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(54) Title: IMPROVED USE OF CANNABINOIDS IN THE TREATMENT OF EPILEPSY

(57) Abstract: A method of treating epilepsy in a subject, whereby the subject in need thereof is administered, via the oral mucosa, a rapidly infusing composition that includes (a) a pharmaceutically acceptable binder and/or excipient system containing gelatin and a sugar alcohol, and (b) a therapeutically effective amount of cannabidiol (CBD) or a derivative/analog thereof.

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TITLE

IMPROVED USE OF CANNABINOIDS IN THE TREATMENT OF EPILEPSY

CROSS REFERENCE TO RELATED APPLICATIONS

5 This application claims priority to U.S. Patent Application No. 17/225,738 filed April 08, 2021, which claims priority to U.S. Provisional Application No. 63/114,194 filed November 16, 2020; U.S. Provisional Application No. 63/114,181 filed November 16, 2020; U.S. Provisional Application No. 63/147,453 filed February 09, 2021; U.S. Provisional Application No. 63/172,343 filed April 08, 2021; U.S. Provisional Application No. 63/172,362 filed April 08, 2021; U.S. Provisional Application No. 63/172,386 filed April 08, 2021; U.S. Provisional Application No. 63/172,368 filed April 08, 2021; and U.S. Provisional Application No. 63/180,193 filed April 27, 2021; which are each incorporated herein by reference in their entirety.

15 BACKGROUND OF THE INVENTION

TECHNICAL FIELD

 The present disclosure relates to methods of treating epilepsy with a rapidly infusing composition formulated with cannabidiol (CBD), cannabinoids or a derivative/analog thereof as the active therapeutic ingredient (ATI).

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DESCRIPTION OF THE RELATED ART

 The “background” description provided herein is for the purpose of generally presenting the context of the disclosure. Work of the presently named inventors, to the extent it is described in this background section, as well as aspects of the description which may not otherwise qualify as prior art at the time of filing, are neither expressly or impliedly admitted as prior art against the present invention.

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Epilepsy, or seizure disorder, is a chronic neurological condition characterized by recurrent seizures that begin in the brain and are associated with excessive or abnormal synchronization of neural activity. It has been estimated that about 1% of the population, or upwards of 65 million individuals worldwide, suffer from some form of epilepsy. While therapeutic intervention with traditional antiepileptic drugs (AEDs) remains a viable approach for a significant number of patients with epilepsy, approximately 25-30% of epilepsy patients remain intractable to current anticonvulsant treatment, and as such are termed as suffering from “drug resistant epilepsy” (DRE). DRE is thought to develop following an initial seizure event early in life, such as a febrile seizure or status epilepticus, with this seizure activity leading to neuronal cell death and subsequent epileptogenesis that causes the development of pharmaco-resistance. Lennox-Gastaut syndrome and Dravet syndrome are examples of life-long epilepsy disorders that begin in early childhood. Drug resistant seizures are a hallmark of these syndromes, which are often frequent, prolonged, and severe.

Epidiolex® is currently the only FDA-approved drug containing cannabidiol (CBD) as the active ingredient. CBD is formulated in an oral liquid dosage form with inactive ingredients dehydrated alcohol, sesame oil, strawberry flavor, and sucralose for the treatment of epilepsy, specifically for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or Tuberous Sclerosis Complex.

However, the oral liquid dosage administration of Epidiolex® suffers from a number of disadvantages. For example, treatment with Epidiolex® requires extremely high doses of CBD, with the FDA-approved recommended dosages of CBD being in the range of 5 mg/kg/day to 25 mg/kg/day, divided between two daily doses. These extremely high doses are an unavoidable consequence of oral liquid administration, which results in low bioavailability and inconsistent levels of CBD in systemic circulation. Specifically, drugs

taken by mouth and swallowed are absorbed first into the blood perfusing the gastrointestinal (GI) tract. The venous drainage from the GI tract is into the blood perfusing the liver, and thus drugs absorbed from the lumen of the GI tract are immediately presented to the liver – the major detoxifying organ of the body – whereby the drugs are metabolized and then
5 returned to the left side of the heart via the hepatic portal vein and sent into systemic circulation. This first pass metabolism through the liver may result in the removal of a substantial portion of an ingested drug and is more pronounced for some drugs than others; in the case of cannabinoids such as CBD, extensive first pass metabolism provides a paltry bioavailability of only about 6 to 11% when ingested orally. This bioavailability is further
10 affected by whether the subject is in a “fasted” or a “fed” state and even the content of the meal for subjects in the “fed” state.

