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(54) Title: PHARMACEUTICAL COMPOSITION AND METHOD FOR TREATING SEIZURE DISORDERS

(57) Abstract: The present disclosure relates to the transdermal administration of cannabidiol (CBD) for the reduction of seizure frequency in the treatment of "treatment-resistant epilepsy" (TRE).

PHARMACEUTICAL COMPOSITION AND METHOD FOR TREATING SEIZURE DISORDERS:

SPECIFICATION

This application claims priority to U.S. Serial No. 17/225,654 filed April 08, 2021, which is a continuation in part of U.S. Serial No. 17/065,851, filed October 8, 2020, which claims priority to U.S. Serial Number 62/913,874, filed October 11, 2019, the entireties of which are incorporated herein by reference.

BACKGROUND

The present disclosure relates to the transdermal administration of cannabidiol (CBD) for the reduction of seizure frequency in the treatment of, for example, "treatment-resistant epilepsy" (TRE), including treatment resistant pediatric epilepsy, or Tuberous Sclerosis Complex (TSC), Dravet Syndrome and Lennox-Gastaut Syndrome. In one embodiment the patients suffering from TRE are children and young adults. CBD appears particularly effective when the TRE is Dravet syndrome; myoclonic absence seizures or febrile infection related epilepsy syndrome (FIRES). In these indications the reduction of total convulsive frequency has surprisingly been shown to be greater than 50%, through 70% to greater than 90% in a significant number of patients. Indeed a significant number of patients have been seizure free at the end of three months treatment.

In certain embodiments as disclosed herein the CBD used is in the form of a highly purified extract of *cannabis* such that the CBD is present at greater than, for example, 98% of the total extract (w/w) and the other components of the extract are characterised. In particular tetrahydrocannabinol (THC) has been substantially removed to a level of not more than, for example, 0.15% (w/w). In certain embodiments as disclosed herein it is a synthetically produced CBD (See U.S. Patent No. 10,195,159).

The CBD may be used concomitantly with one or more other anti-epileptic drugs (AED). Alternatively the CBD may be formulated for administration separately, sequentially or simultaneously with one or more AED or the combination may be provided in a single dosage form. Where the CBD is formulated for administration separately, sequentially or simultaneously it may be provided as a kit or together with instructions to administer the one or more components in the manner

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 cannabinodis have been extracted from the plant. From

all of the phytochemicals, only tetryhydrocannbinol (THC) showed significant psychoactive effect. A number of research papers have been published on THC due to its psychoactive and therapeutic 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, antimicrobial, type-2 related metabolic disorder, decrease 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. FDA approved Marinol and Syndros contains delta 9-THC, which currently using in pain and/or inflammation 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.

Lennox-Gastaut Syndrome (LGS) is a severe form of epilepsy that typically becomes apparent during infancy or early childhood. Onset of LGS is usually between 2-7 years with a peak onset between 3 to 5 years. Affected Children experience several different types of seizures most commonly atonic, tonic and atypical absence seizures.

In 2018, GW Pharmaceutical received FDA approval for its fast track designated drug “Epidiolex” (Cannabidiol) to treat two orphan conditions in children- LGS and Dravet syndrome (DS).

Epidiolex contains naturally derived cannabidiol from Sativex plant in oral solution form (100 mg/ml). According to the FDA Label, the recommended dose of Epidiolex described in Table 1.

Table 1: Recommended dose of Epidiolex for LGS and DS[1]

Recommended Dose	Avg wt of 2 years old Child (kg)	Avg wt of 7-year-old Child (kg)	Total Dose (2-7 yrs)
5 mg/kg/day	12.25 (12-12.5 kg)	22.7 Kg (22.4-22.9 Kg)	61.25-113.5 mg/day
10 mg/kg/day			122.5-227 mg/day

20 mg/kg/day			245- 454 mg/day

Epidiolex has mainly five dose dependent side effects: 1) Hepatocellular injury, 2) Somnolence and sedation, 3) Suicidal Behavior and Ideation, 4) Hypersensitivity Reaction and 5) withdrawal of antiepileptic drugs[1].

The discontinuation rate of Epidiolex is high due to hepatocellular injury and somnolence and sedation side effects. During clinical trial 1.3% patient taking 10mg/kg/day and 5.9% patient taking 20 mg/kg/day Epidiolex discontinue due to hepatocellular injury. Furthermore, there were 0% patient taking dose of 10 mg/kg/day and 3% patient taking 20 mg/kg/day dropped out due to somnolence and sedation. Table 2 provides the dose dependent side effects due to Epidiolex[1].

Table 2: Dose dependent Adverse effects: (FDA)[1]

Adverse Reactions	**EPIDIOLEX**		**Placebo**
	10 mg/kg/day	**20 mg/kg/day**	
	N=75 %	**N=238 %**	**N=227 %**
Hepatic Disorders			
Transaminases elevated	8	16	3
Hepatocellular Injury	1	17	0
Gastrointestinal Disorders			
Decreased appetite	16	22	5
Diarrhea	9	20	9
Weight decreased	3	5	1
Gastroenteritis	0	4	1
Abdominal pain, discomfort	3	3	1
Nervous System Disorders			
Somnolence	23	25	8
Sedation	3	6	1
Lethargy	4	8	2
Fatigue, malaise, asthenia	11	12	4

Insomnia, sleep disorder, poor quality sleep	11	5	4
Irritability, agitation	9	5	2
Aggression, anger	3	5	<1
Drooling, salivary hypersecretion	1	4	<1
Gait disturbance	3	2	<1
Infections			
Infection, all	41	40	31
Infection, viral	7	11	6
Pneumonia	8	5	1
Infection, fungal	1	3	0
Infection, other	25	21	24
Other			
Rash	7	13	3
Hypoxia, respiratory failure	3	3	1

These side effects are dose related and therefore it is required to monitor the patients and reduced the dose if needed.

Many orally delivered drugs irritate the gastrointestinal mucosa and a large number, including CBD, undergo extensive 'first-pass' inactivation by the liver. The compositions and methods of the disclosure are directed to drug delivery directly to the systemic circulation via application to the skin, and thus the compositions and methods of the disclosure overcome the problems gastrointestinal tract irritation and liver first pass metabolism because the active agent avoids being metabolized by the liver after absorption, and also avoids gastrointestinal irritation since it is not orally administered.

However, the TDDS system is delivering the drug molecule constantly at defined input rate. Instead of peaks and valley in plasma concentrations like in oral delivery, the TDDS maintain the average plasma concentration at predetermined constant input rate.

