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(19) **United States**(12) **Patent Application Publication****Nowak et al.**(10) **Pub. No.: US 2021/0038520 A1**(43) **Pub. Date: Feb. 11, 2021**(54) **MULTIPARTICULATE FORMULATIONS OF CANNABINOIDS**(71) Applicant: **Glatt GmbH**, Binzen (DE)(72) Inventors: **Reinhard Nowak**, Lörrach (DE); **Zafar Iqbal**, Sloatsburg, NY (US); **Mohammed Taleb**, Nanuet, NY (US); **Neha Chavan**, Jamaica, NY (US)(73) Assignee: **Glatt GmbH**, Binzen (DE)(21) Appl. No.: **17/081,189**(22) Filed: **Oct. 27, 2020***A61K 36/185* (2006.01)*A61K 31/05* (2006.01)*A61K 9/48* (2006.01)*A61K 31/352* (2006.01)(52) **U.S. Cl.**CPC *A61K 9/1652* (2013.01); *A61K 9/1623* (2013.01); *A61K 9/1664* (2013.01); *A61K 9/1617* (2013.01); *A61K 9/1676* (2013.01); *A61K 9/1635* (2013.01); *A61K 31/352* (2013.01); *A61K 36/185* (2013.01); *A61K 31/05* (2013.01); *A61K 9/1658* (2013.01); *A61K 9/0053* (2013.01); *A61K 9/1611* (2013.01); *A61K 9/48* (2013.01); *A61K 9/0056* (2013.01)**Related U.S. Application Data**

(62) Division of application No. 16/513,238, filed on Jul. 16, 2019.

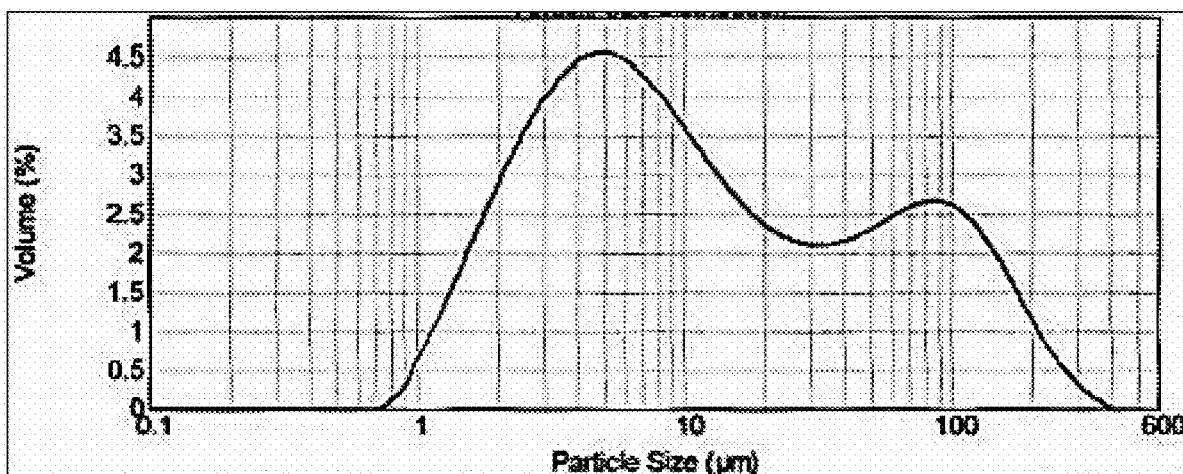
(60) Provisional application No. 62/700,107, filed on Jul. 18, 2018.

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(57)

ABSTRACT

Compositions for the immediate release, extended release, or sustained release of two or more active agents, in which the two or more active agents comprises at least one cannabinoid and at least one non-cannabinoid therapeutic agent. The compositions comprise a population of particles, in which each particles comprises the at least one cannabinoid, the at least one non-cannabinoid therapeutic agent, or a combination thereof.



