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SUSTAINED RELEASE CANNABINOID FORMULATIONS

The present invention provides modified release pharmaceutical composition comprising one or more natural or synthetic cannabinoids and one or more pharmaceutically acceptable excipients. More specifically, the invention relates to modified release pharmaceutical compositions comprising cannabinoids and a process for preparation thereof. The present invention also provides large scale batches of modified release pharmaceutical composition comprising one or more natural or synthetic cannabinoids and one or more pharmaceutically acceptable excipients.
[001] **SUSTAINED RELEASE CANNABINOID FORMULATIONS**

[002] **RELATED APPLICATIONS**

[003] This application claims priority from United States provisional patent applications: serial numbers 62/400,216, filed on September 27, 2016; serial number 62/449,377, filed on January 23, 2017; and serial number 62/551,924, filed on August 30, 2017.

[004] **FIELD OF THE INVENTION**

[005] The present invention relates to modified release pharmaceutical compositions comprising one or more natural or synthetic cannabinoids, one or more release modifying agent(s) and one or more pharmaceutically acceptable excipient(s). More specifically, the invention relates to modified release pharmaceutical compositions comprising cannabinoids and a process for preparation thereof. The invention also relates to production of large scale batches of modified release pharmaceutical compositions comprising cannabinoids and a process for preparation thereof.

[006] **BACKGROUND OF THE INVENTION**

[007] Cannabinoids are a class of diverse chemical compounds that act on cannabinoid receptors on cells that repress neurotransmitter release in the brain. The most notable cannabinoid is the phytocannabinoid tetrahydrocannabinol (THC), the primary psychoactive compound of cannabis. Cannabidiol (CBD) is another major constituent of the plant. There are at least 85 different cannabinoids isolated from cannabis, exhibiting varied effects. From Wikipedia http://en.wikipedia.org/wiki/Tetrahydrocannabinol accessed 5/25/2015. All or any of these cannabinoids can be used in the present invention.

[008] Synthetic cannabinoids encompass a variety of distinct chemical classes: the cannabinoids structurally related to THC, the cannabinoids not related to THC, such as (cannabinimimetics) including the aminoalkylindoles, 1,5-diarylpyrazoles, quinolines, and arylsulfonamides, and eicosanoids related
to the endocannabinoids. All or any of these cannabinoids can be used in the present invention.

[009] Delta-9-Tetrahydrocannabinol (dronabinol) is a naturally occurring compound and is the primary active ingredient in marijuana. Marijuana is dried hemp plant *Cannabis Sativa*. The leaves and stems of the plant contain cannabinoid compounds (including dronabinol). Dronabinol has been approved by the Food and Drug Administration for the control of nausea and vomiting associated with chemotherapy and for appetite stimulation of patients suffering from wasting syndrome. Synthetic dronabinol is a recognized pharmaceutically active ingredient, but natural botanical sources of cannabis rather than synthetic THC are also known in the art. All or any of these cannabinoids can be used in the present invention.

[0010] Dronabinol is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7. After oral administration, dronabinol has an onset of action of approximately 0.5 to 1 hours and peak effect at 2 to 4 hours. Duration of action for psychoactive effects is 4 to 6 hours, but the appetite stimulant effect of dronabinol may continue for 24 hours or longer after administration.

[0011] Dronabinol is the international nonproprietary name for a pure isomer of THC, (-)-\(\Delta^8\)-tetrahydrocannabinol, which is the main isomer, and the principal psychoactive constituent, found in cannabis. Synthesized dronabinol is marketed as Marinol (a registered trademark of Solvay Pharmaceuticals).

[0012] Marinol is manufactured as a gelatin capsule containing synthetic delta-9-tetrahydrocannabinol (THC) in sesame oil. It is taken orally and is available in 2.5mg, 5mg and/or 10mg dosages. Marinol is prescribed for the treatment of cachexia 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. Like other oils provided in gelatin dosage forms there is an urgent need for solid (powder and tablet) dosage forms of this drug as provided in the instant invention.

[0013] Despite FDA approval, it is almost universally accepted that medical marijuana has many benefits over Marinol and that by prohibiting the possession and use of natural cannabis and its cannabinoids, patients are unnecessarily restricted to use a synthetic substitute that lacks much of the therapeutic efficacy of natural cannabis. Sativex, is considered an improvement over Marinol. Sativex is an oral cannabis spray consisting of natural cannabinoid extracts, has greater bioavailability and is faster acting than oral synthetic THC. Of course oral sprays have numerous problems as a dosage form and Sativex has not been widely adopted as a replacement for medical marijuana. *Why Marinol Is Not As Good As Real Marijuana* Posted by Johnny Green on March 5, 2012 - see http://www.theweedblog.com/why-marinol-is-not-as-good-as-real-marijuana/ accessed 9 18 2016. Incorporated by reference in its entirety.

[0014] Marinol lacks several of the therapeutic compounds available in natural cannabis. Chemical compounds in cannabis, known as cannabinoids, are responsible for its numerous therapeutic benefits. Scientists have identified 66 naturally occurring cannabinoids. The active ingredient in Marinol, synthetic delta-9-tetrahyrdocannabinol (THC), is an analogue of one such compound, THC. However, several other cannabinoids available in cannabis — in addition to naturally occurring terpenoids (oils) and flavonoids (phenols) — have also been clinically demonstrated to possess therapeutic utility. Many patients favor natural cannabis to Marinol because it includes these other therapeutically active cannabinoids. *Why Marinol Is Not As Good As Real Marijuana* Posted by Johnny Green on March 5, 2012 - see http://www.theweedblog.com/why-marinol-is-not-as-good-as-real-marijuana/ accessed 9 18 2016.
Cannabidiol (CBD) is a non-psychoactive cannabinoid that has been clinically demonstrated to have analgesic, antispasmodic, anxiolytic, antipsychotic, antinausea, and anti-rheumatoid arthritic properties. Clinical studies have shown CBD to possess anti-convulsant properties, particularly in the treatment of epilepsy. Natural extracts of CBD, when administered in combination with THC, significantly reduce pain, spasticity and other symptoms in multiple sclerosis (MS) patients unresponsive to standard treatment medications. CBD has been shown to be neuroprotective against glutamate neurotoxicity (i.e. stroke), cerebral infarction (localized cell death in the brain), and ethanol-induced neurotoxicity, with CBD being more protective against glutamate neurotoxicity than either ascorbate (vitamin C) or alpha-tocopherol (vitamin E). Clinical trials have also shown CBD to possess anti-tumoral properties, inhibiting the growth of glioma (brain tumor) cells in a dose dependent manner and selectively inducing apoptosis (programmed cell death) in malignant cells. Why Marinol Is Not As Good As Real Marijuana

Posted by Johnny Green on March 5, 2012 - see
http://www.theweekblog.com/why-marinol-is-not-as-good-as-real-marijuana/ accessed 9/18/2016. Dosage formulations of CBD and other natural cannabinoids can also be formulated into solid dosage forms according to the present invention.