While there are patents available on cannabidiol, the shortcomings of these disclosures are overcome by the compounds and methods as disclosed herein. For example, US 9375417 fails to provide any in-vitro or in-vivo data. US 6328992 discloses reservoir and adhesive matrix

patches, however, these examples contain mixture of cannabinoids (such as delta-8-THC, delta-9-THC, cannabidiol, and cannabinol) instead of cannabidiol only. The THC is a psychoactive agent and an addictive substance, so the utility is problematic.

In addition, US 8449908 discloses delivery of the cumulative amount of 60600 ng in 48 hrs through the human cadaver skin. This amount represents the flux of 1925 ng/sqcm/hr. The patch area can be calculated using following equation.

In-Vitro Flux (ug/sqcm/hr) = (Css (ug/l)*CL (L/hr)/ Patch Area (Sqcm)

Patch Area (Sqcm) = (Css (ug/l) * CL (L/ hr)/ In-Vitro Flux (ug/sqcm/hr)

= (10*74.4)/1.925

= 386 sqcm

In order to deliver 5mg/kg/day cannabidiol, the patient has to apply formulation on 386 sqcm surface area. This is an impractical patch size for any Transdermal drug delivery system (TDDS). Furthermore, the '908 patent discloses using receiving media PBS:PEG-400 (60:40). It is very well known that PEG-400 is permeability enhancer and by incorporating it in receiving media, the skin is damaged from the dermis side, this can also increase the permeation amount due to unviable skin samples.

There is a need for an improved drug delivery system of cannabidiol which can overcome the drawbacks associated with oral and IV route. Transdermal delivery of highly purified cannabidiol can address the challenges associated with oral and IV drug delivery as set forth herein. The current invention addresses all the above drawbacks and provides a real-world utility. Furthermore, the current disclosed herein is the use of a synthetic version of cannabidiol which is manufactured in more controlled environment than the botanical source of the same. The synthetic version of cannabidiol provides more permeability as compared to adulterated versions 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.

BRIEF SUMMARY

The disclosure provides compositions and methods for the treatment and/or prevention and/or control of seizure disorders, using transdermal drug delivery. 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 CBD which is currently administered several times a day. Through transdermal delivery, transdermal compositions or transdermal formulations or transdermal patch of highly purified CBD, 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 highly purified CBD, patients can have the therapeutic effect of the drug for extended period of time without drastic changes in drug plasma concentration.

When a medication is orally administered, its bioavailability generally decreases due to incomplete absorption and first-pass metabolism and may vary from patient to patient. The compositions of the disclosure overcome these problems because in transdermal delivery, active agent is delivered directly into systemic circulation through the skin, and it escapes the first pass hepatic metabolism therefore to achieve the desired therapeutic activity less drug is required, resulting into less adverse effects or side effects. Cannabinol has high lipid solubility and after oral administration undergoes hepatic first pass metabolism, therefore of the administered dose only 10% - 20% reaches systemic circulation, thus as compared to oral dose, transdermal delivery a small dose of cannabidiol can give the desired therapeutic effects at a lower dose than oral.

Furthermore, 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.

Therefore, transdermal delivery can overcome the drawbacks of injections which are often painful and requires medical supervision.

With respect to cannabidiol it is expected that interpatient variability in pharmacologic response will be less with transdermal delivery as drug plasma concentration can be controlled by controlling the rate of drug delivery from transdermal composition or transdermal patch. With transdermal delivery a small amount of cannabidiol can be delivered for longer duration than oral administration. Transdermal formulations of cannabidiol also provide more abuse deterrence than immediate release dosage forms.

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.

As per above stated reasons for the treatment and/or prevention and/or control of seizure disorders, transdermal delivery can provide patient friendly, simplified and convenient therapeutic regimen over traditional delivery systems. Transdermal delivery can reduce the dosing frequency of highly purified CBD. 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.

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.

The disclosure provides a pharmaceutical composition comprising at least about 90% (w/w) cannabidiol (CBD), in a dosage form for transdermal delivery. The disclosure provides a pharmaceutical composition which comprises at least about 95% CBD. The disclosure provides a pharmaceutical composition which comprises at least about 98% CBD. The disclosure provides a pharmaceutical composition which comprises at least about 99% CBD. The disclosure provides a pharmaceutical composition formulated as 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 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, 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 the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder disorders include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions. 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. The disclosure provides a pharmaceutical composition co-administered with at least one additional an anti-epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin. The disclosure provides a pharmaceutical composition further comprising at least one additional an anti-epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

The disclosure provides a method for the treatment and/or prevention and/or control of seizure disorder in a patient comprising: selecting a patient in need of treatment and/or prevention and/or control of seizure disorder; topically applying the pharmaceutical composition as disclosed herein. The disclosure provides a method for the treatment and/or prevention and/or control of seizure disorder in a patient wherein the seizure disorder includes complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions. The disclosure provides a method for the treatment and/or prevention and/or control of seizure disorder in a patient wherein the topical application of a transdermal patch for the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions 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 seizure disorder in a patient 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 seizure disorder in a patient 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 seizure disorder in a patient 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 seizure disorder in a patient 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 seizure disorder in a patient 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 a highly purified extract of cannabis which comprises at least about 90% (w/w) cannabidiol (CBD), in a dosage form for transdermal delivery. The disclosure provides a pharmaceutical composition wherein the highly purified extract of cannabis comprises at least about 95% CBD. The disclosure provides a pharmaceutical composition wherein the highly purified extract of cannabis comprises at least about 98% CBD. The disclosure provides a pharmaceutical composition wherein the highly purified extract of cannabis comprises at least about 99% CBD. The disclosure provides a pharmaceutical composition formulated as 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 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, 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 the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder disorders include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions. 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. The disclosure provides a pharmaceutical composition co-administered with at least one additional an anti-epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin. The disclosure provides a pharmaceutical composition further comprising at least one additional an anti-epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

The disclosure provides a pharmaceutical composition comprising a highly purified extract of cannabis which comprises at least about 90% (w/w) cannabidiol (CBD), in a dosage form for transdermal delivery wherein the pharmaceutical composition comprises: about 9% to about 12% w/w of the highly purified 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 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 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% - 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 pressure sensitive adhesive patch, a mucoadhesive patch, and combinations thereof. The disclosure provides a pharmaceutical composition indicated for the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder disorders include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and

progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions. 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. The disclosure provides a pharmaceutical composition co-administered with at least one additional an anti-epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin. The disclosure provides a pharmaceutical composition further comprising at least one additional an anti-epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