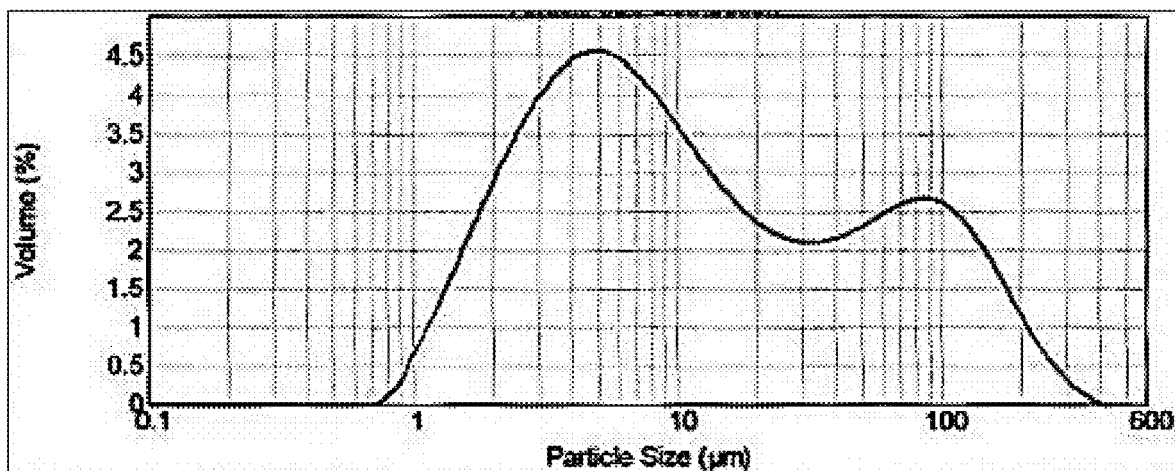


Figure 1A

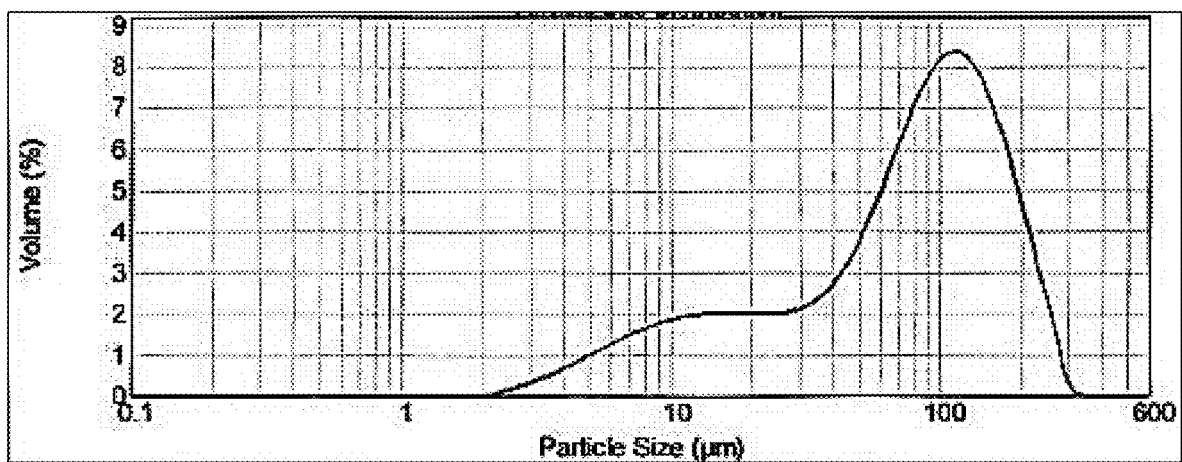


Figure 1B

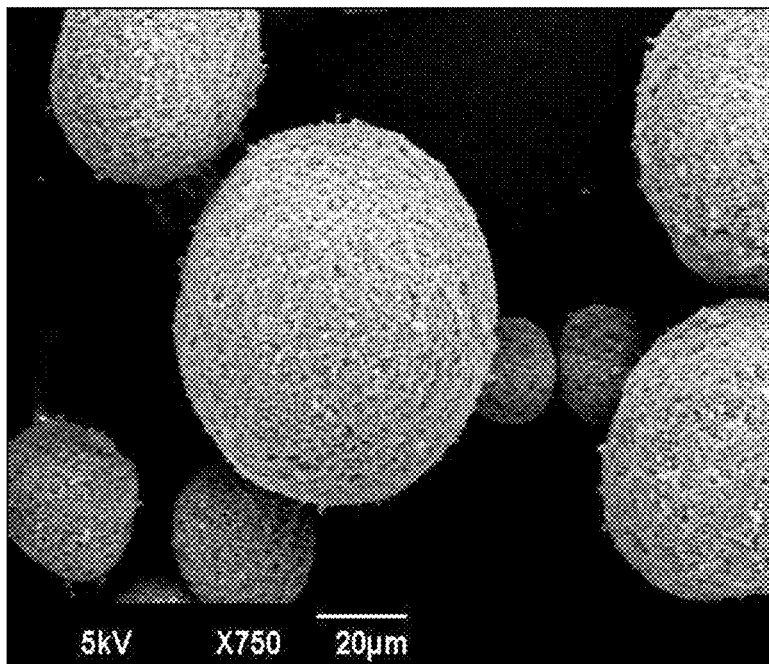


Figure 2A

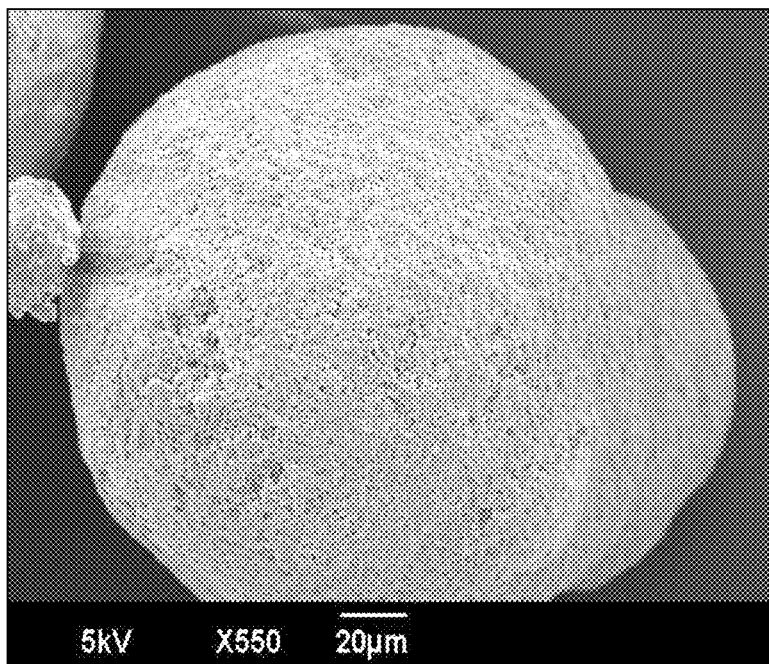


Figure 2B

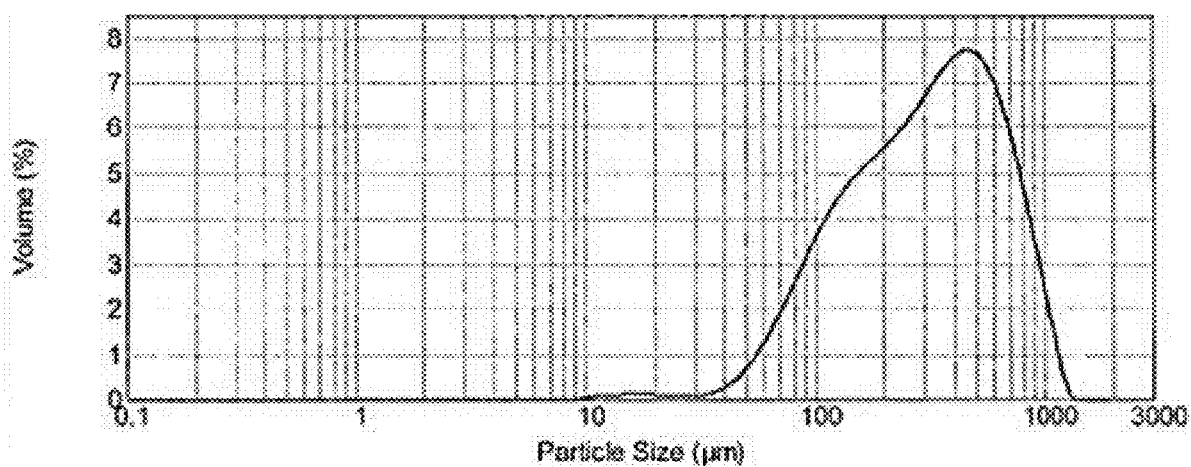


Figure 3

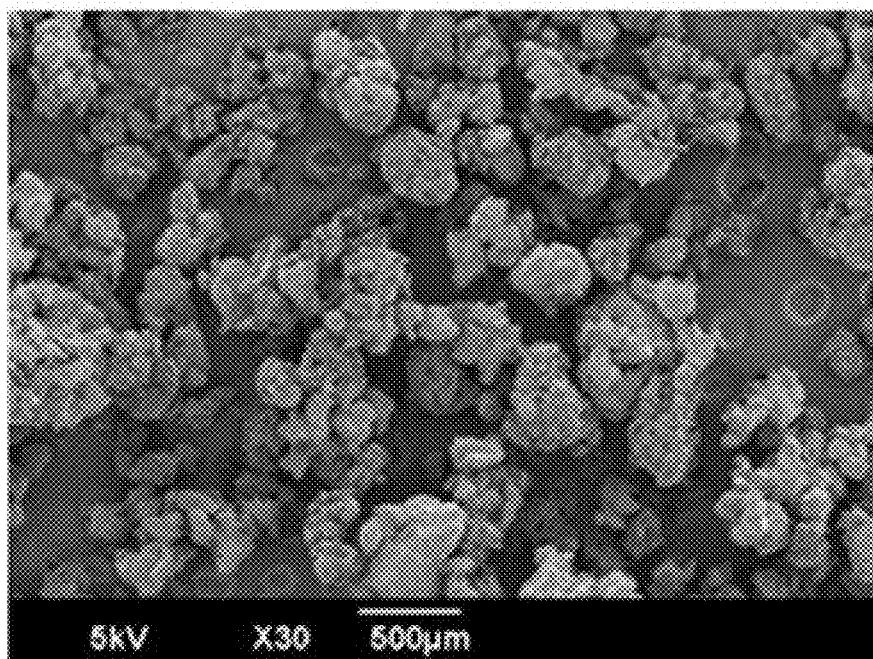


Figure 4A

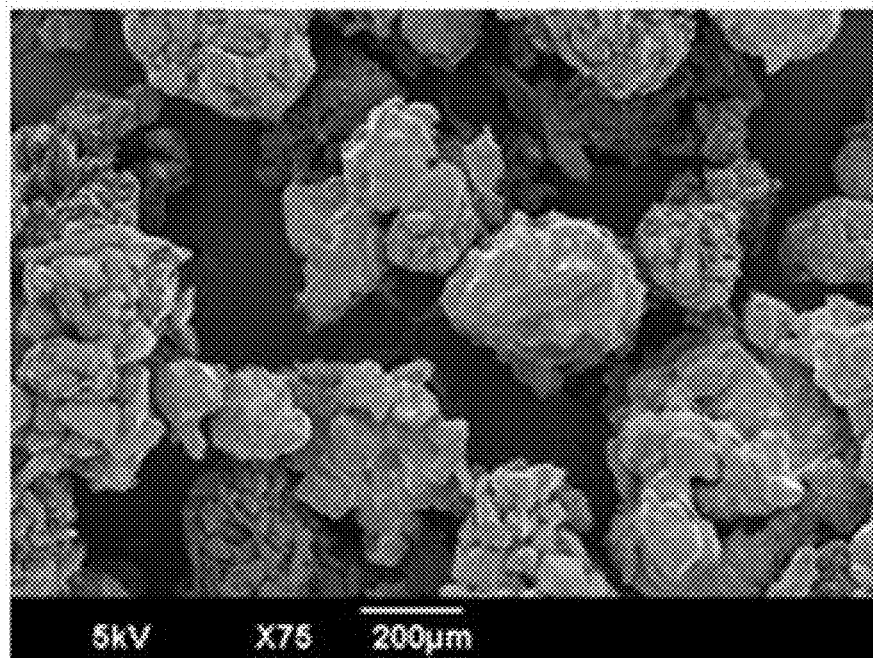


Figure 4B

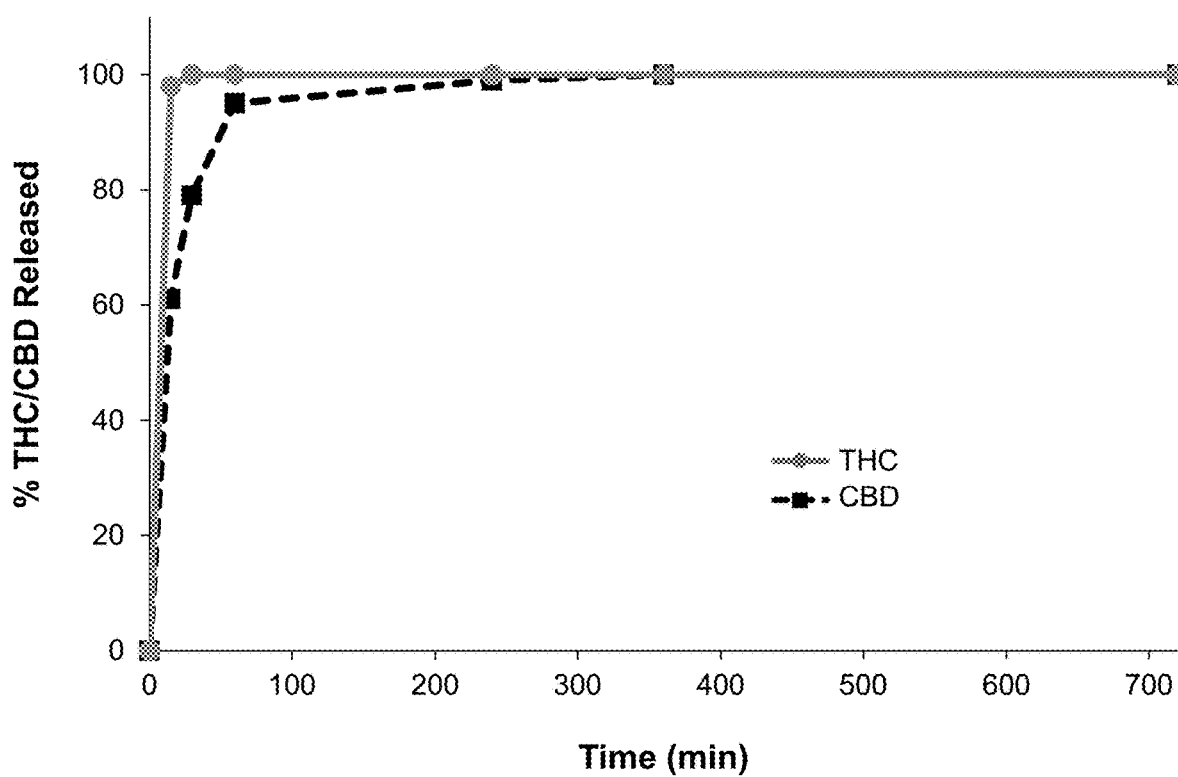


Figure 5

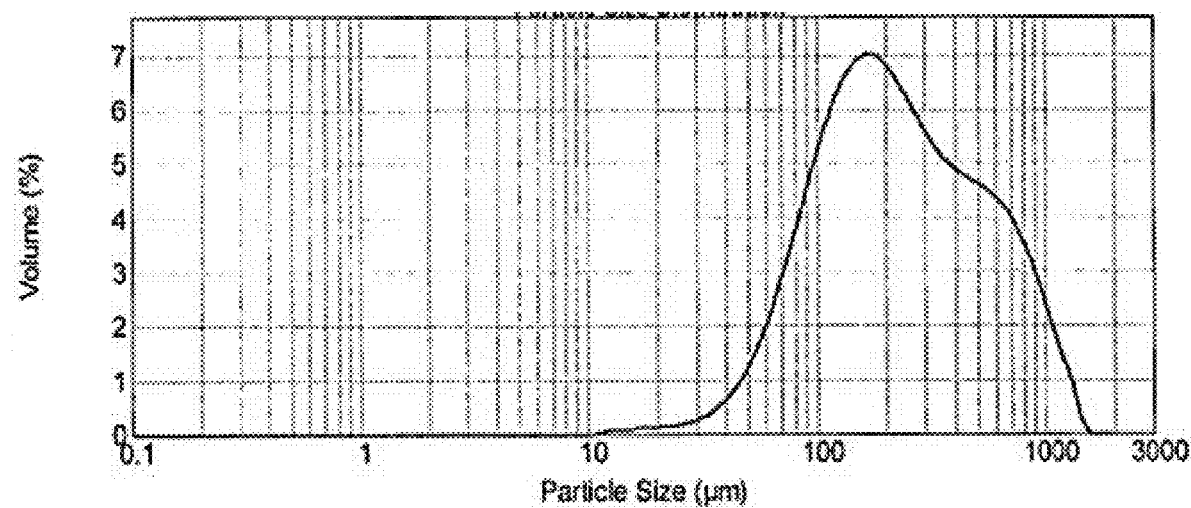


Figure 6

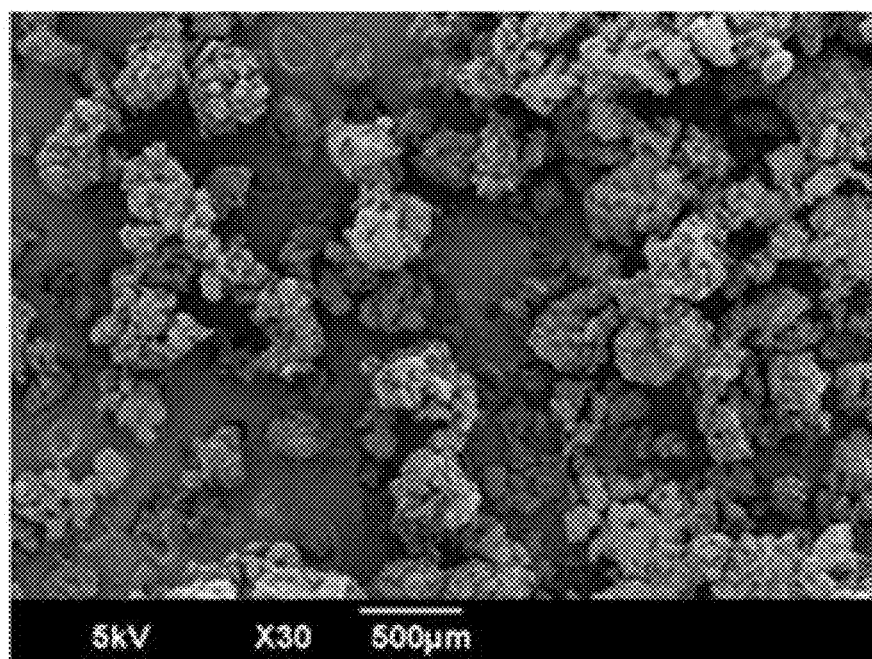


Figure 7A

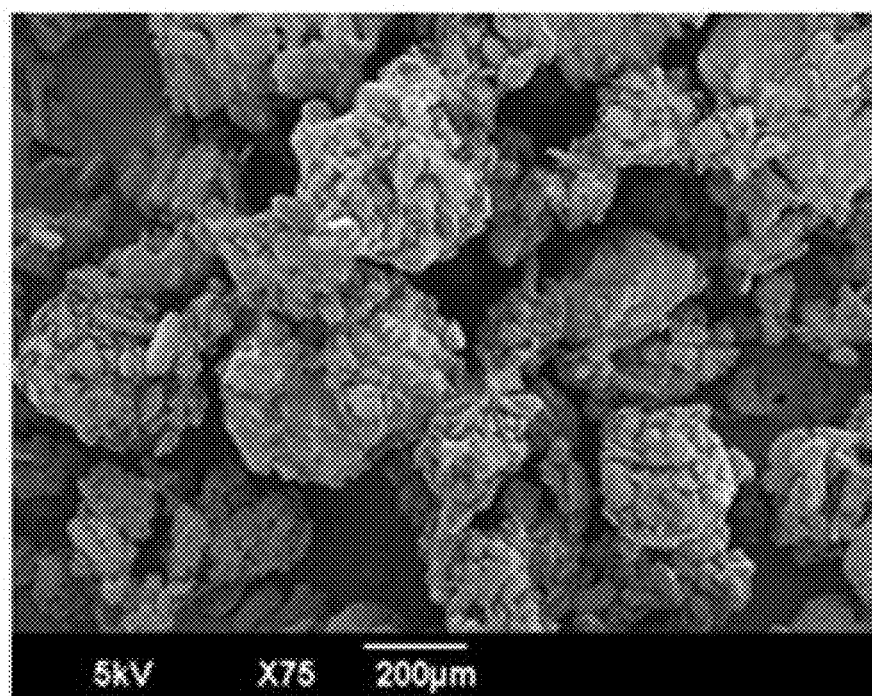


Figure 7B

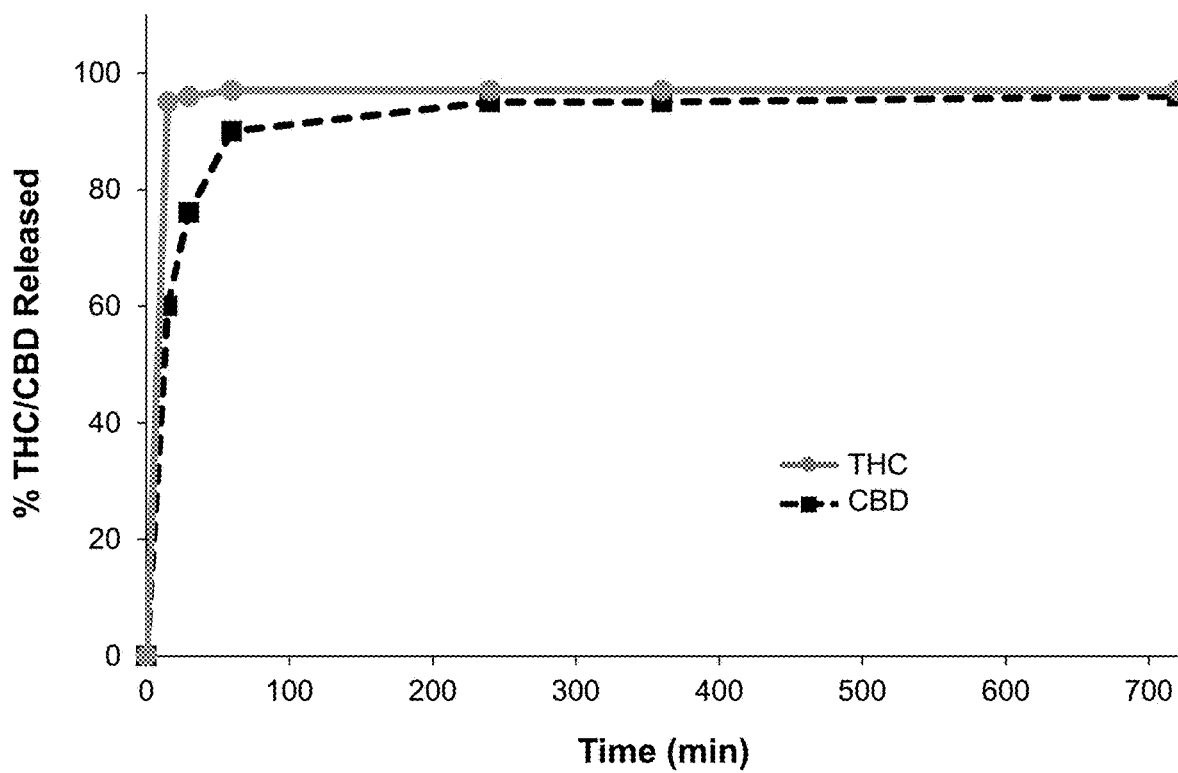


Figure 8

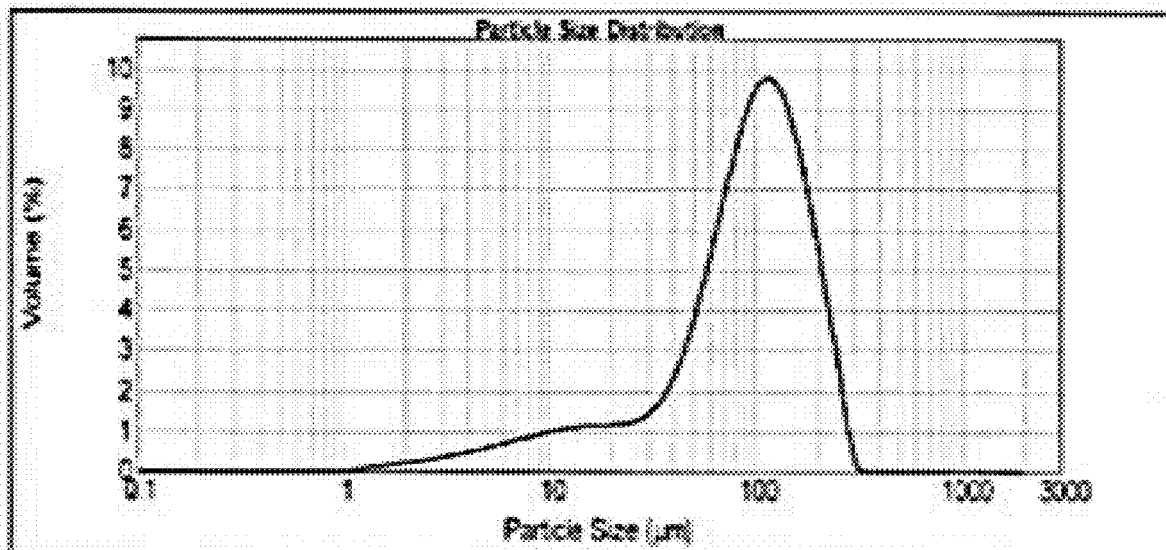


Figure 9A

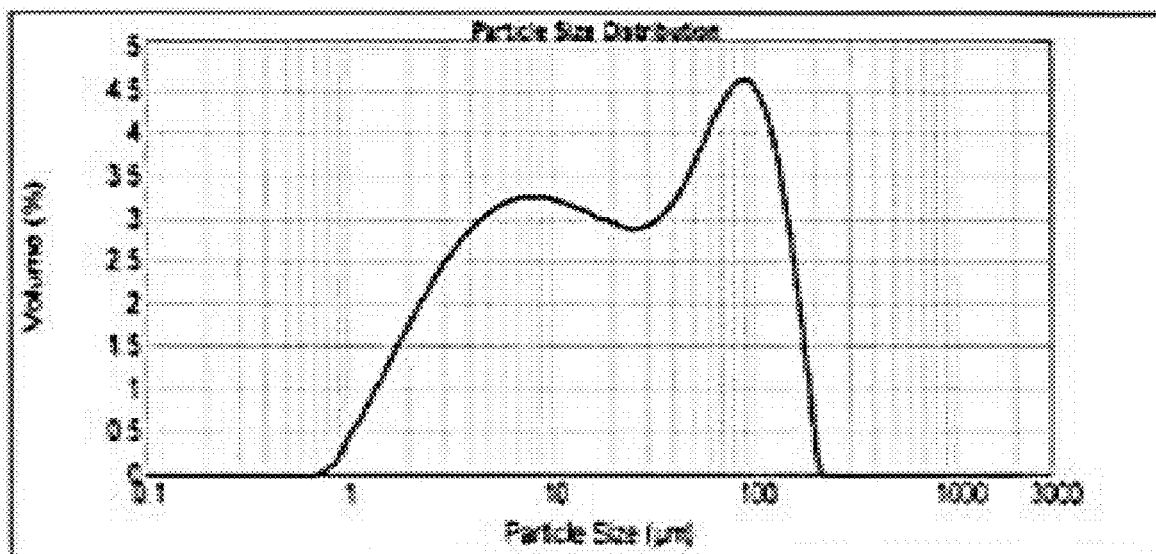


Figure 9B

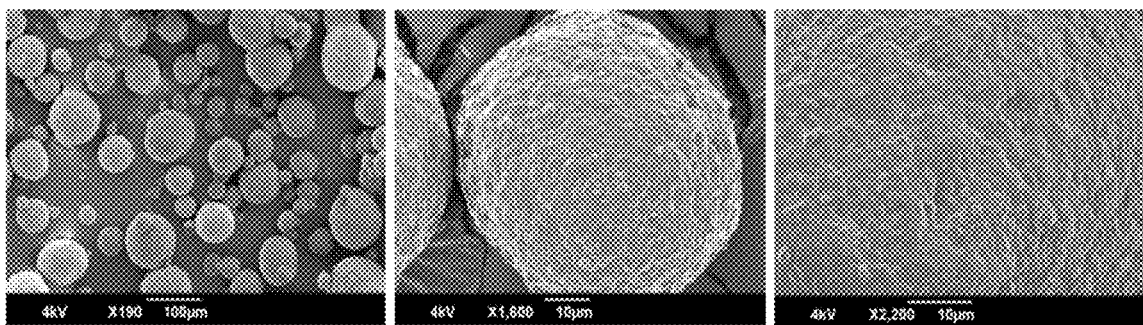


Figure 10A

Figure 10B

Figure 10C

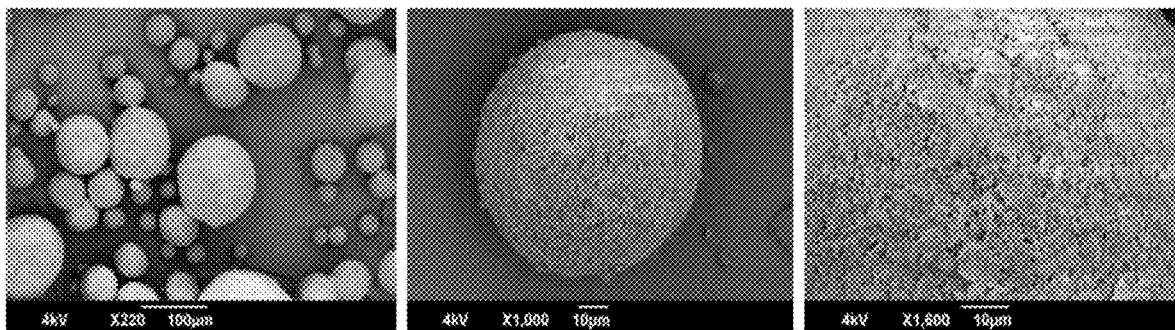


Figure 10D

Figure 10E

Figure 10F

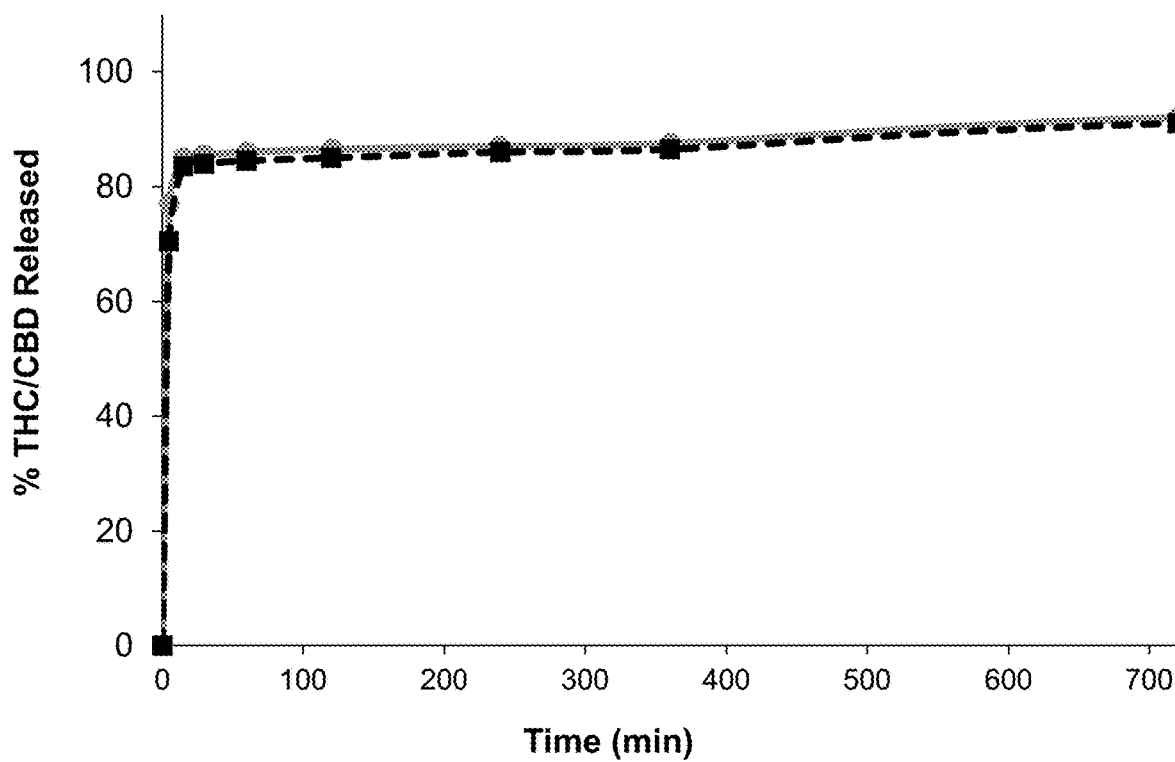


Figure 11

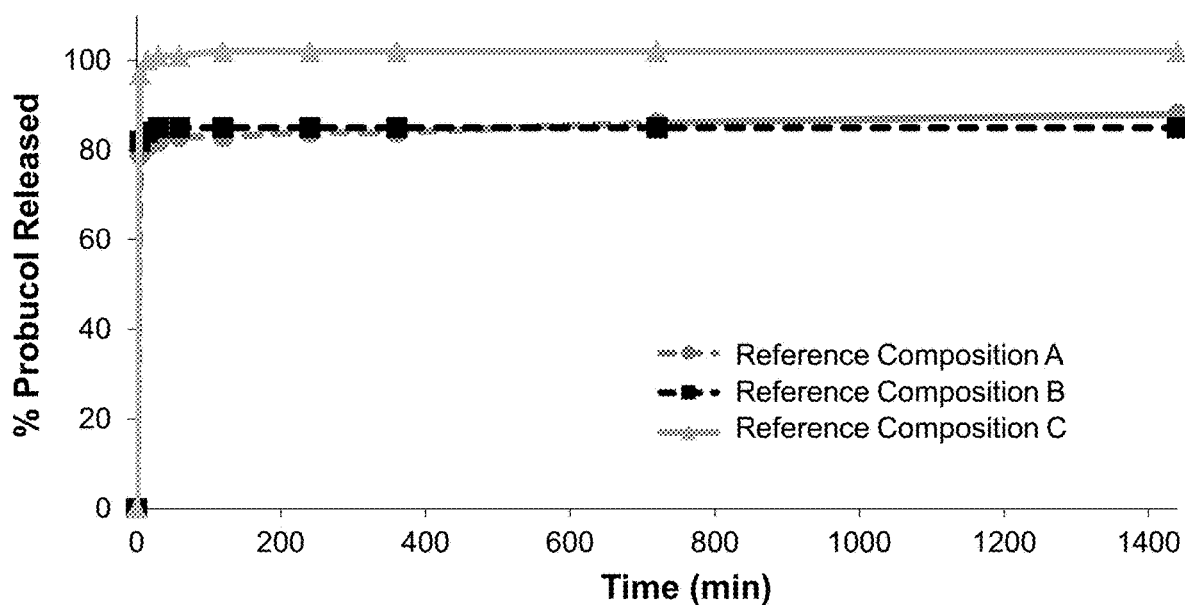


Figure 12A

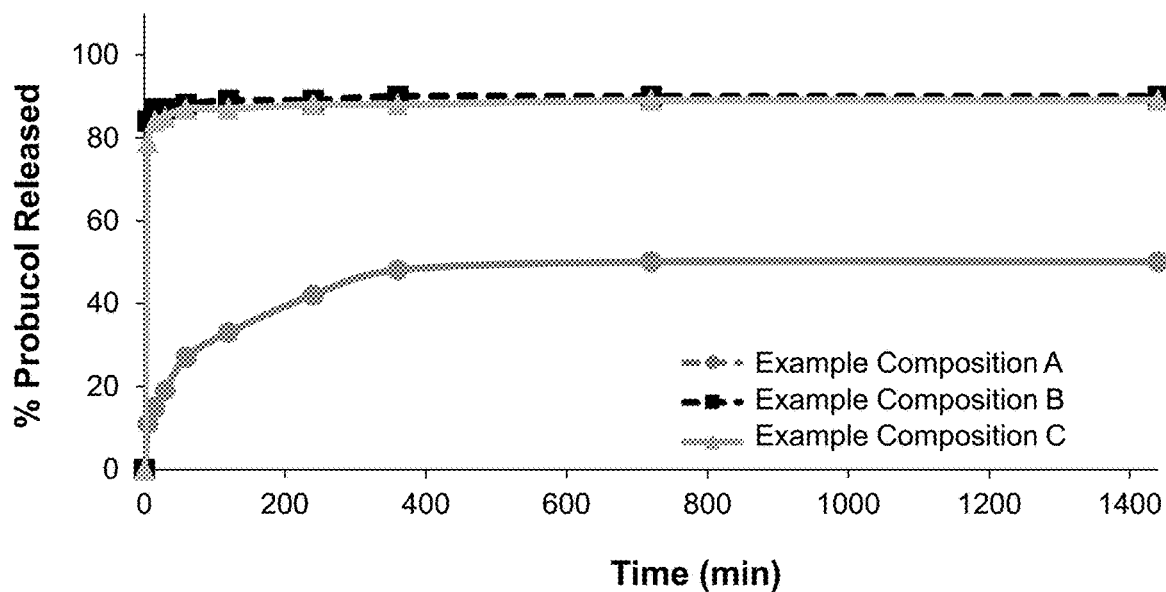


Figure 12B

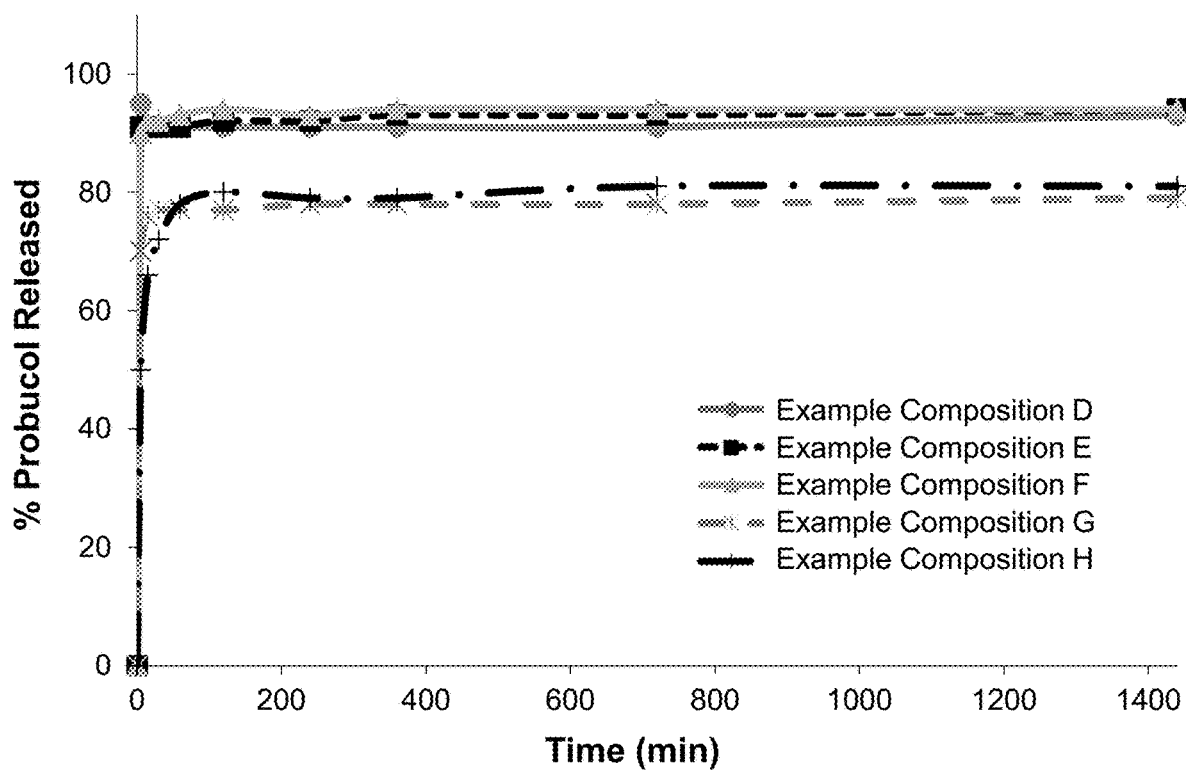


Figure 13

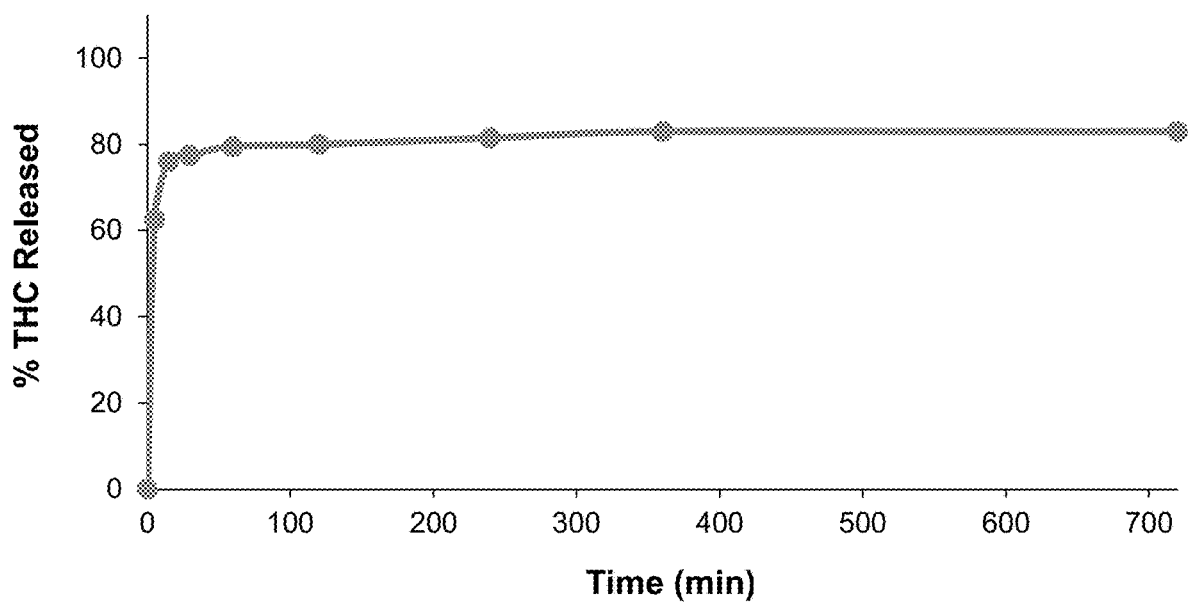


Figure 14A

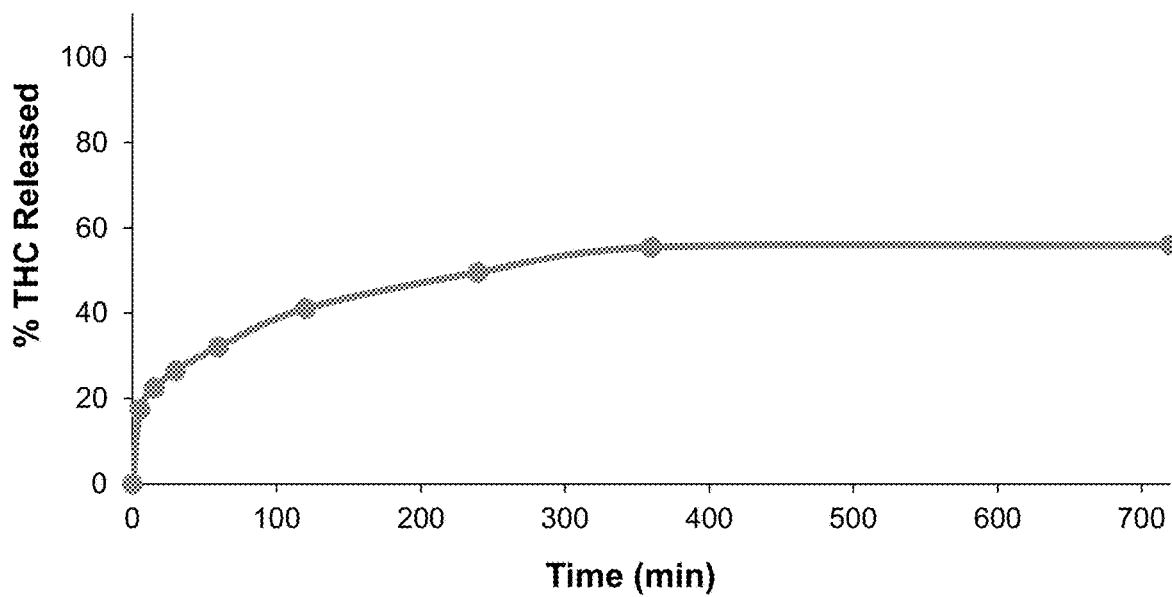


Figure 14B

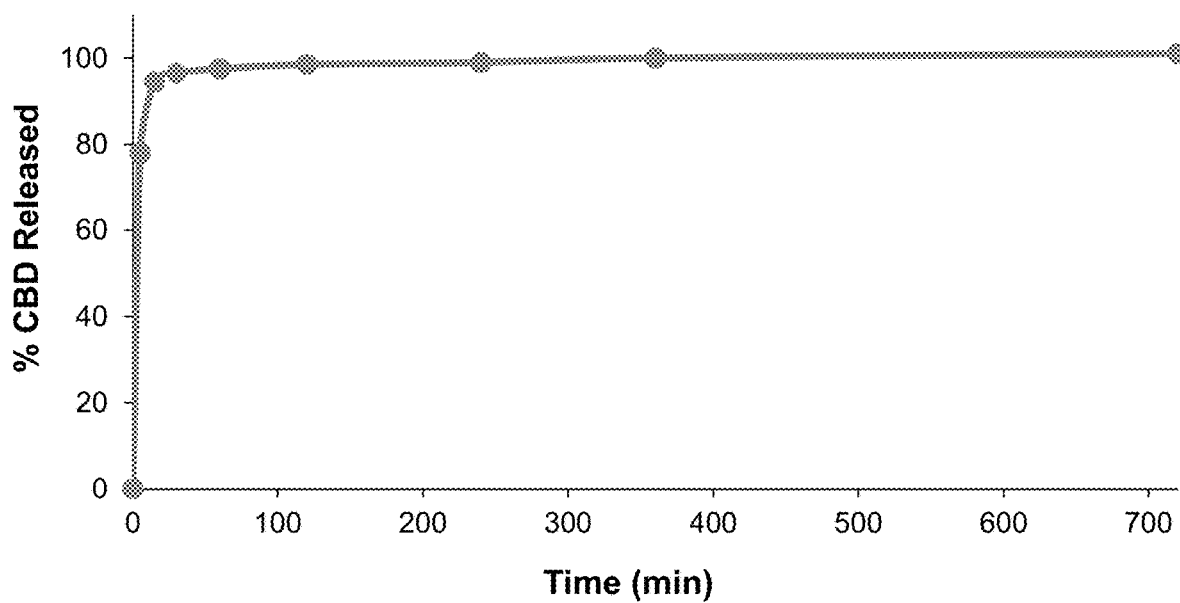


Figure 15A

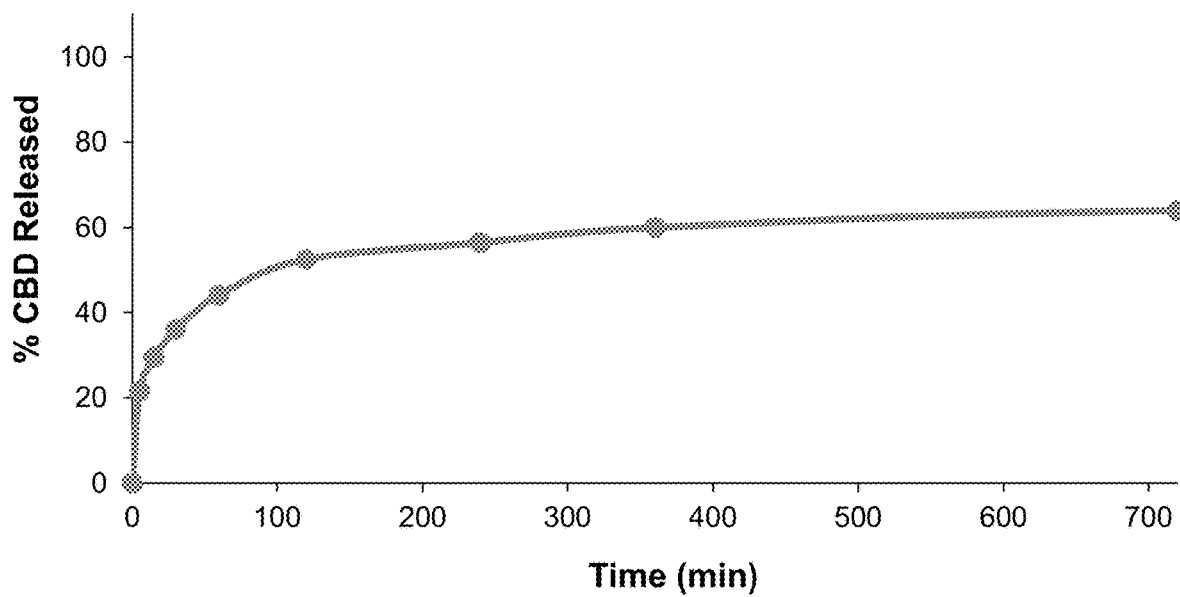


Figure 15B

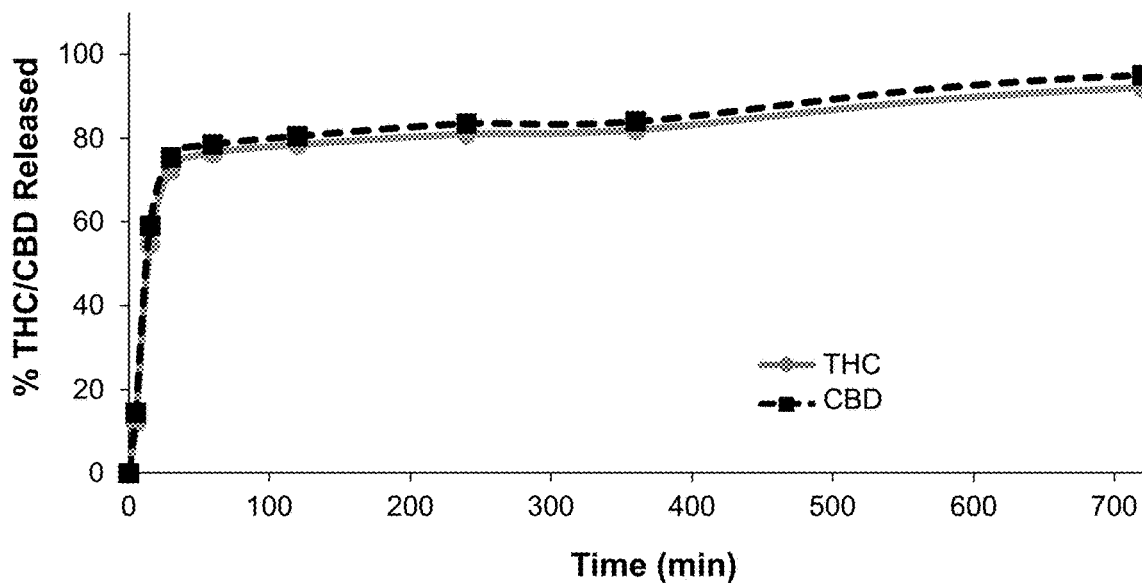


Figure 16A

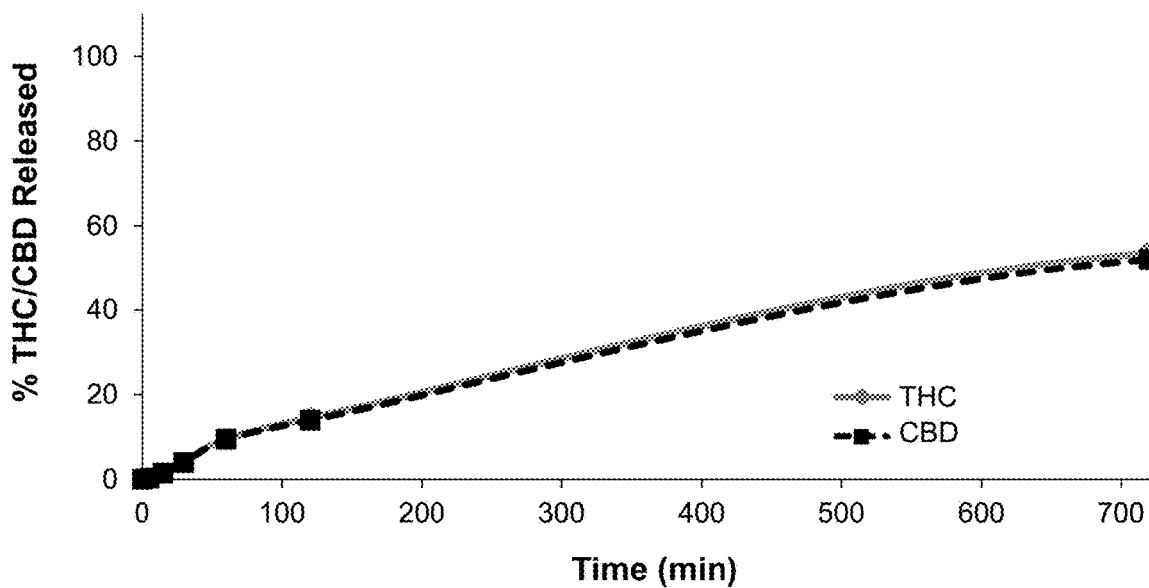


Figure 16B

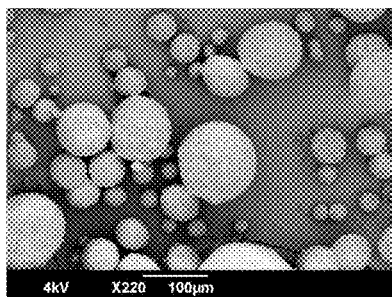


Figure 17A

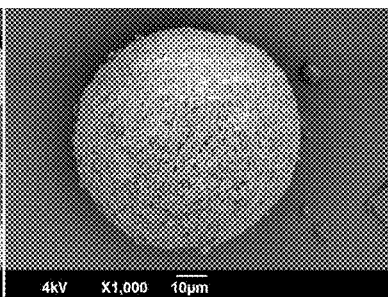


Figure 17B

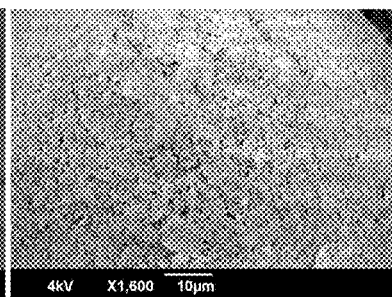


Figure 17C

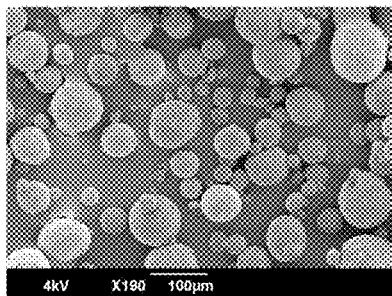


Figure 17D

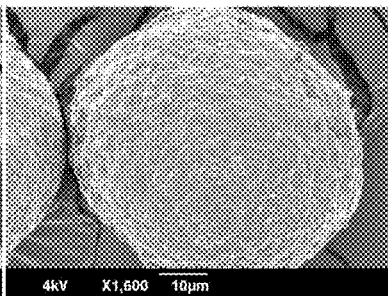


Figure 17E

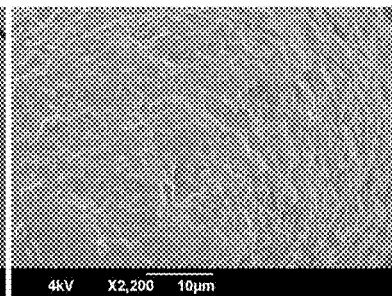


Figure 17F

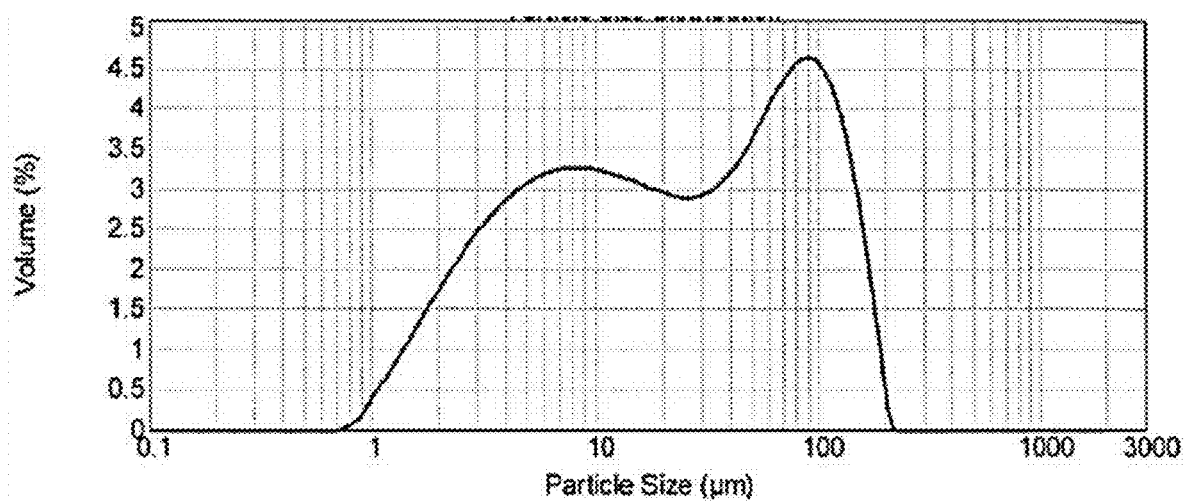


Figure 18A

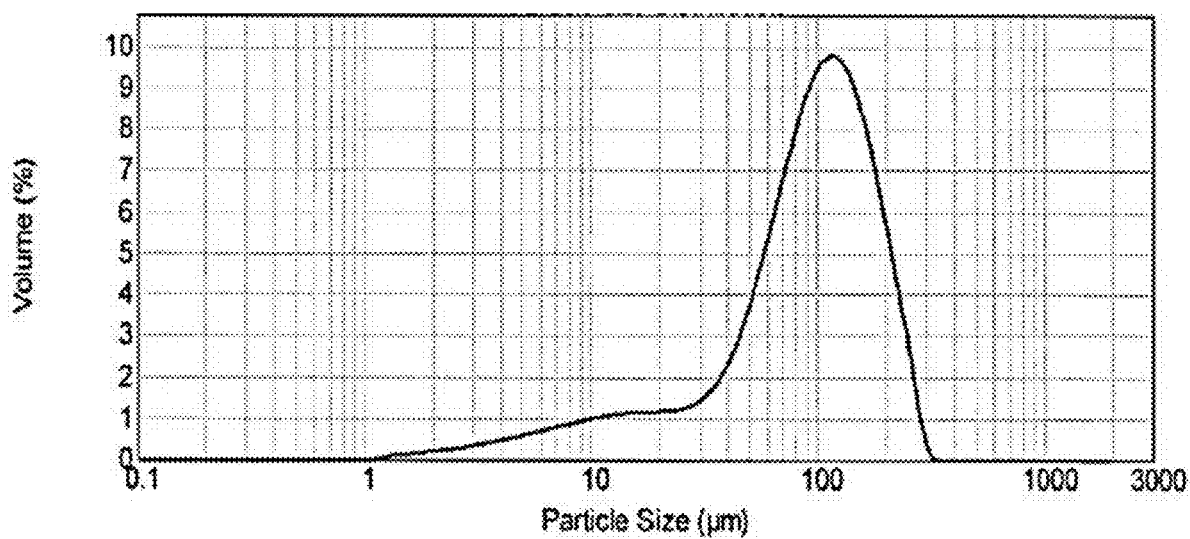


Figure 18B

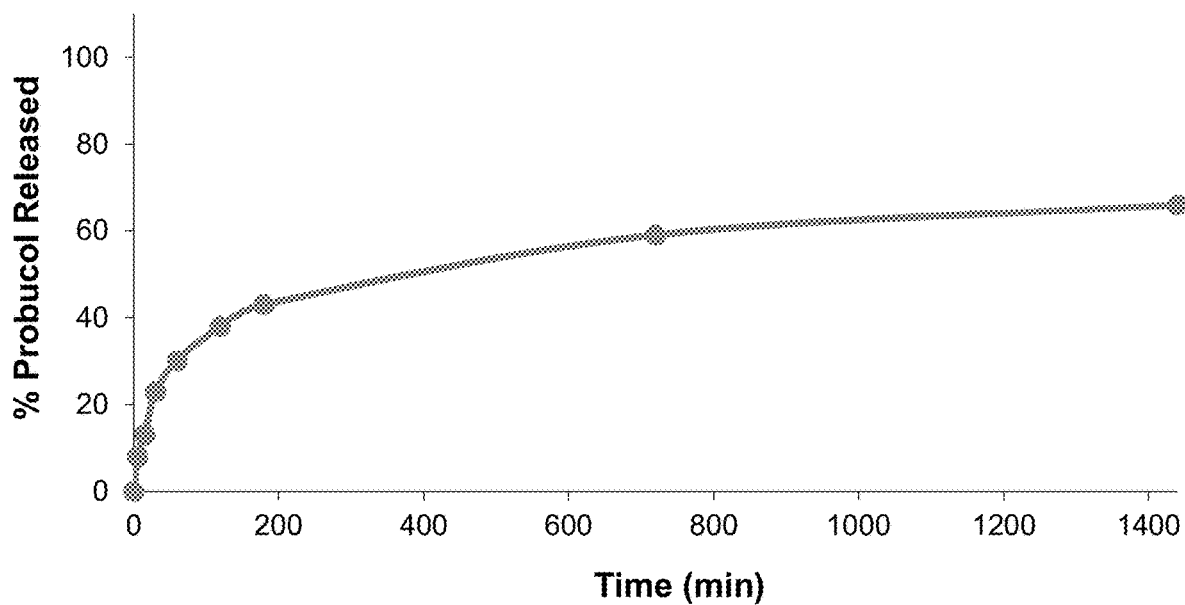


Figure 19A

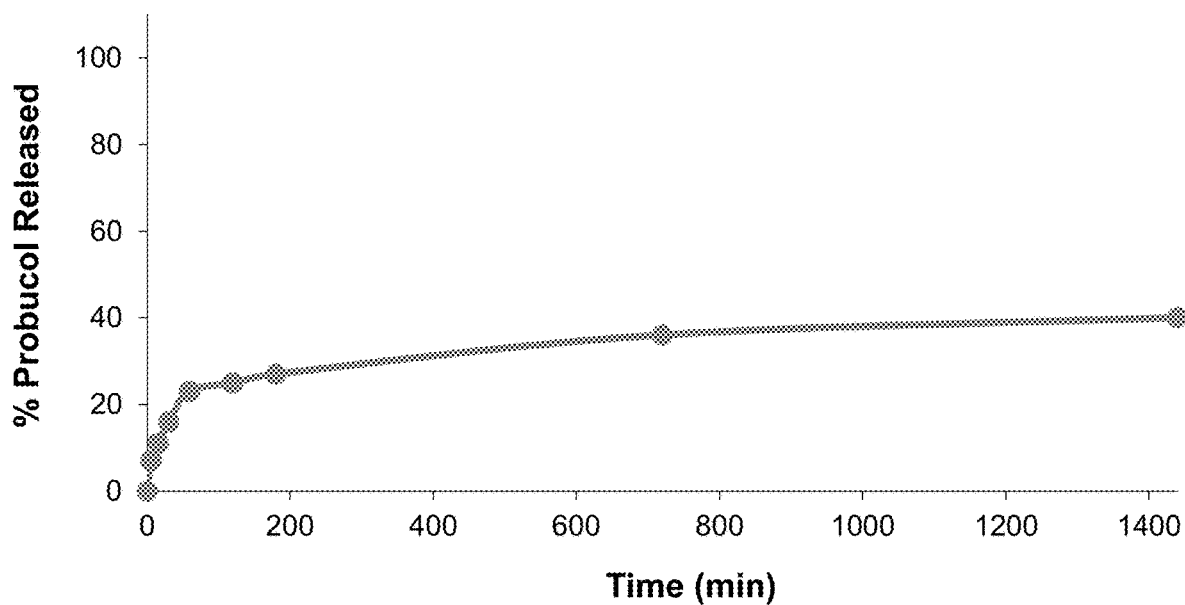


Figure 19B

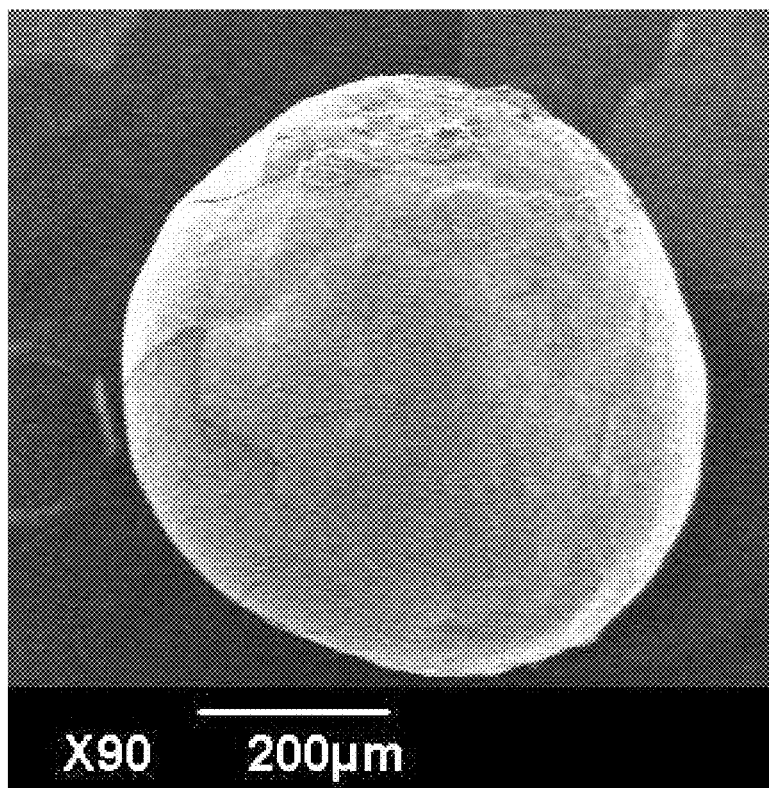


Figure 20

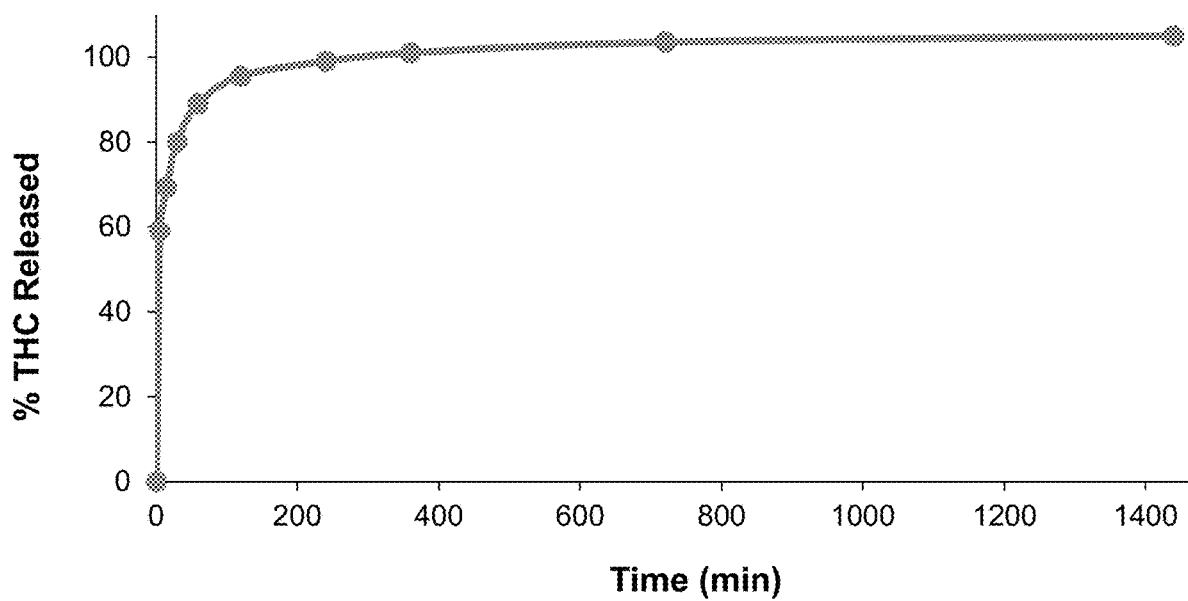


Figure 21A

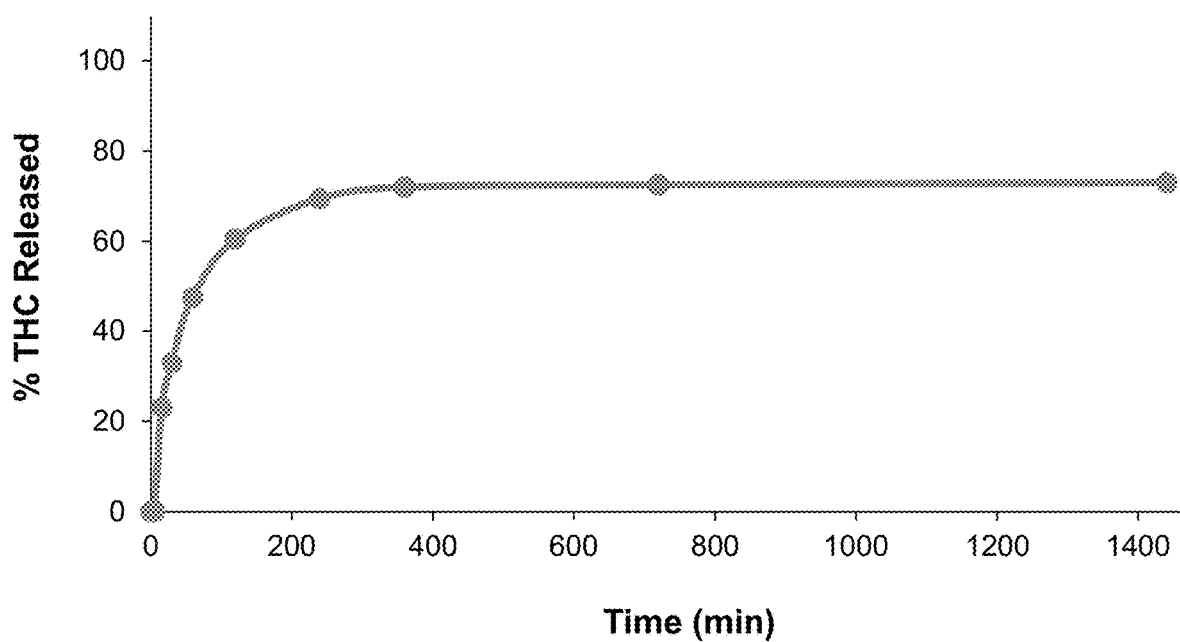


Figure 21B

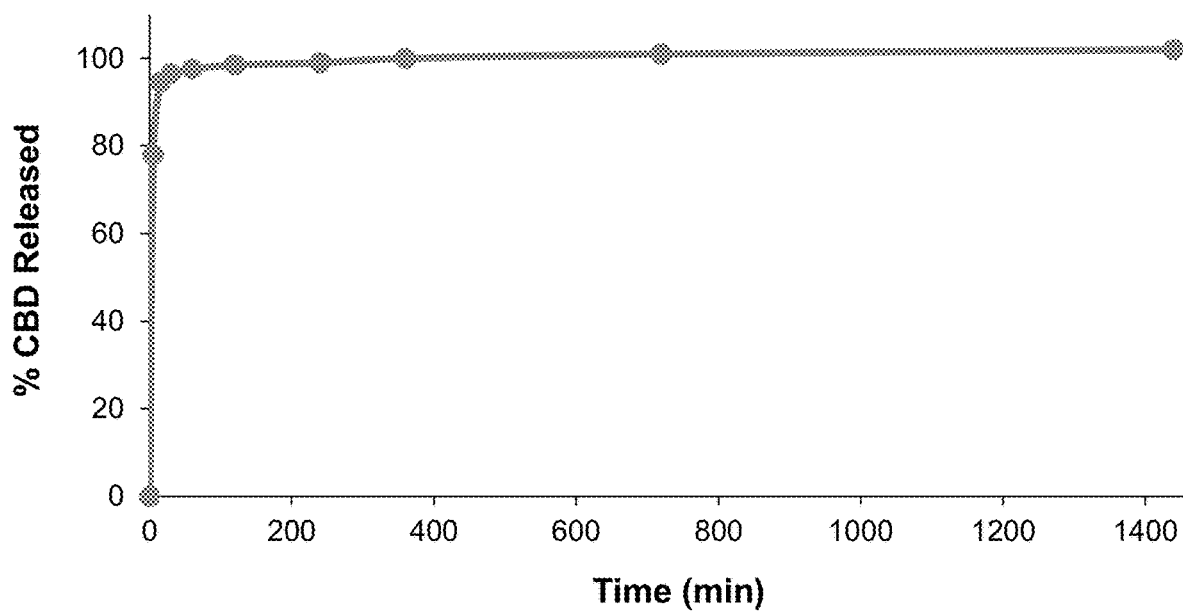


Figure 22A

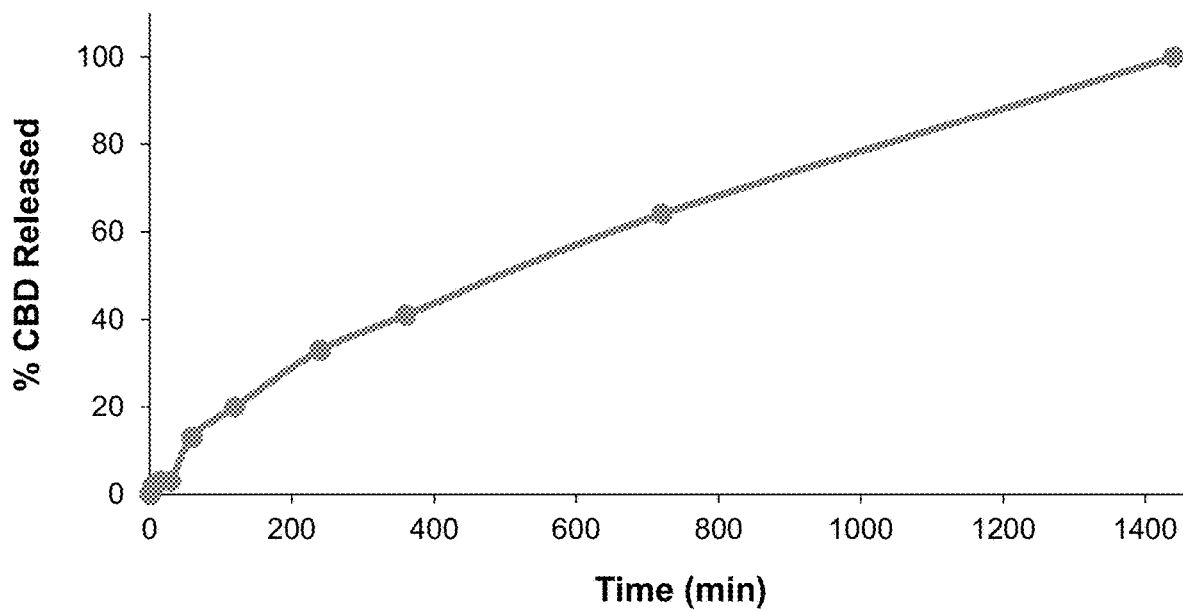


Figure 22B

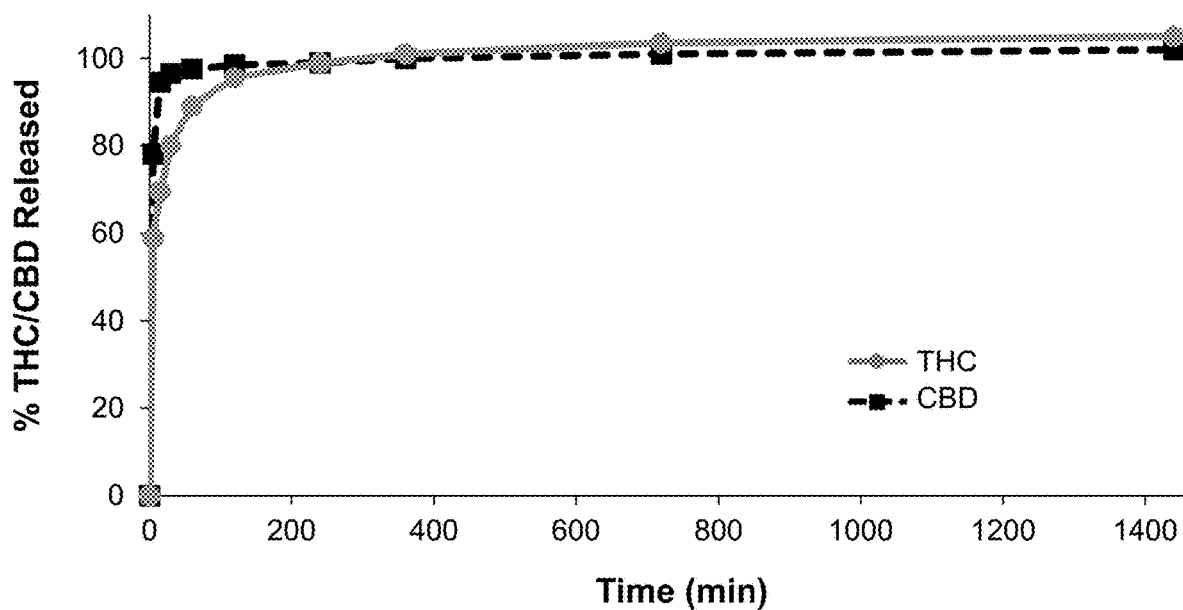


Figure 23A

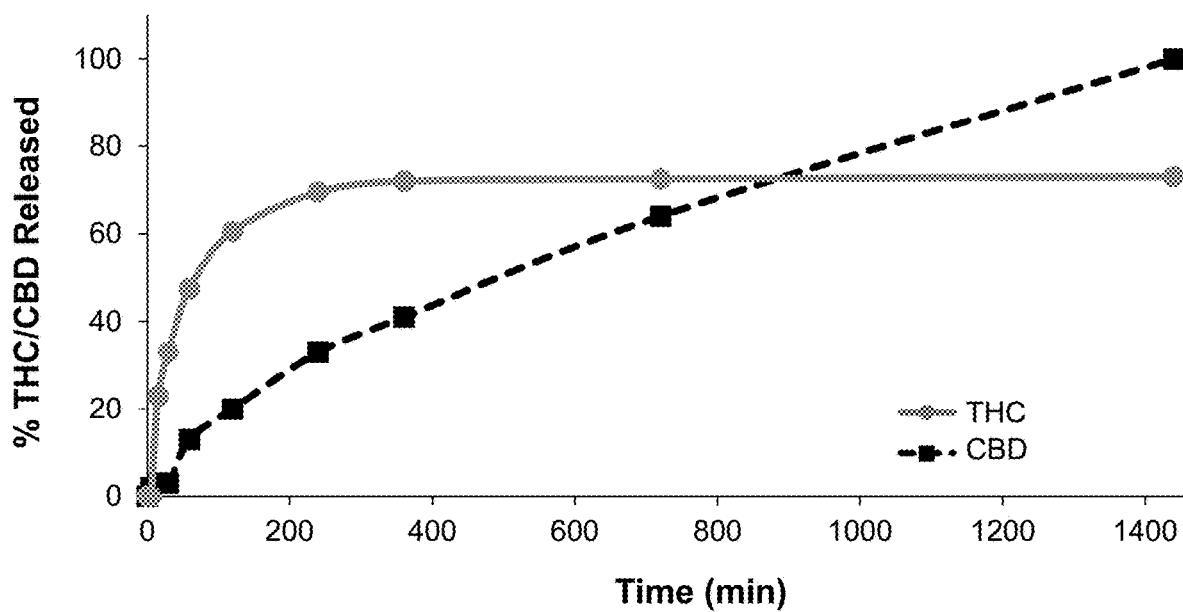


Figure 23B

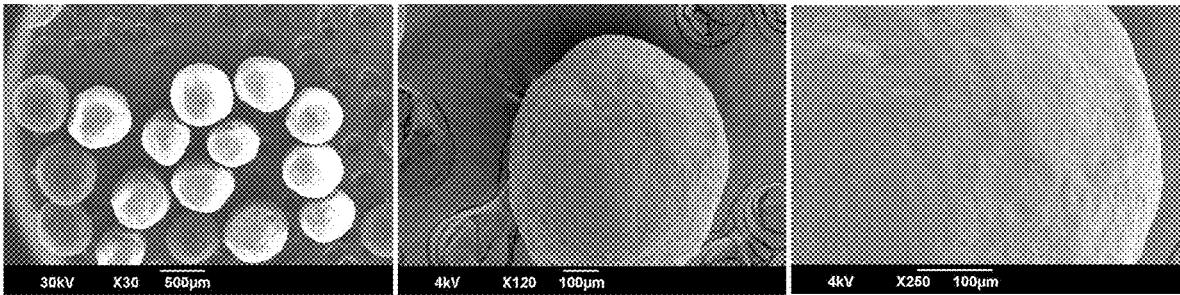


Figure 24A

Figure 24B

Figure 24C

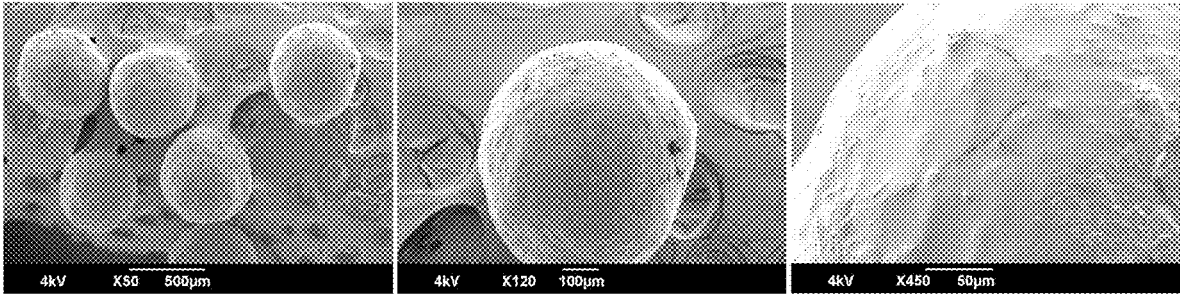


Figure 24D

Figure 24E

Figure 24F

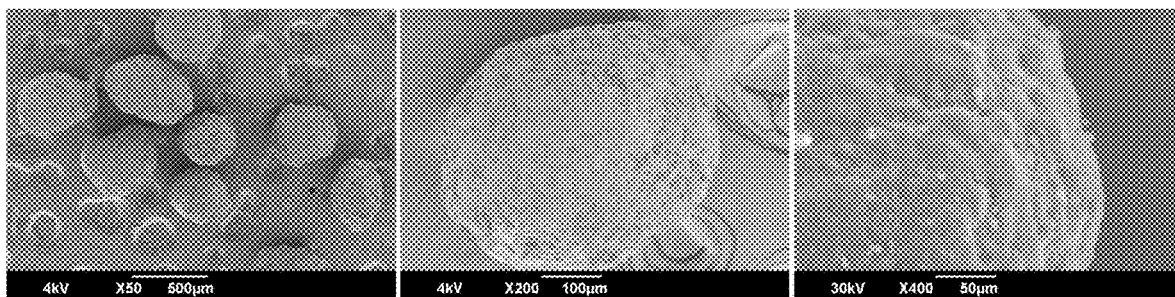


Figure 25A

Figure 25B

Figure 25C

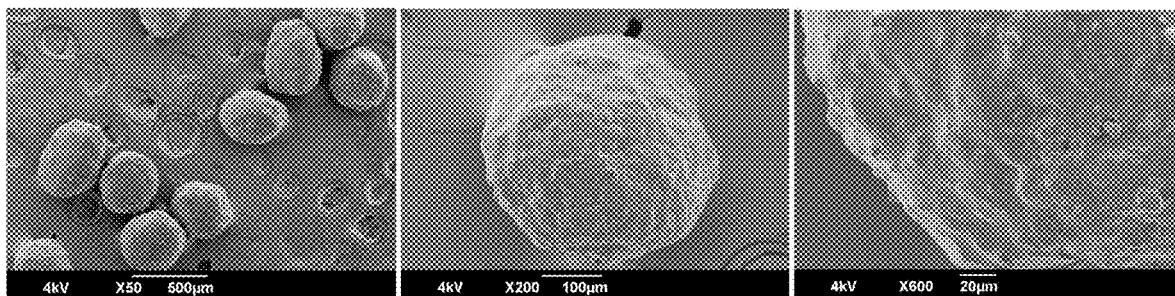


Figure 25D

Figure 25E

Figure 25F

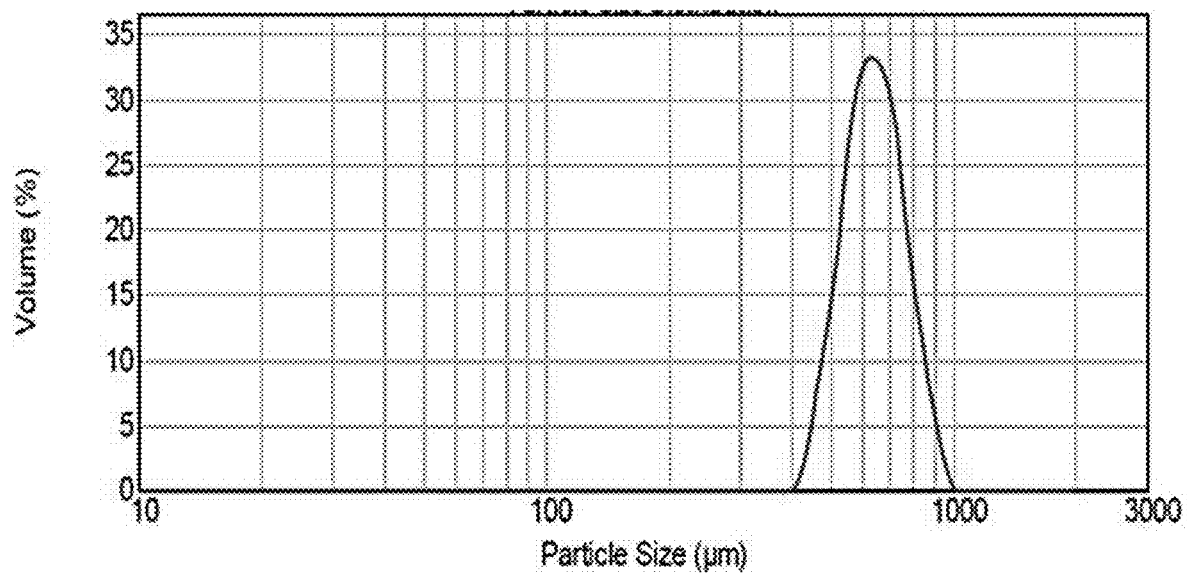


Figure 26A

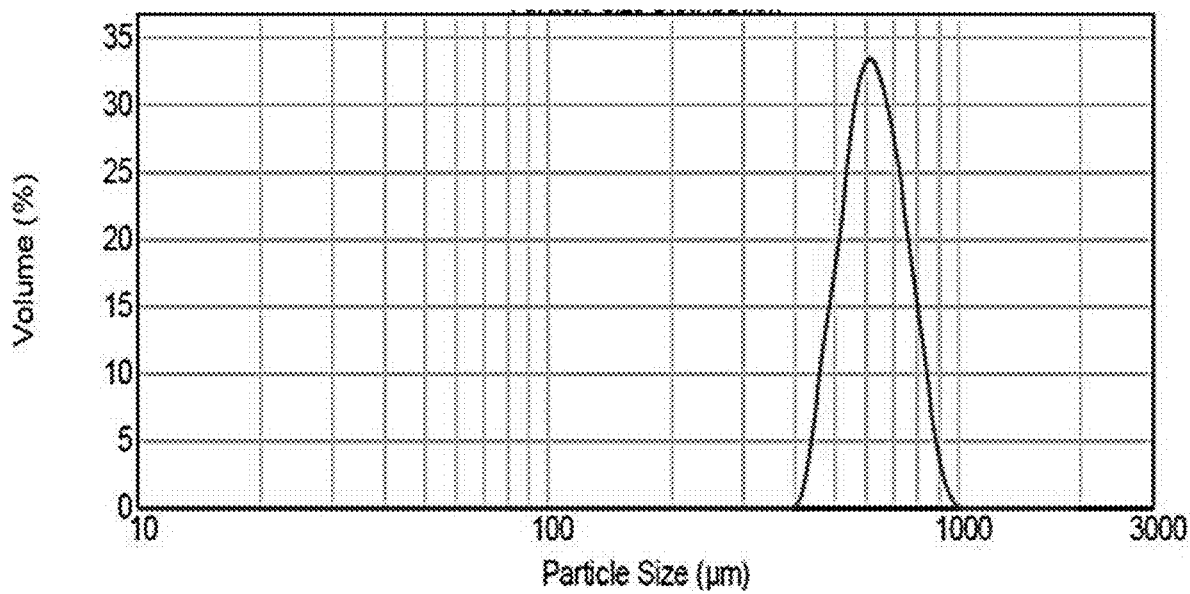


Figure 26B

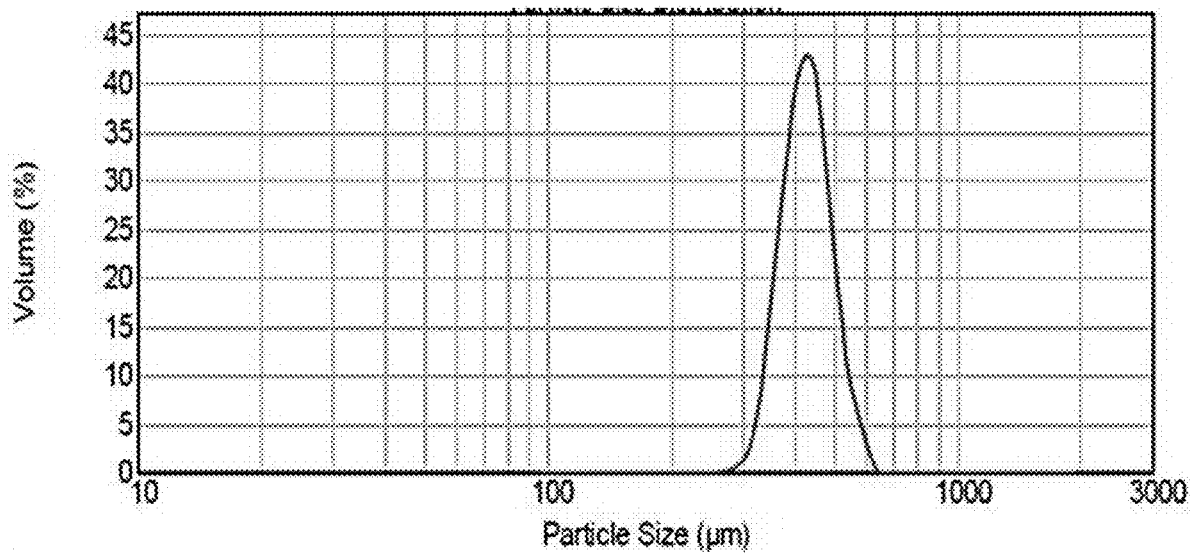


Figure 27A

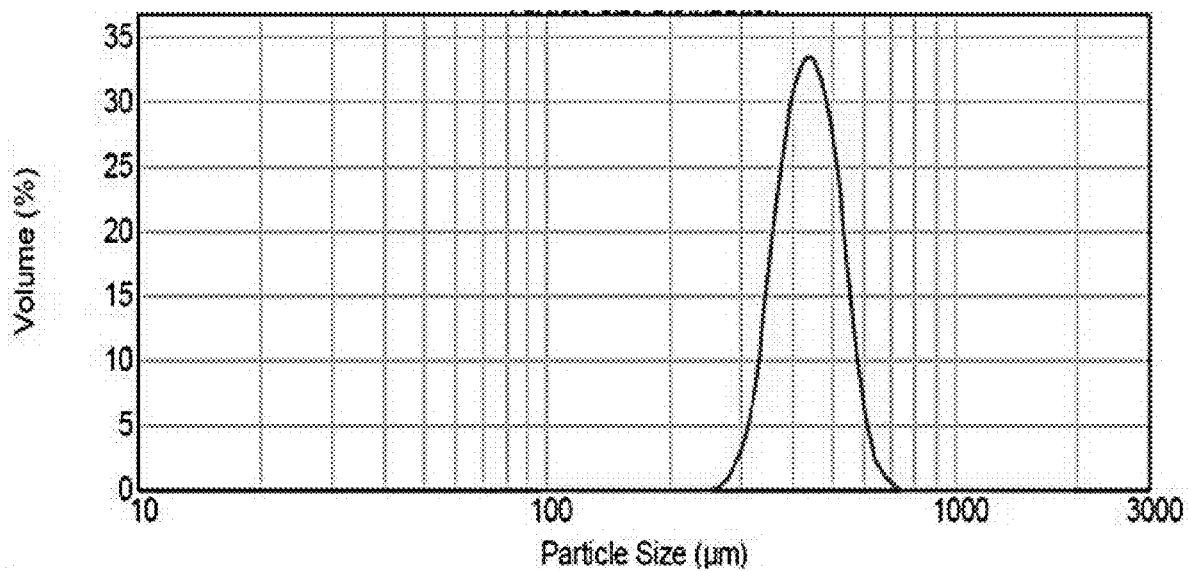


Figure 27B

MULTIPARTICULATE FORMULATIONS OF CANNABINOIDS

FIELD OF INVENTION