Additional cannabinoids possessing clinically demonstrated therapeutic properties include: cannabinol (anticonvulsant and anti-inflammatory activity); cannabichromine (anti-inflammatory and antidepressant activity); and cannabigerol (anti-tumoral and analgesic activity). Natural cannabis' essential oil components (terpenoids) exhibit anti-inflammatory properties and its flavonoids possess antioxidant activity. Emerging clinical evidence indicates that cannabinoids may slow disease progression in certain autoimmune and neurologic diseases, including multiple sclerosis (MS), Amyotrophic Lateral Sclerosis (Lou Gehrig's disease) and Huntington's Disease. Why Marinol Is Not As Good As Real Marijuana

Posted by
Johnny Green on March 5, 2012 - see http://www.theweedblog.com/why-marinol-is-not-as-good-as-real-marijuana/ accessed 9/18/2016. Dosage formulations of these cannabinoids can be formulated into solid dosage forms according to the present invention.


[0018] As a result of Marinol's slow onset and poor bioavailability, scientists are now in the process of developing a new formulation of pulmonary dronabinol, delivered with a pressurized metered dose inhaler. Medical News Today. "New synthetic delta-9-THC Inhaler offers safe, rapid delivery, Phase I study." April 17, 2005. Unlike oral synthetic THC, it's possible that pulmonary Marinol "could offer an alternative for patients when a fast onset of action is desirable." Sativex, an oral cannabis spray consisting of natural cannabinoid extracts, has greater bioavailability and is faster acting than oral synthetic THC. Clinical trials comparing its bioavailability and time of peak onset compared to vaporized cannabis have not been performed, though anecdotal reports indicate that vaporized cannabis and its cannabinoids likely possess greater
bioavailability and are faster acting than the Sativex spray. Thus there is a need for improved bioavailability, simple, inexpensive solid dosage forms of natural and synthetic cannabinoids.


[0020] An analog of dronabinol, nabilone, is available commercially.

[0021] US 20120231083 discloses a sustained release medicament which results in delivery of a therapeutic level of one or more cannabinoids during a clinically relevant therapeutic window. The therapeutic window is a longer window than provided by an immediate release medicament such as Marinol containing an equivalent amount of the cannabinoid. Oral administration of the present compositions provides therapeutic dosing while maintaining safe, side effect sparing, levels of a cannabinoid. The present invention also provides methods of treating cannabinoid-sensitive disorders.

[0022] US 20060257463 discloses a method of transmucosally delivering a cannabinoid to a subject in need of such treatment comprising the steps of: administering to the subject a transmucosal preparation containing the cannabinoid wherein said transmucosal preparation is made by incorporating an effective amount of the cannabinoid via hot-melt extrusion technology, hot-melt molding, admixing or a solvent cast technique into a film matrix or a reservoir containing the cannabinoid, and attaching said transmucosal preparation to the mucosa of the subject.

[0023] Pharmaceutical compositions comprising the cannabinoid active pharmaceutical ingredient, crystalline trans-(±)-A9-tetrahydrocannabinol, and formulations thereof are disclosed in WO 2006133941. The invention also relates to methods for treating or preventing a condition such as pain comprising administering to a patient in need thereof an effective amount of crystalline trans-(±)-A9-tetrahydrocannabinol. In specific embodiments, the crystalline trans-(±)-A9-tetrahydrocannabinol administered according
to the methods for treating or preventing a condition such as pain can have a purity of at least about 98% based on the total weight of cannabinoids.

[0024] US 20140100269 A1 discloses oral cannabinoid formulations, including an aqueous-based oral dronabinol solution, that are stable at room or refrigerated temperatures and may possess improved in vivo absorption profiles with faster onset and lower inter-subject variability.

[0025] US 8632825 discloses the use of a combination of cannabinoids, particularly tetrahydrocannabinol (THC) and cannabidiol (CBD), in the manufacture of a medicament for use in the treatment of cancer.

[0026] US 6630507 discloses that cannabinoids have antioxidant properties. This property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia. Nonpsychoactive cannabinoids, such as cannabidoil, are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present invention.

[0027] US 8808734 discloses stable, fast-acting liposomal and micelle formulations of cannabinoids or cannabinoid analogues.


[0029] DOSAGE AND ADMINISTRATION OF DRONABINOL FROM FDA DOCUMENT NDA 18-651/S-021; 500012 Rev Sep 2004:

- Appetite Stimulation: Initially, 2.5 mg Dronabinol Capsules should be administered orally twice daily (b.i.d.), before lunch and supper.

For patients unable to tolerate this 5 mg/day dosage, the dosage
can be reduced to 2.5 mg/day, administered as a single dose in the evening or at bedtime. If clinically indicated and in the absence of significant adverse effects, the dosage may be gradually increased to a maximum of 20 mg/day, administered in divided oral doses. Caution should be exercised in escalating the dosage because of the increased frequency of dose-related adverse experiences at higher dosages.

- Antiemetic: Best administered at an initial dose of 5 mg/m2, given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy is given, for a total of 4 to 6 doses/day. Should the 5 mg/m2 dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m2 increments to a maximum of 15 mg/m2 per dose. Caution should be exercised in dose escalation, however, as the incidence of disturbing psychiatric symptoms increases significantly at maximum dose.

[0030] Despite all of the work on cannabinoids and dronabinol, there is a need in the art for simple, inexpensive, improved dosage forms that have an improved profile with faster onset, extended release profiles and lower inter-subject variability than currently available cannabinoid products.

[0031] In the 1970s and 1980s there were almost no marketed drugs with less than 10 µg/ml solubility (10-100 µg/ml was considered low) (Solid Dispersions: New Approaches and Technologies in Oral Drug Delivery, Controlled Release Society; Rutgers, NJ 02 June 2009 Craig A. McKelvey Merck & Co., Inc. hereinafter "McKelvey"). Now it is estimated that more than 60% of Active Pharmaceutical Ingredients (API) in development have poor bioavailability due to low aqueous solubility (WO 2013040187 citing Manufacturing chemist, March 2010, 24-25). At least partially as a result of advances in combinatorial chemistry and molecular screening methods for identifying potential drug candidates, an increasing number of insoluble drugs are being identified. Poor solubility of lead compounds results in
ineffective absorption, which is an important part of the high clinical failure rate due to poor pharmacokinetics. Drugs with very low aqueous solubility usually have sizeable within and between subject pharmacokinetic variability making study design and the conduct of Phase I studies very challenging, the assessment of dose-response and exposure response relationships difficult, and resulting in difficult dose determination. Water insoluble drugs usually have high propensity for drug interactions at the absorption level, such as food interactions, and interactions with gastrointestinal "GI" prokinetic agents, especially if these drugs also have narrow therapeutic windows. There is an on-going need in the art for better formulation technologies for poorly soluble drugs (Jain et al. Asian J Pharm Clin Res, Vol 5, Suppl 4, 2012, 15-19).

