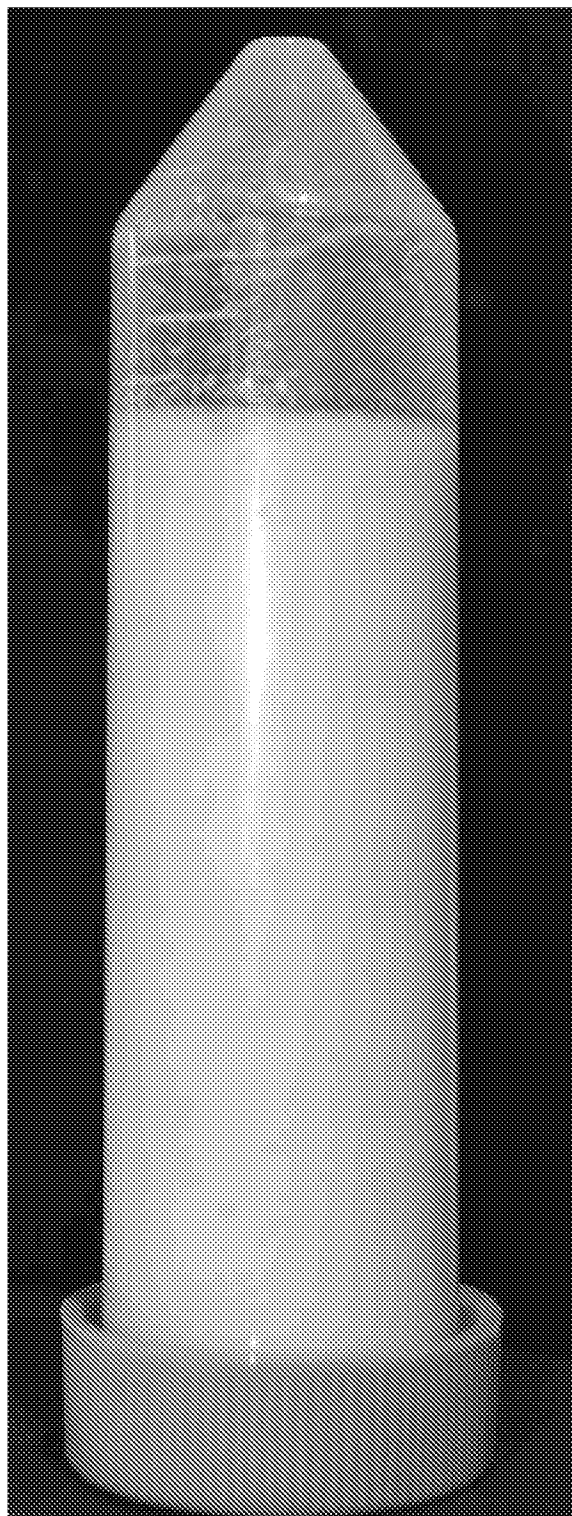


FIG 3

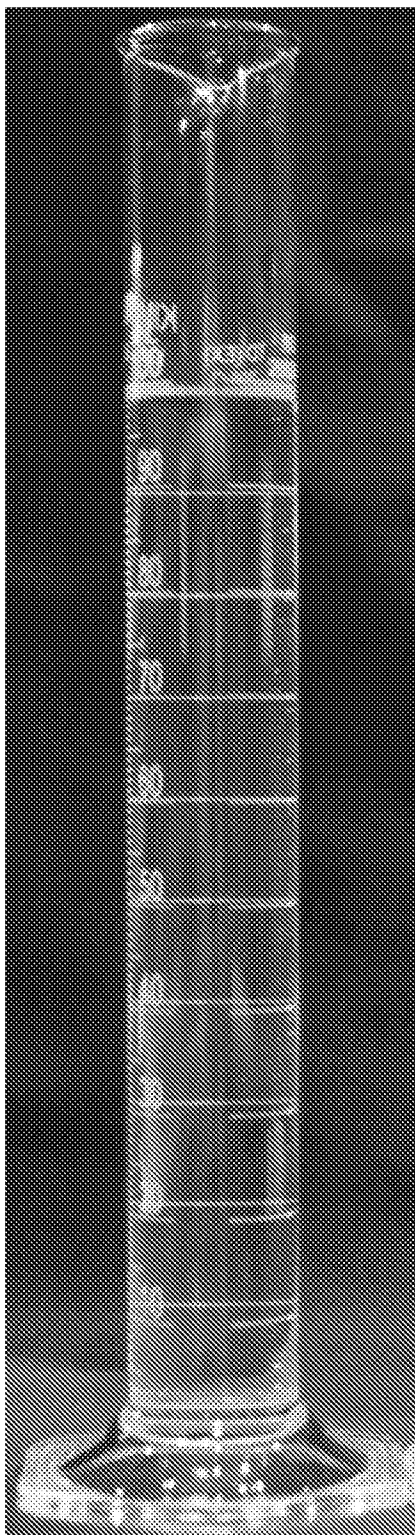


