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(54) Title: TRANSDERMAL DELIVERY OF CANNABIDIOL

(57) Abstract: Provided is a transdermal drug delivery system comprising cannabidiol, or its salt alone or in combinations thereof. Transdermal delivery can provide a drug plasma concentration at predetermined rate for a predetermined period of time with a simplified therapeutic regimen by decreasing dosing frequency for the treatment and/or prevention of pain and/or inflammation.



**WO 2021/074790 A1**

**TRANSDERMAL DELIVERY OF CANNABIDIOL**

## CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims priority to U.S. Serial No. 62/914,662 filed October 14, 2019, the entirety of which is incorporated herein by reference.

## SPECIFICATION

## BACKGROUND

10 Pain and Inflammation are the body's physiological responses to tissue injury, infection and genetic changes. These responses can be divided into two phases: acute and chronic. The acute phase is the early, non-specific phase and is characterized by local vasodilation, increased capillary permeability, the accumulation of fluid and blood proteins in the interstitial spaces, the migration of neutrophils out of the capillaries, and the release of inflammatory mediators. Pain is produced by all these pro-inflammatory agents, that also leads to hyperalgesia through the  
15 activation of the corresponding receptors, which are expressed by nonreceptive terminals. If the condition that causes the damage is not resolved, the inflammatory process progressed toward subacute/chronic inflammation, which is characterized by immunopathological changes such as the infiltration of inflammatory cells, the overexpression of pro-inflammatory genes, the dysregulation of cellular signaling and the loss of barrier function<sup>1</sup>.

20 The chronic pathological pain state, including neuropathic pain, is a leading health problem worldwide as it endures beyond the resolution of the pain source and can deeply impact quality of life<sup>2</sup>. Unlike physiological pain, in which tissue injury and/or inflammation can induce reversible adaptive changes in the sensory nervous system leading to protective sensitization, changes in sensitivity become persistent or chronic in neuropathic pain. Furthermore, the  
25 nervous system, peripheral of central, is injured in neuropathic pain. It is characterized by pain in the absence of a noxious stimulus and may be spontaneous in its temporal characteristics or be evoked by sensory stimuli.

30 Arthritis is a classic example of chronic pain inflammation, as are various diseases and conditions, including, for example, cardiovascular and neurodegenerative diseases, diabetes, cancer, and asthma. Synthetic anti-inflammatory compounds are one of the general ways to control chronic inflammation and pain. There are several common side effects associated with these synthetic anti-inflammatory drug products such as gastric irritation and ulceration, renal and hepatic failure, hemolytic anemia, asthma exacerbation. Increasing amount of evidence

demonstrates that the endocannabinoid system actively participates in the pathophysiology of osteoarthritis-associated joint pain. Overall, preclinical and clinical data support the potentially effective anti-inflammatory properties of endocannabinoids agonist that target CB2 (Cannabinoid receptor 2) receptors<sup>3</sup>.

5 Cannabis (marijuana) is a schedule-I drug in USA. Cannabis is a flowering plant which contains more than 400 phytonutrient (micronutrient). More than 100 different types of terpenoids, essential oils, antioxidants and cannabinoids have been extracted from the plant. From all of the phytochemicals, only tetrahydrocannabinol (THC) showed significant psychoactive effect. A number of research papers have been published on THC due to its psychoactive and therapeutic  
10 effects. Apart from THC, several other constituents have been studied, which also showed some therapeutic effect without psychoactive effect such as cannabidiol (CBD), cannbinol (CBN), cannabichromene (CBC), cannabigerol (CBG), tetrahydrocannbivarin (THCV), delta 9-tetrahydrocannbinol (delta9THC) and many more. It has been showed that cannabis and its derivatives can be used for the treatment of pain, type-2 related metabolic disorder, decrease  
15 intraocular pressure, Dravet syndrome, Lennox-Gastaut Syndrome (LGS), epilepsy, nausea, pain and wasting associated with AIDS, arthritis and rheumatism, migraines, muscle spasticity associated with multiple sclerosis and paralysis, alcohol and narcotics withdrawal, stress and depression, asthma, fibromyalgia, inflammatory pain, and pain and/or inflammation associated with chemotherapy, act as an antimicrobial. FDA approved Marinol and Syndros contains delta  
20 9-THC, which currently used in treatment of nausea, vomiting, and anorexia associated with chemotherapy treatments. Furthermore, in April 2016 FDA gave orphan drug designation to cannabidiol for the treatment of Tuberous Sclerosis Complex (TSC), Dravet Syndrome and Lennox-Gastaut Syndrome. Cannabidiol is an orally effective treatment for pain and inflammation. (Costa, B. The non-psychoactive cannabis constituent cannabidiol is an orally  
25 effective therapeutic agent in rat chronic inflammatory and neuropathic pain. European Journal of Pharmacology. Volume 556, Issues 1–3, 5 February 2007, Pages 75-83).

Currently, 107 different cannabinoids have been identified from cannabis Sativa. These compounds are similar to the endogenous cannabinoid group that consists of long chain polyunsaturated fatty acids<sup>4</sup>. There are two types of cannabinoid receptors: I) CB1 and II) CB2.

30 The endocannabinoid system is a one of the important endogenous lipids signaling pathway, which consists of cannabinoid receptors, the endogenous ligands of cannabinoid receptors (endocannabinoids) and the enzymes that regulate the biosynthesis and inactivation of

endocannabinoids. The lipid signaling system is involved in many important physiological functions in the central and peripheral nervous system and in the endocrine and immune system. These receptors are from family of Guanosine Binding Protein-Coupled Receptors, are widely expressed and distinguished by their specific function, localization and signaling mechanisms<sup>5,3</sup>.

5 Cannabinoid receptor 1 (CB1), inhibits adenylate cyclase and reduce cAMP levels and protein kinase A (PKA) activity, resulting in the activation of the A-type potassium channels and decrease cellular potassium levels. This receptor mainly found in adipose tissue, the GI tract, the spinal cord, the adrenal and thyroid glands, liver, reproductive organ and immune cells<sup>6</sup>.

10 Cannabidiol (CBD), a major non-psychoactive phytocannabinoid has little affinity for CB1 and CB2, and act as a partial antagonist CB1 and as a weak inverse CB2 agonist<sup>7</sup>.

Selective CB2 agonists have shown considerable efficiency in a variety of neuropathic pain preclinical models, while increasing amounts of evidence, derived from clinical studies, have confirmed the potential of the cannabinoid system in affording benefits for patients with chronic pain and chronic inflammatory disease (arthritis). Currently, patients with chronic arthritis and musculoskeletal pain are the most prevalent users of therapeutic cannabis products<sup>8</sup>.

15 Preclinical studies have shown that cannabinoid receptor agonists block pain in various acute and chronic pain models and that inflammation is attenuated<sup>9-11</sup>. Both CB1 and CB2 receptor agonists demonstrate anti-nociceptive activity, whether used singly or in combination, with CB2 activity believed to affect microglial cells and thereby reduce neuro-inflammatory mechanisms<sup>12,13</sup>. The CB2 receptor is thought to be particularly important in central neuronal pain circuits, as agonist activity induces dopamine release in mid-brain areas, contributing to descending pain control and the placebo effect<sup>14</sup>. Inflammatory effects can either be modulated via the upregulation of cannabinoid receptor activity or increased production of endocannabinoids, providing an attenuation in joint destruction in preclinical models of inflammatory arthritis that mimic human rheumatoid arthritis<sup>8,10</sup>. Similarly, CB1 and CB2 receptors, proteins and endocannabinoids are found in the human synovial tissue of patients with  
25 both rheumatoid arthritis and osteoarthritis<sup>15</sup>.

30 It was demonstrated that transdermal CBD delivery has therapeutic potential for the relief of arthritic pain-related behavior and to exert an anti-inflammatory effect without any evident of psychoactive effect using complete Freund's adjuvant-induced monoarthritic knee joint mode.

Result also showed that a dose of 6.2 mg/day reduce knee-joint swelling and that increase the dose of 62 mg/day failed to yield any additional improvement<sup>16</sup>.

5 These side effects related to oral anti-inflammatory drugs can be avoided using transdermal route. Furthermore, the peak and valley in the plasma concentration due to oral administration can be avoided by delivering the drug molecule constantly at predetermined input rate using transdermal dosage forms.

10 There are numerous patents available on cannabidiol, but the utility of those patents is not evaluated. One of the examples is the US 9375417B2. While the '417 patent provides some examples, there is no in-vitro or in-vivo data for those examples. Due to lack of these data, the utility is unfeasible.

US 6328992 provides examples for reservoir and adhesive matrix patches. All these examples contain mixture of cannabinoids (such as delta-8-THC, delta-9-THC, cannabidiol and cannabinol) instead of cannabidiol only. The THC is psychoactive agent and addictive substance, so, the utility of is problematic.

15 There is a need for an improved drug delivery system of cannabidiol which can overcome the drawbacks associated with oral routes. Transdermal delivery of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof  
20 can address the challenges associated with oral drug delivery. The current disclosure addresses all the above drawbacks and provide patent which can have a real world utility. Furthermore, the current disclosure provides for the use of a synthetic version of cannabidiol which is manufactured in more controlled environment than the botanical source of the same. In addition, the synthetic version of cannabidiol can provide more permeability as compared to adulterated  
25 version of it. Moreover, the disclosure is directed to, for example, transdermal matrix patches which can deliver synthetic cannabidiol for 1 day, and/or 2-days, and/or 3-days, and/or 4 days, and/or 5 days, and/or 6 days, and/or 7 days, and/or up to 15 days.

All references cited herein are incorporated herein by reference in their entireties.

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## BRIEF SUMMARY

In Transdermal drug delivery, a transdermal patch or transdermal composition is applied topically to the skin surface. Throughout the duration of topical application of a transdermal patch or transdermal composition drug is continuously released and delivered through the intact skin (via transcellular, intercellular and transappendageal routes) to achieve systemic effect. Therefore, once applied transdermal composition or transdermal patch can deliver drug into systemic circulation throughout the day or even for more than one day depending on the duration of its application which can be even up to a week.

Transdermal delivery can reduce the dosing frequency of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof. Through transdermal delivery, transdermal compositions or transdermal formulations or transdermal patch of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof, can be applied topically to skin thereby delivering the drug throughout the duration of topical application. Depending on the requirement, the duration of topical application can be once in a day, once in two days, once in three days, once in four days, once in five days, once in a week. Therefore, transdermal delivery can overcome the multiple dose regimen of oral delivery by reducing the dosing frequency.

Moreover, in transdermal drug delivery the drug is delivered slowly and continuously throughout the duration of topical application hence there are no peaks and troughs in drug plasma concentration which are associated with multiple dose administration in a day. Therefore, by transdermal delivery of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof, patients can have the therapeutic effect of the drug for extended period of time without drastic changes in drug plasma concentration.