The Biopharmaceutical Classification System (BCS) is a framework for classifying a drug substance on the basis of its equilibrium aqueous solubility and intestinal permeability. (Jain et al. Asian J Pharm Clin Res, Vol 5, Suppl 4, 2012, 15-19 hereinafter "Jain") When combined with the in vitro dissolution characteristics of a drug product, the BCS takes into account three major factors: solubility, intestinal permeability and dissolution rate. These factors govern the rate and extent of oral drug absorption for immediate release solid oral dosage forms. The BCS defines four classes of drug substances based on their solubility and permeability characteristics.

<table>
<thead>
<tr>
<th>Solubility</th>
<th>High Permeability</th>
<th>Low Permeability</th>
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<tr>
<td>High Solubility</td>
<td>BCS Class I</td>
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<tr>
<td>Low Permeability</td>
<td>BCS Class III</td>
<td>BCS Class IV</td>
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A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml water over a pH range of 1 to 7.5. A drug is considered highly permeable when the extent of absorption in humans is determined to be 90% of an administered dose, based on the mass
balance or in comparison to an intravenous dose (drug and metabolite). A drug product is considered to dissolve rapidly when 85% of the labeled amount of substance dissolves within 30 minutes, using USP apparatus I or II in a volume of 900 ml buffer solution. (Gothoskar A.V. Biopharmaceutical classification of drugs. Pharm Rev. 2005; 3:1.)

[0034] For BCS Class II drugs that have low bioavailability resulting from poor solubility and the inability to dissolve rapidly the selection of formulation is often a major hurdle preventing the development of a successful oral drug product. Certain technologies have recently been developed to aid in the formulation of these drugs including: salt formation, size reduction, co-solvency, pH manipulation, surfactant and micelle use, inclusion complexes, lipid formulations, and solid dispersions. Jain et al. Asian J Pharm Clin Res, Vol 5, Suppl 4, 2012, 15-19).

[0035] According to the "Intra-Agency Agreement Between the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA) Oral Formulations Platform—Report 1" dronabinol is a class 2 or class 4 drug with low solubility and unknown permeability. Thus it may be formulated in the same manner as a class 2 drug.

[0036] Absorption and distribution: Dronabinol capsules are almost completely absorbed (90 to 95%) after single oral doses. Due to the combined effects of first pass hepatic metabolism only 10 to 20% of the administered dose reaches the systemic circulation. FDA document NDA 18-651/S-021.

[0037] **Controlled Release Dosage Forms**

[0038] Controlled-release formulations have been one of the major focuses in pharmaceutical research and development.

[0039] The advantages of controlled release products are well known in the pharmaceutical field. Sustained release drug formulations may be useful to reduce the frequency of drug administration (especially in the case of drugs with short compound half-lives), improve patient compliance, reduce drug toxicity (local or systemic associated with high peak exposure),
reduce drug level fluctuation in blood, stabilize medical condition with more uniform drug levels, reduce drug accumulation with chronic therapy, improve bioavailability of some drugs because of spatial control, and reduce total drug usage when compared with immediate release drugs.

[0040] Oral controlled release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and temporal requirements.

[0041] Mechanical devices aside, interaction between a drug and a polymeric material often forms the basis of controlled oral drug delivery. A polymer at certain concentrations in a solution imposes pathways for drug diffusion. Polymers that dissolve in or otherwise hydrate in aqueous media can alter the drug diffusion process in a time-dependent manner. For example, a commonly used material, hydroxypropyl methylcellulose (HPMC), which is water soluble, behaves as a swellable absorptive polymer in the limited volumes of aqueous media in the gastrointestinal tract. Drug dispersed in this polymer, as in monolithic tablets, diffuses through the viscous hydrated polymer at a rate dependent on the movement kinetics of the polymer chains. The faster these relax, the faster the diffusion rate.

[0042] Development of dosage form depends on chemical nature of the drug and polymers, the matrix structure, swelling, diffusion, erosion, the release mechanism and the in vivo environment.

[0043] Hydrophilic polymers like HPMC may also control drug release by erosion mechanisms. After consumption of the dosage form, the GI tract fluid encounters the dosage unit, causing the polymer to hydrate and swell. Weakened mechanical properties in the swollen state may cause the hydrated polymer to break away from the prime particle (compact or pellet). Drug release may therefore be controlled by a combination of diffusion and erosion. Such release mechanisms can apply to systems where drug is dispersed in or coated with polymer.

[0044] Extended release dosage forms of class 2 drugs often require expensive, difficult, and proprietary osmotic delivery systems such as Alza's Oros™
and Duros™ technologies. (See US 4612008; US 4327725; 4,765,989; and 4,783,337). Other technologies have been developed to exploit diffusion, erosion, and other physicochemical mechanisms and provide drug and disease-specific release profiles. Examples also include the release from a Contramid™ tablet controlled by the degree of crosslinking of high amylose starch.

[0045] Different hydrogels have been described for use in controlled release medicines, most of which are semi-synthetic or of natural origin. A few contain both synthetic and non-synthetic material. However, many of the systems require special process and production equipment, and in addition some of these systems are susceptible to variable drug release.

[0046] In another modified release approach, a solid dispersion comprising API with two different polymers is employed. JP Patent Application No. 2004-67606 discloses a tablet comprising fine granules obtained by spraying a solution containing itraconazole, which is a poorly soluble drug, a water-soluble polymer and an enteric polymer, on a mixed powder of an excipient and a disintegrator, granulating and drying. Karel Six et al. (J. Pharm. Sci. 93, 124-131, 2004) discloses a solid dispersion composition of Itraconazole, a class II drug, Eudragit E100 and copovidone. The use of a combination of fast- and slow-dissolving polymers in solid dispersions compositions has resulted in increased physical stability and improved dissolution properties of itraconazole. In another approach, Hirasawa et al. (J. Pharm. Soc. of Japan, 124(1), 19-23, 2004; Chem. Pharm. Bull. 52(2) 244-247, 2004; JP Patent Application No. 2001335483 A) disclose a solid dispersion comprising Nilvadipine (NIL)/ Crospovidone (cl-PVP)/ Methylcellulose (MC). US Patent Publication No. 20070248681 discloses a granule of a solid dispersion of a poorly soluble drug, a water-soluble polymer, an excipient and a disintegrator, wherein the content of the water-soluble polymer is 1 to 10% by weight and the content of the disintegrator is 15 to 50% by weight. A method for producing a tablet of a solid dispersion is also disclosed.
Another method of dealing with poorly soluble drugs is to employ emulsions. Emulsions are formed by mixing two immiscible liquids (in the case of drugs usually water and oil) stabilized by an emulsifying agent. Self-emulsification is thought to take place when (as a result of) the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the emulsion is a function of the energy required to create a new surface between the oil and water phases.