FIG 4A

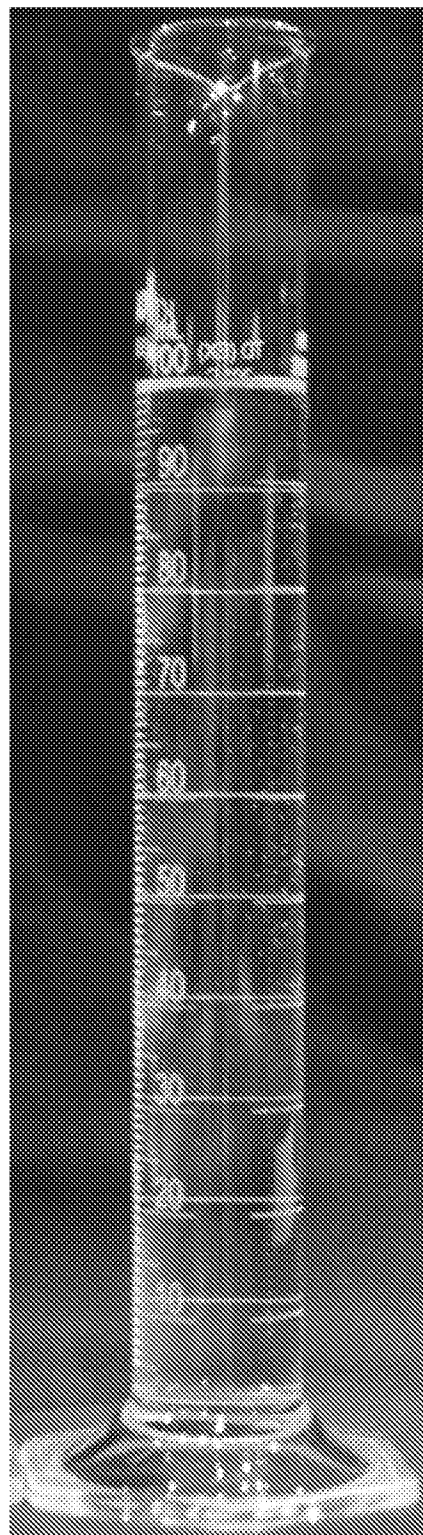
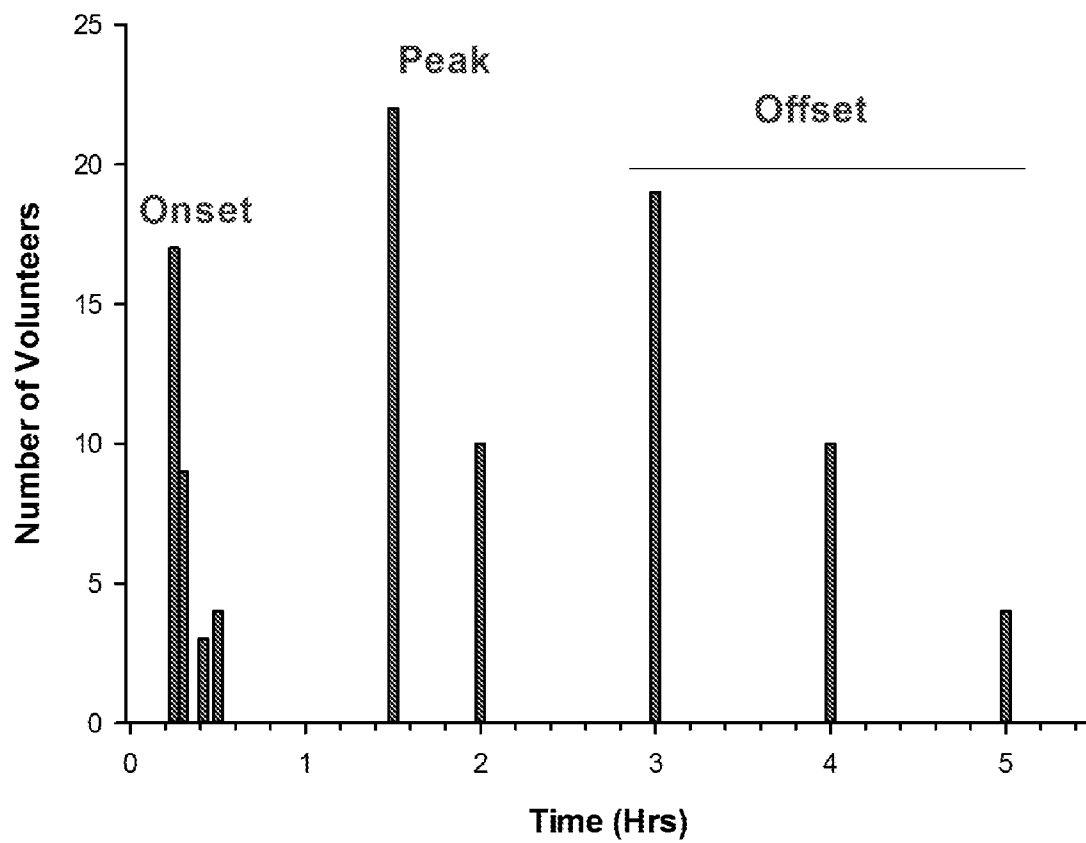