Another disadvantage associated with medications administered thorough oral liquid dosing is inaccurate dosing. To use Epidiolex®, subjects are instructed to fill a 5 mL oral syringe with the required dosage of the oral solution and then to squirt the contents into the
15 mouth. It is recommended to direct the medication against the inside of the cheek because directing the medication towards the back of the mouth may cause choking. Since each mL of Epidiolex® contains 100 mg of CBD, the instructions recognize that many patients will require greater than 5 mL of oral solution during each of the two daily dosing events to reach the recommended dosage amount, requiring multiple loadings and dispensings of the oral
20 syringe. Any inaccuracy in each of the multiple, daily oral syringe loadings and dispensings can result in large variations in the amount of CBD dosed. This process is not only inaccurate, it is cumbersome and generally unpleasant for the patient, particular given that many of the patients will be children, who can be as young as two-years old. Additionally, the oily and foul taste of CBD exacerbates the unpleasant user experience and can result in
25 poor patient compliance when administered orally.

Yet another disadvantage of the oral liquid dosage administration of Epidiolex® is the adverse reactions associated with consuming voluminous amounts of the liquid carrier, specifically sesame oil, needed to meet the high daily dosing requirements of CBD (5 mg/kg/day to 25 mg/kg/day). As a result, taking Epidiolex® is known to cause gastrointestinal ailments such as diarrhea, decrease weight, gastroenteritis, decreased appetite, and abdominal pain/discomfort.

In view of the foregoing, there exists a need for new epilepsy treatment methods based on dosage forms which are bioavailable, are easy to administer, provide for accurate dosing, minimize adverse reactions, and result in high levels of patient compliance.

SUMMARY OF THE INVENTION

In U.S. provisional application 63/114,194 and U.S. non-provisional application 17/225,738—each incorporated herein by reference in its entirety, the instant inventors described a rapidly infusing composition containing cannabidiol (CBD) or a derivative/analog thereof as the active therapeutic ingredient (ATI) and corresponding methods for treating pain using that composition. The inventive rapidly infusing composition provides numerous benefits compared to traditional modes of dosing CBD, such as the oral liquid dosing required with Epidiolex®, including, but not limited to: higher bioavailability; more rapid uptake; more accurate dosing; greater convenience; fewer side effects; and superior patient compliance.

As described in more detail below, the Rapid Infusion Technology™ (RITE) platform formulated with CBD, cannabinoids or a derivative/analog thereof, enables rapid infusion of CBD or a derivative/analog thereof into systemic circulation via the oral mucosa while bypassing the GI tract and hepatic first pass metabolism, and provides for the first time a consistent, repeatable mechanism for the treatment of epilepsy in a bioavailable unit dosage

form for accurate dosing, easy administration, smaller dosages, reduced side effects, and high levels of patient compliance.

Thus, the present invention provides:

(1) A method of treating epilepsy in a subject, comprising:

5 administering to the subject in need thereof, via the oral mucosa, a rapidly infusing composition comprising (a) a pharmaceutically acceptable binder and/or excipient system comprising gelatin and a sugar alcohol, and (b) a therapeutically effective amount of cannabidiol (CBD) or a derivative/analog thereof.

10 (2) The method of (1), wherein the rapidly infusing composition is lyophilized.

(3) The method of (1) or (2), wherein the rapidly infusing composition has a disintegration time of approximately 1 to 30 seconds in deionized water maintained at 37° C ± 2° C.

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(4) The method of any one of (1) to (3), wherein the rapidly infusing composition has a disintegration time of approximately 1 to 5 seconds in deionized water maintained at 37° C ± 2° C.

20 (5) The method of any one of (1) to (4), wherein the gelatin is present in the rapidly infusing composition in an amount of 10 to 35 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

(6) The method of any one of (1) to (5), wherein the gelatin is bovine gelatin.

25

(7) The method of any one of (1) to (6), wherein the sugar alcohol is present in the rapidly infusing composition in an amount of 5 to 35 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

5 (8) The method of any one of (1) to (7), wherein the sugar alcohol comprises mannitol.