The disclosure provides a method for the treatment and/or prevention and/or control of seizure disorder in a patient comprising: selecting a patient in need of treatment and/or prevention and/or control of seizure disorder; topically applying the pharmaceutical composition as disclosed herein. The disclosure provides a method wherein the seizure disorder includes complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions. The disclosure provides a method wherein the topical application of a transdermal patch for the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic),

neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions 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 further providing a constant rate of delivery of the active components of the transdermal patch over a time period. The disclosure provides a method further providing a steady absorption rates of the active components of the transdermal patch over a time period. The disclosure provides a method further achieving a constant blood serum levels of the active components of the transdermal patch over a time period. The disclosure provides a method further achieving a reduced variability in dosage of the active components of the transdermal patches over a time period. The disclosure provides a method 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 transdermal and/or topical pharmaceutical composition comprising: about 0.1% to about 20% of an active agent selected from the group consisting of synthetic cannabidiol, natural cannabidiol, and combinations thereof; about 35% to about 99% of at least one adhesive and/or polymer; optionally about 0.1% to about 30% of at least one penetration enhancer; optionally about 0.1% to about 40% of a gelling agent. The disclosure provides a transdermal and/or topical pharmaceutical composition wherein said CBD or derivative thereof is produced by a synthetic route. The disclosure provides a transdermal and/or topical pharmaceutical composition wherein the active agent is a highly purified synthetic which comprises at least about 90% (w/w) cannabidiol (CBD). The disclosure provides a transdermal and/or topical pharmaceutical composition wherein the adhesive and/or polymer is selected from the group consisting of hydroxylpropylmethyl cellulose, synthetic polymers and its derivatives, carboxyvinyl polymers or carbomers, carbopol 940, carbopol 934, carbopol 971p NF, polyethylene, and its copolymers, clays, silicates, bentonite, silicon dioxide, polyvinyl alcohol, acrylic polymers, eudragit, acrylic acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyrrolidone copolymers, PVP, Kollidon 30,

poloxamer, isobutylene, ethyl vinyl acetate copolymers, natural rubber, synthetic rubber, pressure sensitive adhesives, bio psa 4302, bio-psa 4501, 4202, acrylic pressure sensitive adhesives, duro –tak 87-2156, duro-tak 387-2287, polyisobutylene, polyisobutylene low molecular weight, polyisobutylene medium molecular weight, polyisobutylene 35000 mw, acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers, and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition wherein the at least one penetration enhancer is present and is selected from the group consisting of dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide, 1,3-butanediol, azone, pyrrolidones, N-methyl-2-pyrrolidone, 2-pyrrolidon, esters, fatty acid esters, propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, decyl oleate, glycerol monooleate, glycerol monolaurate, methyl laurate, lauryl laurate, fatty acids, capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid, alcohols, fatty alcohols and glycols, oleyl alcohol, nathanol, dodecanol, propylene glycol, glycerol, ether alcohol, diethylene glycol monoethyl ether, urea, triglycerides, triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers, brij, sodium lauryl sulfate, tween, polysorbate, terpene, terpenoids and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition wherein the at least one gelling agent is present and is selected from the group consisting of natural polymers, polysaccharides and its derivatives, agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium or sodium carrageenan, tragacanth, xanthum gum, copal, starch, chitosan, resin, synthetic polymers and its derivatives, carboxyvinyl polymers or carbomers, carbopol 940, carbopol 934, carbopol 971, polyethylene and its co-polymers, clays, silicate, polyvinyl alcohol, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyyrolidone copolymers, PVP, Poloxamer, acrylic acid its ester, polyacrylate copolymers, isobutylene, ethylene vinyl acetate copolymers, natural rubbers, synthetic rubbers such as styrene-diene copolymers, styrene-butadiene block copolymers, isoprene block copolymers, acrylonitrile butadiene rubber, butyl rubber or neoprene rubber, pressure sensitive adhesive based on silicone, hot-melt adhesive, and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition further comprising carriers or ingredients in effective amount selected from the

group consisting of solvents, 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 transdermal and/or topical pharmaceutical composition which is formulated as a transdermal patch. The disclosure provides a transdermal and/or topical 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, polymer adhesive matrix patch, and combinations thereof. The disclosure provides a transdermal and/or topical pharmaceutical composition indicated for the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder disorders include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions. The disclosure provides a transdermal and/or topical 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 transdermal and/or topical pharmaceutical composition which may be formulated as microneedles. The disclosure provides a transdermal and/or topical pharmaceutical composition co-administered with at least one additional an anti-epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin. The disclosure provides a transdermal and/or topical pharmaceutical composition further comprising at least one additional an anti-

epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

The disclosure provides a method for the treatment and/or prevention and/or control of seizure disorder in a patient comprising: selecting a patient in need of treatment and/or prevention and/or control of seizure disorder; topically applying the pharmaceutical composition as disclosed herein, thereby treating and/or preventing and/or controlling seizure disorder in the patient.

The disclosure provides a method wherein the seizure disorder includes complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions. The disclosure provides a method wherein the topical application of a transdermal patch for the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions 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, and up to 30 days. The disclosure provides a method further providing a constant rate of delivery of the active components of the transdermal patch over a time period 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, and up to 30 days. The disclosure provides a method further providing a steady absorption rates

of the active components of the transdermal patch over a time period 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, and up to 30 days. The disclosure provides a method further achieving a constant therapeutic blood serum levels of the active components of the transdermal patch over a time period 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, and up to 30 days. The disclosure provides a method further achieving a reduced variability in dosage of the active components of the transdermal patches over a time period 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, and up to 30 days. The disclosure provides a method further providing a therapeutic plasma concentration of the active components of the transdermal patch in a therapeutic range over a period of time 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, and up to 30 days.

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

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, for example as disclosed herein.

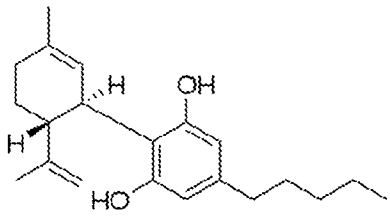
In accordance with yet another embodiment, the present disclosure provides a use of the pharmaceutical compositions described above, and at least one additional therapeutic agent, in an amount effective for use in a medicament, and most preferably for use as a medicament for treating a disease or disorder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

DETAILED DESCRIPTION

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

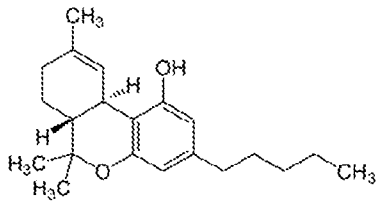
endocannabinoids (produced naturally in the body by humans and animals), the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids. Lipophilic cannabinoids are generally grouped as endocannabinoids (most typically as mammalian endocannabinoids); phytocannabinoids, from plant sources; and synthetic cannabinoids. Such cannabinoids are also often classified into the following subclasses: Cannabigerols (CBG); Cannabichromenes (CBC); Cannabidiol (CBD); Tetrahydrocannabinol (THC); Cannabinol (CBN); Cannabidiol (CBDL); Cannabicyclol (CBL); Cannabielsoin (CBE); and, Cannabitriol (CBT).