When an emulsion is formed surface area expansion is created between the two phases. The emulsion is stabilized by the surfactant 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, 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, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have the ability to form oil-in-water emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. The digestive motility of the stomach and the intestine provides the agitation necessary for self-emulsification.

To date, there are still numerous limitations to SEDDS and SMEDDS, for example, they require high surfactant concentrations in formulations (approximately 30-60%) which may irritate the gastrointestinal tract. They include chemically unstable drugs that tend to precipitate, and the volatile co-solvents in the self-micro emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the
precipitation of the lipophilic drugs. In one example, the SMEDDS showed around 50% degradation after only 30 days (AAPS PharmSciTech. 2009 June; 10(2): 482-487. SMEDDS of Glyburide: Formulation, In Vitro Evaluation, and Stability Studies. Yogeshwar G. Bachhav and Vandana B. Patavale). Further, these systems are hard to develop and tend to be expensive. Such systems have only been useful for immediate release dosage forms, useful, extended release dosage forms have not been regularly achieved.

[0051] SMEDDS generally must be given as a liquid and so oral formulations are often formulated as soft gels, for example: Neoral and Sandimmune; Norvir; Fortase; and Convulex. The present invention represents a considerable advance over such formulations.

[0052] Water insoluble polymers can be used in extended drug release formulations. These include methacrylate- or acrylate-based polymers with low permeability.

[0053] Hydrophilic functional groups such as trimethylaminoethyl methacrylate can improve permeability and swellability in water thus altering release behaviors.

[0054] Various drug candidates such as diltiazem hcl, carbamazepine, metoprolol, exprenolol, nifedipine, glipizide have been formulated as osmotic delivery systems. Problems with such osmotic delivery systems include the need for special equipment for making an orifice in the system; residence time of the system in the body varies with the gastric motility and food intake; such systems may cause irritation or ulcer due to release of saturated solutions of drug. Vol. 1 No. 7 2012. Online Available at www.thepharmajournal.com. THE PHARMA INNOVATION Vol. 1 No. 7 2012 www.thepharmajournal.com Page | 116 Osmotic-Controlled Release Oral Delivery System: An Advanced Oral Delivery Form. Nitika Ahuja, Vikash Kumar, Permender Rathee.
The instant invention solves these problems and provides for cannabinoid sustained release dosage forms in a technically and economically efficient and surprising manner.

In general, the most desirable oral dosage form is a tablet, and it would be advantageous if a cannabinoid containing tablet could be made available which does not suffer from the problems of expense and the need for smoking or "edible" dosage forms. None of the documents described above enable modified release cannabinoid tablets. There is a need for new cheap and stable dosage formulations, especially tablets, comprising an effective dose of cannabinoids or derivatives thereof. There is also a need for a stable cannabinoid powder.

Another aspect the invention provides a pharmaceutical or nutraceutical composition in the form of a tablet for oral administration comprising cannabinoid wherein said tablet is preferably formed from a pharmaceutically or even nutraceutically acceptable powder.

By "nutraceutical" is meant a composition that provides medical or health benefits, including the prevention and treatment of disease. Dietary supplements and natural health products are examples of nutraceuticals. In many places natural cannabinoids are considered nutraceuticals. Within the context of this invention it is understood that the term "drug" is used generically to include prescription and non-prescription pharmaceutical products as well as nutraceuticals including dietary supplements, natural health products, medicinal foods, drinks, candy bars with active ingredients and all other similar delivery methods whether approved or unapproved.

Viewed from another aspect the invention provides a pharmaceutical or nutraceutical tablet as hereinbefore described for use in the treatment or prophylaxis of all of the disorders that medical marijuana and drabinol is used for at the present time.
As used herein, the term "drug" includes not only pharmaceuticals but also natural medicines, alternative medicines, and dietary supplements and generally refers to all forms of cannabinoids.

DETAILED DESCRIPTION OF THE INVENTION

Extending drug release ("sustained release") from a dosage form can prolong its action and attenuate peak plasma levels, thereby obviating concentration-related side effects or optimize efficacy by matching systemic presence with other time-related effects. Sustained release drug forms can be achieved by embedding the drug in a matrix that prevents immediate release and delivers excipient at a desired rate consistent with absorption or disposition requirements. A wide variety of materials can be used to design the most appropriate release profile and provide a viable and consistent mode of manufacture. The present invention approaches this problem systematically and solves it in a unique way.

As discussed above, BCS Class II drugs present immense challenges for oral delivery, let alone attempts at zero order pharmacokinetics. In particular embodiments, the dosage form may provide a zero order release from about 1 hour to about 24 hrs after administration. In certain embodiments, the dosage form releases more than about 90% of the active agent in less than about 24 hrs. In particular embodiments, the dosage form may provide a zero order rate of release for at least a portion of the delivery period. In other embodiments, the dosage form may provide an ascending rate of release for at least a portion of the delivery period. In yet other embodiments, the dosage form may provide a fast initial rate of release followed by a slower rate of release and an ascending rate of release of the remaining active agent.

The sustained release formulations of cannabinoids of the present invention represent a significant improvement over existing formulations and delivery methods of cannabinoids.

The present invention involves a novel granulation method for formulating cannabinoids in a matrix and subsequently into tablets.
The benefits of the invention include maintaining cannabinoids in a soluble, hydrophilic state in contact with body fluids.

The present invention provides a deceptively simple formulation solution to the problem of formulating modified release versions of cannabinoids involving a few simple ingredients combined in an extremely inventive and unique way. The present invention provides tablets and powders of cannabinoid formulations using a novel combination of silica gel, hydrogenated lecithin, glyceryl behenate, peg-6 caprylic/capric glycerides, hydroxypropylmethylcellulose, microcrystalline cellulose, colloidal silicon dioxide, and hydroxypropylcellulose.

Cannabinoid Extract Resin

The cannabinoid extracts of the present invention can be extracted and formulated to provide a number of sustained release combinations useful in the present invention. Of particular interest are 100 percent THC tablets, 100% CBD tablets, 10:1 THC/CBD, 1:10 THC/CBD, and 50:50 THC/CBD although other variations of sustained release granules and tablets may be desirable in specific situations.

Cyclodextrins

Cyclodextrins (sometimes called cycloamyloses) are a family of compounds made up of sugar molecules bound together in a ring (cyclic oligosaccharides).