[0001] The present invention relates to a multiparticulate drug delivery platform for the oral administration of one or more cannabinoids. The drug delivery system of the present invention achieves a targeted pharmacokinetic profile and provides a uniform drug distribution in the gastrointestinal tract. The delivery system of the present invention can be administered as capsules, tablets, sprinkles, or a stick pack for convenience in administration and handling.

BACKGROUND OF THE INVENTION

[0002] Cannabis, the plant genus that includes both hemp and marijuana, possesses many medicinal and psychoactive properties that reportedly alleviate a wide range of symptoms experienced in connection with serious medical conditions, while providing safer and fewer serious side effects than most current prescription drugs. For example, cannabis has been used to combat symptoms associated with cancer, anorexia, AIDS, chronic pain, muscle spasticity, glaucoma, arthritis, migraine, and many other illnesses.

[0003] Cannabinoids are a class of diverse chemical compounds originating from the cannabis plant that act on cannabinoid receptors, which repress neurotransmitter release in the brain. Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most prominent cannabinoids found in Cannabis. While there are over 100 different cannabinoids so far identified in Cannabis by scientists, CBD and THC are by far the most extensively studied and best understood. CBD and THC both interact with the body's endocannabinoid system, a vital signaling system responsible for regulating a wide array of functions.

[0004] THC is a psychotropic chemical derived from marijuana that acts on the body's cannabinoid receptors and resembles chemicals naturally produced by the body. THC is a psychoactive that activates the CB1 and CB2 receptors and affects perception, mood, consciousness, cognition, and behavior. In medicinal application, THC has the properties of an analgesic and an appetite stimulant. THC has also been reported to create a state of relaxation and well-being, induce sleep, and cause a state of euphoria. These effects have been used to treat a variety of health issues, such as pain, inflammation, nausea, sleep apnea, and stress disorders. Additionally, THC has been shown to fight the side effects and symptoms of chemotherapy, multiple sclerosis, glaucoma, AIDS, and spinal injuries.

[0005] Currently, there are only three drug products approved by the Food and Drug Administration (FDA) for THC: Marinol®, Syndros®, and Cesamet®. Marinol® and Syndros® both contain dronabinol, a synthetic THC that is insoluble in water and has a pK_A of 10.6. Marinol® is available as soft gelatin capsules in dosage strengths of 2.5 mg, 5 mg, and 10 mg, and Syndros® is available as an oral solution (5 mg/ml). Both Marinol® and Syndros® are indicated for the treatment of anorexia associated with weight loss in patients with AIDS and for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

[0006] Cesamet® contains nabilone, a synthetic cannabinoid that is chemically similar to THC. As a raw material,