Transdermal delivery is easy, noninvasive and convenient. Administration of a transdermal patch or transdermal composition does not require medical supervision as patients can topically apply the transdermal patch or transdermal composition themselves.

5 Moreover, in case of any adverse effect, side effect or emergency transdermal delivery gives the liberty to terminate the therapy anytime by taking off the transdermal patch or transdermal composition from skin.

10 As per above stated reasons for the prevention of pain and/or inflammation transdermal delivery can provide patient friendly, simplified and convenient therapeutic regimen over traditional delivery systems. Transdermal delivery can reduce the dosing frequency of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof. Depending on the necessity, dosing frequency can be once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week.

15 Through transdermal administration of drug combination, two or more drugs can be delivered simultaneously. Depending on the necessity, dosing frequency of transdermal patch or transdermal composition containing drug combination can be once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week. It would be a great addition to the patient compliance.

20 The disclosure provides a pharmaceutical composition comprising cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof,  
25 in a dosage form for transdermal delivery. The disclosure provides a pharmaceutical composition comprising cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof in the range of 0.01% - 95% w/w or  
30 w/v. The disclosure provides a pharmaceutical composition formulated as transdermal liquid formulation, transdermal semisolid formulation, or matrix patch formulation. The disclosure provides a pharmaceutical composition further comprising carriers or ingredients in effective

amount selected from the group consisting of solvents, gelling agents, polymers, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, and combinations thereof. The disclosure provides a pharmaceutical composition further comprising carriers or ingredients in effective amount selected from the group consisting of solvents, gelling agents, polymers, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, fillers, pressure sensitive adhesives, and combinations thereof in the range of 0.01% - 95% w/w or w/v. The disclosure provides a pharmaceutical composition wherein the carrier is present in the range of 0.01% - 99.8% w/w or w/v. The disclosure provides a pharmaceutical composition which is formulated as a transdermal patch. The disclosure provides a pharmaceutical composition formulated as a transdermal patch, wherein the transdermal patch is selected from the group such as to reservoir patch, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, extended release transdermal film a liquid reservoir system, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, a mucoadhesive patch, and combinations thereof. The disclosure provides a pharmaceutical composition indicated for treatment of headaches, migraine, tension headaches, cluster headaches, acute pain, chronic pain, neuropathic pain, nociceptive pain, central pain, inflammatory pain, fibromyalgia, drug-induced neuropathic pain, causalgia, complex regional pain syndrome types I and II, and reflex sympathetic dystrophy (RSDS), pain and wasting associated with AIDS, arthritis and rheumatism, migraines, and muscle spasticity associated with multiple sclerosis and paralysis. The disclosure provides a pharmaceutical composition which is formulated as the transdermal formulation which can be administered in a dosage regimen selected from the group consisting of once daily, twice daily, three times a day, once in 1-8 hrs, once in 1-24 hrs, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in a 8 to about 13 days, once in two weeks, once in 15 days to about 30 days. The disclosure provides a pharmaceutical composition which may be formulated as microneedles. The disclosure provides a pharmaceutical composition wherein said CBD or derivative thereof is produced by a synthetic route or biosynthetic route.

The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation comprising: selecting a patient in need of treatment and/or prevention



and/or control of pain and/or inflammation; topically applying the pharmaceutical composition as disclosed herein. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation wherein the topical application of a transdermal patch for the treatment and/or prevention and/or control of pain and/or inflammation is selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further providing a constant rate of delivery of the active components of the transdermal patch over a time period. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further providing a steady absorption rates of the active components of the transdermal patch over a time period. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further achieving a constant blood serum levels of the active components of the transdermal patch over a time period. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further achieving a reduced variability in dosage of the active components of the transdermal patches over a time period. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further providing a plasma concentration of the active components of the transdermal patch in a therapeutic range over a period of time.

The disclosure provides a pharmaceutical composition comprising cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof, in a dosage form for transdermal delivery. The disclosure provides a pharmaceutical composition comprising cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof in the range of 0.01% - 95% w/w or w/v. The disclosure provides a pharmaceutical composition formulated as transdermal liquid formulation, transdermal semisolid formulation, or matrix patch formulation. The disclosure provides a pharmaceutical composition further comprising carriers or ingredients in effective amount selected from the group consisting of solvents, gelling agents, polymers, penetration

enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, fillers, pressure sensitive adhesives, and combinations thereof. The disclosure provides a pharmaceutical composition further comprising carriers or ingredients in effective amount selected from the group consisting of solvents, gelling agents, polymers, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, fillers, pressure sensitive adhesives, and combinations thereof in the range of 0.01% - 95% w/w or w/v. The disclosure provides a pharmaceutical composition wherein the carrier is present in the range of 0.01% - 99.8% w/w or w/v. The disclosure provides a pharmaceutical composition which is formulated as a transdermal patch. The disclosure provides a pharmaceutical composition formulated as a transdermal patch, wherein the transdermal patch is selected from the group such as to reservoir patch, a microreservoir patch, , a liquid reservoir system, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, a mucoadhesive patch, and combinations thereof, transdermal matrix patch without any limitations such as adhesive matrix patch, non-adhesive matrix patch, pressure sensitive adhesive matrix patch, extended release transdermal films, drug in adhesive matrix patch. The disclosure provides a pharmaceutical composition indicated for treatment of conditions selected from the group consisting of headaches, migraine, tension headaches, cluster headaches, acute pain, chronic pain, neuropathic pain, nociceptive pain, central pain, inflammatory pain, fibromyalgia, drug-induced neuropathic pain, causalgia, complex regional pain syndrome types I and II, and reflex sympathetic dystrophy (RSDS), pain and wasting associated with AIDS, arthritis and rheumatism, migraines, and muscle spasticity associated with multiple sclerosis and paralysis, Autism Spectrum Disorder (ASD) and Autism Spectrum Disorder (ASD) for Pediatric patients, pain and/or inflammation of patients with liver disease, pain and/or inflammation of patients with kidney disease, pain and/or inflammation for liver cancer patients, treating pain and/or inflammation for kidney cancer patients, pain and/or inflammation for cancer patients, and combinations thereof. The disclosure provides a pharmaceutical composition which is formulated as the transdermal formulation is applied to the patient for a time selected from the group consisting of, for example, about 4 hours, 8 hours, 12 hours, 16 hours, 24 hours, 48 hours, 60 hours, 72 hours, 84 hours, 108 hours, 120 hours, one day, two days, three days, four days, five days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12, days, 13, days, 14 days, one week , two weeks, three weeks, four weeks, one month, two

months, three months, and four months . The disclosure provides a pharmaceutical composition which may be formulated as microneedles. The disclosure provides a pharmaceutical composition wherein said CBD or derivative thereof is produced by a synthetic route or biosynthetic route.

5 The disclosure provides a pharmaceutical composition comprising cannabidiol (CBD), in a dosage form for transdermal delivery wherein the pharmaceutical composition comprises: about 9% to about 12% w/w of CBD; optionally, about 30% to about 99% solvent; optionally, about 1% to about 20% penetration enhancer(s), wherein the pH of the composition is maintained at approximately 4.0 to 8.0. The disclosure provides a pharmaceutical composition formulated as  
10 transdermal liquid formulation, transdermal semisolid formulation, or transdermal polymer matrix formulation. The disclosure provides a pharmaceutical composition further comprising carriers or ingredients in effective amount selected from the group consisting of gelling agents, polymers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, and combinations thereof. The disclosure provides a pharmaceutical  
15 composition further comprising carriers or ingredients in effective amount selected from the group consisting of gelling agents, polymers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, and combinations thereof in the range of 0.01%  
20 - 95% w/w or w/v. The disclosure provides a pharmaceutical composition which is formulated as a transdermal patch. The disclosure provides a pharmaceutical composition formulated as a transdermal patch, wherein the transdermal patch is selected from the group such as to reservoir patch, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, extended release transdermal film a liquid reservoir system, a microreservoir patch, a matrix patch, a  
25 pressure sensitive adhesive patch, a mucoadhesive patch, and combinations thereof. The disclosure provides a pharmaceutical composition which is formulated as the transdermal formulation which can be administered in a dosage regimen selected from the group consisting of once daily, twice daily, three times a day, once in 1-8 hrs, once in 1-24 hrs, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week,  
30 once in a 8 to about 13 days, once in two weeks, once in 15 days to about 30 days. The disclosure provides a pharmaceutical composition which may be formulated as microneedles. The disclosure provides a pharmaceutical composition wherein said CBD or derivative thereof is produced by a synthetic route.

The disclosure provides a method for the treatment and/or prevention and/or decrease and/or control of pain and/or inflammation comprising: selecting a patient in need of treatment and/or prevention and/or control of pain and/or inflammation; topically applying the pharmaceutical composition as disclosed herein. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation wherein the topical application of a transdermal patch for the treatment and/or prevention and/or control of pain and/or inflammation is selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further providing a constant rate of delivery of the active components of the transdermal patch over a time period. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further providing a steady absorption rates of the active components of the transdermal patch over a time period. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further achieving a constant blood serum levels of the active components of the transdermal patch over a time period. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further achieving a reduced variability in dosage of the active components of the transdermal patches over a time period. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation further providing a plasma concentration of the active components of the transdermal patch in a therapeutic range over a period of time. The disclosure provides a method for the treatment and/or prevention and/or control of pain and/or inflammation wherein the topical application of a transdermal patch is for the treatment and/or prevention and/or control of pain and/or inflammation of indications selected from the group consisting of headaches, migraine, tension headaches, cluster headaches, acute pain, chronic pain, neuropathic pain, nociceptive pain, central pain, inflammatory pain, fibromyalgia, drug-induced neuropathic pain, causalgia, complex regional pain syndrome types I and II, and reflex sympathetic dystrophy (RSDS), pain and wasting associated with AIDS, arthritis and rheumatism, migraines, and muscle spasticity associated with multiple sclerosis and paralysis, Autism Spectrum Disorder (ASD) and Autism Spectrum Disorder (ASD) for Pediatric patients, pain and/or inflammation of patients with liver disease, pain and/or inflammation of patients with kidney disease, pain and/or inflammation for liver cancer patients, treating pain and/or inflammation for kidney cancer patients, pain and/or inflammation for cancer patients, and combinations thereof.

The disclosure provides for the use of the compositions of the invention for the production of a medicament for treating the indications as set forth herein.

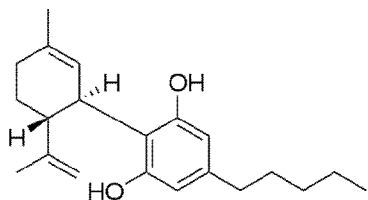
5 In accordance with a further embodiment, the present disclosure provides a use of the pharmaceutical compositions described above, an amount effective for use in a medicament, and most preferably for use as a medicament for treating a disease or disorder in a subject.