FIG 4B

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Pre-Clinical Sensation Timing

**FIG 5**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2019/060799

A. CLASSIFICATION OF SUBJECT MATTER IPC: <i>A61K 47/40</i> (2006.01), <i>A21D 13/00</i> (2017.01), <i>A23G 3/42</i> (2006.01), <i>A23G 3/48</i> (2006.01), <i>A23L 33/10</i> (2016.01), <i>A23L 33/105</i> (2016.01) (more IPCs on the last page) 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) <i>A61K 47/40</i> (2006.01), <i>A21D 13/00</i> (2017.01), <i>A23G 3/42</i> (2006.01), <i>A23G 3/48</i> (2006.01), <i>A23L 33/10</i> (2016.01), <i>A23L 33/105</i> (2016.01) (more IPCs on the last page) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) Questel Orbit (FamPat), STNext (CAPlus), CIPO Library Discovery Tool, Canadian Patent Database: Artiss, *cyclodextrin*, cannabi*, and related terms.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Hazekamp et al., "Structure elucidation of the tetrahydrocannabinol complex with randomly methylated β -cyclodextrin", <i>European Journal of Pharmaceutical Sciences</i> 2006 , 29, 340-347. Entire document Cited in the application	1-20
X	US 2018/0085308 A1 (Renwick et al.) 29 March 2018 (29-03-2018) Entire document	1-20
☒ 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 "D" document cited by the applicant in the international application "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 24 February 2020 (24-02-2020)		Date of mailing of the international search report 04 March 2020 (04-03-2020)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476		Authorized officer Samantha Drouin (819) 639-8652

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2019/060799

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7,592,328 B2 (Jarho et al.) 22 September 2009 (22-09-2009) Entire document Cited in the application	1-20
P, X	CN 109953951 A (Luan et al.) 02 July 2019 (02-07-2019) Embodiment 1	1-20
P, X	CN 110496064 A (Liu et al.) 26 November 2019 (26-11-2019) Examples	1-20
P, X	Lv et al., "Structural analysis and cytotoxicity of host-guest inclusion complexes of cannabidiol with three native cyclodextrins", <i>Journal of Drug Delivery Science and Technology</i> 2019 , 51, 337-344. Published 19 March 2019 (19-03-2019) Entire document	1-20

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2019/060799

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2018085308A1	29 March 2018 (29-03-2018)	AU2017334283A1 CA3005885A1 CA3005889A1 CA3036585A1 US2018250262A1 US2018263953A1 US2018263954A1 WO2018058235A1	04 April 2019 (04-04-2019) 28 February 2019 (28-02-2019) 28 February 2019 (28-02-2019) 05 April 2018 (05-04-2018) 06 September 2018 (06-09-2018) 20 September 2018 (20-09-2018) 20 September 2018 (20-09-2018) 05 April 2018 (05-04-2018)
US7592328B2	22 September 2009 (22-09-2009)	US2005153931A1 AU2003205808A1 AU2003205808B2 AU2003205808C1 CA2476834A1 CA2476834C EP1476473A1 EP1476473B1 FI20020334A FI113340B NZ535154A US2009298929A1 WO03070775A1	14 July 2005 (14-07-2005) 09 September 2003 (09-09-2003) 24 April 2008 (24-04-2008) 09 October 2008 (09-10-2008) 28 August 2003 (28-08-2003) 01 December 2015 (01-12-2015) 17 November 2004 (17-11-2004) 18 June 2014 (18-06-2014) 21 August 2003 (21-08-2003) 15 April 2004 (15-04-2004) 26 January 2007 (26-01-2007) 03 December 2009 (03-12-2009) 28 August 2003 (28-08-2003)
CN109953951A	02 July 2019 (02-07-2019)	None	
CN110496064A	26 November 2019 (26-11-2019)	None	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2019/060799**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 1, 2, 5-7, and 13-17 (each in part)
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:

See the extra sheet

3. ☐ Claim Nos.:
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 claim Nos.:

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of Box No. 2

Claims 1, 2, 5-7, and 13-17 define complexes of α -cyclodextrin and “one or more cannabinoids, one or more terpenes, or mixtures of such complexes” (emphasis added). The expression “one or more terpenes” encompasses a vast number of compounds. By contrast, the present application provides empirical evidence of complexation only for cannabis products. The application provides adequate disclosure within the meaning of Article 5 for specifically only complexes of α -cyclodextrin and one or more cannabinoids or one or more cannabis-derived terpenes. In the present case, the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been established for the parts of the application which appear to be clear and/or supported, namely for complexes of α -cyclodextrin and one or more cannabinoids, one or more cannabis-derived terpenes, or mixtures of such complexes.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2019/060799

A23L 33/125 (2016.01), *A61K 31/05* (2006.01), *A61K 31/352* (2006.01), *A61K 36/185* (2006.01),
C07C 39/23 (2006.01), *C07D 311/60* (2006.01), *C07D 311/80* (2006.01)