nabilone is a white to off-white polymorphic crystalline powder. In aqueous media, the solubility of nabilone is less than 0.5 mg/L, with pH values ranging from 1.2 to 7.0. Cesamet® is available as a powder-filled capsule (1 mg/capsule) for oral administration and is indicated for the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. However, the effects of Cesamet® have been reported to persist for a variable and unpredictable period of time following its oral administration; for example, adverse psychiatric reactions from using Cesamet® can persist for 48 to 72 hours following cessation of treatment.

[0007] CBD is another potent chemical derived from marijuana that is widely inhaled by patients from smoking the hemp leaves. To date, the FDA has only approved Epidiolex®, an oral solution (100 mg/ml) containing plant-derived CBD for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. CBD is a white to pale yellow crystalline solid. It is insoluble in water and is soluble in organic solvents. The primary medical applications of CBD are to combat severe and chronic pain, stress, depression, anxiety, cancer, epilepsy, schizophrenia, multiple sclerosis, migraine, arthritis, and the adverse effects of chemotherapy.

[0008] The presence of CBD can balance the agonistic activity of THC. THC activates the cannabinoid receptors CB1 and CB2 that are present in the brain and that are responsible for THC's psychoactive effects, while CBD suppresses the CB1 and CB2 receptors by operating as an indirect antagonist of cannabinoid agonists. Hence, CBD suppresses the activation of the CB1 and CB2 receptors by a cannabinoid like THC, creating a balanced effect.

[0009] When used in combination, THC and CBD have anti-inflammatory, appetite stimulant, antiemetic, anticonvulsant, antioxidant, neuroprotective, and antitumoral actions. THC and CBD also can be used to combat epilepsy, depression, anxiety, schizophrenia, multiple sclerosis, migraine, and arthritis; and to alleviate the symptoms of cancer, AIDS, and spinal injuries; all of which improves quality of life for patients suffering from those debilitating conditions.

[0010] Because THC and CBD can impact a variety of health conditions, treatment with THC and CBD is ideal for combining with other treatments. To this end, the present invention relates to a dosage form of THC and CBD, either individually or combined, that can be combined with other active agents for treatment of multiple clinical conditions.

SUMMARY OF THE INVENTION

[0011] The present invention provides multiparticulate solid oral dosage forms comprising two or more active agents, wherein the two or more active agents comprise at least one cannabinoid and at least one non-cannabinoid therapeutic agent. The drug loaded system may comprise particles (e.g., granules, particle agglomerates of any shape, beads, or pellets) having a size that may range from about 30 μ m to about 1500 μ m, or about 50 μ m to about 1000 μ m, in diameter, and with uniform loading. The multiparticulate solid oral dosage forms of the present invention may be formulated in a manner to provide immediate, extended, or sustained release of the two or more active agents. The dosage forms of the present invention also may be formu-

lated to achieve a targeted pharmacokinetic profile and to provide uniform distribution in the gastrointestinal tract.