10 In accordance with yet another embodiment, the present disclosure provides a use of the pharmaceutical compositions described above, and at least one additional therapeutic agent, in an amount effective for use in a medicament, and most preferably for use as a medicament for treating a disease or disorder associated with disease in a subject.

#### DETAILED DESCRIPTION

15 Cannabinoids are a group of 21 -carbon-containing terpenophenolic compounds produced by Cannabis species. Cannabinoids may also be synthetically produced. The term "cannabinoid" refers hereinafter to a class of diverse chemical compounds that act on cannabinoid receptors on cells that repress neurotransmitter release in the brain. These receptor proteins include the endocannabinoids (produced naturally in the body by humans and animals), the  
20 phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids. Lipophilic cannabinoids are generally grouped as endocannabinoids (most typically as mammalian endocannabinoids); phytocannabinoids, from plant sources; and synthetic cannabinoids. Such cannabinoids are also often classified into the following subclasses: Cannabigerols (CBG); Cannabichromenes (CBC); Cannabidiol (CBD; CBDL);  
25 Tetrahydrocannabinol (THC); Cannabinol (CBN); Cannabicyclol (CBL); Cannabielsoin (CBE); and, Cannabitrinol (CBT).

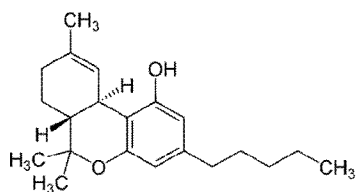
**Cannabidiol** IUPAC Name 2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol Chemical Formula: C<sub>21</sub>H<sub>30</sub>O<sub>2</sub> Molecular weight: 314.46 dalton  
30 Chemical structure is shown below as formula I



Formula I

- 5 **Tetrahydrocannabinol (THC)** IUPAC Name (-)-(6*aR*,10*aR*)-6,6,9-Trimethyl-3-pentyl-6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol  
 Chemical Formula: C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>  
 Molecular weight: 314.47 dalton.

Chemical structure is shown below as formula II



10

Formula II

- As used herein, the word cannabis refers to all pharmaceutically acceptable forms of cannabis  
 15 and its derivatives either alone or in combinations thereof, for example, in following forms but not limited to such as free base or salts or isomers or amorphous or crystalline or co crystalline or solid solution or prodrugs or analogs or derivatives or metabolites. For example, cannabidiol's free base or its salts or its isomers or its amorphous form or its crystalline form or its co crystalline form or its solid solution or its prodrugs or its analogs or its derivatives or synthetic forms. The compound may be in the form of, for example, a  
 20 pharmaceutically acceptable salt, such as an acid addition salt or a base salt, or a solvate thereof, including a hydrate thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts. Suitable base salts are formed from  
 25 bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

- 30 As used herein, the term "cannabidiol" includes the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic

forms thereof, active metabolites thereof, alone or in combinations thereof. As used herein, the term "cannabidiol" includes the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, and synthetic forms thereof, alone or in combinations thereof. In certain embodiments the CBD is highly purified. In certain embodiments the CBD is present as a highly purified extract of cannabis which comprises at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.75% (w/w) CBD. In exemplary embodiments, formulations of the disclosure may comprise CBD as disclosed herein at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 9.1%, about 9.2%, about 9.3%, about 9.4%, about 9.5%, about 9.6%, about 9.7%, about 9.8%, about 9.9% about 9.25%, about 9.5%, about 9.75%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise CBD at a concentration of about 1 to 25%, of about 5% to 20%, about 8% to about 15%, or about 9% to about 14%, about 9% to about 13%, about 9% to about 12%, w/w of the formulation.

In certain embodiments, the dose of CBD is greater than, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, or 45 mg/kg/day. In certain embodiments, the dose of CBD is greater than, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, or 275 mg/day.

In one embodiment the CBD is present as a highly purified extract of cannabis which comprises at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.75% (w/w) CBD.

As used herein, the term "pharmaceutically acceptable salts" includes acid addition salts or addition salts of free bases. The term "pharmaceutically acceptable salts" of the cannabidiol within its scope all the possible isomers and their mixtures, and any pharmaceutically acceptable metabolite, bioprecursor and/or pro-drug, such as, for example, a compound which has a

structural formula different from the one of the compounds of the disclosure, and yet is directly or indirectly converted in vivo into a compound of the disclosure, upon administration to a subject, such as a mammal, particularly a human being.

As used herein, the terms “subject” and “patient” are used interchangeably. As used herein, the term “patient” refers to an animal, preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey and human), and most preferably a human. In some embodiments, the subject is a non-human animal such as a farm animal (e.g., a horse, pig, or cow) or a pet (e.g., a dog or cat). In a specific embodiment, the subject is a human. As used herein, the term “agent” refers to any molecule, compound, methodology and/or substance for use in the prevention, treatment, management and/or diagnosis of a disease or condition. As used herein, the term “effective amount” refers to the amount of a therapy that is sufficient to result in the prevention of the development, recurrence, or onset of a disease or condition, and one or more symptoms thereof, to enhance or improve the prophylactic effect(s) of another therapy, reduce the severity, the duration of a disease or condition, ameliorate one or more symptoms of a disease or condition, prevent the advancement of a disease or condition, cause regression of a disease or condition, and/or enhance or improve the therapeutic effect(s) of another therapy.

As used herein, the phrase “pharmaceutically acceptable” means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia, or other generally recognized pharmacopeia for use in animals, and more particularly, in humans.

As used herein, the term “therapeutic agent” refers to any molecule, compound, and/or substance that is used for treating and/or managing a disease or disorder.

As used herein, the terms “therapies” and “therapy” can refer to any method(s), composition(s), and/or agent(s) that can be used in the prevention, treatment and/or management of a disease or condition, or one or more symptoms thereof. In certain embodiments, the terms “therapy” and “therapies” refer to small molecule therapy.

The term "derivative" or "derivatized" as used herein includes, for example, chemical modification of a compound of the disclosure, or extracted from botanical sources or pharmaceutically acceptable salts thereof or mixtures thereof. That is, a "derivative" may be a



functional equivalent of a compound of the disclosure, which is capable of inducing the improved pharmacological functional activity in a given subject.

As used herein, the terms “composition” and “formulation” are used interchangeably.

As used herein, the terms “transdermal matrix patch” and “matrix patch” are used interchangeably.

As used herein, the term “transdermal delivery” means delivery of drug into systemic circulation through the skin.

As used herein, synthetic cannabinoids include at least the following:

AM-087 is an analgesic drug that is a cannabinoid agonist derivative of  $\Delta^8$ THC substituted on the 3-position side chain and a potent CB1 agonist; AM-251 is an inverse agonist at the CB1 cannabinoid receptor with close structural similarity to SR141716A (rimonabant), both of which are biarylpyrazole cannabinoid receptor antagonists as well as  $\mu$ -opioid receptor antagonist; Methanandamide (AM-356) is a stable chiral analog of anandamide and acts on the cannabinoid receptors with a  $K_i$  of 17.9 nM at CB1 and 868 nM at CB2; AM-374—palmitylsulfonyl fluoride; AM-381—stearyl sulfonyl fluoride; AM404, also known as N-arachidonoylaminophenol, is an active metabolite of paracetamol (acetaminophen) thought to induce its analgesic action through its activity on the endocannabinoid, COX, and TRPV systems, all of which are present in pain and thermoregulatory pathways; AM-411 is an analgesic that is a cannabinoid agonist; AM-411 is a potent and fairly selective CB1 full agonist and produces similar effects to other cannabinoid agonists such as analgesia, sedation, and anxiolysis; AM-630 (6-Iodopravadoline) acts as a potent and selective inverse agonist for the cannabinoid receptor CB2, selectivity over CB1 where it acts as a weak partial agonist; AM-661—1-(N-methyl-2-piperidine)methyl-2-methyl-3-(2-iodo)benzoylindole; JWH-018 (1-pentyl-3-(1-naphthoyl)indole) or AM-678 is an analgesic chemical from the naphthoylindole family that acts as a full agonist at both the CB1 and CB2 cannabinoid receptors, with some selectivity for CB2; AM-679 acts as a moderately potent agonist for the cannabinoid receptors; AM-694 (1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole) acts as a potent and selective agonist for the cannabinoid receptor CB1; AM-735—3-bornyl- $\Delta^8$ -THC, a mixed CB1/CB2 agonist; AM-855 is an analgesic cannabinoid agonist at both CB1 and CB2 with moderate selectivity for CB1; AM-881—a chlorine-substituted stereoisomer of anandamide whose  $K_i=5.3$  nM at CB1 and 95 nM

at CB2; AM-883 an allyl-substituted stereoisomer of anandamide whose  $K_i=9.9$  nM at CB1 and 226 nM at CB2; AM-905 is an analgesic cannabinoid which acts as a potent and reasonably selective agonist for the CB1 cannabinoid receptor; AM-906 is an analgesic drug which is a cannabinoid agonist and is a potent and selective agonist for the CB1 cannabinoid receptor;

5 AM-919 is an analgesic cannabinoid receptor agonist, potent with respect to both CB1 and CB2; AM-926—a potent agonist at both CB1 and CB2 with moderate selectivity for CB1; AM-938 is an analgesic drug which is a cannabinoid receptor agonist and while it is still a potent agonist at both CB1 and CB2, it is reasonably selective for CB2; AM-1116—a dimethylated stereoisomer of anandamide; AM-1172—an endocannabinoid analog specifically designed to be a potent and

10 selective inhibitor of AEA uptake that is resistant to FAAH hydrolysis; AM-1220 is a potent and moderately selective agonist for the cannabinoid receptor CB1; AM-1221 acts as a potent and selective agonist for the cannabinoid receptor CB2; AM-1235 (1-(5-fluoropentyl)-3-(naphthalen-1-oyl)-6-nitroindole) acts as a potent and reasonably selective agonist for the cannabinoid receptor CB1; AM-1241 (1-(methylpiperidin-2-ylmethyl)-3-(2-iodo-5-

15 nitrobenzoyl)indole) is a potent and selective agonist for the cannabinoid receptor CB2, with analgesic effects in mammals, particularly against “atypical” pain such as hyperalgesia and allodynia, and has also shown efficacy in the treatment of amyotrophic lateral sclerosis in mammalian models; AM-1248 acts as a moderately potent agonist for both the cannabinoid receptors CB1 and CB2; AM-1710—a CB2 selective cannabilactone with 54x selectivity over