Cannabidiol IUPAC Name 2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol Chemical Formula: $C_{21}H_{30}O_2$ Molecular weight: 314.46 dalton
Chemical structure is shown below as formula I



Formula I

Tetrahydrocannbinol (THC) IUPAC Name (−)-(6a*R*,10a*R*)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol Chemical Formula: $C_{21}H_{30}O_2$ Molecular weight: 314.47 dalton.
Chemical structure is shown below as formula II



Formula II

As used herein, the word cannabis refers to all pharmaceutically acceptable forms of cannabis 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 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 bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

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 0.1% to about 20%,

about 1 to 25%, about 3% to about 6%, about 5% to about 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.

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 term “transdermal delivery” means delivery of drug into systemic circulation through the skin.

According to certain embodiments, transdermal compositions described herein are for the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder disorders include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions.

Epilepsy

Epilepsy is a brain disorder characterized by repeated seizures over time. Types of epilepsy can include, but are not limited to generalized epilepsy, e.g., childhood absence epilepsy, juvenile myoclonic epilepsy, epilepsy with grand-mal seizures on awakening, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, partial epilepsy, e.g., temporal lobe epilepsy, frontal lobe epilepsy, benign focal epilepsy of childhood.

Status epilepticus (SE) can include, e.g., convulsive status epilepticus, e.g., early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus; non-convulsive status epilepticus, e.g., generalized status epilepticus, complex partial status epilepticus; generalized periodic epileptiform discharges; and periodic lateralized epileptiform discharges. Convulsive status epilepticus is characterized by the presence of convulsive status epileptic seizures, and can include early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus. Early status epilepticus is treated with a first line therapy. Established status epilepticus is characterized by status epileptic seizures which persist despite treatment with a first line therapy, and a second line therapy is administered. Refractory status epilepticus is characterized by status epileptic seizures which persist despite treatment with a first line and a second line therapy, and a general anesthetic is generally administered. Super refractory status epilepticus is characterized by status epileptic seizures which persist despite treatment with a first line therapy, a second line therapy, and a general anesthetic for 24 hours or more.

Non-convulsive status epilepticus can include, e.g., focal non-convulsive status epilepticus, e.g., complex partial non-convulsive status epilepticus, simple partial non-convulsive status epilepticus, subtle non-convulsive status epilepticus; generalized non-convulsive status epilepticus, e.g., late onset absence non-convulsive status epilepticus, atypical absence non-convulsive status epilepticus, or typical absence non-convulsive status epilepticus.

Compositions described herein can also be administered as a prophylactic to a subject having a CNS disorder e.g., a traumatic brain injury, status epilepticus, e.g., convulsive status epilepticus, e.g., early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus; non-convulsive status epilepticus, e.g., generalized status epilepticus, complex partial status epilepticus; generalized periodic

epileptiform discharges; and periodic lateralized epileptiform discharges; prior to the onset of a seizure.

Seizure

A seizure is the physical findings or changes in behavior that occur after an episode of abnormal electrical activity in the brain. The term "seizure" is often used interchangeably with "convulsion." Convulsions are when a person's body shakes rapidly and uncontrollably. During convulsions, the person's muscles contract and relax repeatedly.

Based on the type of behavior and brain activity, seizures are divided into two broad categories: generalized and partial (also called local or focal). Classifying the type of seizure helps doctors diagnose whether or not a patient has epilepsy.

Generalized seizures are produced by electrical impulses from throughout the entire brain, whereas partial seizures are produced (at least initially) by electrical impulses in a relatively small part of the brain. The part of the brain generating the seizures is sometimes called the focus.

There are six types of generalized seizures. The most common and dramatic, and therefore the most well-known, is the generalized convulsion, also called the grand-mal seizure. In this type of seizure, the patient loses consciousness and usually collapses. The loss of consciousness is followed by generalized body stiffening (called the "tonic" phase of the seizure) for 30 to 60 seconds, then by violent jerking (the "clonic" phase) for 30 to 60 seconds, after which the patient goes into a deep sleep (the "postictal" or after-seizure phase). During grand-mal seizures, injuries and accidents may occur, such as tongue biting and urinary incontinence.

Absence seizures cause a short loss of consciousness (just a few seconds) with few or no symptoms. The patient, most often a child, typically interrupts an activity and stares blankly. These seizures begin and end abruptly and may occur several times a day. Patients are usually not aware that they are having a seizure, except that they may be aware of "losing time."

Myoclonic seizures consist of sporadic jerks, usually on both sides of the body. Patients sometimes describe the jerks as brief electrical shocks. When violent, these seizures may result in dropping or involuntarily throwing objects.

Clonic seizures are repetitive, rhythmic jerks that involve both sides of the body at the same time.

Tonic seizures are characterized by stiffening of the muscles.

Atonic seizures consist of a sudden and general loss of muscle tone, particularly in the arms and legs, which often results in a fall.

Seizures described herein can include epileptic seizures; acute repetitive seizures; cluster seizures; continuous seizures; unremitting seizures; prolonged seizures; recurrent seizures; status epilepticus seizures, e.g., refractory convulsive status epilepticus, non-convulsive status epilepticus seizures; refractory seizures; myoclonic seizures; tonic seizures; tonic-clonic seizures; simple partial seizures; complex partial seizures; secondarily generalized seizures; atypical absence seizures; absence seizures; atonic seizures; benign Rolandic seizures; febrile seizures; emotional seizures; focal seizures; gelastic seizures; generalized onset seizures; infantile spasms; Jacksonian seizures; massive bilateral myoclonus seizures; multifocal seizures; neonatal onset seizures; nocturnal seizures; occipital lobe seizures; post traumatic seizures; subtle seizures; Sylvan seizures; visual reflex seizures; or withdrawal seizures.

Purified CBD

The disclosure provides that the CBD is present in an amount that reduces total seizure frequency by greater than 70% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED). More preferably the CBD is present in an amount that reduces total seizure frequency by greater than 90% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED). More preferably still the CBD is present in an amount that reduces total seizure frequency by 100% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED).

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.