[0012] The multiparticulate form can provide uniform drug loading and may be compressed into tablets (regular tablets, oral-disintegrating tablets (ODT), self-disintegrated tablets, chewable tablets), filled into capsules (conventional hard gelatin capsules and easy open capsules to sprinkle) or loaded into stick packs to sprinkle over food or into water or other liquid drinks.

[0013] An aspect of the current invention relates to a composition for the immediate release of two or more active agents, in which the two or more active agents comprise at least one cannabinoid and at least one non-cannabinoid therapeutic agent. In embodiments of the invention, the immediate release composition may comprise a population of particles, wherein each particle comprises: at least one active agent, and one or more intra-granular excipients. The at least one active agent may comprise the at least one cannabinoid, the at least one non-cannabinoid therapeutic agent, or a combination of the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent. In embodiments in which each particle does not comprise both the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent, then the population of particles in the immediate release composition may comprise both particles comprising the at least one cannabinoid and particles comprising the at least one non-cannabinoid therapeutic agent.

[0014] In some embodiments, the one or more intra-granular excipients may comprise one or more diluents, binders, fillers, surfactants/emulsifying agents, disintegrating agents, or a combination thereof. In certain embodiments, the one or more intra-granular excipients may comprise one or more cellulose-derivative diluents. Examples of cellulose-derivative diluents may include lactose, isomalt, cellulose, starch, cyclodextrin, mannitol, and sorbitol.

[0015] In some embodiments, each particle may further comprise one or more surfactants/emulsifying agents.

[0016] In embodiments of the invention, the immediate release composition may comprise a population of particles, wherein each particle comprises at least one active agent, and a porous bead core. The at least one active agent may comprise the at least one cannabinoid, the at least one non-cannabinoid therapeutic agent, or a combination of the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent. In embodiments in which each particle does not comprise both the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent, then the population of particles in the immediate release composition may comprise both particles comprising the at least one cannabinoid and particles comprising the at least one non-cannabinoid therapeutic agent.

[0017] The porous bead core may comprise a mesoporous silica bead or a porous biodegradable glass bead. The particles may comprise a diameter of about 10 μm and 1000 μm . The ratio of pore volume to particle size may range from about 0.001 to about 0.8. Each particle may further comprise one or more surfactants/emulsifying agents.

[0018] An aspect of the present invention relates to a composition for the extended release of two or more active agents, in which the two or more active agents comprise at least one cannabinoid and at least one non-cannabinoid therapeutic agent. In embodiments of the invention, the extended release composition may comprise a population of

particles, wherein each particle comprises: at least one active agent, one or more drug-releasing agents, and a porous core. In some embodiments, the particles may comprise at least one active agent, one or more drug-releasing agents, a porous core, one or more solubilizers, and one or more surfactants. The at least one active agent may comprise the at least one cannabinoid, the at least one non-cannabinoid therapeutic agent, or a combination of the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent. In embodiments in which each particle does not comprise both the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent, then the population of particles in the extended release composition may comprise both particles comprising the at least one cannabinoid and particles comprising the at least one non-cannabinoid therapeutic agent.

[0019] In some embodiments, the drug-releasing agent may comprise one or more gel-forming agents. The one or more gel-forming agents may be selected from glyceryl monooleate, glycerol monostearate, soybean oil, propylene glycol monopalmitostearate, cellulose-based gelling agents, carboxypolymethylenes, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, chitosan, natural gums such as acacia, alginates, carrageen, guar gum, or a combination thereof. The ratio of the one or more gel-forming agents to the one or more surfactants may be about 10:1 to about 1:10, or about 8:1 to about 1:8, or about 5:1 to about 1:5, by weight.

[0020] In some embodiments, the one or more solubilizers may comprise an oil, glyceride, an alcohol, or a combination thereof. The oil may be selected from oils that include, but not limited to, cannabis oil and sesame oil. In some embodiments, the porous core may comprise a porous bead such as a mesoporous silica bead or a porous biodegradable glass bead.

[0021] The weight ratio of pore volume to particle size may range from about 0.001 to about 0.8. In some embodiments, the pores may contain the at least one active agent and the one or more drug-releasing agents. In certain embodiments, the pores may contain the at least one active agent, one or more solubilizers, one or more surfactants, and one or more drug-releasing agents.

[0022] In embodiments of the invention, the extended release composition may comprise a population of particles, wherein each particle comprises: at least one active agent, one or more drug-releasing agents, and an inert core. In some embodiments, the particles may comprise at least one active agent, one or more drug-releasing agents, an inert core, one or more solubilizers, and one or more surfactants. The at least one active agent may comprise the at least one cannabinoid, the at least one non-cannabinoid therapeutic agent, or a combination of the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent. In embodiments in which each particle does not comprise both the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent, then the population of particles in the extended release composition may comprise both particles comprising the at least one cannabinoid and particles comprising the at least one non-cannabinoid therapeutic agent.

[0023] In some embodiments, the one or more drug-releasing agents may comprise one or more release-controlling polymers, one or more release-accelerating polymers (pore-formers), or a combination thereof. In some embodi-

ments, the inert core may comprise an inert material selected from the group consisting of microcrystalline cellulose, celluloses, starches, saccharides, and mixtures thereof. In some embodiments, the core may comprise a coating that comprises the at least one active agent and the one or more drug-releasing agents. In certain embodiments, the core may comprise a coating that comprises the at least one active agent, the one or more drug-releasing agents, the one or more solubilizers, and the one or more surfactants.

[0024] In some embodiments, the one or more solubilizers may comprise an oil, glyceride, an alcohol, or a combination thereof. The oil may be selected from oils that include, but not limited to, cannabis oil and sesame oil.

[0025] An aspect of the present invention relates to a composition for the sustained release of two or more active agents, in which the two or more active agents comprise at least one cannabinoid and at least one non-cannabinoid therapeutic agent. In embodiments of the invention, the sustained release composition may comprise a population of particles comprising one or more of the particles of the immediate release composition of the present invention, and one or more of the particles of the extended release composition of the present invention.

[0026] In some embodiments, the one or more cannabinoids may comprise THC, CBD, or a combination thereof.

[0027] In some embodiments, the one or more non-cannabinoid therapeutic agents may comprise one or more alcohol deterrents, analgesics and/or anti-inflammatory agents; antipyretics, anorexigenic agents and respiratory and central nervous system (CNS) stimulants, antiarrhythmic agents, anticholinergic agents, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheal agents, antidotes, antiemetics, antigout agents, antihistamine drugs, anti-infective agents, antimigraine agents, antineoplastic agents, anti-parkinsonian agents, antipsychotics, antitussives, antiulcer agents and acid suppressants, antivirals, anxiolytics such as sedatives and/or hypnotics, atypical antipsychotics, corticosteroids, gastrointestinal drugs, hypotensive agents, immunosuppressive agents, miscellaneous therapeutic agents, monoamine oxidase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), opiate agonists, opiate partial agonists, respiratory tract agents, skeletal muscle relaxants, thyroid and anti-thyroid agents, tricyclics and other norepinephrine-reuptake inhibitors, vitamins, wakefulness-promoting agents, or a combination thereof.

[0028] In some embodiments, the immediate release, extended release, or sustained release compositions of the present invention may be provided in a dosage form such as a tablet (for example, an ODT, self-disintegrated tablet, or chewable tablet), capsule, or stick pack for oral administration.

[0029] Another aspect of the present invention relates to methods of preparing the immediate release compositions of the invention. In embodiments of the invention, the method of preparing an immediate release composition of particles may comprise combining the at least one active agent with the one or more intra-granular excipients, and granulating the combination to produce immediate release particles. In embodiments of the invention, the method of preparing an immediate release composition of particles may comprise loading the at least one active agent onto porous bead cores. In embodiments in which each particle does not comprise both at least one cannabinoid and the at least one non-cannabinoid therapeutic agent, then the method of preparing

the immediate release compositions of the invention comprises preparing immediate release particles comprising at least one cannabinoid and preparing immediate release particles comprising at least one non-cannabinoid therapeutic agent, and then combining these particles into one population for the immediate release composition. Such a combination may occur, for example, by granulating particles comprising the at least one cannabinoid and particles comprising the at least one non-cannabinoid therapeutic agent into one granulation.

[0030] Alternatively, such a combination may occur, by mixing a population of particles comprising the at least one cannabinoid and a population of particles comprising the at least one non-cannabinoid therapeutic agent.

[0031] Another aspect of the present invention relates to methods of preparing the extended release compositions of the invention. In embodiments of the invention, the method of preparing an extended release composition of particles may comprise mixing the at least one active agent in one or more solubilizers along with one or more gel-forming agents (and in some embodiments one or more surfactants, and optionally one or more stabilizing agents) and loading the mixture onto porous cores. In other embodiments of the invention, the method of preparing an extended release composition of particles may comprise dispersing the at least one active agent in one or more solubilizers (such as an ethanol and water mixture) along with one or more release-controlling polymers and/or one or more release-accelerating polymers (and optionally one or more stabilizing agents), and the drug dispersion may then be applied onto inert cores. In embodiments in which each particle does not comprise both at least one cannabinoid and at least one non-cannabinoid therapeutic agent, then the method of preparing the extended release compositions of the invention comprises preparing extended release particles comprising the at least one cannabinoid and preparing extended release particles comprising the at least one non-cannabinoid therapeutic agent, and then combining these particles into one population for the extended release composition.

[0032] Yet another aspect of the present invention relates to methods of preparing the sustained release compositions of the invention. In embodiments of the invention, the methods may comprise mixing particles of the immediate release compositions of the invention with particles of the extended release compositions of the invention.

[0033] Finally, an aspect of the present invention relates to methods of treating a health issue in a subject in need thereof, wherein the methods comprise administering the immediate release composition of the invention, the extended release composition of the invention, or the sustained release composition of the invention. In some embodiments, the health issue may be selected from the group consisting of pain, nausea, sleep apnea, stress disorders, inflammation, depression, anxiety, epilepsy, schizophrenia, migraines, arthritis, weight loss, poor appetite, and a combination thereof. In some embodiments, the composition may be administered orally. In certain embodiments, prior to administration, the composition may be sprinkled on food or nutrient that is solid, semi-solid, or liquid; into water; or into other types of liquid drink.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] For a better understanding of the present invention, reference is made to the following description of an exemplary embodiment thereof, and the accompanying drawing, wherein:

[0035] FIGS. 1A and 1B shows particle size distribution using dynamic light scattering technique (Malvern Instruments, USA) for: plain Neusilin US2 beads (FIG. 1A) and Neusilin US2 beads loaded with probucol in sesame oil and surfactant (FIG. 1B).

[0036] FIGS. 2A and 2B shows scanning electron microscopic (SEM) images of plain Neusilin US2 beads (FIG. 2A) and Neusilin US2 beads loaded with probucol in sesame oil and surfactant (FIG. 2B).

[0037] FIG. 3 shows the particle size distribution of both THC particles and CBD particles according to embodiments of the invention, as described in Example 1.

[0038] FIGS. 4A and 4B shows scanning electron microscopic (SEM) images at magnifications of 30× (FIG. 4A) and 75× (FIG. 4B) of THC particles and CBD particles according to embodiments of the invention, as described in Example 1.

[0039] FIG. 5 shows the dissolution profile of both THC particles and CBD particles according to embodiments of the invention, as described in Example 1.

[0040] FIG. 6 shows the particle size distribution of both THC particles and CBD particles according to embodiments of the invention, as described in Example 2.

[0041] FIGS. 7A and 7B shows SEM images at magnifications of 30× (FIG. 7A) and 75× (FIG. 7B) of THC particles and CBD particles according to embodiments of the invention, as described in Example 2.

[0042] FIG. 8 shows the dissolution profile of both THC particles and CBD particles according to embodiments of the invention, as described in Example 3.

[0043] FIG. 9A shows the particle size distribution of both THC particles and CBD particles according to embodiments of the invention, and FIG. 9B shows the particle size distribution of blank porous bead cores, as described in Example 3.

[0044] FIGS. 10A-10F shows SEM images of THC and CBD particles and blank porous bead cores particles according to embodiments of the invention, as described in Example 3. FIGS. 10A-10C shows SEM images of THC and CBD particles at magnifications of 190× (FIG. 10A), 1600× (FIG. 10B), and 2200× (FIG. 10C). FIGS. 10D-10F shows blank porous bead cores at magnifications of 220× (FIG. 10D), 1000× (FIG. 10E), and 1600× (FIG. 10F).

[0045] FIG. 11 shows the dissolution profile of both THC particles and CBD particles according to embodiments of the invention, as described in Example 3.

[0046] FIGS. 12A and 12B show the dissolution profile of IR Reference Compositions A-C (FIG. 12A) and the dissolution profile of extended release Example Compositions A-C according to embodiments of the invention (FIG. 12B), as described in Example 4.

[0047] FIG. 13 shows the dissolution profiles of extended release Example Compositions D-H according to embodiments of the invention, as described in Example 5.

[0048] FIGS. 14A and 14B show the dissolution profile of immediate release Reference Composition D (FIG. 14A) and the dissolution profile of extended release Example Composition I according to embodiments of the invention (FIG. 14B), as described in Example 6.

[0049] FIGS. 15A and 15B show the dissolution profile of immediate release Reference Composition E (FIG. 15A) and the dissolution profile of extended release Example Composition J according to embodiments of the invention (FIG. 15B), as described in Example 7.

[0050] FIGS. 16A and 16B show the dissolution profile of immediate release Reference Composition F (FIG. 16A) and the dissolution profile of extended release Example Composition K according to embodiments of the invention (FIG. 16B), as described in Example 8.

[0051] FIGS. 17A-17F shows SEM images of plain Neusilin US2 beads at magnifications of 220× (FIG. 17A), 1000× (FIG. 17B), and 1600× (FIG. 17C); and of Neusilin US2 beads loaded with THC and CBD in sesame oil according to embodiments of the invention at magnifications of 190× (FIG. 17D), 1600× (FIG. 17E), and 2200× (FIG. 17F).

[0052] FIGS. 18A and 18B shows particles size distribution profiles of a composition of plain Neusilin US2 beads (FIG. 18A) and a composition of Neusilin US2 beads loaded with THC and CBD in sesame oil according to embodiments of the invention (FIG. 18B).

[0053] FIGS. 19A and 19B show the dissolution profile of extended release Example Composition L according to embodiments of the invention (FIG. 19A) and the dissolution profile of extended release Example Composition M according to embodiments of the invention (FIG. 19B), as described in Example 9.

[0054] FIG. 20 shows an SEM image of a particle of extended release Example Composition L according to embodiments of the invention, as described in Example 9.

[0055] FIGS. 21A and 21B show the dissolution profile of immediate release Reference Composition F (FIG. 21A) and the dissolution profile of extended release Example Composition N according to embodiments of the invention (FIG. 21B), as described in Example 10.

[0056] FIGS. 22A and 22B show the dissolution profile of immediate release Reference Composition G (FIG. 22A) and the dissolution profile of extended release Example Composition O according to embodiments of the invention (FIG. 22B), as described in Example 11.

[0057] FIGS. 23A and 23B show the dissolution profile of immediate release Reference Composition H (FIG. 23A) and the dissolution profile of extended release Example Composition I according to embodiments of the invention (FIG. 23B), as described in Example 12.

[0058] FIGS. 24A-24F shows SEM images of plain Cellets at magnifications of 30× (FIG. 24A), 120× (FIG. 24B), and 250× (FIG. 24C); and of Cellets loaded with THC and CBD in sesame oil according to embodiments of the invention at magnifications of 50× (FIG. 24D), 120× (FIG. 24E), and 450× (FIG. 24F).

[0059] FIGS. 25A-25F shows SEM images of plain Suglets® 40/45 at magnifications of 50× (FIG. 25A), 200× (FIG. 25B), and 400× (FIG. 25C); and of Suglets® 40/45 loaded with THC and CBD in sesame oil according to embodiments of the invention at magnifications of 50× (FIG. 25D), 200× (FIG. 25E), and 600× (FIG. 25F).

[0060] FIGS. 26A and 26B show particle size distribution of plain Cellets (FIG. 26A) and Cellets loaded with CBD according to embodiments of the invention (FIG. 26B).

[0061] FIGS. 27A and 27B show particle size distribution of plain Suglets® 40/45 (FIG. 27A) and Suglets® 40/45 loaded with CBD according to embodiments of the invention (FIG. 27B).

DETAILED DESCRIPTION

[0062] According to the present invention, multiparticulate dosage forms are provided for administering two or more active agents, in which the two or more active agents comprise at least one cannabinoid and at least one non-cannabinoid therapeutic agent. In certain embodiments, a final composition may comprise the two or more active agents in an amount of about 1% to about 90% w/w, or about 5% to about 50% w/w.

[0063] An aspect of the invention relates to immediate release, extended release, or sustained release compositions comprising a population of particles that contain the two or more active agents. These compositions may be provided in a dosage form such as a tablet (for example, an ODT, self-disintegrated tablet, or chewable tablet), capsule, or stick pack.

[0064] Other aspects of the invention relate to methods of preparing the compositions of the present invention, and methods of treatment involving administering the compositions of the present invention.

Compositions of the Present Invention

[0065] The compositions of the present invention comprise two or more active agents, in which the two or more active agents comprise at least one cannabinoid and at least one non-cannabinoid therapeutic agent. The at least one cannabinoid may comprise THC, CBD, or a combination thereof.

[0066] The at least one non-cannabinoid therapeutic agent may be selected from active agents that can be used to help treat the various health conditions encompassed by the methods of treatment according to the present invention. In some embodiments, the at least one non-cannabinoid therapeutic agent may be selected from a group consisting of alcohol deterrents, such as disulfiram, naltrexone, acamprosate, gabapentin, and topiramate; analgesics and/or anti-inflammatory agents such as aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, and sulindac; antipyretics, such as acetaminophen, aspirin, ibuprofen, sodium salicylate, acetylsalicylic acid and naproxen; anorexigenic agents and respiratory and CNS stimulants, such as caffeine, mazindol, carboxymethylcellulose, phenylpropanolamine, ephedrine, pseudoephedrine, amfepramone, methamphetamine, phentermine, and chlorphenamine; antiarrhythmic agents, such as amiodarone, disopyramide, flecainide acetate, and quinidine sulphate; anticholinergic agents, such as amitriptyline, atropine, benztropine, chlorpheniramine, chlorpromazine, clomipramine, clozapine, cyclobenzaprine, cyproheptadine, desipramine, dexchlorpheniramine, dicyclomine, diphenhydramine, doxepin, fesoterodine, hydroxyzine, hyoscyamine, imipramine, meclizine, nortriptyline, olanzapine, orphenadrine, oxybutynin, paroxetine, perphenazine, prochlorperazine, promethazine, protriptyline, pseudoephedrine hcl/triprolidine hcl, scopolamine, thioridazine, tolterodine, trifluoperazine, and trimipramine; anticonvulsants, such as acetazolamide, carbamazepine, clobaz, clonazepam, diazepam, ethosuximide, fosphenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, lorazepam, methsuximide, nitrazepam, oxcarbazepine, paraldehyde,

phenobarbital, phenytoin, pregabalin, primidone, rufinamide, stiripentol, topiramate, valproic acid, vigabatrin, felbamate, tiagabine hydrochloride, zonisamide; antidepressants, such as amoxapine, ciclazindol, maprotiline, mianserin, nortriptyline, trazodone, trimipramine maleate, acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, and tolbutamide; antidiabetic agents, such as acarbose, miglitol, pramlintide, alogliptan, linagliptan, saxagliptin, sitagliptin, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, insulin, nateglinide, repaglinide, metformin, canagliflozin, dapagliflozin, empagliflozin, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, rosiglitazone, and pioglitazone; antidiarrheal agents, such as attapulgite, bismuth subgallate, bismuth subsalicylate, atropine, loperamide, and diphenoxylate; antidotes; antiemetics, such as hyoscyamine, methscopolamine, scopolamine, cyclizine, dimenhydrinate, hydroxyzine, meclizine, promethazine, dronabinol, nabilone, tetrahydrocannabinol, chlorpromazine, prochlorperazine, alosetron, dolasetron, granisetron, ondansetron, palonosetron, aprepitant, fosaprepitant, rolapitant, dexamethasone, metoclopramide, and trimethobenzamide; anti-out agents, such as probenecid, sulfinpyrazone, allopurinol, and colchicine; antihistamine drugs, such as acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadine, dimenhydrinate, flunarizine, loratadine, meclozine, oxatamide, terfenadine, and triprolidine; anti-infective agents, including antibiotics, antifungals, antiparasitic agents, and antivirals; antimigraine agents, such as dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, pizotifen maleate, and sumatriptan succinate; antineoplastic agents, including alkylating agents, antimetabolites, mitotic inhibitors, and hormonal agents; antiparkinsonian agents, such as bromocriptine mesylate and lysuride maleate; antipsychotics, such as chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, haloperidol, lithium, loxapine, molindone, pimozide, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, and ziprasidone; antitussives, anti-ulcer agents and acid suppressants, antivirals, anxiolytics including sedatives and/or hypnotics, such as alprazolam, amyobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, clobazam, clonazepam, clozapine, diazepam, droperidol, ethinamate, flunarisone, flunitrazepam, fluopromazine, flupenitixol decanoate, fluphenazine decanoate, flurazepam, haloperidol, lorazepam, lorazepam, medazepam, meprobamate, methaqualone, midazolam, nitrazepam, oxazepam, pentobarbitone, perphenazine pimozide, prochlorperazine, suipiride, temazepam, thioridazine, triazolam, and zopiclone; atypical antipsychotics, corticosteroids, such as beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, flucortolone, fluticasone, propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone; gastrointestinal drugs, hypotensive agents, such as amlodipine, carvedilol, benidipine, darodipine, diltiazem, diazoxide, felodipine, guanabenz acetate, indoramin, isradipine, minoxidil, nicardipine, nifedipine, nimodipine, phenoxymethylamine, prazosin, reserpine, and terazosin; immunosuppressive agents, miscellaneous therapeutic agents, monoamine oxidase inhibitors, NSAIDs,

opiate agonists or opiate partial agonists, such as codeine, dextropropoxyphene, diamorphine, dihydrocodeine, meptazinol, methadone, morphine, nalbuphine, and pentazocine; respiratory tract agents, skeletal muscle relaxants, thyroid and anti-thyroid agents, such as carbimazole and propylthiouracil; tricyclics and other norepinephrine-reuptake inhibitors, vitamins, wakefulness-promoting agents, sildenafil, tadalafil or combinations thereof.

[0067] The compositions of the present invention may be an immediate release composition, extended release composition, or a sustained release composition.

Immediate Release Compositions

[0068] In embodiments of the invention, the immediate release compositions of the present invention may comprise particles, in which each particle may comprise at least one active agent and one or more intra-granular excipients. The one or more intra-granular excipients may comprise one or more diluents, one or more binders, one or more fillers, one or more surfactants/emulsifying agents, one or more disinfectants, or a combination thereof.

[0069] In embodiments of the invention, the immediate release compositions of the present invention may comprise particles, in which each particle may comprise at least one active agent and a porous bead core. The porous bead core may be a carrier for the absorption and release of liquids, e.g., silica bead. In some embodiments of the invention, the core may comprise a silica bead, a biodegradable glass bead, or any other bead made of any compatible materials known in the art as suitable for oral administration (e.g., porous ceramics, porous calcium carbonate particles, porous zeolite particles, etc.).

[0070] The core may comprise one or more pores that extend from the surface of the core. The core may contain the one or more cannabinoids. According to some embodiments, the ratio of pore volume to particle size of the core may be between about 0.001 to about 0.8.

[0071] According to the present invention, the core is selected to achieve a free flowing multiparticulate system. According to some embodiments, the core may comprise mesoporous silica (e.g. Syloid® XDP 3150 (Grace, USA), Davisil® LC150A (Grace, USA), Neusilin® US2 (Fuji Chemicals, Japan)).

[0072] The at least one active agent may comprise at least one cannabinoid, at least one non-cannabinoid therapeutic agent, or a combination of at least one cannabinoid and the at least one non-cannabinoid therapeutic agent. In embodiments in which each particle does not comprise both at least one cannabinoid and at least one non-cannabinoid therapeutic agent, then the particles in the immediate release composition may comprise both particles comprising the at least one cannabinoid and particles comprising the at least one non-cannabinoid therapeutic agent.

[0073] The immediate release composition of the present invention may release a particular percentage of the active agents (i.e., the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent) within a certain amount of time, as determined by dissolution testing.

[0074] The dissolution test may be performed under the conditions summarized in Table 1 below.

TABLE 1

Conditions used for dissolution testing according to embodiments of the invention.	
Parameter	Condition
Apparatus	USP II (Paddle)
Paddle Speed	100 rpm
Media	1% Polysorbate 80 in DW
Media Volume	500 ml
Temperature	37° C.
Sampling Time Point(s)	15, 30, 60, 240, 360, 720 min

[0075] In some embodiments, the composition of the present invention may release about 30% or greater of the one or more cannabinoids over a period of about 30 minutes (0.5 hours) or less, or about 15 minutes (0.25 hours) or less, or about 10 minutes or less, from the start of the dissolution test. In some embodiments, the composition may release about 50% or greater of the one or more cannabinoids over a period of about 60 minutes (1 hour) or less, or about 30 minutes (0.5 hours) or less, or about 15 minutes (0.25 hours) or less, or about 10 minutes or less, from the start of the dissolution test. In some embodiments, the composition may release about 80% or greater of the one or more cannabinoids over a period of about 90 minutes (1.5 hours) or less, or about 60 minutes (1 hour) or less, or about 30 minutes (0.5 hours) or less, or about 15 minutes (0.25 hours) or less, or about 10 minutes or less, from the start of the dissolution test.

[0076] The composition of the present invention may comprise particles having a particular size distribution. For example, in some embodiments, about 80% of the particles may be between about 20 μm and about 2000 μm in diameter, or between about 30 μm and about 1000 μm in diameter, or between about 40 μm and about 900 μm in diameter. In some embodiments, about 80% of the particles may be between about 2 μm and about 500 μm in diameter, or between about 4 μm and about 300 μm in diameter, or between about 5 μm and about 200 μm in diameter.