20 CB1; AM-1714 acts as a reasonably selective agonist of the peripheral cannabinoid receptor CB2 and has both analgesic and anti-allodynia effects; AM-2201 (1-(5-fluoropentyl)-3-(1-naphthoyl)indole) acts as a potent but nonselective full agonist for the cannabinoid receptor; AM-2212—a potent agonist at both CB1 and CB2; AM-2213—a potent agonist at both CB1 and CB2; AM-2232 (1-(4-cyanobutyl)-3-(naphthalen-1-oyl)indole) acts as a potent but

25 unselective agonist for the cannabinoid receptors CB1 and CB2; AM-2233 acts as a highly potent full agonist for the cannabinoid receptors CB1 and CB2 and has been found to fully substitute for THC in certain mammalian studies, with a potency lower than that of JWH-018 but higher than WIN 55,212-2; AM-2389 acts as a potent and reasonably selective agonist for the CB1 receptor; AM-3102—an analog of oleoylethanolamide, (the endogenous agonist for proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ )) it acts as a weak cannabinoid agonist at CB1 and at

30 CB2; AM-4030 an analgesic which is potent agonist at both CB1 and CB2, but also reasonably selective for CB1; AM-4054 is a potent but slow-onset agonist with CB1 affinity and selectivity CB1 over CB2; AM-4113—a CB1 selective neutral antagonist; AM-6545 acts as a peripherally

selective silent antagonist for the CB1 and was developed for the treatment of obesity; JWH-007—an analgesic which acts as a cannabinoid agonist at both the CB1 receptor and CB2 receptors, with some selectivity for CB2, JWH-007 is an analgesic which acts as a cannabinoid agonist at both the CB1 and CB2 receptors; JWH-015 acts as a subtype-selective cannabinoid agonist which binds almost 28× more strongly to CB2 than CB1. and has been shown to have immunomodulatory effects, and may be useful in the treatment of pain and inflammation; JWH-018 an analgesic which acts as a full agonist at both the CB1 and CB2 cannabinoid receptors and produces effects similar to those of THC; JWH-019—an agonist at both CB1 and CB2 receptors and is an analgesic from the naphthoylindole family that acts as a cannabinoid agonist at both the CB1 and CB2 receptors; JWH-030—an analgesic which is a partial agonist at CB1 receptors; JWH-047—a potent and selective agonist for the CB2 receptor, JWH-048—a potent and selective agonist for the CB2 receptor, JWH-051—an analgesic with a high affinity for the CB1 receptor, but is a much stronger agonist for CB2, JWH-057—a 1-deoxy analog of Δ8-THC that has very high affinity for the CB2 receptor, but also has high affinity for the CB1 receptor; JWH-073—an analgesic which acts as a cannabinoid agonist at both the CB1 and CB2 receptors. It is somewhat selective for the CB1 subtype; JWH-081—an analgesic which acts as an agonist at both the cannabinoid CB1 AND CB2 receptors; JWH-098—a potent and fairly selective CB2 agonist; JWH-116—a CB1 ligand; JWH-120—a potent and 173-fold selective CB2 agonist; JWH-122—a potent and fairly selective CB1 agonist; JWH-133—a potent and highly selective CB2 receptor agonist; JWH-139—3-(1,1-dimethylpropyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6H-benzo[c]chromene; JWH-147—an analgesic from the naphthoylpyrrole family, which acts as a cannabinoid agonist at both the CB1 and CB2 receptors; JWH-148—a moderately selective ligand for the CB2 receptor, with more than 8 times selectivity over the CB1 subtype; JWH-149—a potent and fairly selective CB2 agonist; JWH-161—a CB1 ligand; JWH-164—a potent cannabinoid agonist; JWH-166—a potent and highly selective CB2 agonist; JWH-167—a weak cannabinoid agonist from the phenylacetylindole family; JWH-171—an analgesic which acts as a cannabinoid receptor agonist; JWH-175—(1-pentylindol-3-yl)naphthalen-1-ylmethane, 22 nM at CB1, JWH-176—1-([(1E)-3-pentylinden-1-ylidene]methyl)naphthalene; JWH-181—a potent cannabinoid agonist; JWH-182—a potent cannabinoid agonist with some selectivity for CB1; JWH-184—1-pentyl-1H-indol-3-yl-(4-methyl-1-naphthyl)methane; JWH-185—1-pentyl-1H-indol-3-yl-(4-methoxy-1-naphthyl)methane; JWH-192—(1-(2-morpholin-4-ylethyl)indol-3-yl)-4-methylnaphthalen-1-ylmethane; JWH-193—(1-(2-morpholin-4-ylethyl)indol-3-yl)-4-methylnaphthalen-1-

ylmethanone; JWH-194—2-methyl-1-pentyl-1H-indol-3-yl-(4-methyl-1-naphthyl)methane; JWH-195—(1-(2-morpholin-4-ylethyl)indol-3-yl)-naphthalen-1-ylmethane; JWH-196—2-methyl-3-(1-naphthalenylmethyl)-1-pentyl-1H-Indole; JWH-197—2-methyl-1-pentyl-1H-indol-3-yl-(4-methoxy-1-naphthyl)methane; JWH-198—(1-(2-morpholin-4-ylethyl)indol-3-yl)-4-methoxynaphthalen-1-ylmethanone; JWH-199—(1-(2-morpholin-4-ylethyl)indol-3-yl)-4-methoxynaphthalen-1-ylmethane; JWH-200—an analgesic from the aminoalkylindole family, which acts as a cannabinoid receptor agonist; JWH-203—an analgesic from the phenylacetylindole family, which acts as a cannabinoid agonist with approximately equal affinity at both the CB1 and CB2 receptors; JWH-205—142-methyl-1-pentylindol-3-yl)-2-phenylethanone; JWH-210—an analgesic from the naphthoylindole family, which acts as a potent cannabinoid agonist at both the CB1 and CB2 receptors; JWH-213—a potent and fairly selective CB2 agonist; JWH-229—1-methoxy-3-(1',1'-dimethylhexyl)- $\Delta$ 8-THC, a dibenzopyran cannabinoid which is a potent CB2 agonist; JWH-234—a cannabinoid agonist with selectivity for CB2; JWH-250—an analgesic from the phenylacetylindole family, which acts as a cannabinoid agonist at both the CB1 and CB2 receptors; JWH-251—(1-pentyl-3-(2-methylphenylacetyl)indole); JWH-258—a potent and mildly selective CB1 agonist; JWH-302—(1-pentyl-3-(3-methoxyphenylacetyl)indole); JWH-307—an analgesic from the naphthoylpyrrole family, which acts as a cannabinoid agonist at both the CB1 and CB2 receptors that is somewhat selective for the CB2 subtype; JWH-350—a 11-nor-1-methoxy-3-(1',1'-dimethylheptyl)-9 $\alpha$ -hydroxyhexahydrocannabinol has a 33-fold selectivity for the CB2 receptor and high CB2receptor affinity with little affinity for the CB1 receptor; JWH-359—a dibenzopyran cannabinoid that is a potent and selective CB2 receptor agonist; JWH-387—1-pentyl-3-(4-bromo-1-naphthoyl)indole, an analgesic from the naphthoylindole family, which acts as a potent cannabinoid agonist at both receptors CB1 and CB2; JWH-398—an analgesic chemical from the naphthoylindole family, which acts as a potent cannabinoid agonist at both receptors with a  $K_i$  of 2.3 nM at CB1 and 2.8 nM at CB2; JWH-424—a potent and moderately selective CB2 agonist with a  $K_i$  of 5.44 nM at CB2 and 20.9 nM at CB1; HU-210 is a cannabinoid that is 100 to 800 times more potent than natural THC from cannabis and has an extended duration of action and is a ponntent analgesic with many of the same effects as natural THC; Ajulemic acid (AB-III-56, HU-239, IP-751, CPL 7075, CT-3, Resunab) is a cannabinoid derivative of the non-psychoactive THC metabolite 11-nor-9-carboxy-THC that shows useful analgesic and anti-inflammatory effects without causing a subjective “high”. It is being developed for the treatment of neuropathic pain and inflammatory conditions such as arthritis

and for the treatment of orphan life-threatening inflammatory diseases; HU-243 (AM-4056) is a cannabinoid which is a potent agonist at both the CB1 and CB2 receptors; HU-308 acts as a cannabinoid agonist and is highly selective for the CB2 receptor subtype. It has analgesic effects, promotes proliferation of neural stem cells, and protects both liver and blood vessel tissues against oxidative stress via inhibition of TNF- $\alpha$ ; HU-331 is a quinone anticarcinogenic synthesized from cannabidiol; HU-336 is a strongly antiangiogenic compound, it inhibits angiogenesis by directly inducing apoptosis of vascular endothelial cells without changing the expression of pro- and anti-angiogenic cytokines and their receptors; HU-345 (cannabinol quinone) is a drug that is able to inhibit aortic ring angiogenesis more potently than its parent compound cannabinol; CP 47,497 or (C7)-CP 47,497 is a cannabinoid receptor agonist drug.

The disclosure also provides methods for the biosynthesis of cannabinoids and for the use of a eukaryotic or prokaryotic expression system for the production of biosynthetic enzymes that can be used for the manufacture of cannabinoids and cannabinoid analogs. Yeast as well as eukaryotic and prokaryotic cells are suitable for the cloning and expression of the cannabinoid acid synthase enzymes and include without limitation E coli, yeast and baculovirus hosts. Thus, the present disclosure provides a method for the production of biosynthetic cannabinoids, such as for example THC and/or CBD, using cannabinoid acid synthase enzymes including, but not limited to, tetrahydrocannabinolic acid (THCA) synthase and cannabidiolic acid (CBDA) synthase. The disclosure further provides for the transdermal compositions as disclosed herein comprising, for example, biosynthetic CBD, alone or in combination with other active agents.

According to certain embodiments, transdermal compositions described herein are for the prevention and/or treatment of pain and/or inflammation. According to certain embodiments, transdermal compositions described herein are for the reduction in severity of pain and/or inflammation.

According to certain embodiments described herein, pharmaceutical composition or transdermal formulation of contains cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof. More preferably transdermal formulation may include cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs

thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof.

5 One embodiment of the present disclosure can be a transdermal drug delivery system which may include without any limitation to transdermal formulation, transdermal patches, topical formulation, microneedles, iontophoresis, metered dose transdermal spray.

10 Transdermal formulation which includes liquids for example without any limitation like solutions, suspensions, dispersions, emulsion. Transdermal formulation includes semisolids for example without any limitations like gels, ointments, emulsions, creams, suspension, paste, lotion, balm. Liquid formulation and/or gel formulation incorporated in transdermal patch is preferred. Transdermal formulations which includes matrix patch without any limitations like adhesive matrix patch, non-adhesive matrix patch, pressure sensitive adhesive matrix patch, extended release transdermal films, drug in adhesive matrix patch.