The one or more AED is preferably selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin. In certain embodiments the CBD is used in combination with

clobazam. Preferably the number of different anti-epileptic drugs or the dose of AED that are used in combination with the CBD is reduced. More preferably the dose of AED which is reduced is of clobazam.

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. For example, a for a 15 kg patient a dose of greater than 75 mg of CBD per day would be provided. Doses greater than 5 mg/kg/day such as greater than 10/mg/kg/day, greater than 15 mg/kg/day, greater than 20 mg/kg/day and greater than 25 mg/kg/day are also envisaged to be effective. 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.

The disclosure provides a method of treating treatment-resistant epilepsy comprising administering cannabidiol (CBD) to a subject, wherein the epilepsy is febrile infection related epilepsy syndrome (FIRES).

The disclosure provides a method of treating treatment-resistant epilepsy comprising administering cannabidiol (CBD) to a subject in an amount sufficient to reduce total seizure frequency by greater than 50% with respect to the seizure frequency achieved on one or more concomitant anti-epileptic drugs (AED).

Pharmaceutical Compositions

According to certain embodiments described herein, pharmaceutical composition or transdermal formulation of contains highly purified CBD. More preferably transdermal formulation may include highly purified CBD.

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.

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 polymer matrix without any limitations like adhesive matrix, non-adhesive matrix.

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.

In certain embodiments of the present disclosure, a transdermal patch comprises transdermal formulation containing highly purified CBD 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 highly purified CBD 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.

The transdermal formulation comprising highly purified CBD 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 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.

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.

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.

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.

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, semisolids 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 highly purified CBD 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, chelating agents, complexing agents, diluents, excipients, material to prepare patch, material to prepare 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 11 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_1-C_{20} 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, butyene 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. 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) 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.

Example 2

The transdermal formulation and/or topical formulation of the disclosure may comprise gelling agents and/or thickening and/or suspending agents 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, xantham, 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, hydroxylpropyl cellulose, hydroxylpropylmethyl cellulose etc.), synthetic polymers and its derivatives such as 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 silicone polymers such as but not limited to (bio psa 4302, bio-psa 4501, 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, plyisobutylene medium molecular weight, polyisobutylene 35000 mw, etc), acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers, etc. More preferably in the range of 0.1% 70% 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.

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-pyrrolidon 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 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%, 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 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.

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, 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-polyoxy1-6-glycerides, lauroyl polyoxyl-6-gylcerides, ethyl oleate, polyglycery1-3- 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 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.

Example 7

Different techniques and ingredients can be used to increase the stability and/or solubility of highly purified CBD 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.

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, matrix patch, drug in adhesives, transdermal films 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 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, 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.

The transdermal formulation and/or topical formulation and/or transdermal delivery system of the disclosure may deliver at least therapeutic effective dose of highly purified CBD. Therapeutic effective highly purified CBD, alone or in combinations thereof in human plasma required for treating and/or preventing pain and/or inflammation. Therapeutic effective highly purified CBD dose refers to the therapeutic concentration of in human plasma required for treating and/or preventing pain and/or inflammation. Furthermore, the precise therapeutic effective dose of highly purified CBD in the transdermal formulation or topical formulation or transdermal delivery system can be 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 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 of the disclosure may deliver at least therapeutic effective dose of highly purified CBD. Therapeutic effective highly purified CBD refers to the therapeutic concentration of highly purified CBD thereof in human plasma required for the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder disorders include, for example, complex partial seizures, simple partial seizures, partial seizures with

secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions.

The transdermal formulation or transdermal patch of highly purified CBD 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 12

Theoretical Flux calculation for Cannabidiol:

Oral bioavailability of CBD is only 13-19%. For our calculation purpose, TRPL took average bioavailability of 15%[2]. So, the actual dose delivering to patient upon oral delivery is described in Table 3

Table 3: Theoretical dose required from Transdermal Dosage form.

Oral Dose	**Dose range (mg/day) (based on Table 1)**	**Transdermal Dose range (mg/day)**	**Oral AUC (hr*ng/ml)[3]**	**Avg. Oral Plasma Concentration (ng/ml)**
5 mg/kg/day	61-113	9-17	241	10.0 ng/ml
10 mg/kg/day	122-227	18-34	722	30.0 ng/ml

Flux Required = Dose/Surface area

= 9 mg/day/surface area

= 9000 ug /24 hr/50 sqcm

= 7.5 ug/sqcm/hr

So, 50 sqcm patch with 7.5 ug/sqcm/hr flux will deliver 9 mg of drug in one day. And 100 sqcm of patch will deliver 18 mg of drug with same flux profile. Some research articles showed oral bioavailability of CBD is in the range of 5-6% [2,8]

Example 13

Synthetic cannabidiol (CBD) formulations for transdermal delivery ((Formulation Nos. 001, 002, 003, 004, and 005) were prepared by mixing ingredients as shown in Table 4:

Table 4: Transdermal Synthetic Cannabidiol formulations

Ingredients	001 (% W/W)	002 (% W/W)	003 (% W/W)	004 (% W/W)	005 (% W/W)
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 2, 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 keep the CBD concentration in receptor compartment less than 10% of its solubility. The experimental conditions are provided in Table 3:

Table 5. Experimental Condition for In-vitro Permeability testing	
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 96 Hrs (4 days) and results of the flux measurement are provided in Table 4.

Table 6: CBD Flux Results

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

Example 14

Additional synthetic Cannabidiol (CBD) formulations for transdermal delivery (Formulation Nos. 006 through 014) were prepared by mixing ingredients as shown in Table 7:

Table 7: Transdermal Synthetic Cannabidiol formulation nos. 006 to 014

Ingredients	006 (% W/W)	007 (% W/W)	008 (% W/W)	009 (% W/W)	010 (% W/W)	011 (% W/W)	012 (% W/W)	013 (% W/W)	014 (% W/W)
CBD	9.95	9.64	9.77	9.98	9.98	9.64	9.87	9.52	10.27
PG	42.70	42.58	42.51	42.51	42.02	42.45	42.47	42.34	42.09
Hexylene Glycol	42.36	42.48	42.40	42.63	42.66	42.77	42.50	42.64	42.39
Tween-20	4.99								
Triacetin		5.30							
PGML			5.32						
OA				4.88					
ML					5.34				
EO						5.18			
IPM							5.16		
IPP								5.51	
Labrasol									5.25

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

Synthetic Cannabidiol formulations for transdermal delivery (006-014) were prepared by the same procedure described in Example 2. Flux measurement was also performed as described in Example 2. The experimental conditions are the same as provided in Table 5 of Example 2.

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 8.

Table 8: CBD Flux Results

	Formulation No.