Cyclodextrins are composed of 5 or more α-D-glucopyranoside units linked 1->4, as in amylose (a fragment of starch). The 5-membered
A macrocycle is not natural. Recently, the largest well-characterized cyclodextrin contains 32 1,4-anhydroglucopyranoside units, while as a poorly characterized mixture, at least 150-membered cyclic oligosaccharides are also known. Typical cyclodextrins contain a number of glucose monomers ranging from six to eight units in a ring, creating a cone shape:

- a (alpha)-cyclodextrin: 6-membered sugar ring molecule
- β (beta)-cyclodextrin: 7-membered sugar ring molecule
- Y (gamma)-cyclodextrin: 8-membered sugar ring molecule
- α- and γ-cyclodextrin are being used in the food industry.

All of these cyclodextrins can be employed in the present invention.

Cyclodextrins are able to form host-guest complexes with hydrophobic molecules given the unique nature imparted by their structure. As a result, these molecules have found a number of applications in a wide range of fields.

Because cyclodextrins are hydrophobic inside and hydrophilic outside, they can form complexes with hydrophobic compounds. Thus they can enhance the solubility and bioavailability of such compounds. This is of high interest for pharmaceutical as well as dietary supplement applications in which hydrophobic compounds shall be delivered.

Cyclodextrins can solubilize hydrophobic drugs in pharmaceutical applications, and crosslink to form polymers used for drug delivery. [Laza-Knoerr, A. L, Gref, R., & Couvreur, P. (2010). Cyclodextrins for drug delivery. Journal of Drug Targeting, 18(9), 645-656. One example is Sugammadex, a modified γ-cyclodextrin which reverses neuromuscular blockade by binding the drug rocuronium. Other than the above-mentioned pharmaceutical applications, cyclodextrins can be employed in environmental protection: these molecules can effectively immobilise inside their rings toxic compounds, like trichloroethane or heavy metals, or can form complexes with stable substances, like trichlorfon (an
organophosphorus insecticide) or sewage sludge, enhancing their decomposition.

[0078] Typical cyclodextrins are constituted by 6-8 glucopyranoside units, can be topologically represented as toroids with the larger and the smaller openings of the toroid exposing to the solvent secondary and primary hydroxyl groups respectively. Because of this arrangement, the interior of the toroids is not hydrophobic, but considerably less hydrophilic than the aqueous environment and thus able to host other hydrophobic molecules. In contrast, the exterior is sufficiently hydrophilic to impart cyclodextrins (or their complexes) water solubility.

[0079] The formation of the inclusion compounds greatly modifies the physical and chemical properties of the guest molecule, mostly in terms of water solubility. This is the reason why cyclodextrins have attracted much interest in many fields, especially pharmaceutical applications: because inclusion compounds of cyclodextrins with hydrophobic molecules are able to penetrate body tissues, these can be used to release biologically active compounds under specific conditions. In most cases the mechanism of controlled degradation of such complexes is based on pH change of water solutions, leading to the loss of hydrogen or ionic bonds between the host and the guest molecules. Alternative means for the disruption of the complexes take advantage of heating or action of enzymes able to cleave a-1,4 linkages between glucose monomers.

[0080] α-Cyclodextrin has been authorized for use as a dietary fiber in the European Union since 2008. In 2013 the EU commission has verified a health claim for alpha-cyclodextrin. The EU assessment report confirms that consumption of alpha-cyclodextrin can reduce blood sugar peaks following a high-starch meal. Weight loss supplements are marketed from alpha-cyclodextrin which claim to bind to fat and be an alternative to other anti-obesity medications.
Due to its surface-active properties, a-cyclodextrin can also be used as emulsifying fiber, for example in mayonnaise as well as a whipping aid, for example in desserts and confectionary applications.

β-cyclodextrins are the main ingredient in P&G's product Febreze which claims that the β-cyclodextrins "trap" odor causing compounds, thereby reducing the odor.


Alkylation of β-cyclodextrin functions with different substituents results in derivatives having a drastically increased aqueous solubility, while also preserving the complexing properties of the starting compound and allowing for solubilization [Muller B, Brauns U. Solubilization of drugs by modified β-cyclodextrins. *Intl J Pharm* 1985; 26: 77-88.] In addition, studies have shown a stabilizing effect on aqueous solutions, in which decomposition was delayed.

As mentioned above, the formation of inclusion compounds or "inclusion complexes" modifies the physical and chemical properties of the guest molecule, mostly in terms of water solubility, and allows hydrophobic molecules to penetrate body tissues and release biologically active compounds. Studies conducted on the use of indomethacin as a guest molecule, which normally undergoes controlled degradation by hydrolytic cleavage with a rate constant depending on the pH of the solution [Krasowska, H. (1974) Kinetics of indomethacin hydrolysis. *Acta. Pharm.*]
Jugoslav. 24:13-200.], was found to undergo delayed decomposition when it was solubilized by hydroxyethyl-p-cyclodextrin. Both of the above factors have important implications for the absorption of the EHA and DPA contained in omega 3 oils.

[0086] The silica gel is used herein as an adsorbant and solid carrier and should be selected for properties making it ideal for use with lipid formulations; able to adsorb large amounts of oils with a resulting density and flowability that is useful for maximum loading into tablets. It is also desirable that the oil will release from the silica gel without the use of additional surfactants.

[0087] Lecithin is a naturally occurring mixture of the diglycerides of stearic, palmitic, and oleic acids, linked to the choline ester of phosphoric acid, commonly called phosphatidylcholine. Hydrogenated Lecithin is the product of controlled hydrogenation of Lecithin. Bilayers of these phospholipids in water may form liposomes, a spherical structure in which the acyl chains are inside and not exposed to the aqueous phase. Lecithin and Hydrogenated Lecithin are used in a large number of cosmetic formulations as skin conditioning agents-miscellaneous and as surfactant-emulsifying agents. Hydrogenated Lecithin is also used as a nonsurfactant suspending agent. Lecithin is virtually nontoxic in acute oral studies, short-term oral studies, and subchronic dermal studies in animals. Lecithin is not a reproductive toxicant, nor is it mutagenic in several assays. Fiume Z. Int J Toxicol. 2001 ;20 Suppl 1:21-45.

[0088] Soy lecithin one of the most widely used food additives on the market today. It is used as an emulsifier. It helps to emulsify numerous foods, even unlikely emulsions such as chocolate. In chocolate, lecithin stabilizes the cocoa butter fat so it doesn't separate from the moisture, cocoa solids and dairy.

[0089] Lecithin also extends shelf life by stabilizing emulsions, and it also reduces "stickiness" and is often used as a "releasing agent."

[0090] Chemically, glyceryl behenate is a mixture of various esters of behenic acid and glycerol (glycerides). The mixture predominately contains the
diester glyceryl dibehenate. 21 C.F.R. 184.1328. Glyceryl behenate is a tablet and capsule lubricant and a lipidic coating excipient. It has been used for the encapsulation of various drugs such as retinoids. It has also been used as a matrix-forming agent for the controlled release of water-soluble drugs and as a lubricant in oral solid dosage formulations. It is also used widely as ingredient for preparation of lipidic nanoparticles such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC).