15 Without any limitation, transdermal patch may include all transdermal drug delivery systems stated in art preferably but not limited to reservoir patch, matrix patch, bilayer matrix patch, multilayer matrix patch, microreservoir patch, adhesive systems, transdermally applicable tape and other.

20 In certain embodiments of the present disclosure, a transdermal patch comprises transdermal formulation containing cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof,, alone or in combinations thereof contained in a reservoir or a matrix, and an adhesive which allows the transdermal patch to adhere to the skin, allowing the passage of the cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof from the transdermal patch through the skin of the patient. The transdermal delivery system can be occlusive, semi-occlusive or non-occlusive, and can be adhesive or non-adhesive.

30 The transdermal formulation comprising cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms

thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof can be incorporated within the patch and patch can be applied topically to the skin surface. The patch can be left on the subject for any suitable period of time. In certain embodiments, the transdermal patch is applied to the patient for, for example, about 4 hours, 8 hours, 12 hours, 16 hours, 24 hours, 48 hours, 60 hours, 72 hours, 84 hours, 108 hours, 120 hours, one day, two days, three days, four days, five days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12, days, 13, days, 14 days, one week, two weeks, three weeks, four weeks, one month, two months, three months, four months.

10 In some embodiments, the transdermal patches provide for a constant rate of delivery of the active components of the transdermal patch over a predetermined time period. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

15 In yet further embodiments, the transdermal patches described herein provide a steady absorption rate of the active components of the transdermal patches by the patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

20 In yet further embodiments, the transdermal patches described herein provide a constant blood serum level of the active components of the transdermal patches in a patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

25 In yet further embodiments, the transdermal patches described herein provide a plasma concentration of the active components of the transdermal patches in a therapeutic range in a patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

30 In some embodiments the matrix patch comprising cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof can be

prepared as transdermal matrix patch and matrix patch can be applied topically to the skin surface. The matrix patch can be left on the subject for any suitable period of time.

In some embodiments, the matrix patch provides for a constant rate of delivery of the active components of the matrix patch over a predetermined time period. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the matrix patch described herein provide a steady absorption rate of the active components of the matrix patch by the patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the matrix patch described herein provide a constant blood serum level of the active components of the matrix patch in a patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the matrix patch described herein provide a plasma concentration of the active components of the matrix patch in a therapeutic range in a patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the matrix patch described herein allow for reduced variability in dosage of active components in a patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

In yet further embodiments, the transdermal patches described herein allow for reduced variability in dosage of active components in a patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

The topical formulation stated in the art which include, for example without any limitation, semisolid such as ointment, cream, emulsion, micro emulsion, nano emulsion, paste, balms, gels, lotions, mousses. Liquids such as solutions, suspensions, micro suspension, nano



suspension, dispersions, nano dispersion etc. Sprays, aerosols, magma, etc. The topical formulation comprising cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof can be topically applied to the skin surface for transdermal delivery of cannabidiol.

The transdermal formulation and/or topical formulation of some embodiments of the present disclosure may include carriers or ingredients in effective amount either alone or in combinations thereof without any limitation to the following carriers or ingredients such as solvents, gelling agents, polymers, biodegradable polymers, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, tackifiers, surfactants, volatile chemicals, antioxidants, oxidants, fillers, pressure sensitive adhesives, chelating agents, complexing agents, excipients, material to prepare patch, material to prepare transdermal matrix patch, material to prepare reservoir patch etc.

Cannabidiol may be dissolved, suspended, dispersed or uniformly mixed in the above stated single carrier, mixture of carriers and combinations of carrier. Any combination of two or more drugs such as cannabidiol may be dissolved, suspended, dispersed or uniformly mixed in the above stated single carrier, mixture of carriers and combinations of carrier.

The desired optimum transdermal and/or topical formulation of cannabidiol alone or in combinations thereof may comprise without any limitation to following carriers as stated from example 1 to example 13 either alone or in combinations thereof.

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

## EXAMPLES

### Example 1

The transdermal formulation and/or topical formulation of the disclosure may comprise solvents known to those skilled in the art either alone or in combinations thereof without any limitation to following like alcohol C<sub>1</sub>-C<sub>20</sub> such as but not limited to (methanol, ethanol, isopropyl alcohol,

butanol, propanol etc.), polyhydric alcohols, glycols such as but not limited to (propylene glycol, polyethylene glycol, dipropylene glycol, hexylene glycol, butylene glycol, glycerine etc.), derivative of glycols, pyrrolidone such as but not limited to (N methyl 2- pyrrolidone, 2-pyrrolidone etc.), sulfoxides such as but not limited to (dimethyl sulfoxide, decymethylsulfoxide etc), dimethylisosorbide, mineral oils, vegetable oils, water, polar solvents, semi polar solvents, non polar solvents, volatile chemicals which can be used to make matrix patch such as but not limited to (ethanol, propanol, ethyl acetate, acetone, methanol, dichloromethane, chloroform, toluene, IPA), acids such as but not limited to acetic acid, lactic acid, levulinic acid, bases and others. More preferably in the range of 0.01% - 95% w/w or w/v.

10 In exemplary embodiments, formulations of the disclosure may comprise solvent(s) at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise solvent(s)

15 at a concentration of about 30 to 99%, of about 35% to 95%, about 40% to about 90% w/w. In exemplary formulations of the disclosure, the solvent(s) will represent approximately 1 wt% to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation.

20

### Example 2

The transdermal formulation and/or topical formulation of the disclosure may comprise gelling agents and/or thickening and/or suspending agents and/or polymers and/or pressure sensitive adhesives known to those skilled in the art either alone or in combinations thereof without any limitation to following like natural polymers, polysaccharides and its derivatives such as but not limited to (agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium, or sodium carageenan, tragacanth, xanthan, gum copal, chitosan, resin etc.), semisynthetic polymers and its derivatives such as without any limitation to cellulose and its derivatives (methylcellulose, ethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose etc.), synthetic polymers and its derivatives such as

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without any limitation to carboxyvinyl polymers or carbomers (carbopol 940, carbopol 934, carbopol 971p NF), polyethylene, and its copolymers etc, clays such as but not limited to (silicates, bentonite), silicon dioxide, polyvinyl alcohol, acrylic polymers (eudragit), acrylic acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyrrolidone copolymers such as but not limited to (PVP, Kollidon 30, poloxamer), isobutylene, ethyl vinyl acetate copolymers, natural rubber, synthetic rubber, pressure sensitive adhesives such as without any limitation silicone polymers such as but not limited to (bio psa 4302, bio-psa 4202 etc.), acrylic pressure sensitive adhesives such as but not limited to (duro – tak 87-2156, duro-tak 387-2287, etc.), polyisobutylene such as but not limited to (polyisobutylene low molecular weight, polyisobutylene medium molecular weight, polyisobutylene 35000 mw, etc), acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, all water and/or organic solvent swellable polymers, etc. More preferably in the range of 0.1% - 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise gelling agents and/or thickening and/or suspending agents at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise gelling agents and/or thickening and/or suspending agents at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the gelling agents and/or thickening and/or suspending agents will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation.

### 30 **Example 3**

The transdermal formulation and/or topical formulation of the disclosure may comprise penetration or permeation enhancers known to those skilled in the art either alone or in

combination thereof without any limitation to the following, such as sulfoxides, and similar chemicals such as but not limited to (dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide etc), 1,3-butanediol, azone, pyrrolidones such as but not limited to (N-methyl-2-pyrrolidone, 2-pyrrolidone etc.), esters, fatty acid esters such as but not limited to (propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, decyl oleate, glycerol monooleate, glycerol monolaurate, methyl laurate, lauryl laurate, lauryl lactate, oleyl oleate, ethyl oleate, methyl laurate, etc.), fatty acids such as but not limited to (capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid etc.), alcohols, fatty alcohols and glycols such as but not limited to (oleyl alcohol, nathanol, dodecanol, propylene glycol, glycerol etc.), ethers alcohol such as but not limited to (diethylene glycol monoethyl ether), urea, triglycerides such as but not limited to triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers such as but not limited to (brij, sodium lauryl sulfate, tween, polysorbate), terpene, terpenoids and all penetration or permeation enhancers referred in the book "Percutaneous Penetration Enhancers" (*Eric W. Smith, Howard I. Maibach, 2005. Nov, CRC press*). More preferably in the range of 0.01% - 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise permeation enhancer(s) at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise penetration or permeation enhancer(s) at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the permeation enhancer(s) will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation.

**Example 4**

The transdermal formulation and/or topical formulation of the disclosure may comprise plasticizers known to those skilled in the art either alone or in combination thereof without any limitation to following like glycerol and its esters, phosphate esters, glycol derivatives, sugar alcohols, sebacic acid esters, citric acid esters, tartaric acid esters, adipate, phthalic acid esters, triacetin, oleic acid esters and all the plasticizers which can be used in transdermal drug delivery system referred in the book "Handbook of Plasticizers" (*George Wypych, 2004, Chem Tec Publishing*). More preferably in the range of 0.01% - 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise plasticizer(s) at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise plasticizer(s) at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the plasticizer(s) will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation.

**Example 5**

The transdermal formulation and/or topical formulation of the disclosure may comprise emollients, humectants, skin irritation reducing agents and the similar compounds or chemicals known to those skilled in the art either alone or in combinations thereof without any limitation to following like petrolatum, lanolin, mineral oil, dimethicone, zinc oxide, glycerin, propylene glycol and others. More preferably in the range of 0.01% - 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise emollients, humectants, skin irritation reducing agents and the similar compounds or chemicals at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about

0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%,  
5 about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise emollients, humectants, skin irritation reducing agents and the similar compounds or chemicals at a concentration of about 1  
10 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the emollients, humectants, skin irritation reducing agents and the similar compounds or chemicals will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation.

#### 15 **Example 6**

The transdermal formulation and/or topical formulation of the disclosure may comprise solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds or chemicals known to those skilled in the art either alone or in combination thereof without any limitation to following like polysorbate (e.g., TWEEN®) such as but not limited to (polysorbate  
20 20, polysorbate 40, polysorbate 60, polysorbate 80 etc.), span such as but not limited to (span 80, span 20 etc.), surfactants such as (anionic, cationic, nonionic and amphoteric), propylene glycol monocaprylate type I, propylene glycol monocaprylate type II, propylene glycol dicaprylate, medium chain triglycerides, propylene glycol monolaurate type II, linoleoyl polyoxyl-6 glycerides, oleoyl-polyoxyl-6-glycerides, lauroyl polyoxyl-6-glycerides, ethyl  
25 oleate, polyglyceryl-3- dioleate, diethylene glycol monoethyl ether, propylene glycol monolaurate type I, polyglyceryl-3-dioleate, caprylocaproyl polyoxyl — 8 glycerides etc, cyclodextrins, LABRASOL® (a caprylocaproyl macrogolglyceride, Caprylocaproyl macrogol-8 glycerides EP, Caprylocaproyl polyoxyl-8 glycerides NF), and others. More preferably in the range of 0.01% 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure  
30 may comprise solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds or chemicals at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%,

about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds or chemicals at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds or chemicals will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation.