	006	007	008	009	010	011	012	013	014
Total Amount of CBD Permeated at 48 hrs (ng/cm^2)	27272	34091	39205	44318	34659	40341	38068	66477	28977
Flux ($ng/cm^2/hr$)	568.16	710.23	816.77	923.29	722.06	840.43	793.08	1384.94	603.69

Example 15

Additional synthetic cannabidiol (CBD) formulations for transdermal delivery patches (Formulation Nos. 015 to 018) were prepared by mixing ingredients as shown in Table 9:

Table 9: Transdermal Synthetic cannabidiol formulation nos. 015 to 018

Ingredients	015 (% W/W)	016 (% W/W)	017 (% W/W)	018 (% W/W)
CBD	2.0	2.0	2.0	2.0
PG	27.8	27.8	27.8	27.8
Hexylene Glycol	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 9, 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 place 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^2) 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 (Example 15, Table 9 only). 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 5 of Example 13.

Example 16

Synthetic cannabidiol (CBD) formulations for transdermal delivery (Formulation Nos. 047-055) were prepared by mixing ingredients as shown in Table 10:

Table 10: Transdermal Synthetic Cannabidiol formulations

Excipients	CBD 047	CBD 048	CBD 049	CBD 050	CBD 051	CBD 052	CBD 053	CBD 054	CBD 055
CBD	4.84%	4.98%	4.73%	4.99%	4.87%	4.89%	5.04%	4.83%	5.00%
DURO-TAK 2516	95.16%	-	-	-	-	-	-	-	-
DURO-TAK 9301	-	95.02%	-	-	-	-	-	-	-
DURO-TAK 2287	-	-	95.27%	-	-	-	-	-	-
DURO-TAK 2054	-	-	-	95.01%	-	-	-	-	-
DURO-TAK 2852	-	-	-	-	95.13%	-	-	-	-
DURO-TAK 2074	-	-	-	-	-	95.11%	-	-	-
DURO-TAK 2194	-	-	-	-	-	-	94.96%	-	-
BIO-PSA 4501	-	-	-	-	-	-	-	95.17%	-
BIO-PSA 4201	-	-	-	-	-	-	-	-	95.00%

The above ingredients (Table 10) are blended by stirring for 18 hours and then, using a commercial benchtop spreader, the 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 place in an oven at 86 F for 120 min to evaporate off the ethyl acetate adhesive solvent. An opaque backing membrane (such as 3M 9730 NR film) with low permeability to oxygen to inhibit photo and oxidative degradation, is then carefully applied by hand to avoid formation of bubbles and voids. A circular die (1.5 inches diameter) is used to cut patches (1.76 sqcm) for subsequent studies. After drying, the drug adhesive matrix has a surface density of 2-30 mg/sqcm, containing CBD in 5% w/w.

The prepared formulations where then subjected to a release study as follows: After weighing the patches (n=3), the release liner was removed, and the patches were placed in 20ml scintillation vials with 15ml of receiving media. The receiving media was PBS solution of pH 7.4 with 0.5% Brij(O)20. Vials were placed on the roller overnight at 20 RPM. Samples were withdrawn every 24 hours, up to 48 hours, and media was fully replaced each time. Samples were then run in the HPLC in order to determine the % release of CBD from the different formulations.

The prepared formulations also analyze for the uniformity of drug content. The patches (n=3) were weight out for each formulation, the release liner was removed, and the

patches (including the release liner) were placed in 20ml scintillation vials with 15ml of solution IPA:Ethanol (190proof) (50:50). The vials were then placed on the roller at 20 RPM and left overnight. Samples were withdrawn from each vial and analyzed on the HPLC in order to determine the drug content of each formulation.

Table 11. Experimental Condition for In-vitro Permeability testing	
Receiving Media	PBS (pH 7.4) + 0.5% Brij-O(20) +0.01% Sodium Azide
Receiving Media Volume (mL)	15
Sample Volume (mL)	15
Sampling Interval (hr)	24,48
Diffusion area (sqcm)	1.76

% Release of CBD through the matrix system was measured for a minimum period of 48Hrs (2 days) and results of the % release are provided in Table 12.

Table 12. % CBD Release Results

	CBD 047	**CBD 048**	**CBD 049**	**CBD 050**	**CBD 051**	**CBD 052**	**CBD 053**	**CBD 054**	**CBD 055**
Av. % Release at 24 hours	26 (3)	9 (7)	20 (7)	**40 (2)**	23 (8)	**35 (12)**	**37 (6)**	**93 (2)**	Did not solubilize the CBD 98% (0.05)
Av. % Release at 48 hours	18 (7)	6 (12)	13 (13)	22 (1)	13 (9)	12 (1)	22 (5)	2 (2)	
% Release 0-48hours (cumulative)	44	15	33	**62**	36	**47**	**59**	**95**	
% CBD from extraction (STD)	104 (2)	100 (1)	100 (5)	102 (1)	103 (6)	96 (15)	104 (4)	107	

Drug content study showed that the % recover of CBD in extraction is between 96-107% for all the manufactured formulations. Furthermore, the release study showed that the silicone adhesive 4501 showed more than 90% release within first 24 hrs. Based on the release profile following are the best adhesive for CBD formulation: BIOPSA-4501 > 2054=2194 >2074 >2516 >2852=2287 >9301.

Release studies indicate that the functional group and crosslinker affect the CBD release from acrylic adhesive. According to current study, acrylic adhesive containing -COOH functional group with crosslinker showed the maximum release of CBD from all the acrylic adhesive patches.

Example 17

Additional synthetic Cannabidiol (CBD) formulations for transdermal delivery (Formulation Nos. 057 through 064) were prepared by mixing ingredients as shown in Table 13:

Table 13: Transdermal Synthetic Cannabidiol formulation no. 057 to 064

Excipients	CBD 057	CBD 058	CBD 059	CBD 060	CBD 061	CBD 062	CBD 063	CBD 064
CBD	5.0%	5.0%	5.0%	4.9%	4.8%	4.8%	4.9%	4.8%
BIO-PSA 4501	95.0%	84.6%	84.5%	85.0%	83.3%	89.7%	86.9%	89.6%
IPM	-	10.4%	-	-	-	-	-	-
IPP	-	-	10.5%	-	-	-	-	-
Oleic Acid	-	-	-	10.1%	-	-	-	-
Transcutol P	-	-	-	-	11.9%	-	-	-
Brij O20	-	-	-	-	-	5.5%	-	-
Poloxamer 124	-	-	-	-	-	-	8.2%	-
PGML	-	-	-	-	-	-	-	5.6%

Synthetic Cannabidiol formulations for transdermal delivery (057-064) were prepared by the same procedure described in Example 16.