[0091] Peg-6 caprylic/capric glycerides (Labrasol) is a polyethylene glycol derivative of a mixture of mono-, di-, and triglycerides of caprylic and capric acids with an average of 6 moles of ethylene oxide. It is used in the present invention as an emulsifying agent. A preferred form is caprylocaproyl macrogol-8 glycerides, a non-ionic water dispersible surfactant composed of polyethylene glycol (PEG) esters, a glyceride fraction, and free PEG. This form is able to self-emulsify on contact with aqueous media to form a fine micro-emulsion. It is a solubilizer and wetting agent: its surfactive power improves the solubility and wettability of active pharmaceutical ingredients in vitro and in vivo. See for example, http://www.gattefosse.com.

[0092] Hydroxypropyl methylcellulose (HPMC), which is water soluble, behaves as a swellable absorptive polymer in the limited volumes of aqueous media in the gastrointestinal tract. Drug dispersed in this polymer, as in the monolithic tablets of the instant invention, diffuses through the viscous hydrated polymer at a rate dependent on the movement kinetics of the polymer chains. The faster these relax, the faster the diffusion rate.

[0093] Hydrophilic polymers like HPMC also control drug release by erosion mechanisms. After consumption of the dosage form, the GI tract fluid encounters the dosage unit, causing the polymer to hydrate and swell. Weakened mechanical properties in the swollen state may cause the hydrated polymer to break away from the prime particle (compact or pellet). Drug release may therefore be controlled by a combination of
diffusion and erosion. Such release mechanisms can apply to systems where drug is dispersed in or coated with polymer.

[0094] Microcrystalline cellulose is derived from refined wood pulp and is used in the present invention as an anti-caking agent and emulsifier.

[0095] Microcrystalline cellulose (MCC) is pure partially depolymerized cellulose synthesized from α-cellulose precursor. The MCC can be synthesized by different processes such as reactive extrusion, enzyme mediated, steam explosion and acid hydrolysis. The later process can be done using mineral acids such as H2SO4, HCl and HBr as well as ionic liquids. The role of these reagents is usually to destroy the amorphous regions remaining in the crystalline domains. The degree of polymerization is typically less than 400. The MCC particles with size lower than 5 μm not be more than 10%. The MCC is a valuable additive in pharmaceutical, food, cosmetic and other industries. Different properties of MCC are measured to qualify its suitability to such utilization, namely particle size, density, compressibility index, angle of repose, powder porosity, hydration swelling capacity, moisture sorption capacity, moisture content, crystallinity index, crystallite size and mechanical properties such as hardness and tensile strength. https://en.wikipedia.org/wiki/ Microcrystalline cellulose. Accessed September 16, 2016.

[0096] Microcrystalline cellulose is a naturally occurring polymer, it is composed of glucose units connected by a 1-4 beta glycosidic bond. These linear cellulose chains are bundled together as microfibril spiralled together in the walls of plant cell. Each microfibril exhibits a high degree of three-dimensional internal bonding resulting in a crystalline structure that is insoluble in water and resistant to reagents. There are, however, relatively weak segments of the microfibril with weaker internal bonding. These are called amorphous regions. The crystalline region is isolated to produce microcrystalline cellulose. https://en.wikipedia.org/wiki/ Microcrystalline cellulose. Accessed September 16, 2016.
[0097] Colloidal silicon dioxide or silicon dioxide is used in the instant invention as an anti-caking agent, adsorbent, disintegrant, and glidant to allow powder to flow freely when tablets are processed.

[0098] Hydroxypropylcellulose (HPC) is an ether of cellulose in which some of the hydroxyl groups in the repeating glucose units have been hydroxypropylated. In the instant invention it is used as a tablet binder and emulsifier.

[0099] Examples

[00100] Example 1: Ingredients useful for 25 mg cannabinoid tablet (total 287.70mg) components

[00101] Granules - 229.0mg granules

- beta-cyclodextrin 150.0mg
- Sesame Oil 25.0mg
- Cannabinoid Resin 25.0mg
- Compritol 888 4.0mg
- Soy Lecithin 2.5mg
- Labrasol 22.5mg

[00102] Blend

- Syloid XDP 3150 2.5mg
- Klucel LF Pharm 5.0mg
- ProSolv90 25.0mg
- HPMC LVCR K100 12.5mg

[00103] Coating

- Green Colour 5% 13.70mg
Example 2: Formulation Methods

The formulation according to the present example may be prepared as follows:

1. mix cyclodextrin with water for approximately 2.5 hours to form a slurry;
2. mix a cannabinoid resin and sesame oil together at a temp of about 60°C until a uniform mixture is obtained;
3. add the uniform mixture or resin and oil to the cyclodextrin slurry and mix for about 1 hour;
4. mix soy lecithin and water together at a temperature of about 60°C, until a uniform slurry mixture is obtained;
5. slowly sprinkle the glyceryl behenate on to the resin, cyclodextrin mixture obtained in step 3 and mix for about 15 minutes;
6. slowly add the soy lecithin slurry to the mixture obtained in step 5 while increasing the mixer speed to achieve a uniform mixture;
7. slowly add Labrasol to the mixture obtained in step 6 while maintaining the uniform mixture;
8. continue mixing until a uniform mixture is obtained and being careful to not over mix;
9. transfer the mixture to stainless steel (or other suitable) trays;
10. place in an oven and dry at about 70°C until the moisture content is less than 2.0% to form granules;
11. screen the granules through a 30 mesh;
12. screen each of the silica gel, hydroxypropylcellulose, microcrystalline cellulose/colloidal silicon dioxide, and hydroxypropylmethylcellulose together with through a 30 mesh;
13. add the resin granules and blend for about 10 minutes;
14. form tablets;
15. mix colour and water together for about 30 minutes;
16. preheat the coating machine to 70°C with the guns blowing air, to stabilize the temperature; and
17. coat tablets to a 5% uniform coating.