Extended Release Compositions

[0077] As used herein, the term “extended release” is characterized by the gradual release of the active agents from the particles of the composition over an extended period of time, optionally greater than about 30 minutes. With extended release, the rate of release of the active agents from the particles is controlled in order to maintain therapeutic activity of the active agents for a longer period of time. In some embodiments of the current invention, the composition may release greater than about 40% of the one or more active agents over a period of about 6 hours or more. In certain embodiments, the composition may release the one or more active agents over a period of about 12 hours to about 24 hours.

[0078] As used herein, the term “solubilizer” refers to a solubility enhancement excipient that increases the bioavailability of the one or more active agents. The purpose of the one or more solubilizers is to achieve a concentrated, homogenous, and stable solution in order to deliver the one or more active agents in an efficient way. The one or more solubilizers for use in the present invention may include, but are not limited to, oil, glyceride, an alcohol, or a combination thereof. The oil may be selected from the group consisting of cannabis oil, borage oil, coconut oil, cotton-

seed oil, soybean oil, safflower oil, sunflower oil, castor oil, corn oil, olive oil, palm oil, peanut oil, almond oil, sesame oil, rapeseed oil, peppermint oil, poppy seed oil, canola oil, palm kernel oil, hydrogenated soybean oil, hydrogenated vegetable oil, and a combination thereof. The glyceride may be selected from the group consisting of a monoglyceride, diglyceride, triglyceride, and a combination thereof. The alcohol may be a monohydric alcohol, e.g., ethanol, methanol, or isopropyl alcohol. In some embodiments, the one or more solubilizers may be a hydroalcoholic mixture.

[0079] As used herein, the term “drug-releasing agents” relates to agents that control drug delivery so that the active agents are released in a predesigned manner. As a result, the drug-releasing agents contribute to the rate and extent of the cannabinoids’ active availability to the body.

[0080] As used herein “stabilizing agents” may include, but are not limited to, tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, isoascorbic acid, potassium salt of sulfurous acid (e.g., potassium metabisulfite), sodium salt of sulfurous acid (e.g., sodium metabisulfite), vitamin E, lecithin, ascorbyl palmitate, edetic acid, edetate salt (e.g., EDTA), or a combination thereof. The stabilizing agents may be present in the composition in an amount of about 0.001% to about 5% by weight, or as suitable in order to achieve a stabilized composition.

[0081] In embodiments of the invention, the extended release composition may comprise a population of particles, wherein each particle comprises: at least one active agent, one or more lipid-based gel-forming agents, and a porous core. In some embodiments, the particles may comprise at least one active agent, one or more lipid-based gel-forming agents, a porous core, one or more solubilizers, and one or more surfactants. The at least one active agent may comprise the at least one cannabinoid, the at least one non-cannabinoid therapeutic agent, or a combination of the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent. In embodiments in which each particle does not comprise both the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent, then the population of particles in the extended release composition may comprise both particles comprising the at least one cannabinoid and particles comprising the at least one non-cannabinoid therapeutic agent.

[0082] In some embodiments, the particles may comprise one or more stabilizing agents.

[0083] The one or more gel-forming agents may be selected from glyceryl monooleate (e.g., Capmul GMO-50; Abitec Corp., USA), glycerol monostearate (e.g., Geleol™ Mono and Diglycerides; Gattefosse, USA), glyceryl distearate, polyglyceryl-3 diolate (Gelolil®; Gattefosse, USA), soybean oil, propylene glycol monopalmitostearate (e.g., Monosteol™; Gattefosse, USA), cellulose-based gelling agents, carboxypolymethylenes (e.g., Carbopol® or Carbomer®), hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, chitosan, natural gums (e.g., acacia, alginates, carrageen, guar gum), and a combination thereof. In certain embodiments, the one or more gel-forming agents may comprise glycerol monooleate.

[0084] In embodiments in which the composition comprises one or more gel-forming agents and one or more surfactants, the weight ratio of the one or more gel-forming agents to the one or more surfactants may be about 10:1 to about 1:10, or about 8:1 to about 1:8, or about 5:1 to about

1:5. According to certain embodiments, the ratio of the one or more gel-forming agents to the one or more surfactants may be about 1:1. In certain embodiments, cellulose-based and gum-based gelling agents can be added with or without surfactants.

[0085] The porous core may be the same as the porous bead core described above for the immediate release composition. The core may contain the at least one active agent, the one or more solubilizers, and the one or more gel-forming agents. According to some embodiments, the ratio of pore volume to particle size of the core may be between about 0.001 to about 0.8. Within that range, the pores may be configured such that the one or more gel-forming agents are located in the pores closer to the surface of the core than the at least one active agent and the one or more solubilizers. In embodiments wherein one or more solubilizers and one or more surfactants are in the composition, the pores may be configured such that the one or more gel-forming agents are located in the pores closer to the surface of the core than the at least one active agent, the one or more solubilizers, and the one or more surfactants.

[0086] According to the present invention, the core is selected in consideration of loading capacity and its capability of achieving a free-flowing multiparticulate system. According to some embodiments, the core comprises mesoporous silica (e.g., Syloid® XDP 3150 (Grace, USA), Davisil® LC150A (Grace, USA), Neusilin® US2 (Fuji Chemicals, Japan)). Particle size, pore volume and specific surface area for the silica beads are given in Table 2 below.

TABLE 2

Physical properties of silica beads			
Physical properties	Syloid ® XDP 3150	Davisil ® LC150A	Neusilin ® US2
Particle Size Distribution (µm)	120-170	315-500	44-177
Specific Surface Area (m ² /g)	320	340	300
Pore Volume (ml/g)	1.7	1.23	1.2
Ratio of pore volume to particle size	0.014	0.003	0.020
Oil Adsorption Capacity (g/100 g)	300	—	270-340
Angle of Repose (°)	36	36	30

[0087] The ratio of pore volume to particle size was determined using dynamic light scattering technique and was highest for Neusilin US2 beads. The particle size distribution for the Neusilin US2 beads is shown in FIG. 1A having d₉₀ as 108 µm and a bimodal distribution. Upon loading of 2:1 ratio of probucol (as a surrogate active ingredient), sesame oil, surfactant, and gel-forming lipid excipient to silica, the particle size distribution of the Neusilin US2 beads was changed to d₉₀ of 182 µm having a unimodal distribution curve, as shown in FIG. 1B. Scanning electron microscopy images for both plain and loaded Neusilin US2 beads are illustrated in FIGS. 2A and 2B. In particular, FIG. 2A depicts plain Neusilin US2 beads and FIG. 2B depicts Neusilin US2 beads loaded with probucol (as a surrogate active ingredient) in sesame oil and a surfactant.

[0088] Selection of silica beads considered their flowability upon maximum drug loading. Weight ratios 2:1, 3:1, and 4:1 of probucol (as a surrogate active ingredient) in sesame oil and surfactant to silica were evaluated for the maximum drug loading capacity while retaining the free flowing capac-

ity of the silica beads. Angle of repose of Syloid® XDP 3150 beads and Davisil® LC150A beads is between 35-40° representing passable flowability, as shown in Table 1. However, the angle of repose of Neusilin® US2 beads is 30°, shown in Table 2, which represents better flowability as compared to Syloid® XDP 3150 beads and Davisil® LC150A beads. Upon maximum drug loading, Syloid® XDP 3150 beads and Davisil® LC150A beads displayed a loss in their flowability when loaded with the 2:1 weight ratio of probucol (as a surrogate active ingredient) in sesame oil, surfactant, and gel-forming excipient to silica. Neusilin® US2 beads retained their free flowing properties at the 2:1 and 3:1 weight ratio of probucol (as a surrogate active ingredient) in sesame oil, surfactant, and gel-forming excipient to silica. However, at 4:1 ratio, the flowability of Neusilin® US2 beads appeared to be reduced. Therefore, based on evaluation, Neusilin® US2 beads were identified as a carrier substrate with optimized drug loading of 2:1 and 3:1 weight ratio of probucol (as a surrogate active ingredient) in sesame oil, surfactant, and gel-forming excipient to silica. However, Syloid® XDP 3150 and Davisil® LC150A carrier substrates nonetheless display properties that are conducive for use as the core in the compositions of the present invention.

[0089] In embodiments of the invention, one or more surfactants are used in the composition. In the current invention, surfactants are included to maximize the complete release of the one or more active agents from the pores of the cores. The active agents may be hydrophobic and their release upon dissolution in aqueous medium of the gastrointestinal tract is determined by various intrinsic factors such as fluid volume, peristaltic movement, concentration gradient, food effect, bile salts, and transit time. Since the loading of the one or more active agents onto porous cores is achieved by the capillary action and in consideration of the greater affinity of hydrophobic active agents to the cores, the release of the one or more active agents from the pores warrants an emulsification action.

[0090] In embodiments of the invention, the extended release composition may comprise a population of particles, wherein each particle comprises: at least one active agent; one or more drug-releasing agents that comprise one or more release-controlling polymers, one or more release-accelerating polymers, or a combination thereof; and an inert core. In some embodiments, the particles may comprise at least one active agent; one or more drug-releasing agents that comprise one or more release-controlling polymers, one or more release-accelerating polymers, or a combination thereof; an inert core; and one or more solubilizers. The at least one active agent may comprise the at least one cannabinoid, the at least one non-cannabinoid therapeutic agent, or a combination of the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent. In embodiments in which each particle does not comprise both the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent, then the population of particles in the extended release composition may comprise both particles comprising the at least one cannabinoid and particles comprising the at least one non-cannabinoid therapeutic agent.

[0091] In some embodiments, the particles may comprise one or more stabilizing agents.

[0092] The one or more release-controlling polymers may be selected from, for example, ethyl cellulose, polymethacrylate copolymers, copolymers derived from esters of

acrylic and methacrylic acid (e.g., Eudragit® such as Eudragit® L-30D, Eudragit® FS-30D), polyacrylic acid-based polymers, polyacrylates, methacrylic acid co-polymers, polyvinyl acetate (e.g., Kollicoat® SR-30D), polyvinyl alcohol, and combinations thereof. The one or more release-accelerating polymers may be selected from polyvinylpyrrolidones or cellulose derivatives that are water soluble. The early dissolution of these ingredients leave pores on and around the coated material applied on the inert substrates through which one or a combination of active agents is released by diffusion. Diffusion is defined as a process of drug transport from a region of high concentration to a region of low concentration.

[0093] According to embodiments of the current invention, the core may comprise an inert material selected from the group consisting of microcrystalline cellulose, celluloses, starches, and saccharides; natural polymers that include, but are not limited to, chitosan, alginate, and collagen protein/polypeptides; synthetic polymer-based materials that include, but are not limited to, polylactic acid, polycaprolactone, polyglycolic acid, and polylactic-co-glycolic acid; ceramics that include, but are not limited to, calcium phosphate, hydroxyapatite, and α -tricalcium phosphate; glass that include, but are not limited to, borate-based glass, silicate-based glass, and phosphate-based glass; and combinations thereof.

[0094] In some embodiments, the core may comprise a coating that comprises the one or more active agents; and the one or more release-controlling polymers, the one or more release-accelerating polymers, or a combination thereof.

[0095] In embodiments of the present invention, the composition of the present invention can exhibit a dissolution profile that is characteristic of extended release. In some embodiments, when subjected to water as a dissolution medium, the composition of the present invention may exhibit a percent release of the one or more active agents of not more than about 20%, or not more than about 30%, or not more than about 40%, or not more than about 50% by weight, after 30 minutes; or not more than about 30%, or not more than about 40%, or not more than about 50%, or not more than about 60% by weight, after 60 minutes; or not more than about 40%, or not more than about 50%, or not more than about 60%, or not more than about 70% by weight, after 120 minutes.

Dosage Forms

[0096] The composition of the present invention may be in various dosage forms, for example, in capsules, tablets (including regular tablets, ODT, self-disintegrated tablets, chewable tablets), sachets, sprinkles, or a stick pack. To this end, the composition may comprise excipients such as binding agents, fillers, lubricants, disintegrants, antioxidants, wetting agents, flavors/sweeteners, or a combination thereof.

Excipients

[0097] The compositions of the present invention may comprise one or more excipients. As described herein, in some embodiments the immediate release composition may comprise a population of particles, in which each particle includes one or more intra-granule excipients, such as one or more diluents, one or more binders, one or more fillers, one or more surfactants/emulsifying agents, one or more disin-

tegrating agents, or a combination thereof. Also, in some embodiments the extended release composition may comprise a population of particles, in which each particle may comprise one or more excipients such as one or more surfactants. In addition, the dosage forms of the compositions may comprise one or more excipients such as one or more binding agents, fillers, surfactants, lubricants, disintegrants, antioxidants, wetting agents, or flavors/sweeteners.

[0098] Diluents may serve different functions, such as to increase weight and improve content uniformity, improve cohesion, and/or promote flow. Examples of diluents include, but are not limited to, cellulose derivatives such as lactose, sucrose, isomalt, cellulose, starch, cyclodextrin, mannitol, microcrystalline cellulose, and sorbitol; calcium carbonate; plain or anhydrous calcium phosphate; calcium hydrogen phosphate dehydrate; calcium phosphate di- or tri-basic; magnesium carbonate; magnesium oxide; starch; sodium chloride; and a combination thereof.

[0099] Binders are excipients that may act as an adhesive to "bind together" particles and, in some cases, impart mechanical strength. In addition, binders can also provide volume to the composition. Examples of binders may include, but are not limited to, sugars such as sucrose, lactose, and glucose; corn syrup; soy polysaccharide; gelatin; povidone (e.g., Kollidon®, Plasdane®); Pullulan; cellulose derivatives such as microcrystalline cellulose, hydroxypropylmethyl cellulose (e.g., Methocel), hydroxypropyl cellulose (e.g., Klucel®), ethylcellulose, hydroxyethyl cellulose, carboxymethylcellulose sodium, and methylcellulose; acrylic and methacrylic acid co-polymers; carbomer (e.g., Carbopol®); polyvinylpyrrolidone, polyethylene glycol (Carbowax®); pharmaceutical glaze; alginates such as alginic acid and sodium alginate; gums such as acacia, guar gum, and arabic gums; tragacanth; dextrin and maltodextrin; milk derivatives such as whey; starches such as pregelatinized starch and starch paste; hydrogenated vegetable oil; magnesium aluminum silicate; and a combination thereof.

[0100] Fillers may increase the bulk of the composition and may make it easier to handle. Examples of fillers may include, but are not limited to, lactose, dextrose, saccharose, cellulose, starch, calcium phosphate, sucrose, dextrates, dextrin, maltodextrin, microcrystalline cellulose (e.g., PH102 or PH200, Avicel®), microfibrillated cellulose, powdered cellulose, pregelatinized starch (e.g., Starch 1500®), calcium phosphate dihydrate, soy polysaccharide (e.g., Emcosoy®), gelatin, silicon dioxide, calcium sulfate, calcium carbonate, magnesium carbonate, magnesium oxide, sorbitol, mannitol, kaolin, polymethacrylates (e.g., Eudragit®), potassium chloride, sodium chloride, talc, and a combination thereof.

[0101] Disintegrants may assist in breaking up the particles when exposed to an aqueous environment. Examples of disintegrants may include, but are not limited to, modified sodium starch glycolate, cross-linked povidone or croscopolvidone (e.g., Kollidon®), hydroxyl propyl cellulose, starch, alginic acid, sodium alginate, sodium carboxy-methylcellulose, croscarmellose sodium, carmellose sodium, microcrystalline cellulose, carboxystarch sodium, carboxymethyl starch sodium, potato starch, wheat starch, corn starch, rice starch, partly pregelatinized starch, hydroxypropyl starch, alginates, carbonates, and a combination thereof.

[0102] Surfactants/emulsifying agents promote self-emulsification. When an emulsion is formed, surface area expansion

is created between the two phases. The emulsion is stabilized by the surfactant/emulsifying agent molecules that form a film around the internal phase droplet. In emulsion formation, the excess surface free energy is dependent on the droplet size and the interfacial tension. If the emulsion is not stabilized using surfactants/emulsifying agents, the two phases will separate reducing the interfacial tension and the free energy. Self-emulsifying drug delivery systems ("SEDDS") including self-micro-emulsifying drug delivery systems ("SMDDS") are mixtures of natural or synthetic oils, solid or liquid surfactants/emulsifying agents, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants/emulsifying agents that have the ability to form oil-in-water emulsions upon mild agitation followed by dilution in aqueous media, such as gastrointestinal fluids. Examples of surfactants/emulsifying agents may include, but are not limited to, sorbitan esters, ethoxylated sorbitan esters (Tween® 80; Sigma Aldrich, USA), ethoxylated linear alcohols, ethoxylated alkyl phenols, fatty acid esters, amine and amide derivatives, alkylpolyglucosides, ethylene-oxide/propylene oxide copolymers, polyalcohols and ethoxylated polyalcohols, thiols (e.g., mercaptans) and derivatives, poloxamers, polyethylene glycol-fatty acid esters, lecithins, and mixtures thereof. In certain embodiments, the surfactant/emulsifying agent may be selected from polysorbates (Tween® 80; Sigma Aldrich, USA), and polyethylene glycol esters of ricinoleic acid (Kolliphor® RH40, Kolliphor® EL; BASF, Germany).

[0103] Lubricants may reduce friction between granules and thus enhance followability, as well as prevent sticking to the wall in tablet compression and facilitate powder-filling in encapsulation. Lubricants may also assist with disintegration time and impact dissolution rate. Examples of lubricants may include, but are not limited to, calcium stearate, castor oil hydrogenated, glyceryl monostearate, glyceryl behenate, magnesium stearate, mineral oil, polyethylene glycol, polaxamer 407 or 188 or plain, sodium lauryl sulfate, sodium benzoate, stearic acid, sodium stearyl fumarate, silica, talc, and a combination thereof.

[0104] Antioxidants can have positive effects on the stability and efficacy of the composition. Examples of antioxidants may include, but are not limited to, acetylcysteine, ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), monothioglycerol, potassium nitrate, sodium ascorbate, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium bisulfite, vitamin E or a derivative thereof, propyl gallate, edetate (EDTA) (e.g., disodium edetate), diethylenetriaminepentaacetic acid (DTPA), triglycollamate (NT), and a combination thereof. Antioxidants may also comprise amino acids such as methionine, histidine, cysteine and those carrying a charged side chain, such as arginine, lysine, aspartic acid, and glutamic acid. Any stereoisomer (e.g., L-, D-, or a combination thereof) of any particular amino acid (e.g., methionine, histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine and combinations thereof) or combinations of these stereoisomers, may be present so long as the amino acid is present either in its free base form or its salt form. For example, the L-stereoisomer may be used.

[0105] Flavors/sweeteners can help make the composition more palatable. Examples of flavors/sweeteners may include, but are not limited to, sugar, dextrose, fructose, aspartame, glycerin, mannitol, sucrose, saccharin sodium, acesulfame potassium, dextrates, liquid glucose, maltitol,

saccharin, saccharin calcium; saccharin sodium, sodium cyclamate, sorbitol, stevia, syrup, xylitol, and a combination thereof.

Sustained Release Compositions

[0106] As used herein, the term “sustained release” is characterized by the continuous release of the active agents from the particles of the composition over a prolonged period of time, optionally greater than about 60 minutes.

[0107] The sustained release composition may comprise a population of particles comprising one or more of the particles of the immediate release composition of the present invention, and one or more of the particles of the extended release composition of the present invention. The amounts of the particles of the immediate release composition and the particles of the extended release composition may be based on achieving a pre-determined release profile.

[0108] In some embodiments, the release profile may comprise a rapid release of the active agents, followed by a more gradual release of the active agents. For example, the rapid release may comprise about 30% to about 70% by weight of the total active agents, or about 40% to about 60% by weight of the total active agents, released within about 60 minutes (1 hour) or less, or about 30 minutes or less, or about 15 minutes or less. The gradual release may comprise the remaining about 30% to about 70% by weight of the total active agents, or the remaining about 40% to about 60% by weight of the total active agents, released after about 60 minutes (1 hour), or after about 120 minutes (2 hours), or after about 180 minutes (3 hours), or after about 240 minutes (4 hours). In some embodiments, the release of the active agents may be prolonged up to 1440 minutes (24 hours), as intended for the therapeutic effect.

Methods of Preparing the Compositions of the Invention

Methods of Preparing Immediate Release Compositions

[0109] In embodiments of the invention, methods of preparing immediate release compositions of the present invention may comprise (a) combining the at least one active agent with one or more intra-granular excipients, and granulating the combination to produce immediate release particles; or (b) loading the at least one active agent onto porous bead cores to produce immediate release particles.

[0110] The at least one active agent used in the methods above may comprise at least one cannabinoid, or at least one non-cannabinoid therapeutic agent, or a combination of the at least one cannabinoid and at least one non-cannabinoid therapeutic agent. In embodiments in which the at least one active agent used in the methods above is not a combination of the at least one cannabinoid and at least one non-cannabinoid therapeutic agent, then the methods may comprise preparing immediate release particles that comprises the at least one cannabinoid as the at least one active agent, preparing immediate release particles that comprises the at least one non-cannabinoid therapeutic agent as the at least one active agent, and then combining the immediate release particles comprising at least one cannabinoid and the immediate release particles comprising the at least one non-cannabinoid therapeutic agent to form the immediate release composition. Such a combination may occur, for example, by granulating particles comprising the at least one cannabinoid and particles comprising the at least one non-cannabi-

noid therapeutic agent into one granulation. Alternatively, such a combination may occur, by mixing a population of particles comprising the at least one cannabinoid and a population of particles comprising the at least one non-cannabinoid therapeutic agent.

[0111] The at least one active agent that is combined with the one or more intra-granular excipients or that is loaded onto porous bead cores may be in a granulating liquid. The granulating liquid may be an emulsion, suspension, hydroalcoholic mixture, or a combination thereof. In some embodiments, the granulating liquid may comprise one or more solubilizing agents. The one or more solubilizing agents may be an oil, a glyceride, an alcohol, a hydroalcoholic solution, or a combination thereof. Examples of an oil may include, but are not limited to, sesame oil, cannabis oil, borage oil, coconut oil, cottonseed oil, soybean oil, safflower oil, sunflower oil, castor oil, corn oil, olive oil, palm oil, peanut oil, almond oil, rapeseed oil, peppermint oil, poppy seed oil, canola oil, palm kernel oil, hydrogenated soybean oil, hydrogenated vegetable oil, and a combination thereof. Examples of a glyceride may include, but are not limited to, a monoglyceride, diglyceride, triglyceride, and a combination thereof. Examples of an alcohol may include, but are not limited to, a monohydric alcohol, e.g., ethanol, methanol, or isopropyl alcohol. Examples of a hydroalcoholic mixture may include, but are not limited to, isopropyl alcohol mixed with water, or ethanol mixed with water, in varying ratios.

[0112] In some embodiments, the granulating liquid may further comprise one or more surfactants/emulsifying agents.

[0113] In some embodiments, the methods of the invention further comprise preparing the granulating liquid comprising the at least one active agent. Preparation of the granulating liquid may involve mixing the at least one active agent with the one or more solubilizing agents until the at least one active agent is dissolved. In some embodiments, preparation of the granulating liquid may comprise mixing other components, such as one or more surfactants/emulsifying agents, with the at least one active agent and the one or more solubilizing agents. The mixing of the contents may be by methods known in the art. For example, the contents may be mixed by simple mixing, or may be mixed with a mixing device continuously, periodically, or a combination thereof. Examples of mixing devices may include, but are not limited to, a magnetic stirrer, shaker, a paddle mixer, homogenizer, and any combination thereof.

[0114] In embodiments in which the particles comprise both at least one cannabinoid and at least one non-cannabinoid therapeutic agent, the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent may be in the same granulating liquid, or may be in different granulating liquid.

[0115] In embodiments in which the particles comprise both THC and CBD, the THC and CBD may be in the same granulating liquid, or may be in different granulating liquids.

[0116] In embodiments of the invention, the granulating liquid may be combined with one or more intra-granular excipients, and the combination may be granulated to produce immediate release particles. The combination of the granulating liquid may occur before granulation, or may occur concurrently in whole or in part with granulation.

[0117] In embodiments in which the particles comprise both the at least one cannabinoid and the at least one non-cannabinoid therapeutic agent, and in which the at least

one cannabinoid and the at least one non-cannabinoid therapeutic agent are in different granulating liquids, the granulating liquid may be combined together before combining with the one or more intra-granular excipients. Alternatively, the granulating liquid may be combined together simultaneously with combining with the one or more intra-granular excipients.

[0118] In embodiments in which the particles comprise both THC and CBD, and in which the THC and CBD are in different granulating liquids, the granulating liquids may be combined together before combining with the one or more intra-granular excipients. Alternatively, the granulating liquids may be combined together simultaneously with combining with the one or more intra-granular excipients.

[0119] In some embodiments, the combination of the granulating liquid(s) with the one or more intra-granular excipients and granulation may be performed by a fluid bed granulation process. The one or more intra-granular excipients may be loaded into a granulator bowl of a fluid bed granulator and fluidized. The granulating liquid(s) may be added into the granulator bowl and onto the one or more intra-granular excipients. The addition of the granulating liquid(s) may be via a top spray, bottom spray, tangential spray, or an equivalent thereof. The parameters of this process, including the amount of pressure necessary to fluidize the one or more excipients in the granulator bowl, the inlet air temperature in the granulator bowl, the humidity level in the granulator bowl, the spray rate of the granulating liquid(s), and the fluid bed spray nozzle size and height, can all be determined by one of ordinary skill in the art. Examples of fluid bed granulators that may be used in these methods of the invention may include those manufactured by Glatt GMBH, Sainty International Group, GEA Group, Senieer, LB Bohle, Robert Bosch Packaging Technology GmbH, and SPX FLOW Danmark.

[0120] In some embodiments, the combination of the granulating liquid(s) with the one or more intra-granular excipients and granulation may be performed by a wet granulation process. In certain embodiments, the wet granulation process may be performed with a high-shear granulator. The one or more intra-granular excipients may be loaded into a bowl of a high-shear granulator and mixed at speeds ranging from about 25 rpm to about 1000 rpm, or about 100 rpm to about 500 rpm. The granulating liquid(s) may be added into the granulator bowl and onto the one or more intra-granular excipients, and the combination of the granulating liquid(s) and the one or more excipients is mixed under high shear at speeds ranging from about 500 rpm to about 5000 rpm, or about 1000 rpm to about 3000 rpm. The parameters of this process, such as the addition rate of the granulating liquid(s), can all be determined by one of ordinary skill in the art. In some embodiments, the high-shear granulator may be a vertical high-shear granulator. The vertical high-shear granulator may be top-driven or bottom-driven. In other embodiments, the high-shear granulator may be a horizontal high-shear granulator. Examples of high-shear granulators that may be used in these methods of the invention may include those manufactured by Glatt GMBH, SERVOLIIFT LLC, Sainty International Group, GEA Group, Senieer, LB Bohle, and Robert Bosch Packaging Technology GmbH.