(9) The method of any one of (1) to (8), wherein the CBD or derivative/analog thereof is present in the rapidly infusing composition in an amount of 20 to 70 wt.%, based on a total
10 weight of the rapidly infusing composition on a dry basis.

(10) The method of any one of (1) to (9), wherein the rapidly infusing composition is formulated with a solid form of the CBD.

15 (11) The method of any one of (1) to (10), wherein the rapidly infusing composition is formulated with a solid form of the CBD having a purity between 95 and 99.9 wt.%.

(12) The method of any one of (1) to (11), wherein the rapidly infusing composition is formulated with a solid form of the CBD that has been micronized to have a D50 diameter
20 between 1 and 50 μm .

(13) The method of any one of (1) to (9), wherein the rapidly infusing composition is formulated with a CBD derivative/analog.

(14) The method of (13), wherein the CBD derivative/analog is cannabidiolic acid methyl ester.

(15) The method of any one of (1) to (14), wherein the rapidly infusing composition
5 further comprises at least one selected from the group consisting of a sweetener, a flavorant, and a colorant.

(16) The method of (15), wherein the rapidly infusing composition comprises the flavorant, and the flavorant comprises lemon-lime flavor.

10

(17) The method of (15) or (16), wherein the rapidly infusing composition comprises the colorant, and the colorant comprises FD&C Yellow #5.

15

(18) The method of any one of (15) to (17), wherein the rapidly infusing composition comprises the sweetener, and the sweetener comprises a mixture of sucralose and acesulfame-K.

20

(19) The method of any one of (1) to (18), wherein the rapidly infusing composition is administered to the subject via the buccal mucosa.

(20) The method of any one of (1) to (19), wherein the therapeutically effective amount of CBD or derivative/analog thereof is from 0.1 mg/kg/day to less than 5 mg/kg/day.

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(21) The method of any one of (1) to (20), wherein the rapidly infusing composition is administered to the subject 1 to 3 times per day.

(22) The method of any one of (1) to (21), wherein the subject presents with focal onset seizures.

5 (23) The method of any one of (1) to (21), wherein the subject presents with generalized onset seizures.

(24) The method of any one of (1) to (21), wherein the subject presents with both generalized onset and focal onset seizures.

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(25) The method of any one of (1) to (24), wherein the epilepsy is childhood epilepsy.

(26) The method of (25), wherein the subject has Dravet Syndrome, myoclonic-absence epilepsy, Lennox-Gastaut syndrome, generalized epilepsy of unknown origin,
15 CDKL5 deficiency disease, PCDH19-epilepsy, continuous spikes and waves during sleep (CSWS), electrical status epilepticus during slow-wave sleep (ESES) epilepsy, Aicardi syndrome, Ohtahara syndrome, bilateral polymicrogyria, Dup15q syndrome, SNAP25-associated epilepsy, febrile infection related epilepsy syndrome (FIRES), benign rolandic epilepsy, juvenile myoclonic epilepsy, Doose syndrome, infantile spasm (West syndrome), or
20 Landau-Kleffner syndrome.

(27) The method of any one of (1) to (24), wherein the epilepsy is drug resistant epilepsy.

(28) The method of (27), wherein the subject has Dravet syndrome, Lennox-Gastaut syndrome, myoclonic absence seizures, febrile infection related epilepsy syndrome (FIRES), treatment-resistant adult focal epilepsy (TRAFF), or PCDH19-epilepsy.

5 (29) The method of any one of (1) to (24), wherein the subject presents with atonic seizures.

(30) The method of (29), wherein the subject has Lennox-Gastaut syndrome, tuberous sclerosis complex, Dravet syndrome, Doose syndrome, Aicardi syndrome, CDKL5
10 deficiency, or Dup15q syndrome.

(31) The method of any one of (1) to (24), wherein the subject has Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex.

15 (32) The method of any one of (1) to (31), wherein a total convulsive frequency of the subject is reduced by at least 50%, relative to the total convulsive frequency observed prior to administration of the rapidly infusing composition.

(33) The method of any one of (1) to (32), wherein a total convulsive frequency of the
20 subject is reduced by at least 70%, relative to the total convulsive frequency observed prior to administration of the rapidly infusing composition.