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 14:

Table 14. Experimental Condition for In-vitro Permeability testing

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
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 96 Hrs (4 days) and results of the flux measurement are provided in Table 15.

Upon completion of the flux study, the used patches were carefully removed and extract the CBD from the use patches using IPA:Ethanol (50:50). The human cadaver skin was also soaked in IPA:Ethanol (50:50), in order to extract the CBD from it. The samples were analyzed using HPLC. The data in table 6 showed the amount of CBD present in the skin and the left-over patches.

Table 15: CBD Flux Results

Excipients	CBD 057	CBD 058	CBD 059	CBD 060	CBD 061	CBD 062	CBD 063	CBD 064
Av. cumulative amount permeated at 96 hrs (µg)	52	31	16	120	86	BLLQ	BLLQ	53
Av. flux 24-96 hrs (µg/hr/sqcm)	0.41	0.37	0.37	0.69	0.51	BLLQ	BLLQ	0.42
Peak flux (µg/hr/sqcm)	0.44	0.38	0.38	0.82	0.60	-	-	0.44
Time to peak flux (hrs)	72	72	72	72	72	-	-	72
Av. CBD Amount in patch (mg)	1.57	-	-	1.14	2.26	1.81	1.88	1.56
Av. CBD Amount in skin (mg)	0.01	-	-	0.59	0.13	0.54	0.24	0.10

Example 18

The effect of gelling agents and their concentration on the permeation of CBD through human cadaver skin. CBD gel formulation can be gelled by gelling agents including but not limited to, natural polymers such as 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 carrageenan, tragacanth, xanthum gum, copal, starch, chitosan, resin etc.), synthetic polymers and its derivatives such as without any limitation to carboxyvinyl polymers or carbomers (carbopol 940, carbopol 934, carbopol 971), polyethylene and its co-polymers etc. clays such as silicate etc. polyvinyl alcohol, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyyrolidone copolymers (PVP, Poloxamer), acrylic acid its ester, polyacrylate copolymers, isobutylene, ethylene vinyl acetate copolymers, natural rubbers, synthetic rubbers such as styrene-diene copolymers, styrene-butadiene block copolymers, isoprene block copolymers, acrylonitrile butadiene rubber, butyl rubber or neoprene rubber, as well as pressure sensitive adhesive based on silicone, or “hot-melt adhesive”. In addition, other than human cadaver skin, cannabidiol can be evaluated with other artificial membranes including but not limited to cellulose membrane, silicone membranes (polydimethylsiloxane), liposome

coated membranes, solid-supported liquid membranes, lecithin organogel membrane and other. Besides the gel formulation of CBD, other dosage forms including but not limited to ointment, creams, emulsion, liposomes, etc. may be used.

Example 19

The effect of enhancers or solubilizers on the flux of cannabidiol through human cadaver skin was evaluated. The desire optimum composition of cannabidiol gel formulation contained dimethylsulfoxide (DMSO), dimethylisosorbide (DMI), Lactic acid, Tween-20, highly purified diethylene glycol monoethyl ether (Transcutol P), dipropylene glycol, polyethylene glycol-400, propylene glycol (PG), Hexylene Glycol (HG), Lauroglycol-90. Apart from above mentioned enhancers and/or solubilizers , the cannabidiol transdermal delivery can be influenced by enhancers and/or solubilizers including but not limited water, sulfoxides, and similar chemicals such as but not limited to (dimethylsulfoxide, dimethylacetamide, dimethylformamide, decylmethylsulfoxide, dimethylisosorbide etc), azone, pyrrolidones such as but not limited to (N-methyl-2-pyrrolidone, 2-pyrrolidon etc), 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, lauryl 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 such as but not limited to (diethylene glycol monoethyl ether), urea, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, esters of long chain fatty acids with methyl, ethyl or isopropyl alcohol, esters of fatty alcohols with acetic acid, lactic acid, as well as oleic acid diethanolamine, essential oils, terpene and terpenoids such as but not limited to (terpineol, limonene, thymol, cineole etc), surfactant type enhancers (polysorbate 80, polysorbate 20 etc.), liposomes, niosomes, transferomes, ethanosomes, polysorbate such as but not limited to (polysorbate 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, Caprylic glyceride, oleoyl-polyoxyl-6-glycerides, lauroyl polyoxyl-6-

gylcerides, polyglyceryl-3- dioleate, diethylene glycol monoethyl ether, propylene glycol monolaurate type I etc, cyclodextrins, polyhydric alcohol, especially 1,2-propanediol, butanediol, glycerine, polyethylene glycol (m.w. 100 and higher), Dimethyl Sulfoxide, Dimethyl Isosorbide, tetrahydrofurfuryl alcohol, diethyl tolumide, monoisopropylidene glycerine and others Solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds or chemicals known to those skilled in the art can be used either alone or in combination thereof

References:

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3. Devinsky et. al., "Randomized dose-ranging safety trial of cannabidiol in Dravet Syndrome", Neurology, 90(14), 2018
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While the disclosure 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.

CLAIMS

WHAT IS CLAIMED IS:

1. A transdermal and/or topical pharmaceutical composition comprising:

-about 0.1% to about 20% of an active agent selected from the group consisting of synthetic cannabidiol, natural cannabidiol, and combinations thereof;

- about 35% to about 99% of at least one adhesive and/or polymer;

- optionally about 0.1% to about 30% of at least one penetration enhancer;

- optionally about 0.1% to about 40% of a gelling agent.

2. The pharmaceutical composition of claim 1 wherein said CBD or derivative thereof is produced by a synthetic route.

3. The pharmaceutical composition of any one of claims 1 to 2 wherein the active agent is a highly purified synthetic which comprises at least about 90% (w/w) cannabidiol (CBD).

4. The pharmaceutical composition of any one of claim 1 to 3 wherein the adhesive and/or polymer is selected from the group consisting of hydroxylpropylmethyl cellulose, synthetic polymers and its derivatives, carboxyvinyl polymers or carbomers, carbopol 940, carbopol 934, carbopol 971p NF, polyethylene, and its copolymers, clays, silicates, bentonite, silicon dioxide, polyvinyl alcohol, acrylic polymers, eudragit, acrylic acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyrrolidone copolymers, PVP, Kollidon 30, poloxamer, isobutylene, ethyl vinyl acetate copolymers, natural rubber, synthetic rubber, pressure sensitive adhesives, bio psa 4302, bio-psa 4501, 4202, acrylic pressure sensitive adhesives, duro –tak 87-2156, duro-tak 387-2287, polyisobutylene, polyisobutylene low molecular weight, polyisobutylene medium molecular weight, polyisobutylene 35000 mw, acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers, and combinations thereof.