[00106] Example 3: Branded ingredients useful for 25 mg cannabinoid tablet components

**Granules**

- beta-cyclodextrin 150.0mg
- Sesame Oil 25.0mg
- Cannabinoid Resin 25.0 mg
- Compritol 888 4.0mg
- Soy Lecithin 2.5mg
- Labrasol 22.5mg

**Blend**

- Syloid XDP 3150 2.5mg
- Klucel LF Pharm 5.0mg
- ProSolv90 25.0mg
- HPMC LVCR K100 12.5mg

**Coating**

- Green Colour 5% 13.7mg

[00107] Example 4: Branded ingredients useful for 15.5 mg cannabinoid tablet components

[00108] Granules

- beta-cyclodextrin 150.0mg
- Sesame Oil 25.0mg
- Cannabinoid Resin 15.5mg
- Compritol 888 4.0mg
- Soy Lecithin 2.5mg
- Labrasol 15.0mg
[00109] Blend

Syloid XDP 3150 2.5mg
Klucel LF Pharm 5.0mg
ProSolv90 25.0mg
HPMC LVCR K100 12.5mg

[00110] Coating

Green Colour 5% 12.85mg

[00111] Example 5: Ingredients useful for preparing larger scale 25 mg cannabinoid tablets (total weight 323mg) components

[00112] Granules

Beta-cyclodextrin 1.5kg
Sesame Oil 0.250kg
Cannabinoid Resin 0.250kg
Compritol 888 0.050kg
Soy Lecithin 0.050kg
Labrasol 0.230kg

[00113] Blend - using 1.864kg of above

Syloid XDP 3150 0.040kg
Klucel LF Pharm 0.080kg
ProSolv90 0.400kg
HPMC LVCR K100 0.200kg
Coating

Green Colour 5%

Example 6: Formulation Methods

The formulation according to the present example may be prepared as follows:

1. mix cyclodextrin with water for approximately 2.5 hours to form a slurry;
2. mix a cannabinoid resin and sesame oil together at a temp of about 60°C until a uniform mixture is obtained;
3. add the uniform mixture or resin and oil to the cyclodextrin slurry and mix for about 1 hour;
4. mix soy lecithin and water together at a temperature of about 60°C, until a uniform slurry mixture is obtained;
5. slowly sprinkle the glyceryl behenate (Comp888) on to the resin, cyclodextrin mixture obtained in step 3 and mix for about 15 minutes;
6. slowly add the soy lecithin slurry to the mixture obtained in step 5 while increasing the mixer speed to achieve a uniform mixture;
7. slowly add Labrasoi to the mixture obtained in step 6 while maintaining the uniform mixture;
8. continue mixing until a uniform mixture is obtained and being careful to not over mix;
9. transfer the mixture to stainless steel (or other suitable) trays;
10. place in an oven and dry at about 70°C until the moisture content is less than 2.0% to form granules;

Surprisingly, the amounts of glyceryl behenate and soy lecithin are crucial to control, as too little will result in very long drying times for the granules and a loss of efficiency.

11. screen the granules through a 30 mesh;
12. screen each of the silica gel, hydroxypropylcellulose, microcrystalline cellulose/colloidal silicon dioxide, and hydroxypropylmethylcellulose together with through a 30 mesh; The amounts of hydroxypropyl methylcellulose and microcrystalline cellulose are crucial in order to get tablets with desirable dissolution profiles.

13. add the resin granules and blend for about 10 minutes;
14. form tablets;
15. mix colour and water together for about 30 minutes;
16. preheat the coating machine to 70°C with the guns blowing air, to stabilize the temperature; and
17. coat tablets to a 5% uniform coating.

[0017] Example 7: Branded ingredients useful for 2.5 mg cannabinoid tablet components

[0018] Granules

Beta-cyclodextrin 150.0mg
Sesame Oil 25.0mg
Cannabinoid Resin 2.5mg
Compritol 888 4.0mg
Soy Lecithin 2.5mg
Labrasol 15.0mg

[0019] Blend

Syloid XDP 3150 2.5mg
Klucel LF Pharm 5.0mg
ProSolv90 25.0mg
[00120] Coating

Colour 5% 12.85mg

[00121] Example 8: Branded ingredients useful for 5 mg cannabinoid tablet components

[00122] Granules

- Beta-cyclodextrin 150.0mg
- Sesame Oil 25.0mg
- Cannabinoid Resin 5mg
- Compritol 888 4.0mg
- Soy Lecithin 2.5mg
- Labrasol 15.0mg

[00123] Blend

- Syloid XDP 3150 2.5mg
- Klucel LF Pharm 5.0mg
- ProSolv90 25.0mg
- HPMC LVCR K100 12.5mg

[00124] Coating

Colour 5% 12.85mg

[00125] Example 9: Branded ingredients useful for 10 mg cannabinoid tablet components

[00126] Granules
Beta-cyclodextrin 150.0mg
Sesame Oil 25.0mg
Cannabinoid Resin 10mg
Compritol 888 4.0mg
Soy Lecithin 2.5mg
Labrasol 15.0mg

[00127] Blend

Syloid XDP 3150 2.5mg
Klucel LF Pharm 5.0mg
ProSolv90 25.0mg
HPMC LVCR K100 12.5mg

[00128] Coating

Colour 5% 12.85mg

[00129] Example 10: Branded ingredients useful for cannabinoid tablet components

[00130] In each of the foregoing examples cannabinoid isolates may be advantages substituted for cannabinoid resin.

[00131] As will be immediately apparent to the skilled artisan after reading the present disclosure, some of the steps may be carried out simultaneously or in a different order, such variations form part of the present invention.

[00132] All publications mentioned above are hereby specifically incorporated herein by reference in full for the teachings for which they are cited. The examples and claims of the present invention are not limiting. Having read the present disclosure, those skilled in the art will readily recognize that numerous modifications, substitutions and variations can be made to
the description without substantially deviating from the invention described herein. Such modifications, substitutions and variations constitute part of the invention described herein.
Claims

1. A composition comprising granules including cannabinoid resin, sesame oil, a cyclodextrin, glyceryl behenate, lecithin, and polyethylene glycol -6 caprylic/capric glycerides.
2. The composition according to claim 1 further comprising a tablet.
3. A composition according to claim 1 wherein the cannabinoid comprises a tetrahydrocannabinol.
4. A composition according to claim 1 wherein the cannabinoid comprises a CBD.
5. A composition according to claim 1 wherein the cannabinoid comprises a natural extract of Cannabis Sativa.
6. A composition according to claim 2 comprising about 25mg, 15mg, 10mg, 5mg, or 2.5mg of cannabinoid per tablet.
7. A composition according to claim 6 wherein the composition comprises about 25mg of cannabinoid per tablet.
8. A composition according to claim 6 wherein the composition comprises about 15mg of cannabinoid per tablet.
9. A composition according to claim 6 wherein the composition comprises about 10mg of cannabinoid per tablet.
10. A composition according to claim 6 wherein the composition comprises about 5mg of cannabinoid per tablet.
11. A composition according to claim 6 wherein the composition comprises about 2.5mg of cannabinoid per tablet.
12. A composition according to claim 3 wherein the cannabinoid further comprises a CBD.
13. A composition according to claim 12 wherein the cannabinoid has a THC to CBD ratio of about 10:1 to 1:10.
14. A composition according to claim 13 wherein the THC to CBD ratio is about 50:50.
15. A method of formulating a drug comprising forming granules by:
i) mixing a cannabinoid with a non-toxic organic solvent to form a slurry;

ii) mixing a cyclodextrin with water;

iii) combining the slurry from i) and the mixture from ii) to form a uniform slurry;

iv) mixing lecithin with water until a uniform mixture is obtained;

v) sprinkling glyceryl behenate into the mixture from step iii);

vi) slowly add the lecithin mixture from step iv) to the slurry formed in step v);

vii) adding slowly polyethylene glycol -6 caprylic/capric glycerides to the mixture of step vi);

viii) mixing until a uniform mixture is obtained and being careful to not over mix;

ix) transferring the mixture to stainless steel trays;

x) placing the trays to an oven and drying at about 70°C until the moisture content of the mixture is less than 2.0% to form granules.