#### 15 **Example 7**

Different techniques and ingredients can be used to increase the stability and/or solubility of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof in formulation such as without any limitation to coating, encapsulation, microencapsulation, nanoencapsulation, lyophilization, chelating agents, complexing agents, etc.

#### **Example 8**

The transdermal formulation and/or topical formulation of the disclosure may comprise auxiliary pH buffering agents and pH stabilizers and similar compounds known to those skilled in the art which helps to maintain the appropriate pH of formulation preferably in the range of 4.0-8.0 either alone or in combination thereof without any limitation to following such as phosphate buffer, acetate buffer, citrate buffer, etc., acids such as but not limited to (carboxylic acids, inorganic acids, sulfonic acids, vinylogous carboxylic acids and others), base such as but not limited to (sodium hydroxide, potassium hydroxide, ammonium hydroxide, triethylamine, sodium carbonate, sodium bicarbonate) etc. More preferably in the range of 0.01% - 30% w/w

or w/v. In exemplary embodiments, formulations of the disclosure may comprise auxiliary pH buffering agents and pH stabilizers and similar compounds at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise auxiliary pH buffering agents and pH stabilizers and similar compounds at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the auxiliary pH buffering agents and pH stabilizers and similar compounds will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation. In certain embodiments, the pH of the formulation is maintained at about 4.0, about 4.5, about 5.0, about 5.5, about 6.0, about 6.5, about 7.0, about 7.5, or about 8.0. In certain embodiments, the pH of the formulation is maintained at a range of about 4.0 to about 8.0, about 4.5 to about 7.5, or about 5.0 to about 7.0.

### Example 9

The transdermal formulation and/or topical formulation of the disclosure may comprise antioxidants such as but not limited to (sodium metabisulfite, citric acid, ascorbic acid, BHA, BHT), oxidizing agents, stabilizers, discoloring agents, preservatives and similar compounds or chemicals known to those skilled in the art which helps to get a stable formulation can be used either alone or in combination thereof without any limitation. More preferably in the range of 0.01% - 50% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise antioxidants at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about



24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise antioxidants at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the antioxidants will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation.

#### 10 **Example 10**

The transdermal formulation and/or topical formulation of the disclosure may be formulated in ointment and/or cream base known to those skilled in the art.

#### **Example 11**

Materials to make the transdermal delivery system of the disclosure in patch form known to those skilled in the art, for example, such as but not limited to reservoir patch, transdermal matrix patch, and may include, such as but are not limited to polymers, copolymers, derivatives, backing film, release membranes, release liners, etc. either alone or in combinations thereof. Pressure sensitive adhesives (such as but not limited to silicone polymers, rubber based adhesives, acrylic polymers, acrylic copolymers, polyisobutylene, acrylic acid – isooctyl acrylate copolymer, hot melt adhesives, polybutylene, acrylic pressure sensitive adhesives, for example, Duro-Tak 9301, Duro-Tak 2516, Duro-Tak 2207, Duro-Tak 87-2516, Duro-Tak 87-4287, Duro-Tak 87-900A, Duro-Tak 87-9301 etc.), backing film (such as but not limited to ethylene vinyl acetate copolymers, vinyl acetate resins, polyurethane, polyvinyl chloride, metal foils, polyester, aluminized films, polyethylene, light resistant backing film, etc.), release membrane (such as but not limited to microporous polyethylene membrane, microporous polypropylene membrane, rate controlling ethylene vinyl acetate copolymer membrane etc.), release liners (such as but not limited to siliconized polyester films, fluoropolymer coated polyester film, polyester film, siliconized polyethylene terephthalate film, etc.), tapes, etc.

30

**Example 12**

The transdermal formulation and/or topical formulation of the invention may comprise fillers such as but not limited to colloidal silicon dioxide, lactose, mannitol, talc, titanium dioxide, etc. clays such as but not limited to kaolin, bentonite, etc. etc. either alone or in combinations thereof. More preferably in the range of 0.01% - 70% w/w or w/v.

**Example 13**

The transdermal formulation and/or topical formulation of the invention may comprise crystallization inhibitors, tackifiers, cross – linking agents, resins etc. either alone or in combinations thereof.

10 The transdermal formulation and/or topical formulation and/or transdermal delivery system of the disclosure may deliver at least therapeutic effective dose of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof.

15 Therapeutic effective cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof in human plasma required for treating and/or preventing pain and/or inflammation. Therapeutic effective cannabidiol, the free

20 base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof dose refers to the therapeutic concentration of of these forms of cannabidiol in human plasma required for treating and/or preventing pain and/or inflammation. Furthermore, the

25 precise therapeutic effective dose of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof in the transdermal formulation or topical formulation or transdermal delivery system or transdermal patch can be

30 determined by those skilled in the art based on factors such as but not limited to the patient's condition etc. The transdermal formulation or topical formulation or transdermal delivery

system or transdermal patch will be available in different dosage strengths and patch sizes in order to achieve optimum therapeutic outcome based on patient's requirement.

In yet another embodiment, the transdermal formulation and/or topical formulation and/or transdermal delivery system or transdermal patch of the disclosure may deliver at least  
5 therapeutic effective dose of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof. Therapeutic effective cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms  
10 thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof refers to the therapeutic concentration of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms  
15 thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof in human plasma required for treating and/or preventing and/or controlling the conditions and/or diseases and/or disorders associated with pain: Pain syndromes include, for example, headaches, migraine, tension headaches, cluster headaches, acute pain, chronic pain, neuropathic pain, nociceptive pain, central pain, inflammatory pain, fibromyalgia, drug-induced neuropathic pain, causalgia, complex regional pain syndrome types I and II, and reflex sympathetic dystrophy  
20 (RSDS), pain and wasting associated with AIDS, arthritis and rheumatism, migraines, and muscle spasticity associated with multiple sclerosis and paralysis, Autism Spectrum Disorder (ASD), and Autism Spectrum Disorder (ASD) for Pediatric patients, pain and/or inflammation of patients with liver disease, pain and/or inflammation of patients with kidney disease.

25 Another aspect of the present disclosure is directed to the use of the transdermal compositions as disclosed herein as a therapeutic agent for the prophylaxis and/or treatment of, for example, treating pain and/or inflammation for liver cancer patients, and to treat pain as a side effect of liver cancer medications and treatments. Another aspect of the present disclosure is directed to  
30 the use of the transdermal compositions as disclosed herein as a therapeutic agent for the prophylaxis and/or treatment of, for example, treating pain and/or inflammation for kidney cancer patients, and to treat pain as a side effect of kidney cancer medications and treatments. Another aspect of the present disclosure is directed to the use of the transdermal compositions as

disclosed herein as a therapeutic agent for the prophylaxis and/or treatment of, for example, treating pain and/or inflammation for cancer patients, and to treat pain as a side effect of cancer medications and treatments.

Another aspect of the present disclosure is directed to the use of the transdermal compositions as disclosed herein as a therapeutic agent for the prophylaxis and/or treatment of, for example, immunoinflammatory disorder. The term "immunoinflammatory disorder" encompasses a variety of conditions, including autoimmune diseases, proliferative skin diseases, and inflammatory dermatoses. Immunoinflammatory disorders result in the destruction of healthy tissue by an inflammatory process, dysregulation of the immune system, and unwanted proliferation of cells. Examples of immunoinflammatory disorders are acne vulgaris; acute respiratory distress syndrome; Addison's disease; allergic rhinitis; allergic intraocular inflammatory diseases, antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitis; ankylosing spondylitis; arthritis, asthma; atherosclerosis; atopic dermatitis; autoimmune hepatitis; autoimmune hemolytic anemia; autoimmune hepatitis; Behcet's disease; Bell's palsy; bullous pemphigoid; cerebral ischemia; chronic obstructive pulmonary disease; cirrhosis; Cogan's syndrome; contact dermatitis; COPD; Crohn's disease; Cushing's syndrome; dermatomyositis; diabetes mellitus; discoid lupus erythematosus; eosinophilic fasciitis; erythema nodosum; exfoliative dermatitis; fibromyalgia; focal glomerulosclerosis; focal segmental glomerulosclerosis; giant cell arteritis; gout; gouty arthritis; graft versus host disease; hand eczema; Henoch-Schonlein purpura; herpes gestationis; hirsutism; idiopathic cerato-scleritis; idiopathic pulmonary fibrosis; idiopathic thrombocytopenic purpura; immune thrombocytopenic purpura inflammatory bowel or gastrointestinal disorders, inflammatory dermatoses; lichen planus; lupus nephritis; lymphomatous tracheobronchitis; macular edema; multiple sclerosis; myasthenia gravis; myositis; nonspecific fibrosing lung disease; osteoarthritis; pancreatitis; pemphigoid gestationis; pemphigus vulgaris; periodontitis; polyarteritis nodosa; polymyalgia rheumatica; pruritus scroti; pruritis/inflammation, psoriasis; psoriatic arthritis; pulmonary histoplasmosis; rheumatoid arthritis; relapsing polychondritis; rosacea caused by sarcoidosis; rosacea caused by scleroderma; rosacea caused by Sweet's syndrome; rosacea caused by systemic lupus erythematosus; rosacea caused by urticaria; rosacea caused by zoster-associated pain; sarcoidosis; scleroderma; segmental glomerulosclerosis; septic shock syndrome; shoulder tendinitis or bursitis; Sjogren's syndrome; Still's disease; stroke-induced brain cell death; Sweet's disease; systemic lupus erythematosus; systemic sclerosis; Takayasu's arteritis; temporal arteritis; toxic epidermal necrolysis; transplant-

rejection and transplant-rejection-related syndromes; tuberculosis; type-1 diabetes; ulcerative colitis; uveitis; vasculitis; and Wegener's granulomatosis.