(34) The method of any one of (1) to (33), wherein the rapidly infusing composition is administered in combination with an antiepileptic drug.

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(35) The method of (34), wherein the antiepileptic drug is at least one selected from the group consisting of phenobarbital, eslicarbazepine, ethosuximide, everolimus, tiagabine, acetazolamide, brivaracetam, cenobamate, clorazepate, lorazepam, methsuximide, primidone, diazepam, divalproex, felbamate, fenfluramine, carbamazepine, oxcarbazepine, lacosamide, vigabatrin, gabapentin, lamotrigine, pregabalin, baclofen, phenytoin, valproic acid or its salts such as sodium valproate, topiramate, zonisamide, levetiracetam, clonazepam, rufinamide, stiripentol, perampanel, and fosphenytoin.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, it is understood that other embodiments may be utilized and structural and operational changes may be made without departure from the scope of the present embodiments disclosed herein.

Definitions

As used herein, the terms “compound” and “product” are used interchangeably, and are intended to refer to a chemical entity, whether in the solid, liquid or gaseous phase, and whether in a crude mixture or purified and isolated. Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the disclosure. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present, and all such stable isomers are contemplated in the present disclosure. Cis- and trans- (or E- and Z-) geometric isomers, when present, may be isolated as a mixture of isomers or as separated isomeric forms. Compounds referenced in the disclosure can be isolated in optically active or racemic forms. Optically active forms may be prepared

by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare these compounds and intermediates made therein are considered to be part of the present disclosure. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography, fractional crystallization, or through the use of a chiral agent. Depending on the process conditions, the end products referenced in the present disclosure are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the disclosure. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds may be separated into the individual isomers. Compounds referenced in the present disclosure, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the disclosure. Further, a given chemical formula or name shall encompass all conformers, rotamers, or conformational isomers thereof where such isomers exist. Different conformations can have different energies, can usually interconvert, and are very rarely isolatable. There are some molecules that can be isolated in several conformations. For example, atropisomers are isomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. It should be understood that all conformers, rotamers, or conformational isomer forms, insofar as they may exist, are included within the present disclosure.

As used herein, the term "solvate" refers to a physical association of a referenced compound with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances, the solvate will be capable of

isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. Solvate encompasses both solution phase and isolable solvates. Exemplary solvent molecules which may form the solvate include, but are not limited to, water, methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, isobutanol, tert-butanol, ethyl acetate and other lower alkanols, glycerin, acetone, dichloromethane (DCM), dimethyl sulfoxide (DMSO), dimethyl acetate (DMA), dimethylformamide (DMF), isopropyl ether, acetonitrile, toluene, *N*-methylpyrrolidone (NMP), tetrahydrofuran (THF), tetrahydropyran, other cyclic mono-, di- and tri-ethers, polyalkylene glycols (e.g., polyethylene glycol, polypropylene glycol, propylene glycol), and mixtures thereof in suitable proportions. Exemplary solvates include, but are not limited to, hydrates, ethanlates, methanlates, isopropanolates and mixtures thereof. Methods of solvation are generally known to those of ordinary skill in the art.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, “pharmaceutically acceptable salt” refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids and phenols. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound

formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Company, Easton, Pa. (1990)—which is incorporated herein by reference in its entirety.

When referencing a particular composition/material, the phrase “consists essentially of”, means that the particular composition/material may include minor amounts of impurities so long as those impurities do not affect the basic and novel property of the invention—the ability to treat epilepsy.

As used herein, the terms “optional” or “optionally” means that the subsequently described event(s) can or cannot occur or the subsequently described component(s) may or may not be present (e.g., 0 wt.%).

As used herein, the terms “treat”, “treatment”, and “treating” in the context of the administration of a therapy to a subject in need thereof refers to the reduction or amelioration of severity of symptoms of the condition being treated; reduction of duration of symptoms of

the condition being treated; reduction, inhibition, slowing, or arresting of the progression of symptoms associated with the condition; reduction of frequency of symptoms of the condition being treated; elimination of symptoms and/or underlying cause of the condition; prevention of the occurrence of symptoms of the condition, for example in a subject that may
5 be predisposed to the condition but does not yet experience or exhibit symptoms of the condition; improvement or remediation or amelioration of damage following a condition, for example improving, remediating, or ameliorating neurological damage or other physical damage associated with epileptic seizures; and/or causing regression of the condition.