[0121] In certain embodiments, the wet granulation process may be performed with the Glatt CPS' technology (Complex Perfect Spheres Technology). CPS™ is a patented

technology by Glatt GMBH in which spherical granules are manufactured in two phases (i) nucleation of powders in which the solvent acts as a binder to create bridges between the particles of the active ingredient and a filler (e.g., microcrystalline cellulose), resulting in agglomeration; and (ii) spheronization of the granules due to centrifugal force exerted by the simultaneous spinning of the modified rotor disc to produce the smooth spherical granules/pellets. The CPS technology is disclosed in U.S. Pat. No. 6,354,728 and PCT Publication No. WO04052607, which are incorporated herein by reference. The one or more intra-granular excipients may be loaded into a bowl and the granulating liquid(s) may be added into the bowl and onto the one or more excipients.

[0122] In certain embodiments, the wet granulation process may be performed by extrusion-spheronization. The one or more intra-granular excipients may be loaded into a bowl and the granulating liquid(s) may be added into the bowl and onto the one or more intra-granular excipients. The combination of the granulating liquid(s) and the one or more excipients may be mixed, such as with a planetary mixer, a high-shear mixer as described above, or a sigma blade mixer. The combination mixture may then undergo extrusion, in which pressure is applied to the combination mixture until it flows out through one or more orifices to produce the extrudates. Extrusion may be performed using a screw extruder, which uses a screw to develop the necessary pressure to force the combination mixture to flow through the one or more orifices; sieve extruder, which uses a rotating or oscillating arm to press the combination mixture through a sieve; basket extruder, which uses a rotating or oscillating arm to press the combination mixture through a sieve that is part of a vertical cylindrical wall; roll extruder, in which the combination mixture is fed between a roller and a perforated plate or ring die; ram extruder, in which the combination mixture compressed and forced through one or more orifices by a piston that is inside a cylinder or channel; or other types of extruders known in the art. The extruded combination mixture may then undergo spheronization, in which the mixture is broken into uniform lengths and are gradually transformed into spherical shapes. The parameters of the extrusion-spheronization process can be determined by one of ordinary skill in the art. Examples of extrusion-spheronization equipment that may be used in these methods of the invention may include those manufactured by Glatt GMBH, Sainty International Group, GEA Group, LB Bohle, and Robert Bosch Packaging Technology GmbH.

[0123] In certain embodiments, the wet granulation process may be performed with a connection mixer, roller compactor, or "V" blender, using methods known in the art.

[0124] Following wet granulation, the particles may be dried using methods known in the art, for example, using a fluid bed processor.

[0125] In some embodiments, the combination of the granulating liquid(s) with the one or more intra-granular excipients and granulation may be performed by a spray granulation process. The granulating liquid(s), which includes one or more surfactants as described above, is mixed well with the one or more intra-granular excipients, resulting in a dispersion. This dispersion may comprise about 5% to about 90% of solid content. The dispersion is then sprayed onto a fluidized or spouted bed to produce particles. The parameters of this process can be determined by one of ordinary skill in the art. Examples of spray

granulators that may be used in these methods of the invention may include those manufactured by Glatt GMBH, GEA Group, LB Bohle, Robert Bosch Packaging Technology GmbH, and Allgaier Werke GmbH.

[0126] In certain embodiments, the spray granulation process may be performed using Procell® sprouted bed technology. The Procell technology is disclosed in U.S. Pat. Nos. 7,993,595 and 8,597,685, and in European Patent Nos. 1125629 and 1325775, which are all incorporated herein by reference.

[0127] In embodiments of the invention, the granulating liquid(s) comprising the at least one active agent may be loaded onto porous bead cores. The granulating liquid(s) may be loaded onto the porous bead cores by mixing the granulating liquid(s) with the cores. In certain embodiments, a high shear granulator may be used to mix the granulating liquid(s) with the porous bead cores. In some embodiments, the mixing may occur until a free-flowing powder mixture is produced. Thereafter, a composition according to the present invention is formed.

[0128] According to embodiments of the invention, the particles comprising the at least one active agent prepared by the methods described above may be sized, milled, and screened according to methods known in the art. The particles may be blended with extra-granular excipients as described above, and the resulting blend may be processed into a dosage form such as a tablet, capsule, or stick pack using conventional methodologies. Particles comprising different active agents may be combined prior to processing them into the dosage form.

Methods of Preparing Extended Release Compositions

[0129] In embodiments of the invention, methods of preparing extended release compositions of the present invention may comprise (a) mixing the at least one active agent in one or more solubilizers along with one or more gel-forming agents (and in some embodiments one or more surfactants, and optionally one or more stabilizing agents) and loading the mixture onto a porous core; or (b) dispersing the at least one active agent in one or more solubilizers along with one or more release-controlling polymers and/or one or more release-accelerating polymers (and optionally one or more stabilizing agents), and the drug dispersion may then be applied onto inert cores (such as microcrystalline celleds or sugar spheres).

[0130] The at least one active agent used in the methods above may comprise at least one cannabinoid, or at least one non-cannabinoid therapeutic agent, or a combination of the at least one cannabinoid and at least one non-cannabinoid therapeutic agent. In embodiments in which the at least one active agent used in the methods above is not a combination of the at least one cannabinoid and at least one non-cannabinoid therapeutic agent, then the methods may comprise preparing extended release particles that comprises the at least one cannabinoid as the at least one active agent, preparing extended release particles that comprises the at least one non-cannabinoid therapeutic agent as the at least one active agent, and then combining the extended release particles comprising at least one cannabinoid and the extended release particles comprising the at least one non-cannabinoid therapeutic agent to form the extended release composition.

[0131] In embodiments of the present invention, the methods comprise mixing the at least one active agent and the one

or more gel-forming agents (and in some embodiments one or more surfactants, and optionally one or more stabilizing agents) in one or more solubilizers using, for example, a sonicator and/or a vortex mixer. These components may be mixed in the solubilizer(s) in any order (e.g., first mixing the at least one active agent in the one or more solubilizers and then adding the one or more gel-forming agents and in some embodiments the one or more surfactants, or first mixing one or more surfactants in the one or more solubilizers and then adding the at least one active agent and the one or more gel-forming agents, or adding and mixing each component simultaneously together, etc.). In some embodiments, the at least one active agent and the one or more solubilizers may be mixed with a sonicator until uniform, and then the one or more surfactants (in some embodiments) and the one or more gel-forming agents (and optionally one or more stabilizing agents) may be added and mixed using a vortex mixer. The mixture may then be loaded onto the porous cores by mixing the mixture with the cores. In certain embodiments, a high shear granulator may be used to mix the at least one active agent/one or more gel-forming agents/other components mixture with the porous cores. Thereafter, a composition according to the present invention is formed.

[0132] In embodiments of the invention, the methods comprise mixing the at least one active agent in the one or more solubilizers to form a homogenous dispersion. The one or more release-controlling polymers and/or the one or more release-accelerating polymers (and optionally one or more stabilizing agents) may be then mixed with the dispersion using, for example, a vortex mixer, until a homogenous mixture is formed. The mixture may be then loaded onto the cores. In some embodiments, the mixture may be sprayed onto the cores using, for instance, a fluid bed processor. The particle size and size distribution of the cores can be narrowed/adjusted to achieve uniform drug distribution and targeted delivery profile.

[0133] The particles may be blended with extra-granular excipients as described above, and the resulting blend may be processed into a dosage form such as a tablet, capsule, or stick pack using conventional methodologies. Particles comprising different active agents may be combined prior to processing them into the dosage form.

Methods of Preparing Sustained Release Compositions

[0134] In embodiments of the invention, methods of preparing sustained release compositions of the present invention may comprise mixing particles of the immediate release compositions of the invention with particles of the extended release compositions of the invention. The amount of the particles of the immediate release compositions and the amount of the particles of the extended release compositions may be based on achieving a pre-determined release profile.

[0135] The particles may be mixed by simple mixing, or may be mixed with a mixing device continuously, periodically, or a combination thereof. Examples of mixing devices may include, but are not limited to, a magnetic stirrer, shaker, a paddle mixer, homogenizer, and any combination thereof.

[0136] The particles may be blended with extra-granular excipients as described above, and the resulting blend may be processed into a dosage form such as a tablet, capsule, or stick pack using conventional methodologies. Particles com-

prising different active agents may be combined prior to processing them into the dosage form.

Application of the Compositions of the Invention

[0137] An aspect of the invention relates to methods of treating a health issue in a subject in need thereof, wherein the methods comprise administering an immediate release composition of the invention, an extended release composition of the invention, or a sustained release composition of the invention to the subject.

[0138] The present invention also relates to the use of an immediate release composition of the invention, an extended release composition of the invention, or a sustained release composition of the invention for treating a health issue in a subject in need thereof. The use may comprise administering the composition to the subject.

[0139] The present invention relates to the use of an immediate release composition of the invention, an extended release composition of the invention, or a sustained release composition of the invention in the manufacture of a medicament for treating a health issue in a subject in need thereof.

[0140] The present invention further relates to an immediate release composition of the invention, an extended release composition of the invention, or a sustained release composition of the invention for use in treating a health issue in a subject in need thereof. The use may comprise administering the composition to the subject.

[0141] The health issue may be selected from the group consisting of pain, nausea, sleep apnea, stress disorders, inflammation, depression, anxiety, epilepsy, schizophrenia, migraines, arthritis, weight loss, poor appetite, and combinations thereof.

[0142] In some embodiments, the composition may be administered orally.

[0143] In some embodiments, prior to administration, the composition may be sprinkled on food or nutrient that is solid, semi-solid, or liquid; into water; or into other types of liquid drink.

EXAMPLES

Example 1

[0144] A study was performed to prepare and assess a composition according to embodiments of the invention, in which the composition comprises both particles that comprise THC and particles that comprise CBD, as shown in Table 3 below. The particles were prepared using the top spray fluid bed granulation process according to embodiments of the invention.

TABLE 3

Composition of Example 1.			
	Component	Function	% of Total Weight
Granulating liquid	THC (20% Dronabinol in Ethanol)	Active in solubilizing agent	5.54
	Kolliphor® EL	Surfactant/emulsifying agent	0.2

TABLE 3-continued

Composition of Example 1.			
	Component	Function	% of Total Weight
Granulating liquid	CBD	Active	11.08
	Sesame oil	Solubilizing agent	8.6
	Polysorbate 80	Surfactant/emulsifying agent	6
Intra-granular Excipient	Pharmatose® 200M (EU)	Diluent	45.28
	(Milled Lactose Monohydrate)		
	Kollidon® 30	Binder	3
	Vivapur® 101 (Microcrystalline Cellulose)	Disintegrant	20.3
Granulation Process	Methanol	Processing solvent	Non-residual
	Purified water	Processing solvent	Non-residual
TOTAL			100

[0145] The particle size distribution of the composition, shown in FIG. 3, was obtained using dynamic light scattering technique (Malvern Instruments, USA). As shown in the figure, over 70% of the particles are between about 100 nm and about 700 nm in diameter.

[0146] SEM images of the granules obtained using Electronic Scanning Microscopy Imaging technique are shown in FIGS. 4A and 4B.

[0147] A dissolution test was performed using purified water, USP, as the dissolution medium in a dissolution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-μm porous filter was used to sample aliquots. The resulting dissolution profiles for both the THC particles and the CBD particles are shown in FIG. 5. Dissolution of both the THC particles and CBD particles exhibited an immediate release dissolution profile.

Example 2

[0148] A study was performed to prepare and assess a composition according to embodiments of the invention, in which the composition comprises both particles that comprise THC and particles that comprise CBD, as shown in Table 4 below. The particles were prepared using the high-shear granulation process with the CPS technology according to embodiments of the invention.

TABLE 4

Composition of Example 2.			
	Component	Function	% of Total Weight
Granulating liquid	THC (20% Dronabinol in Ethanol)	Active in solubilizing agent	5.54
	Kolliphor® EL	Surfactant/emulsifying agent	0.2
Granulating liquid	CBD	Active	11.08
	Sesame oil	Solubilizing agent	8.6
	Polysorbate 80	Surfactant/emulsifying agent	6

TABLE 4-continued

Composition of Example 2.			
	Component	Function	% of Total Weight
Intra-granular Excipient	Pharmatose® 200M (EU)	Diluent	45.28
	(Milled Lactose Monohydrate)		
	Kollidon® 30	Binder	3
	Vivapur® 101 (Microcrystalline Cellulose)	Disintegrant	20.3
Granulation Process	Methanol	Processing solvent	Non-residual
	Purified water	Processing solvent	Non-residual
TOTAL			100

[0149] The particle size distribution of the composition, shown in FIG. 6, was obtained using dynamic light scattering technique (Malvern Instruments, USA). As shown in the figure, over 70% of the particles are between about 80 μm and about 700 μm in diameter.

[0150] SEM images of the granules obtained using Electronic Scanning Microscopy Imaging technique are shown in FIGS. 7A and 7B.

[0151] A dissolution test was performed using 1% polysorbate 80 in distilled water as the dissolution medium in a dissolution volume of 500 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 100 rpm. The bath temperature was 37° C.

[0152] The resulting dissolution profiles for both the THC particles and the CBD particles are shown in FIG. 8. Dissolution of both the THC particles and CBD particles exhibited an immediate release dissolution profile.

Example 3

[0153] A study was performed to prepare and assess a composition according to embodiments of the invention, in which the composition comprises both particles that comprise THC and particles that comprise CBD, as shown in Table 5 below. The particles were prepared by loading the THC and CBD onto porous bead cores according to embodiments of the invention.

TABLE 5

Composition of Example 3.		
Component	Function	% of Total Weight
THC in sesame oil	Active in solubilizing agent	14
CBD	Active	1.4
Tween® 80	Surfactant/emulsifying agent	51.6
Neusilin® US2 (Silica)	Porous bead core	33
Total		100

[0154] Particle size distribution was obtained using dynamic light scattering technique (Malvern Instruments, USA) for the composition as well as for blank porous bead cores. As shown in FIGS. 9A and 9B, over 70% of the particles of the composition are between about 20 μm and about 200 μm in diameter (FIG. 9A), while over 70% of the particles of the blank porous bead cores are between about 2 μm and about 100 μm in diameter (FIG. 9B).

[0155] SEM images of the granules obtained using Electronic Scanning Microscopy Imaging technique are shown in FIGS. 10A-10F.

[0156] A dissolution test was performed using 1% polysorbate 80 in distilled water as the dissolution medium in a dissolution volume of 500 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 100 rpm. The bath temperature was 37° C.

[0157] The resulting dissolution profiles for both the THC particles and the CBD particles are shown in FIG. 11. The dissolution profile of the THC particles was nearly the same as the dissolution profile of the CBD particles, and both particles achieved 80% release in less than 20 minutes.

Example 4

[0158] A study was performed to assess immediate release compositions (Reference Composition A-C) and extended release compositions (Example Compositions A-C) that comprise different surfactants. This study examined the dissolution profile of the compositions in order to assess the emulsification capacity of each surfactant, and to evaluate the drug-releasing agent in the extended release compositions.

[0159] The immediate release compositions are particles comprising a porous silica bead core; a surrogate active ingredient, probucol; and a surfactant selected from Tween® 80 (Reference Composition A), Kolliphor® RH40 (Reference Composition B), or Kolliphor® EL (Reference Composition C). Table 6 provides a summary of these compositions, including the quantity of each component. The weight ratio of sesame oil to surfactant was 1:5 in each immediate release composition. To prepare the compositions, the probucol was added to sesame oil in a glass beaker, and a sonicator was used to obtain a uniform mixture. The surfactant was added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then loaded into pores of the Neusilin® US2 silica beads using a high shear granulator to achieve uniform drug-loaded beads.

TABLE 6

Summary of the components and their quantities (% w/w) of Reference Compositions A-C.			
Component	Reference Composition A	Reference Composition B	Reference Composition C
Probuco	1.25%	1.25%	1.25%
Sesame oil	11.25%	11.25%	11.25%
Surfactant	62.5%	62.5%	62.5%
	(Tween® 80)	(Kolliphor® RH 40)	(Kolliphor® EL)
Neusilin US2 beads	25%	25%	25%
TOTAL	100%	100%	100%

[0160] The extended release compositions are particles comprising a porous silica bead core; a surrogate active ingredient, probucol; glyceryl monooleate as a gel-forming agent; and a surfactant selected from Tween® 80 in a weight ratio of 1:1 with the glyceryl monooleate (Example Composition A), Kolliphor® RH40 in a weight ratio of 11.5:1 with the glyceryl monooleate (Example Composition B), and Kolliphor® EL in a weight ratio of about 5.25:1 with the glyceryl monooleate (Example Composition C). Table 7 provides a summary of these compositions, including the quantity of each component. To prepare the compositions, the probucol was added to sesame oil in a glass beaker, and a sonicator was used to obtain a uniform mixture. The surfactant and the glyceryl monooleate were added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then loaded into pores of the Neusilin® US2 silica beads using a high shear granulator.

TABLE 7

Summary of the components and their quantities (% w/w) of Example Compositions A-C.			
Component	Example Composition A	Example Composition B	Example Composition C
Probutcol	1.3%	1.25%	1.25%
Sesame oil	12%	11.25%	11.25%
Glyceryl monooleate	26.7%	5%	10%
Surfactant	26.7%	57.5%	52.5%
	(Tween® 80)	(Kolliphor® RH 40)	(Kolliphor® EL)
Neusilin	33.3%	25%	25%
US2 beads			
TOTAL	100%	100%	100%

of 100% w/w drug from the silica pores as compared to 85% w/w with Kolliphor® RH40 and 88% w/w with Tween® 80.

[0164] The dissolution profiles of each extended release Example Composition A-C are provided in Table 9 and in FIG. 12B. The dissolution profile of Example Composition A, in which Tween® 80 was used as the surfactant, showed that drug release was extended for the first 6 hours to achieve 50% w/w drug release—and thereby zero order release—for up to 24 hours (see Table 9 and FIG. 12B).

The dissolution profile of Example Composition B, in which Kolliphor® RH40 was used as the surfactant, showed over 80% w/w drug release by 5 minutes (see Table 9 and FIG. 12B). Similarly, the dissolution profile of Example Composition C, which used Kolliphor® EL as the surfactant, showed 79% w/w drug release by 5 minutes and over 80% w/w drug release by 15 minutes (see Table 9 and FIG. 12B).

TABLE 9

Dissolution profile of Example Compositions A-C.									
Composition	% Drug Release of Probutcol								
	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min	1440 min
Example Composition A	11	15	19	27	33	42	48	50	50
Example Composition B	84	87	87	88	89	89	90	90	90
Example Composition C	79	84	85	87	87	88	88	89	89

[0161] A dissolution test was conducted on the compositions using purified water, USP, as the dissolution medium in a dissolution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-µm porous filter was used to sample aliquots.

[0162] The dissolution profiles of each immediate release Reference Compositions A-C are provided in Table 8 and in FIG. 12A. Surfactant Tween® 80 was able to facilitate over 80% w/w release of probucol from the Neusilin® in the dissolution medium within 15 minutes as shown in Table 8. Surfactants Kolliphor® RH 40 and Kolliphor® EL were both able to facilitate over 80% w/w release of Probutcol in sesame oil from the Neusilin® silica pores in the dissolution medium within 5 minutes, as shown in Table 8.

These results demonstrate that glyceryl monooleate as a gel-forming agent is capable of providing an extended release profile. In addition, it is hypothesized that the hydrophilicity of glyceryl monooleate may have increased the emulsification action of the beads leading to higher drug release in dissolution medium.

Example 5

[0165] A study was performed to assess five extended release compositions (XR Example Compositions D-H) of particles comprising a porous silica bead core; a surrogate active ingredient, probucol; glyceryl monooleate as a gel-forming agent; and a surfactant Kolliphor® EL at varying ratios with the glyceryl monooleate. Table 10 provides a summary of these compositions, including the quantity of each component

TABLE 8

Dissolution profile of Reference Compositions A-C.									
Composition	% Drug Release of Probutcol								
	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min	1440 min
Reference Composition A	79	81	82	83	83	84	84	86	88
Reference Composition B	82	84	85	85	85	85	85	85	85
Reference Composition C	100	99	98	98	98	98	99	99	100

[0163] FIG. 12A illustrates that all the surfactants evaluated attributed greater than 80% w/w drug release in the dissolution medium. Kolliphor® EL demonstrated the highest emulsification capacity yielding a release after 24 hours

[0166] To prepare the compositions, the probucol was added to sesame oil in a glass beaker, and a sonicator was used to obtain a uniform mixture. Kolliphor® EL and the glyceryl monooleate were added to the mixture, and a vortex

mixer was used to form a homogenous mixture. The mixture was then loaded into pores of the Neusilin® US2 silica beads using a high shear granulator.

[0167] A dissolution test was conducted on XR Example Compositions D-H using purified water, USP, as the dissolution medium in a dissolution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-μm porous filter was used to sample aliquots.

[0168] The dissolution profiles of each composition are provided in Table 11 and FIG. 13. The dissolution profiles of XR Example Compositions D-F showed that 90% w/w or greater drug release within 5 minutes, which indicates that no extended release was achieved. The dissolution profile of XR Example Composition G exhibited 70% w/w drug release within 5 minutes, but release remained below 80% w/w through 24 hours. The dissolution profile of XR Example Composition H showed 50% w/w drug release at 5 minutes, which climbed to 80% w/w by 120 minutes.

noid THC; and surfactant Tween® 80. The particles of the extended release composition additionally comprise glyceryl monooleate as a gel-forming agent. Table 12 provides a summary of these compositions, including the quantity of each component.

[0171] To prepare the IR Reference Composition D, the THC was added to sesame oil in a glass beaker, and a sonicator was used to obtain a uniform mixture. The surfactant Tween® 80 was added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then loaded into pores of the Neusilin® US2 silica beads using a high shear granulator.

[0172] To prepare the XR Example Composition I, the THC was added to sesame oil in a glass beaker, and a sonicator was used to obtain a uniform mixture. The surfactant Tween® 80 and the glyceryl monooleate were added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then loaded into pores of the Neusilin® US2 silica beads using a high shear granulator.

TABLE 10

Summary of the components and their quantities (% w/w) of XR Example Compositions D-H.					
Components	XR Example Composition D	XR Example Composition E	XR Example Composition F	XR Example Composition G	XR Example Composition H
Probucol	1.2%	1.1%	1.1%	1%	1%
Sesame Oil	10.7%	10%	9.7%	9.4%	9%
Glyceryl monooleate	4.7%	9%	13%	16.7%	20%
Kolliphor® EL	59.5%	56.8%	54.3%	52.1%	50%
Neusilin US2 beads	23.8%	22.7%	25%	20.1%	20%
TOTAL	100%	100%	100%	100%	100%

TABLE 11

Dissolution profile of XR Example Compositions D-H.									
Composition	% Drug Release of Probucol								
	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min	1440 min
XR Example Composition D	95	91	91	91	91	91	91	91	93
XR Example Composition E	91	91	91	91	92	92	93	93	94
XR Example Composition F	90	92	92	93	94	93	94	94	94
XR Example Composition G	70	76	77	77	77	78	78	78	79
XR Example Composition H	50	66	72	78	80	79	79	81	81

[0169] These results demonstrate that glyceryl monooleate as a gel-forming agent is capable of providing an extended release profile.

Example 6

[0170] A study was performed to compare an immediate release composition (IR Reference Composition D) and an extended release composition (XR Example Composition I) of particles comprising a porous silica bead core; cannabi-

[0173] A dissolution test was conducted on IR Reference Composition D and XR Example Composition I using purified water, USP, as the dissolution medium in a dissolution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-μm porous filter was used to sample aliquots.

[0174] The dissolution profiles of each composition are provided in Table 13 and FIGS. 14A and 14B. The dissolution profile of IR Reference Composition D showed 80%

w/w THC release after 5 minutes, and about 100% w/w THC release by 12 hours (see Table 13 and FIG. 14A). In contrast, the dissolution profile of XR Example Composition I showed less than 20% w/w THC release after 5 minutes, and less than 60% w/w drug release after 12 hours (see Table 13 and FIG. 14B).

TABLE 12

Summary of the components and their quantities (% w/w) of IR Reference Composition D and XR Example Composition I.		
Component	IR Reference Composition D	XR Example Composition I
THC in sesame oil	1.4%	1.4%
Sesame oil	12.6%	12.6%
Surfactant Tween® 80	53%	26.5%
Capmul GMO-50 (glyceryl monooleate)	—	26.5%
Neusilin US2 beads	33%	33%
TOTAL	100%	100%

TABLE 13

Dissolution profile of IR Reference Composition D and XR Example Composition I.								
% Drug Release of THC								
Composition	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min
IR Reference Composition D	80	92	93.5	95.5	96.5	98	97.5	100
XR Example Composition I	17.5	22.5	26.5	32	41	49.5	55.5	56

[0175] These results demonstrate that glyceryl monooleate as a gel-forming agent is capable of extending the release of THC.

Example 7

[0176] A study was performed to compare an immediate release composition (IR Reference Composition E) and an extended release composition (XR Example Composition J) of particles comprising a porous silica bead core; cannabinoid CBD; and surfactant Tween® 80. The particles of the extended release composition additionally comprise glyceryl monooleate as a gel-forming agent. Table 14 provides a summary of these compositions, including the quantity of each component.

[0177] To prepare the IR Reference Composition E, the CBD was added to sesame oil in a glass beaker, and a sonicator was used to obtain a uniform mixture. The surfactant Tween® 80 was added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then loaded into pores of the Neusilin US2 silica beads using a high shear granulator.

[0178] To prepare the XR Example Composition J, the CBD was added to sesame oil in a glass beaker, and a sonicator was used to obtain a uniform mixture. The surfactant Tween® 80 and the glyceryl monooleate were added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then loaded into pores of the Neusilin® US2 silica beads using a high shear granulator.