Another aspect of the present disclosure is directed to the use of the transdermal compositions as disclosed herein as a therapeutic agent for the prophylaxis and/or treatment of, for example, inflammation. Symptoms and signs of inflammation associated with specific conditions include: rheumatoid arthritis: pain, swelling, warmth and tenderness of the involved joints; generalized and morning stiffness; insulin-dependent diabetes mellitus-insulinitis; this condition can lead to a variety of complications with an inflammatory component, including: retinopathy, neuropathy, nephropathy; coronary artery disease, peripheral vascular disease, and cerebrovascular disease; autoimmune thyroiditis: --weakness, constipation, shortness of breath, puffiness of the face, hands and feet, peripheral edema, bradycardia; multiple sclerosis: spasticity, blurry vision, vertigo, limb weakness, paresthesias; uveoretinitis: decreased night vision, loss of peripheral vision; lupus erythematosus: joint pain, rash, photosensitivity, fever, muscle pain, puffiness of the hands and feet, abnormal urinalysis (hematuria, cylinduria, proteinuria), glomerulonephritis, cognitive dysfunction, vessel thrombosis, pericarditis; scleroderma: Raynaud's disease; swelling of the hands, arms, legs and face; skin thickening; pain, swelling and stiffness of the fingers and knees, gastrointestinal dysfunction, restrictive lung disease; pericarditis; renal failure; other arthritic conditions having an inflammatory component such as rheumatoid spondylitis, osteoarthritis, septic arthritis and polyarthritis: fever, pain, swelling, tenderness; other inflammatory brain disorders, such as meningitis, Alzheimer's disease, AIDS dementia encephalitis: photophobia, cognitive dysfunction, memory loss; other inflammatory eye inflammations, such as retinitis: decreased visual acuity; inflammatory skin disorders, such as, eczema, other dermatites (e.g., atopic, contact), psoriasis, burns induced by UV radiation (sun rays and similar UV sources): erythema, pain, scaling, swelling, tenderness; inflammatory bowel disease, such as Crohn's disease, ulcerative colitis: pain, diarrhea, constipation, rectal bleeding, fever, arthritis; asthma: shortness of breath, wheezing; other allergy disorders, such as allergic rhinitis: sneezing, itching, runny nose conditions associated with acute trauma such as cerebral injury following stroke-sensory loss, motor loss, cognitive loss; heart tissue injury due to myocardial ischemia: pain, shortness of breath; lung injury such as that which occurs in adult respiratory distress syndrome: shortness of breath, hyperventilation, decreased oxygenation, pulmonary infiltrates; inflammation accompanying infection, such as sepsis, septic shock, toxic shock syndrome: fever, respiratory failure, tachycardia, hypotension, leukocytosis; other

inflammatory conditions associated with particular organs or tissues, such as: (i) nephritis (e.g., glomerulonephritis): oliguria, abnormal urinalysis; (ii) inflamed appendix: fever, pain, tenderness, leukocytosis; (iii) gout: -pain, tenderness, swelling and erythema of the involved joint, elevated serum and/or urinary uric acid; (iv) inflamed gall bladder: -abdominal pain and tenderness, fever, nausea, leukocytosis; (v) congestive heart failure: shortness of breath, rales, peripheral edema; (vi) Type II diabetes: end organ complications including cardiovascular, ocular, renal, and peripheral vascular disease; (vii) lung (pulmonary) fibrosis: hyperventilation, shortness of breath, decreased oxygenation; (viii) vascular disease, such as atherosclerosis and restenosis: pain, loss of sensation, diminished pulses, loss of function; and (ix) alloimmunity leading to transplant rejection: pain, tenderness, fever. Another aspect of the present disclosure is directed to the use of the transdermal compositions as disclosed herein as a therapeutic agent for the prophylaxis and/or treatment of, for example, Autism Spectrum Disorder (ASD), and Autism Spectrum Disorder (ASD) for Pediatric patients.

The transdermal formulation or transdermal patch of cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof preferably but not limited to can be applied to the skin surface in any of the following dosage regimens such as once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in a 8 to about 13 days, once in two weeks, once in 15 days.

#### Example 14

Synthetic cannabidiol (CBD) formulations for transdermal delivery ((Formulation Nos. 001, 002, 003, 004, and 005) were prepared by mixing ingredients as shown in Table 1:

**Table 1: Transdermal Synthetic Cannabidiol formulations**

<b>Ingredients</b>	<b>001</b> <b>(% W/W)</b>	<b>002</b> <b>(% W/W)</b>	<b>003</b> <b>(% W/W)</b>	<b>004</b> <b>(% W/W)</b>	<b>005</b> <b>(% W/W)</b>
CBD	9.35	9.06	9.34	9.09	9.13

PG	90.65	45.51	45.17	45.54	45.33
Hexylene Glycol		45.43			
1,3 Butanediol			45.49		
PEG-400				45.37	
Dipropylene Glycol					45.53

Abbreviations: PG = propylene glycol; CBD = Cannabidiol; PEG-400: Polyethylene Glycol-400.

All of the components from Table 1, with the exception of the CBD, were mixed together with stirring for 18 hours. Next, the CBD was added into the excipient mixture to prepare the final transdermal formulations.

The prepared transdermal formulations were then subjected to a flux measurement test as follows. Human cadaver skin, stored at -80°C, was thawed at room temperature in phosphate buffered saline (PBS), and visually inspected for defects before using in the study. Transdermal flux was then measured using standard Franz diffusion cells composed of a cylindrical donor compartment and a separate water jacketed cylindrical receptor compartment with the volume of 13 mL. The human cadaver skin was clamped between the two compartments with the dermis side facing toward the receptor compartment. The donor compartment was filled with the transdermal CBD formulations prepared as described above. The receptor compartment was filled with receptor medium, held at constant temperature, and constantly stirred to collect the CBD as it diffuses through the skin and into receptor compartment. It is important to confirm that the receptor fluid is always in contact with the skin. The receptor compartment was emptied at 24 hr intervals for assay of CBD and replaced with fresh receptor solution. In order to maintain the sink condition in receptor compartment, it is important to keep the CBD concentration in receptor compartment less than 10% of its solubility. The experimental conditions are provided in Table 5:

<b>Table 2. Experimental Condition for In-vitro Permeability testing</b>	
Receiving Media	De-ionized water + 0.5% Brij-O(20) +0.01% Sodium Azide
Receiving Media Volume (mL)	13
Sample Volume (mL)	13
Sampling Interval (hr)	24,48,72,96,120,144
Franz-cell diffusion area (sqcm)	1.76
Membrane Type	Human Cadaver Skin

Flux of CBD through the human cadaver skin was measured for a minimum period of 144 Hrs (6 days) and results of the flux measurement are provided in Table 6.

**Table 3. CBD Flux Results**

	<b>001</b>	<b>002</b>	<b>003</b>	<b>004</b>	<b>005</b>
Total Amount of CBD Permeated at 144 hrs (ng/cm <sup>2</sup> )	85795	167045	150000	59091	166477
Flux (ng/cm <sup>2</sup> /hr)	338.5	1160.03	1041.66	410.35	1156.09

5 **Example 15**

Additional synthetic Cannabidiol (CBD) formulations for transdermal delivery (Formulation Nos. 006 through 014) were prepared by mixing ingredients as shown in Table 4:



**Table 4: Transdermal Synthetic Cannabidiol formulation no. 015 to 022**

<b>Ingredients</b>	<b>015</b>	<b>016</b>	<b>017</b>	<b>018</b>	<b>019</b>	<b>020</b>	<b>021</b>	<b>022</b>
	<b>(% W/W)</b>	<b>(% W/W)</b>	<b>(% W/W)</b>	<b>(% W/W)</b>	<b>(% W/W)</b>	<b>(% W/W)</b>	<b>(% W/W)</b>	<b>(% W/W)</b>
CBD	9.95	9.64	9.77	9.98	9.98	9.64	9.87	9.52
PG	42.70	42.58	42.51	42.51	42.02	42.45	42.47	42.34
1,3 Butanediol	42.36	42.48	42.40	42.63	42.66	42.77	42.50	42.64
Tween-20	4.99							
Triacetin		5.30						
PGML			5.32					
OA				4.88				
ML					5.34			
IPM						5.16		
IPP							5.04	
Labrasol								4.91

Abbreviations: CBD= Cannabidiol; PGML: Propylene glycol monolaurate; PG = propylene glycol; OA= Oleyl Alcohol; ML= Methyl Laurate; IPM= Isopropyl Myristate; IPP: Isopropyl Palmitate.

5

Synthetic Cannabidiol formulations for transdermal delivery (006-014) were prepared by the same procedure described in Example 1. Flux measurement was also performed as described in Example 1. The experimental conditions are the same as provided in Table 2 of Example 1.

Flux of CBD through the human cadaver skin was measured for a minimum period of 48 Hrs and results of the flux measurement experiments are provided in Table 5.

**Table 5. CBD Flux Results**

	Formulation No.							
	015	016	017	018	019	020	021	022
Total Amount of CBD Permeated at 48 hrs (ng/cm <sup>2</sup> )	25791	22851	29098	37085	37351	45008	59954	21524
Flux (ng/cm <sup>2</sup> /hr)	537.31	476.06	606.20	772.60	778.14	937.67	1249.04	448.41

5 **Example 16**

Additional synthetic cannabidiol (CBD) formulations for transdermal delivery patches (Formulation Nos. 015 to 018) were prepared by mixing ingredients as shown in Table 6:

**Table 6: Transdermal Synthetic cannabidiol formulation nos. 023 to 026**

Ingredients	023	024	025	026
	(% W/W)	(% W/W)	(% W/W)	(% W/W)
CBD	2.0	2.0	2.0	2.0
PG	27.8	27.8	27.8	27.8
1,3 Butane diol	27.8	27.8	27.8	27.8
Durotak 9301	42.4			

Durotak 2516		42.4		
Durotak 2207			42.4	
Silicone Adhesive				42.4

To prepare a transdermal patch containing synthetic cannabidiol, all of the components from Table 6, with the exception of the CBD, were mixed together with stirring for 18 hours. Next, the CBD was added 30 minutes before spreading the formulation. The formulation was spread using a commercial benchtop spreader. Specifically, the formulation matrix is evenly spread onto an 8x14 inch sheet of release liner (such as 3M 9744) to a thickness of 0.5mm. The sheet is then placed in an oven at 100° F for one hour to evaporate off the ethyl acetate and ethanol adhesive solvent. An opaque backing membrane (such as 3M 9730 NR film) with low permeability to oxygen, for inhibition of photo and oxidative degradation, is then carefully applied to the sheet by hand to avoid formation of bubbles and voids. A circular die (1.5 inches diameter) was used to cut patches (7 cm<sup>2</sup>) for subsequent studies.

The general procedure for flux measurements of transdermal formulations in the examples above was as follows. The human cadaver skin, stored at -80 °C, was thawed at room temperature in PBS, and visually inspected for defects before use. Transdermal flux was measured using standard Franz diffusion cells composed of a cylindrical donor compartment and a separate water jacketed cylindrical receptor compartment with the volume of 13 mL. The human cadaver skin was clamped between the two compartments with the dermis side facing toward the receptor compartment. The general procedure for flux measurement of the transdermal adhesive patch is as follows. The release liner is peeled off the patch and the adhesive surface is applied to a piece of human cadaver skin. The transdermal patch was adhered to the skin with the patch on the side of the skin in contact with the donor compartment. The receptor compartment was filled with receptor medium, held at constant temperature, and constantly stirred to collect the CBD as it diffuses from the adhered patch, through the skin and into receptor compartment. It was confirmed that the receptor fluid was always in contact with the skin. The receptor compartment was emptied at 24 hour intervals for assay of CBD and replaced with fresh receptor solution. In order to maintain the sink condition in receptor compartment, the CBD concentration in the receptor compartment was maintained at less than 10% of its solubility. The experimental conditions are the same as provided in Table 2 of Example 15.