As used herein, “seizure freedom” is defined as freedom from all types of seizures for
10 12 months or longer or three times the preintervention interseizure interval, whichever is longer. With continued and sustained seizure freedom, the subject’s epilepsy may be considered to be “resolved”—the subject has remained seizure-free for the past 10 years, while taking no seizure medication for the last 5 years.

As used herein, “drug resistant epilepsy” (DRE), is defined as epilepsy that does not
15 achieve sustained seizure freedom status after adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination), per the International League Against Epilepsy (ILAE) guidance, *see* Kwan et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies, 2010, *Epilepsia*, 51(6):1069–1077.

20 The term “subject” and “patient” are used interchangeably. As used herein, they refer to any subject for whom or which therapy is desired. In most embodiments, the subject is a human.

The terms “administer”, “administering”, “administration”, and the like, as used herein, refer to the methods that may be used to enable delivery of the active therapeutic

ingredient (ATI) to the desired site of biological action. Routes or modes of administration are as set forth herein.

The term “Rapid Infusion Technology™ (RITE) platform” or “rapidly infusing composition”, as used herein means a solid dosage form containing medicinal substances that disintegrates rapidly in the oral cavity (when contacted with saliva) with no need for chewing or drinking/swallowing liquids (e.g., water, liquid carriers, saliva, etc.) to ingest these medicinal substances, with an *in-vitro* disintegration time of 30 second or less according to the United States Pharmacopeia (USP) <701> Disintegration Test. The disclosed rapidly infusing compositions are thus a different dosage form than, for example, a chewable tablet, a lozenge intended to be dissolved slowly in the mouth, an orally disintegrating film or tablet designed to be dissolved/disintegrated in the mouth and swallowed (also called “orodispersible” formulations), a tablet that should be swallowed whole with food or liquid, oral liquid dosage forms, or any other oral dosage form designed for absorption from the GI tract.

The dosage amount and treatment duration are dependent on factors, such as bioavailability of a drug, administration mode, toxicity of a drug, gender, age, lifestyle, body weight, the use of other drugs and dietary supplements, the disease stage, tolerance and resistance of the body to the administered drug, etc., and then determined and adjusted accordingly. The terms “effective amount” or “therapeutically effective amount” refer to a sufficient amount of an active therapeutic ingredient (ATI) being administered which provides the desired therapeutic or physiological effect or outcome, for example, the amount of ATI sufficient for reducing convulsive seizure frequency or elimination of epileptic seizures altogether. The result can be a reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. Undesirable effects, e.g. side effects, are sometimes manifested along with the desired therapeutic effect; hence, a

practitioner balances the potential benefits against the potential risks in determining what is an appropriate “effective amount”. The exact amount required will vary from subject to subject, depending on the age and general condition of the subject, mode of administration, and the like. An appropriate “effective amount” in any individual case may be determined by one of ordinary skill in the art using only routine experimentation, for example through the use of dose escalation studies.

Rapid Infusion Technology™ (RITE) Platform

The present disclosure provides a therapeutic formulation presented in the form of a rapidly infusing composition which is suitable for administration of lipophilic active therapeutic ingredients (ATIs) such as cannabidiol (CBD) via a non-gastric mucosal surface. As described in more detail below, the novel delivery platform allows otherwise difficult to formulate ATIs—such as CBD—to be presented in unit dosage form for accurate dosing and in an easy-to-take format for high levels of patient compliance. For example, the rapidly infusing composition may be presented in tablet form and packaged in individual blister units.

In particular, the rapidly infusing composition enables oral mucosal administration of lipophilic ATIs in a solid dosage form directly into systemic circulation via the sublingual mucosa or the buccal mucosa and avoidance of first pass metabolism. The rapidly infusing composition thus presents lipophilic ATIs such as CBD (which may otherwise be susceptible to extensive first pass metabolism) in a highly bioavailable dosage form, typically with a bioavailability of at least 50%, preferably at least 55%, preferably at least 60%, preferably at least 65%, preferably at least 70%, preferably at least 75%, preferably at least 80%, preferably at least 85%, preferably at least 90%, and up to 99%, preferably up to 98%, preferably up to 96%, preferably up to 95%, preferably up to 92%. Such high bioavailability

allows the dosage amount of ATI to be reduced, whilst maintaining the same pharmacological effect. For example, the RITe™ platform allows CBD or its derivatives/analogues to be dosed in an amount of under 5 mg/kg/day for the treatment of epilepsy.