16. A method of formulating a drug comprising:

a. mixing cyclodextrin with water for approximately 2.5 hours to form a slurry;

b. mixing a cannabinoid resin and sesame oil together at a temp of about 60°C until a uniform mixture is obtained;

c. adding the uniform mixture or resin and oil to the cyclodextrin slurry and mix for about 1 hour;
d. mixing soy lecithin and water together at a temperature of about 60°C, until a uniform slurry mixture is obtained;
e. slowly sprinkling the glyceryl behenate on to the resin, cyclodextrin mixture obtained in step 3 and mix for about 15 minutes;
f. slowly adding the soy lecithin slurry to the mixture obtained in step 5 while increasing the mixer speed to achieve a uniform mixture;
g. slowly adding Labrasol to the mixture obtained in step 6 while maintaining the uniform mixture;
h. mixing the uniform mixture obtained in step g for about an additional 30;
i. transferring the mixture to stainless steel trays;
j. placing the trays in an oven and drying at about 70°C until the moisture content is less than 2.0% to form granules;
k. screening the granules through a 30 mesh;
l. screening each of silica gel, hydroxypropylcellulose, microcrystalline cellulose/colloidal silicon dioxide, and hydroxypropylmethylcellulose together through a 30 mesh screen to obtain a uniform blend;
m. adding the resin granules to the blend obtained in step l and blending for about 10 minutes;
n. forming tablets;
o. mixing colour and water together for about 30 minutes;
p. preheating the coating machine to 70°C with the guns blowing air to stabilize the temperature; and
q. coating tablets to a 5% uniform coating.

17. A modified release oral drug composition comprising granules including cannabinoid resin, sesame oil, a cyclodextrin, glyceryl behenate, lecithin, and polyethylene glycol -6 caprylic/capric glycerides.
18. A composition according to claim 17 wherein the cannabinoid comprises a natural extract of *Cannabis Sativa*.

19. A composition according to claim 17 comprising about 25mg, 15mg, 10mg, 5mg, or 2.5mg of cannabinoid per tablet.

20. A composition according to claim 19 wherein the composition comprises about 25mg of cannabinoid per tablet.

21. A composition according to claim 19 wherein the composition comprises about 15mg of cannabinoid per tablet.

22. A composition according to claim 19 wherein the composition comprises about 10mg of cannabinoid per tablet.

23. A composition according to claim 19 wherein the composition comprises about 5mg of cannabinoid per tablet.

24. A composition according to claim 19 wherein the composition comprises about 2.5mg of cannabinoid per tablet.

25. A method of formulating a drug comprising forming granules by:

   xi) mixing a cannabinoid with a non-toxic organic solvent to form a slurry;

   xii) mixing a cyclodextrin with water;

   xiii) combining the slurry from i) and the mixture from ii) to form a uniform slurry;

   xiv) mixing lecithin with water until a uniform mixture is obtained;

   xv) sprinkling glyceryl behenate into the mixture from step iii);

   xvi) slowly add the lecithin mixture from step iv) to the slurry formed in step v);

   xvii) adding slowly polyethylene glycol -6 caprylic/capric glycerides to the mixture of step vi);
xviii) mixing until a uniform mixture is obtained and being careful to not over mix;

xix) transferring the mixture to stainless steel trays;

xx) placing the trays to an oven and drying at about 70°C until the moisture content of the mixture is less than 2.0% to form granules.

26. A method of formulating a drug tablet comprising:

r. mixing 1.5kg of cyclodextrin with water for approximately 2.5 hours to form a slurry;

s. mixing 0.250kg of a cannabinoid resin and 0.250kg of sesame oil together at a temp of about 60°C until a uniform mixture is obtained;

t. adding the uniform mixture or resin and oil to the cyclodextrin slurry and mix for about 1 hour;

u. mixing 0.050kg soy lecithin and water together at a temperature of about 60°C, until a uniform slurry mixture is obtained;

v. slowly sprinkling 0.050kg of glyceryl behenate on to the resin, cyclodextrin mixture obtained in step c and mix for about 15 minutes;

w. slowly adding the slurry obtained in step d to the mixture obtained in step e while increasing the mixer speed to achieve a uniform mixture;

x. slowly adding 0.230kg of Labrasol to the mixture obtained in step f while maintaining the uniform mixture;

y. mixing the uniform mixture obtained in step g for about an additional 30 minutes;

z. transferring the mixture obtained in step h to stainless steel trays;
aa. placing the trays in an oven and drying at about 70°C until the moisture content is less than 2.0% to form granules;
bb. screening the granules formed in step j through a 30 mesh;
cc. screening each of 0.040kg of silica gel, 0.080 hydroxypropylcellulose, 0.400kg microcrystalline cellulose/colloidal silicon dioxide, and 0.200kg hydroxypropylmethylcellulose together through a 30 mesh screen to obtain a uniform blend;
dd. adding the resin granules screened in step k (1.864kg of screened granules) to the blend obtained in step l and blending for about 10 minutes;
ee. forming tablets;
ff. mixing colour and water together for about 30 minutes;
gg. preheating the coating machine to 70°C with the guns blowing air to stabilize the temperature; and
hh. coating tablets to a 5% uniform coating.
INTERNATIONAL SEARCH REPORT

INTERNATIONAL APPLICATION NO.
PCT/CA2017/000211

A. CLASSIFICATION OF SUBJECT MATTER
   IPC: A61K 47/44 (2017.01) , A61K 31/05 (2006.01) , A61K31/352 (2006.01) , A61K 36/185 (2006.01) , A61K 47/10 (2017.01) , A61K 47/24 (2006.01) (more IPCs on the last page)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Databases: STN, Google Scholar, PubMed, Canadian Patent Database and Orbit; Keywords: tablet, solid, granule, powder, cannabinoid, cannabidiol, cannabis, marijuana, CDB, THC, dronabinol, marinol, formulation, composition, dosage form, polyethylene glycol, sesame oil, behenate, compritol, cyclodextrin, polyethylene glycol, caprylic, capric

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

P See patent family annex.

Date of the actual completion of the international search
04 December 2017 (04-12-2017)

Date of mailing of the international search report
18 December 2017 (18-12-2017)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C14 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 819-953-2476

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