5. The pharmaceutical composition of any one of claims 1 to 4 wherein the at least one penetration enhancer is present and is selected from the group consisting of dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide, 1,3-butanediol, azone, pyrrolidones, N-methyl-2-pyrrolidone, 2-pyrrolidon, esters, fatty acid esters,

propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, decyl oleate, glycerol monooleate, glycerol monolaurate, methyl laurate, lauryl laurate, fatty acids, capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid, alcohols, fatty alcohols and glycols, oleyl alcohol, nathanol, dodecanol, propylene glycol, glycerol, ether alcohol, diethylene glycol monoethyl ether, urea, triglycerides, triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers, brij, sodium lauryl sulfate, tween, polysorbate, terpene, terpenoids and combinations thereof.

6. The pharmaceutical composition of any one of claims 1 to 5 wherein the at least one gelling agent is present and is selected from the group consisting of natural polymers, polysaccharides and its derivatives, agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium or sodium carrageenan, tragacanth, xanthum gum, copal, starch, chitosan, resin, synthetic polymers and its derivatives, carboxyvinyl polymers or carbomers, carbopol 940, carbopol 934, carbopol 971, polyethylene and its co-polymers, clays, silicate, polyvinyl alcohol, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyyrolidone copolymers, PVP, Poloxamer, acrylic acid its ester, polyacrylate copolymers, isobutylene, ethylene vinyl acetate copolymers, natural rubbers, synthetic rubbers such as styrene-diene copolymers, styrene-butadiene block copolymers, isoprene block copolymers, acrylonitrile butadiene rubber, butyl rubber or neoprene rubber, pressure sensitive adhesive based on silicone, hot-melt adhesive, and combinations thereof.

7. The pharmaceutical composition of any one of claims 1 to 6 further comprising carriers or ingredients in effective amount selected from the group consisting of solvents, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, oxidants, and combinations thereof.

8. The pharmaceutical composition of any one of claims 1 to 7 which is formulated as a transdermal patch.

9. The pharmaceutical composition of any one of claims 1 to 8 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, polymer adhesive matrix patch, and combinations thereof.

10. The pharmaceutical composition of any one of claims 1 to 9 indicated for the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder disorders include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions.

11. The pharmaceutical composition of any one of claims 1 to 10 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.

12. The pharmaceutical composition of any one of claims 1 to 11 which may be formulated as microneedles.

13. The pharmaceutical composition of any one of claims 1 to 12 co-administered with at least one additional an anti-epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

14. The pharmaceutical composition any one of claims 1 to 13 further comprising at least one additional an anti-epileptic agent selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

15. A method for the treatment and/or prevention and/or control of seizure disorder in a patient comprising:

- selecting a patient in need of treatment and/or prevention and/or control of seizure disorder;

- topically applying the pharmaceutical composition of any one of claims 1 to 14,

thereby treating and/or preventing and/or controlling seizure disorder in the patient.

16. The method of claim 15, wherein the seizure disorder includes complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions.

17. The method of any one of claims 15 to 16 wherein the topical application of a transdermal patch for the treatment and/or prevention and/or control of seizure disorder in a patient, wherein the seizure disorder include, for example, complex partial seizures, simple partial seizures, partial seizures with secondary generalization, generalized seizures (including absence, grand mal (tonic clonic), status epilepticus, tonic, atonic, myoclonic), neonatal and infantile spasms, drug-induced seizures, trauma-induced seizures, and febrile seizures, and additional specific epilepsy syndromes such as juvenile myoclonic epilepsy, Lennox-Gastaut, Dravet syndrome, Tuberous Sclerosis Complex (TSC), Treatment-Resistant Epilepsy, Treatment Resistant Pediatric Epilepsy, mesial temporal lobe epilepsy, nocturnal frontal lobe epilepsy, progressive epilepsy with mental retardation, and progressive myoclonic epilepsy, as well as seizures associated with CNS mass lesions 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, and up to 30 days.

18. The method of any one of claims 15 to 17 further providing a constant rate of delivery of the active components of the transdermal patch over a time period 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, and up to 30 days.

19. The method of any one of claims 15 to 18 further providing a steady absorption rates of the active components of the transdermal patch over a time period 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, and up to 30 days.

20. The method of any one of claims 15 to 19 further achieving a constant therapeutic blood serum levels of the active components of the transdermal patch over a time period 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, and up to 30 days.

21. The method of any one of claims 15 to 20 further achieving a reduced variability in dosage of the active components of the transdermal patches over a time period 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, and up to 30 days.

22. The method of any one of claims 15 to 21 further providing a therapeutic plasma concentration of the active components of the transdermal patch in a therapeutic range over a period of time 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, and up to 30 days.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/05*** (2006.01), ***A61K 9/00*** (2006.01), ***A61K 9/70*** (2006.01), ***A61P 25/08*** (2006.01), ***C07C 39/23*** (2006.01)

CPC: **A61K 31/05** (2020.01), A61K 9/00 (2021.05), A61K 9/0014 (2020.01), A61K 9/0021 (2020.01), A61K 9/7023 (2020.01), A61P 25/08 (2020.01) (more CPCs on the last page)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: ***A61K 31/05*** (2006.01), ***A61K 9/00*** (2006.01), ***A61K 9/70*** (2006.01), ***A61P 25/08*** (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)

Databases: Canadian Patent Database, Questel Orbit, CIPO Library Discovery Tool, Google
Keywords: cannabidiol, transdermal, transdermal patch, topical, pharmaceutical composition, adhesive and/or polymer, penetration enhancer, gelling agent, thickening agent, microneedle, seizure disorder, epilepsy, convulsant

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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) see the entire document, in particular claims, paragraphs [0006], [0008], [0013], [0014], [0021], [0022], [0025], [0033], [0088]-[0095], [00102]-[00107], [00138]-[00145], example 11	1-12, 15-22
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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

Date of the actual completion of the international search 27 June 2022 (27-06-2022)	Date of mailing of the international search report 12 July 2022 (12-07-2022)
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 Connie Kuang (819) 639-8664

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 2010/0273895 A1 (STINCHCOMB et al.) 28 October 2010 (28-10-2010) see the entire document, in particular claims, paragraphs [0020], [0022], [0039], [0043]-[0044], [0051], [0053], [0056]-[0067], [0073], [0075], [0080]-[0081], [0098], [00103], [00109], [00111], [00113], [00118], [00143], [00147]	1-11, 15-22
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IPC:

CPC:
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