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15

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

20

## CLAIMS

## WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co-crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof, in a dosage form for transdermal delivery.  
5
2. The pharmaceutical composition of claim 1 comprising cannabidiol, the free base thereof, salts thereof, isomers thereof, amorphous forms thereof, crystalline forms thereof, co crystalline forms thereof, prodrugs thereof, analogs thereof, derivatives thereof, synthetic forms thereof, biosynthetic forms thereof, active metabolites thereof, alone or in combinations thereof in the range of 0.01% - 95% w/w or w/v.  
10
3. The pharmaceutical composition of any one of claims 1 to 2 formulated as transdermal liquid formulation, transdermal semisolid formulation, or transdermal matrix patch formulation.
4. The pharmaceutical composition of any one of claims 1 to 3 further comprising carriers or ingredients in effective amount selected from the group consisting of solvents, gelling agents, polymers, pressure sensitive adhesives, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, fillers, tackifiers, cross-linking agents, resins, and combinations thereof.  
15  
20
5. The pharmaceutical composition of any one of claims 1 to 4 further comprising carriers or ingredients in effective amount selected from the group consisting of solvents, gelling agents, polymers, pressure sensitive adhesives, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, fillers, tackifiers, cross – linking agents, resins, and combinations thereof in the range of 0.01% - 95% w/w or w/v.  
25
6. The pharmaceutical composition of any one of claims 1 to 5 wherein the carrier is present in the range of 0.01% - 99.8% w/w or w/v.
7. The pharmaceutical composition of any one of claims 1 to 6 which is formulated as a transdermal patch.  
30

8. The pharmaceutical composition of any one of claims 1 to 7 formulated as a transdermal patch, wherein the transdermal patch is selected from the group such as to reservoir patch, a microreservoir patch, a liquid reservoir patch, a mucoadhesive patch, a matrix patch wherein matrix patch is selected from the group such as a pressure sensitive adhesive matrix patch,  
5 extended release transdermal film, drug in adhesive matrix patch.
9. The pharmaceutical composition of any one of claims 1 to 8 indicated for treatment of conditions selected from the group consisting of headaches, migraine, tension headaches, cluster headaches, acute pain, chronic pain, neuropathic pain, nociceptive pain, central pain,  
10 inflammatory pain, fibromyalgia, drug-induced neuropathic pain, causalgia, complex regional pain syndrome types I and II, and reflex sympathetic dystrophy (RSDS), pain and wasting associated with AIDS, arthritis and rheumatism, migraines, and muscle spasticity associated with multiple sclerosis and paralysis, Autism Spectrum Disorder (ASD) and Autism Spectrum Disorder (ASD) for Pediatric patients, pain and/or inflammation of patients with liver disease,  
15 pain and/or inflammation of patients with kidney disease, pain and/or inflammation for liver cancer patients, treating pain and/or inflammation for kidney cancer patients, pain and/or inflammation for cancer patients, and combinations thereof.
10. The pharmaceutical composition of any one of claims 1 to 9 which is formulated as the transdermal formulation is applied to the patient for a time selected from the group consisting of, for example, about 4 hours, 8 hours, 12 hours, 16 hours, 24 hours, 48 hours, 60 hours, 72  
20 hours, 84 hours, 108 hours, 120 hours, one day, two days, three days, four days, five days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12, days, 13, days, 14 days, one week , two weeks, three weeks, four weeks, one month, two months, three months, and four months.
11. The pharmaceutical composition of any one of claims 1 to 10 which may be formulated as microneedles.
- 25 12. The pharmaceutical composition of any one of claims 1 to 11, wherein said CBD or derivative thereof is produced by a synthetic route or biosynthetic route.
13. A pharmaceutical composition comprising cannabidiol (CBD), in a dosage form for transdermal delivery wherein the pharmaceutical composition comprises:
- about 9% to about 12% w/w of CBD;

- optionally, about 30% to about 99% solvent;
- optionally, about 1% to about 20% penetration enhancer(s),

wherein the pH of the composition is maintained at approximately 4.0 to 8.0.

5 14. The pharmaceutical composition of claim 13 formulated as transdermal liquid formulation, transdermal semisolid formulation, or transdermal polymer matrix formulation.

10 15. The pharmaceutical composition of any one of claims 13 to 14 further comprising carriers or ingredients in effective amount selected from the group consisting of gelling agents, polymers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, and combinations thereof.

15 16. The pharmaceutical composition of any one of claims 13 to 15 further comprising carriers or ingredients in effective amount selected from the group consisting of gelling agents, polymers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, and combinations thereof in the range of 0.01% - 95% w/w or w/v.

17. The pharmaceutical composition of any one of claims 13 to 16 which is formulated as a transdermal patch.

20 18. The pharmaceutical composition of any one of claims 13 to 17 formulated as a transdermal patch, wherein the transdermal patch is selected from the group such as to reservoir patch, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, extended release transdermal film a liquid reservoir system, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, a mucoadhesive patch, and combinations thereof.

25 19. The pharmaceutical composition of any one of claims 13 to 18 which is formulated as the transdermal formulation which can be administered in a dosage regimen selected from the group consisting of once daily, twice daily, three times a day, once in 1-8 hrs, once in 1-24 hrs, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in a 8 to about 13 days, once in two weeks, once in 15 days to about 30 days.



20. The pharmaceutical composition of any one of claims 13 to 19 which may be formulated as microneedles.
21. The pharmaceutical composition of any one of claims 13 to 20, wherein said CBD or derivative thereof is produced by a synthetic route.
- 5 22. A method for the treatment and/or prevention and/or decrease and/or control of pain and/or inflammation comprising:
- selecting a patient in need of treatment and/or prevention and/or control of pain and/or inflammation;
  - topically applying the pharmaceutical composition of any one of claim 1 - 21.
- 10 23. The method of claims 22, wherein the topical application of a transdermal patch for the treatment and/or prevention and/or control of pain and/or inflammation is selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days.
- 15 24. The method of any one of claims 22 to 23 further providing a constant rate of delivery of the active components of the transdermal patch over a time period.
25. The method of any one of claims 22 to 24 further providing a steady absorption rates of the active components of the transdermal patch over a time period.
26. The method of any one of claims 22 to 25 further achieving a constant blood serum levels of the active components of the transdermal patch over a time period.
- 20 27. The method of any one of claims 22 to 26 further achieving a reduced variability in dosage of the active components of the transdermal patches over a time period.
28. The method of any one of claims 22 to 27 further providing a plasma concentration of the active components of the transdermal patch in a therapeutic range over a period of time.
- 25 29. The method of any one of claims 22 to 28, wherein the topical application of a transdermal patch is for the treatment and/or prevention and/or control of pain and/or inflammation of indications selected from the group consisting of headaches, migraine, tension headaches, cluster headaches, acute pain, chronic pain, neuropathic pain, nociceptive pain, central pain,

inflammatory pain, fibromyalgia, drug-induced neuropathic pain, causalgia, complex regional pain syndrome types I and II, and reflex sympathetic dystrophy (RSDS), pain and wasting associated with AIDS, arthritis and rheumatism, migraines, and muscle spasticity associated with multiple sclerosis and paralysis, Autism Spectrum Disorder (ASD) and Autism Spectrum Disorder (ASD) for Pediatric patients, pain and/or inflammation of patients with liver disease, 5 pain and/or inflammation of patients with kidney disease, pain and/or inflammation for liver cancer patients, treating pain and/or inflammation for kidney cancer patients, pain and/or inflammation for cancer patients, and combinations thereof.

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## INTERNATIONAL SEARCH REPORT

International application No.

**PCT/IB2020/059608**

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC: <b>A61K 31/05</b> (2006.01), <b>A61K 9/00</b> (2006.01), <b>A61K 9/70</b> (2006.01), <b>A61M 37/00</b> (2006.01), <b>A61P 29/00</b> (2006.01), <b>C07C 39/23</b> (2006.01).  According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>  Minimum documentation searched (classification system followed by classification symbols) IPC: A61K 31/05(2006.01), A61K 9/00(2006.01), A61K 9/70(2006.01), A61M 37/00(2006.01), A61P 29/00(2006.01), C07C 39/23(2006.01).  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) QUESTEL(FAMPAT)/ STN(CAPLUS)/GOOGLE PATENT+SCHOLAR:Cannabinoid/Cannabidiol/CBD; transdermal/ skin penetration /patch/microneedle*.		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/026144 A1 STINCHCOMB et al. 03 March 2011 (03-03-2011) <b>D1:</b> See paragraph 0006, 0008, 0012-0015, 0021-0022, 0025, 0033, 0039, 0072, 0086-0098, 0111 00122; examples 11; claims 5, 7-11.	1-29
X	CA3075668 A1 YU et al. 21 March 2019 (21-03-2019) <b>D2:</b> See paragraphs 0002, 0027-0030, 0033, 0040-0041; examples 3-8, 11-13.	1-10, 12-19, and 21-29
X	US2010/0273895 A1 STINCHCOMB et al. 28 October 2010 (28-10-2010) <b>D3:</b> See paragraphs 0020, 0022, 0034-0035, 0039, 0043-0044, 0053, 0061-0068, 0071, 0073, 0082-0083, 0096, 00103, 00109, 00111, 00113, 00118, 00143, 00147.	1-10, 12, 21-29
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.		
<input checked="" type="checkbox"/> See patent family annex.		
* "A" "D" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance document cited by the applicant in the international application earlier application or patent but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"I" "X" "Y" "&" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
Date of the actual completion of the international search 30 November 2020 (30-11-2020)		Date of mailing of the international search report 01 February 2021 (01-02-2021)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476		Authorized officer  Christine Bourque (819) 576-2951

## INTERNATIONAL SEARCH REPORT

International application No.

**PCT/IB2020/059608**

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/140321 A1 WITOWSKI et al. 18 July 2019 (18-07-2019) <b>D4:</b> See paragraphs 0015, 0017, 0019, 0022, 0027-0028, 0034-0036, 0059, 0061, 0075; examples 2, 4, 5.	1-10, 12-19, 21-29
X	US2017/0071870 A1 WEIMANN, L. 16 March 2017 (16-03-2017) <b>D5:</b> See paragraphs 0020, 0024-0025, 0027, 0029-0030, 0041, 0049, 0055, 0068-0069, 0089, 0109, figures; claims 4-6).	1-10, 12-19, 21-29

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

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