[0179] A dissolution test was conducted on IR Reference Composition E and XR Example Composition J using purified water, USP, as the dissolution medium in a dissolution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-μm porous filter was used to sample aliquots.

[0180] The dissolution profiles of each composition are provided in Table 15 and FIGS. 15A and 15B. The dissolution profile of IR Reference Composition E showed over 70% w/w CBD release after 5 minutes, and over 90% w/w

CBD release by 15 minutes (see Table 15 and FIG. 15A). In contrast, the dissolution profile of XR Example Composition J showed less than 25% w/w CBD release after 5 minutes, and less than 70% w/w CBD release after 12 hours (see Table 15 and FIG. 15B).

TABLE 14

Summary of the components and their quantities (% w/w) of IR Reference Composition E and XR Example Composition J.		
Component	IR Reference Composition E	XR Example Composition J
CBD	1.4%	1.4%
Sesame oil	12.6%	12.6%
Surfactant Tween® 80	53%	26.5%
Capmul GMO-50 (glyceryl monooleate)	—	26.5%
Neusilin US2 beads	33%	33%
TOTAL	100%	100%

TABLE 15

Dissolution profile of IR Reference Composition E and XR Example Composition J.								
Composition	% Drug Release of CBD							
	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min
IR Reference Composition E	78	94.5	96.5	97.5	98.5	99	100	101
XR Example Composition J	21.5	29.5	36	44	52.5	56.5	60	64

[0181] These results demonstrate that glyceryl monooleate as a gel-forming agent is capable of extending the release of CBD.

Example 8

[0182] A study was performed to compare an immediate release composition (IR Reference Composition F) and an extended release composition (XR Example Composition K) of particles comprising a porous silica bead core; cannabinoids THC and CBD; and surfactant Tween® 80 in a capsule. The particles of the extended release composition additionally comprise glyceryl monooleate as a gel-forming agent. Table 16 provides a summary of these compositions, including the quantity of each component.

[0183] To prepare the IR Reference Composition F, the THC and CBD were added to sesame oil in a glass beaker, and a sonicator was used to obtain a uniform mixture. The surfactant Tween® 80 was added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then loaded into pores of the Neusilin® US2 silica beads using a high shear granulator, and resulting particles were placed in a capsule.

[0184] To prepare the XR Example Composition K, the THC and CBD were added to sesame oil in a glass beaker, and a sonicator was used to obtain a uniform mixture. The surfactant Tween® 80 and the glyceryl monooleate were added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then loaded into pores of the Neusilin® US2 silica beads using a high shear granulator, and resulting particles were placed in a capsule.

[0185] A dissolution test was conducted on IR Reference Composition F and XR Example Composition K using purified water, USP, as the dissolution medium in a disso-

lution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-μm porous filter was used to sample aliquots.

[0186] The dissolution profiles of each composition are provided in Table 17 (for release of THC of both compositions) and Table 18 (for release of CBD of both compositions) and in FIG. 16A (release of THC and CBD in IR Reference Composition F) and FIG. 16B (release of THC and CBD in XR Example Composition K). The dissolution profile of IR Reference Composition F showed, for both THC and CBD, over 60% w/w release within 30 minutes, and over 90% w/w release by 12 hours (see Tables 17 and 18, and FIG. 16A). In contrast, the dissolution profile of XR Example Composition K showed, for both THC and CBD, less than 5% w/w release after 30 minutes, and less than 60% w/w release after 12 hours (see Tables 17 and 18, and FIG. 16B).

TABLE 16

Summary of the components and their quantities (% w/w) of IR Reference Composition F and XR Example Composition K.		
Component	IR Reference Composition F	XR Example Composition K
THC in sesame oil	14%	14%
CBD	1.4%	1.4%
Surfactant Tween® 80	53%	26.5%
Capmul GMO-50 (glyceryl monooleate)	—	26.5%
Neusilin US2 beads	33%	33%
TOTAL	100%	100%

TABLE 17

Dissolution profile of THC of IR Reference Composition F and XR Example Composition K.								
Composition	% Drug Release of THC							
	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min
IR Reference Composition F	12	54.5	72.5	76.5	78.5	81	82	92
XR Example Composition K	0.35	1.5	4	9.5	14.5			53.5

TABLE 18

Dissolution profile of CBD of IR Reference Composition F and XR Example Composition K.								
Composition	% Drug Release of CBD							
	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min
IR Reference Composition F	14.5	59	75.5	78.5	80.5	83.5	84	95
XR Example Composition K	0.3	1.5	4	9.5				52

[0187] These results demonstrate that glyceryl monooleate as a gel-forming agent is capable of extending the release of THC and CBD.

[0188] An analysis was also performed to examine the impact on physical characteristics of loading THC and CBD onto the silica beads. FIGS. 17A-17C and FIGS. 17D-17E compare the physical appearance of plain Neusilin US2 silica beads and of the particles of IR Reference Composition F, respectively. The particles loaded with THC and CBD have a more textured surface as compared to the plain Neusilin US2 silica beads.

[0189] In addition, a comparison of the particle size distribution of the plain Neusilin US2 silica beads and the particles of IR Reference Composition F is shown in FIGS. 18A and 18B. The plain Neusilin US2 silica beads exhibited a wider distribution of particle sizes and fewer particles having a diameter of about 40 nm or larger, as compared to the particles of IR Reference Composition F (see FIG. 18A compared to FIG. 18B).

Example 9

[0190] THC is added in sesame oil in a glass beaker using a sonicator to obtain a uniform mixture. Tween® 80 and the gel-forming agent, glyceryl monooleate, is added to the mixture and mixed homogeneously using a vortex mixer. The mixture is loaded into pores of the Neusilin® US2 silica beads using a high shear granulator to achieve uniform drug loaded beads. Tween® 80 is used as a surfactant with glyceryl monooleate in ratio of 1:1. The resultant multiparticulates are loaded into a capsule.

Example 10

[0191] CBD is added in sesame oil in a glass beaker using a sonicator to obtain a uniform mixture. Tween® 80 and the gel-forming agent, glyceryl monooleate, is added to the mixture and mixed homogeneously using a vortex mixer. The mixture is loaded into pores of the Neusilin® US2 silica beads using a high shear granulator to achieve uniform drug loaded beads. Tween® 80 is used as a surfactant with glyceryl monooleate in ratio of 1:1. The resultant multiparticulate composition is compressed into a tablet.

Example 11

[0192] THC and CBD, in combination, are added to sesame oil in a glass beaker using a sonicator to obtain a uniform mixture. Tween® 80 and the gel-forming agent,

glyceryl monooleate, are added to the mixture and mixed homogeneously using a vortex mixer. The mixture is loaded into pores of the Neusilin® US2 silica beads using a high shear granulator to achieve uniform drug loaded beads. Tween® 80 is used as a surfactant with glyceryl monooleate in ratio of 1:1. The resultant multiparticulates containing CBD and THC are filled into capsules.

Example 12

[0193] A study was performed to assess two different extended release compositions (XR Example Compositions L and M) of particles comprising an inert core and a coating having the following: a surrogate active ingredient, probucol; two or more release-controlling polymers; and a release-accelerating polymer. Table 19 provides a summary of these compositions, including the quantity of each component.

[0194] To prepare the compositions, the probucol was mixed with ethanol and water (50:50) in a glass beaker to form a homogeneous dispersion. The release-controlling polymers (Eudragit® RS and Ethocel® E-10 in Example Composition L; Eudragit® RS, Eudragit® RL, and Ethocel® E-10 in Example Composition M) and release-accelerating polymer (Kollidon® K30) were added to the mixture, and a vortex mixer was used to form a homogeneous mixture. The mixture was then applied onto Cellets® (Glatt GmbH, Germany) in a beaker and the coated pellets were dried.

[0195] A dissolution test was conducted on XR Example Compositions L and M using purified water, USP, as the dissolution medium in a dissolution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-μm porous filter was used to sample aliquots.

[0196] The dissolution profiles of each composition are provided in Table 20 and in FIGS. 19A and 19B. The dissolution profile of XR Example Composition L showed about 13% w/w drug release within 15 minutes and about 38% w/w drug release at 120 minutes (see Table 20 and FIG. 19A). The amount of drug released achieved 66% w/w at 24 hours. FIG. 20 is an SEM image for the Cellets coated with probucol, the release-controlling polymer, and the release-accelerating polymer. The dissolution profile of XR Example Composition M showed about 25% w/w drug release within 2 hours and the extended release profile was maintained through 24 hours (see Table 20, FIG. 19B).

[0197] In addition, an assay was performed on both XR Example Compositions L and M. The results are presented in Table 21.

TABLE 19

Summary of the components and their quantities (% w/w) of XR Example Compositions L and M.		
Component	XR Example Composition L	XR Example Composition M
Probutol	14.3%	14.3%
Ethanol	To make 10% solution of Probutol in ethanol and water (50:50)	To make 10% solution of Probutol in ethanol and water (50:50)
Eudragit® RS	14.3%	7.15%
Eudragit® RL	—	7.15%
Ethocel® E-10	14.3%	14.3%
Kollidon® K30	7.1%	7.1%
Cellets®	50%	50%
TOTAL	100%	100%

TABLE 20

Dissolution profile of XR Example Compositions L and M.								
% Drug Release of Probutol								
Composition	5 min	15 min	30 min	60 min	120 min	180 min	720 min	1440 min
XR Example Composition L	8	13	23	30	38	43	59	66
XR Example Composition M	7	11	16	23	25	27	36	40

TABLE 21

Assay of XR Example Compositions L and M.	
Composition	Assay
XR Example Composition L	71% w/w
XR Example Composition M	73% w/w

[0198] These results demonstrate that Eudragit® RS 30D and Eudragit® RL 30D can be used as release-controlling polymers in a coating to provide an extended release profile.

Example 13

[0199] A study was performed to compare an immediate release composition (IR Reference Composition F) and an extended release composition (XR Example Composition N) of particles comprising an inert core and a coating having cannabinoid THC. The coating for the particles of the extended release composition additionally comprise release-controlling polymers Eudragit® RS 30D and Eudragit® RL 30D. Table 22 provides a summary of these compositions, including the quantity of each component.

[0200] To prepare the IR Reference Composition F, the THC was mixed with methanol in a glass beaker to form a

homogenous dispersion. The dispersion was then applied onto Suglets® 40/45 in a beaker and the coated pellets were dried.

[0201] To prepare the XR Example Composition N, the THC was mixed with methanol in a glass beaker to form a homogenous dispersion. The Eudragit® RS 30D and Eudragit® RL 30D were added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then applied onto Suglets® 40/45 in a beaker and the coated pellets were dried.

[0202] A dissolution test was conducted on IR Reference Composition F and XR Example Composition N using purified water, USP, as the dissolution medium in a dissolution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-μm porous filter was used to sample aliquots.

[0203] The dissolution profiles of each composition are provided in Table 23 and FIGS. 21A and 21B. The dissolution profile of IR Reference Composition F showed nearly

70% w/w THC release after 15 minutes, and over 95% w/w THC release by 120 minutes (see Table 23 and FIG. 21A). In contrast, the dissolution profile of XR Example Composition N showed less than 25% w/w THC release after 15 minutes, about 60% w/w THC release after 120 minutes, and less than 75% w/w THC release after 24 hours (see Table 23 and FIG. 21B).

TABLE 22

Summary of the components and their quantities (% w/w) of IR Reference Composition F and XR Example Composition N.		
Component	IR Reference Composition F	XR Example Composition N
THC	0.5%	0.5%
Methanol	q.s.	q.s.
Eudragit® RS 30D	—	4%
Eudragit® RL 30D	—	4%
Suglets® 40/45	99.5%	91.5%
TOTAL	100%	100%

TABLE 23

Dissolution profile of IR Reference Composition F and XR Example Composition N.									
Composition	% Drug Release of THC								
	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min	1440 min
IR Reference Composition F	59	69.5	80	89	95.5	99	101	103.5	105
XR Example Composition N	—	22	32	44	60	70	72	73	73

[0204] These results demonstrate that Eudragit® RS 30D and Eudragit® RL 30D can be used as release-controlling polymers in a coating to extend the release of THC.

Example 14

[0205] A study was performed to compare an immediate release composition (IR Reference Composition G) and an extended release composition (XR Example Composition O) of particles comprising an inert core and a coating having cannabinoid CBD. The coating for the particles of the extended release composition additionally comprise release-controlling polymers Eudragit® RS 30D and Eudragit® RL 30D. Table 24 provides a summary of these compositions, including the quantity of each component.

[0206] To prepare the IR Reference Composition G, the CBD was mixed with ethanol in a glass beaker to form a homogenous dispersion. The dispersion was then applied onto Suglets® 40/45 in a beaker and the coated pellets were dried.

[0207] To prepare the XR Example Composition O, the CBD was mixed with ethanol in a glass beaker to form a homogenous dispersion. The Eudragit® RS 30D and Eudragit® RL 30D were added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then applied onto Suglets® 40/45 in a beaker and the coated pellets were dried.

[0208] A dissolution test was conducted on IR Reference Composition G and XR Example Composition O using

CBD release by 15 minutes (see Table 25 and FIG. 22A). In contrast, the dissolution profile of XR Example Composition O showed less than 20% w/w CBD release through 60 minutes and less than 40% w/w CBD release after 240 minutes, although at 24 hours there was about 100% w/w CBD release (see Table 25 and FIG. 22B).

TABLE 24

Summary of the components and their quantities (% w/w) of IR Reference Composition G and XR Example Composition O.		
Component	IR Reference Composition G	XR Example Composition O
CBD	2%	2%
Methanol	q.s.	q.s.
Eudragit® RS 30D	—	4%
Eudragit® RL 30D	—	4%
Suglets® 40/45	98%	90%
TOTAL	100%	100%

TABLE 25

Dissolution profile of IR Reference Composition G and XR Example Composition O.									
Composition	% Drug Release of CBD								
	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min	1440 min
IR Reference Composition G	78	94.5	96.5	97.5	98.5	99	100	101	
XR Example Composition O	—	1	2	12	20	31	—	—	100

purified water, USP, as the dissolution medium in a dissolution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-μm porous filter was used to sample aliquots.

[0209] The dissolution profiles of each composition are provided in Table 25 and FIGS. 22A and 22B. The dissolution profile of IR Reference Composition G showed nearly 80% w/w CBD release after 5 minutes, and over 90% w/w

[0210] These results demonstrate that Eudragit® RS 30D and Eudragit® RL 30D can be used as release-controlling polymers in a coating to extend the release of CBD.

Example 15

[0211] A study was performed to compare an immediate release composition (IR Reference Composition H) and an extended release composition (XR Example Composition P)

of particles comprising an inert core and a coating having cannabinoids THC and CBD. The coating for the particles of the extended release composition additionally comprise release-controlling polymers Eudragit® RS 30D and Eudragit® RL 30D. Table 26 provides a summary of these compositions, including the quantity of each component.

[0212] To prepare the IR Reference Composition H, the THC and CBD were mixed with methanol in a glass beaker to form a homogenous dispersion. The dispersion was then applied onto Suglets® 40/45 in a beaker and the coated pellets were dried.

[0213] To prepare the XR Example Composition P, the THC and CBD were mixed with methanol in a glass beaker to form a homogenous dispersion. The Eudragit® RS 30D and Eudragit® RL 30D were added to the mixture, and a vortex mixer was used to form a homogenous mixture. The mixture was then applied onto Suglets® 40/45 in a beaker and the coated pellets were dried.

THC and CBD, less than 30% w/w release after 15 minutes, and less than 70% w/w release after 120 minutes (see Tables 27 and 28, and FIG. 23B).

TABLE 26

Summary of the components and their quantities (% w/w) of IR Reference Composition H and XR Example Composition P.		
Component	IR Reference Composition H	XR Example Composition P
THC	0.5%	0.5%
CBD	2%	2%
Methanol	q.s.	q.s.
Eudragit® RS 30D	—	4%
Eudragit® RL 30D	—	4%
Suglets® 40/45	97.5%	89.5%
TOTAL	100%	100%

TABLE 27

Dissolution profile of THC of IR Reference Composition H and XR Example Composition P.									
% Drug Release of THC									
Composition	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min	1440 min
IR Reference Composition H	59	69	79	88	98	99	100	102	104
XR Example Composition P	—	21	31	48	60	70	72	73	74

TABLE 28

Dissolution profile of CBD of IR Reference Composition H and XR Example Composition P.									
% Drug Release of CBD									
Composition	5 min	15 min	30 min	60 min	120 min	240 min	360 min	720 min	1440 min
IR Reference Composition H	79	95	97	98	99	100	100	100	101
XR Example Composition P	—	1	3	15	20	32	—	—	100

[0214] A dissolution test was conducted on IR Reference Composition H and XR Example Composition P using purified water, USP, as the dissolution medium in a dissolution volume of 900 ml. A USP Type II paddle apparatus was used to mix the dissolution medium at a paddle speed of 75 rpm. The bath temperature was 37° C., and a 10-μm porous filter was used to sample aliquots.

[0215] The dissolution profiles of each composition are provided in Table 27 (for release of THC of both compositions) and Table 28 (for release of CBD of both compositions) and in FIG. 23A (release of THC and CBD in IR Reference Composition H) and FIG. 23B (release of THC and CBD in XR Example Composition P). The dissolution profile of IR Reference Composition H showed, for both THC and CBD, about 70% w/w or greater release within 15 minutes, and over 95% w/w release by 120 minutes (see Tables 27 and 28, and FIG. 23A). In contrast, the dissolution profile of XR Example Composition P showed, for both

[0216] These results demonstrate that Eudragit® RS 30D and Eudragit® RL 30D as release-controlling polymers can be used in a coating to extend the release of THC and CBD.

Example 16

[0217] A study was performed to examine the impact on physical characteristics assessed by SEM imaging of loading THC and CBD onto inert cores selected from Cellets and Suglets® 40/45.

[0218] To prepare Cellets loaded with THC and CBD, the THC and CBD were mixed with methanol in a glass beaker to form a homogenous dispersion. The dispersion was then applied onto Cellets in a beaker and the coated pellets were dried.

[0219] To prepare Suglets® 40/45 loaded with THC and CBD, the THC and CBD were mixed with methanol in a glass beaker to form a homogenous dispersion. The dispersion was then applied onto Suglets® 40/45 in a beaker and the coated pellets were dried.

[0220] FIGS. 24A-24C and FIGS. 24D-24E compare the physical appearance of plain Cellets and of Cellets coated with THC and CBD, respectively. The Cellets loaded with THC and CBD have the appearance of coated surface morphology as compared to the plain Cellets.

[0221] FIGS. 25A-25C and FIGS. 25D-25E compare the physical appearance of plain Suglets® 40/45 and of Suglets® 40/45 coated with THC and CBD, respectively. The Suglets® 40/45 loaded with THC and CBD have the appearance of coated surface morphology as compared to the plain Suglets® 40/45.

Example 17

[0222] A study was performed to examine the impact on particle size distribution of loading CBD onto inert cores selected from Cellets and Suglets® 40/45.

[0223] To prepare Cellets loaded with CBD, the CBD was mixed with ethanol in a glass beaker to form a homogenous dispersion. The dispersion was then applied onto Cellets in a beaker and the coated pellets were dried.

[0224] To prepare Suglets® 40/45 loaded with CBD, the CBD was mixed with ethanol in a glass beaker to form a homogenous dispersion. The dispersion was then applied onto Suglets® 40/45 in a beaker and the coated pellets were dried.

[0225] FIGS. 26A and 26B compare the particle size distribution of the plain Cellets and the Cellets loaded with CBD. As shown in these figures, there was no notable difference in particle size distribution between the plain Cellets and the Cellets loaded with CBD.

[0226] FIGS. 27A and 27B compare the particle size distribution of the plain Suglets® 40/45 and the Suglets® 40/45 loaded with CBD. As shown in these figures, the plain Suglets® 40/45 exhibited a slightly wider distribution of particle sizes as compared to the Suglets® 40/45 coated with CBD.

Example 18

[0227] THC is mixed with ethanol and water (50:50) in a glass beaker to form a homogenous dispersion. The release-controlling polymers Eudragit® RS and Ethocel® E-10 along with release-accelerating polymer Kollidon® K30 is added to the mixture and mixed homogeneously using a vortex mixer. The mixture is then applied onto Cellets® in a beaker and the coated pellets are dried. The multiparticulates are then filled into a No. 2 capsule.

Example 19

[0228] CBD is mixed with ethanol and water (50:50) in a glass beaker to form a homogenous dispersion. The release-controlling polymers Eudragit® RS and Ethocel® E-10 along with release-accelerating polymer Kollidon® K30 are added to the mixture and mixed homogeneously using a vortex mixer. The mixture is then applied onto Cellets® in a beaker and the coated pellets are dried. The multiparticulates are then formed into a tablet.

Example 20

[0229] THC and CBD, in combination, are mixed with ethanol and water (50:50) in a glass beaker to form a homogenous dispersion. The release-controlling polymers Eudragit® RS and Ethocel® E-10 along with release-accelerating polymer Kollidon® K30 are added to the mixture

and mixed homogeneously using a vortex mixer. The mixture is then applied onto Cellets® in a beaker and the coated pellets are dried. The multiparticulates are then provided in a sachet.

Example 21

[0230] THC is mixed with ethanol and water (50:50) in a glass beaker to form a homogenous dispersion. The release-controlling polymers Eudragit® RS, Eudragit® RL, and Ethocel® E-10 along with release-accelerating polymer Kollidon® K30 are added to the mixture and mixed homogeneously using a vortex mixer. The mixture is then applied onto Cellets® in a beaker and the coated pellets are dried. The multiparticulates are then formed into tablets.

Example 22

[0231] CBD is mixed with ethanol and water (50:50) in a glass beaker to form a homogenous dispersion. The release-controlling polymers Eudragit® RS, Eudragit® RL, and Ethocel® E-10 along with release-accelerating polymer Kollidon® K30 are added to the mixture and mixed homogeneously using a vortex mixer. The mixture is then applied onto Cellets® in a beaker and the coated pellets are dried. The resultant multiparticulates are then provided in a capsule, which is opened and admixed with apple sauce prior to administration.

Example 23

[0232] THC and CBD, in combination, are mixed with ethanol and water (50:50) in a glass beaker to form a homogenous dispersion. The release-controlling polymers Eudragit® RS, Eudragit® RL, and Ethocel® E-10 along with release-accelerating polymer Kollidon® K30 are added to the mixture and mixed homogeneously using a vortex mixer. The mixture is then applied onto Cellets® in a beaker and the coated pellets are dried.

Example 24

[0233] CBD and the antipsychotic agent clozapine are dissolved in a hydroalcoholic solution comprising ethanol, and then mixed with Tween® 80. The mixture is loaded onto Neusilin® US2 (Silica) and mixed homogeneously using a vortex mixer to obtain immediate release particles.

Example 25

[0234] THC and CBD, in combination in sesame oil, are sprayed onto Pharmatose® 200M (EU) (Milled Lactose Monohydrate), Kollidon® 30, and Vivapur® 101 (Microcrystalline Cellulose) in a granulator bowl, and the mixture undergoes fluid bed granulation. The resulting granules are sized, milled, and screened to generate immediate release particles.

[0235] THC and CBD, in combination, are mixed with ethanol and water (50:50) in a glass beaker to form a homogenous dispersion. The release-controlling polymers Eudragit® RS and Ethocel® E-10 along with release-accelerating polymer Kollidon® K30 are added to the mixture and mixed homogeneously using a vortex mixer. The mixture is then applied onto Cellets® in a beaker and the coated pellets are dried to generate extended release particles.

[0236] The immediate release particles and the extended release particles are then mixed together in a 50:50 ratio by weight to generate a sustained release composition.

[0237] Although specific embodiments of the present invention have been disclosed herein, those having ordinary skill in the art will understand that changes can be made to the specific embodiments without departing from the spirit of the invention. The scope of the invention is not to be restricted, therefore, to the specific embodiments. Furthermore, it is intended that the appended claims cover any and all such applications, modifications, and embodiments within the scope of the present invention.

What is claimed is:

1. A composition for extended release of two or more active agents, wherein the two or more active agents comprise at least one cannabinoid and at least one non-cannabinoid therapeutic agent,

the composition comprising a population of particles, wherein each particle comprises:

- (a) the at least one cannabinoid, the at least one non-cannabinoid therapeutic agent, or a combination thereof;
- (b) one or more drug releasing agents;
- (c) a core; and
- (d) one or more surfactants;

wherein the composition releases the two or more actives over a period of at least 6 hours.

2. The composition of claim 1, wherein the one or more drug releasing agents comprises one or more gel-forming agents.

3. The composition of claim 2, wherein the one or more gel-forming agents is selected from glyceryl monooleate, glycerol monostearate, soybean oil, propylene glycol monopalmitostearate, carboxypolymethylene, hydroxypro-

pyl cellulose, hydroxypropyl methycellulose, carboxymethyl cellulose, chitosan, acacia, alginates, carrageen, and guar gum.

4. The composition of claim 1, wherein the core comprises a silica bead or porous biodegradable glass bead.

5. The composition of claim 1, wherein the core comprises one or more pores that extend from the surface of the core.

6. A composition for extended release of two or more active agents, wherein the two or more active agents comprise at least one cannabinoid and at least one non-cannabinoid therapeutic agent,

the composition comprising a population of particles, wherein each particle comprises:

- (a) the at least one cannabinoid, the at least one non-cannabinoid therapeutic agent, or a combination thereof;
- (b) one or more drug releasing agents; and
- (c) a core,

wherein the composition releases the two or more active agents over a period of at least 6 hours.

7. The composition of claim 6, wherein the core comprises a coating that comprises the two or more active agents and the one or more drug releasing agents.

8. The composition of claim 6, wherein the one or more drug releasing agents comprise one or more release-controlling polymers, one or more release-accelerating polymers, or a combination thereof.

9. The composition of claim 8, wherein the one or more release-controlling polymers are selected from the group consisting of ethyl cellulose, polyvinyl acetate-based polymers, polyvinyl acetate-based co-polymers, polyacrylic acid-based polymers, polyacrylic acid-based co-polymers, methacrylic acid polymers, methacrylic acid polymers copolymers, polyvinyl alcohol, and a combination thereof.

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