5 Additionally, the rapidly infusing composition enables a defined dose of ATI to be absorbed via the oral mucosae, prior to the gastric mucosa, thereby presenting a defined and consistent level of ATI into systemic circulation for consistent and reliable pharmacological effects. Consistency in pharmacological effects helps to improve patient adherence during treatment. The aforementioned high levels of bioavailability may be consistently achieved
10 because the RITe™ platform reduces the tendency for enteral oral administration through voluntary or involuntary swallowing by shortening the residence time the ATI spends in the oral cavity. Any amount of ATI (e.g., CBD) that is swallowed would be subject to first-pass metabolism and thus overall lower bioavailability. Swallowing further results in greater variability in the effective amount of dosing, as a result of variability in the amount
15 swallowed and the greater subject variability of bioavailability through first-pass metabolism for the amount swallowed.

Administration may be carried out by simply placing the rapidly infusing composition directly in the buccal cavity (between the cheek and gum) or over the sublingual mucous gland (under the ventral surface of the tongue). Preferred rapidly infusing compositions are
20 those which are lyophilized products formulated for rapid disintegration when placed in such an oral environment for rapid release of the ATI. The rapidly infusing compositions of the present disclosure may have a disintegration time of from approximately 1 second to 30 seconds or less, preferably 25 seconds or less, preferably 20 seconds or less, preferably 15 seconds or less, preferably 10 seconds or less, preferably 5 seconds or less, preferably 3
25 seconds or less, according to the United States Pharmacopeia (USP) <701> Disintegration

Test performed in deionized water maintained at $37^{\circ}\text{C} \pm 2^{\circ}$. In particular, preferred rapidly infusing compositions are those formulated for oral disintegration in 5 seconds or less, preferably 4 seconds or less, preferably 3 seconds or less, preferably 2 seconds or less, preferably in approximately 1 second, according to the United States Pharmacopeia (USP)

- 5 <701> Disintegration Test performed in deionized water maintained at $37^{\circ}\text{C} \pm 2^{\circ}$. A disintegration profile no higher than the above-mentioned upper limit when in intimate contact with a non-gastric mucosal surface provides for rapid absorption of the ATI and short onset times to therapeutic relief.

The easy-to-take oral mucosal dosage form presented herein is a vast improvement
10 over the cumbersome and generally unpleasant oral liquid dosage form of Epidiolex®, which as discussed heretofore, is known to cause gastrointestinal side effects and often requires multiple loadings and dispensings of the oral syringe to meet the prescribed high dosages—a particular concern given that a large percent of the patient population receiving Epidiolex® will be children, some as young as two-years old. In contrast, administration of the rapidly
15 infusing composition of the present disclosure is easy, one simply “takes it and it’s gone,” with no need for swallowing, thus offering improved patient compliance whether self-administered or administered by a healthcare provider, a care-taker, etc.

Patient compliance may also be improved in terms of temporary abstinence from swallowing, which is often triggered when a patient is presented with foul-tasting oral
20 medications. Any issues related to foul taste may be minimized with the above rapid disintegration times, which reduces the tendency for enteral oral administration through voluntary or involuntary swallowing, and as a result, the aforementioned high levels of bioavailability may be achieved.

The rapid disintegration profile disclosed herein, coupled with the direct introduction
25 of the ATI into systemic circulation through the sublingual mucosa or the buccal mucosa,

preferably through the buccal mucosa, provides a rapid onset of therapeutic effect. For example, the rapidly infusing composition may provide the desired relief from epileptic seizure episodes in (has an onset time of) under 15 minutes, preferably under 10 minutes, preferably under 5 minutes, preferably under 4 minutes, preferably under 3 minutes, preferably under 2 minutes, preferably under 1 minute, preferably under 45 seconds, preferably under 30 seconds, preferably under 20 seconds, preferably under 10 seconds, preferably approximately 5 seconds. Such short onset times are superior to those which can be obtained with traditional oral dosage forms such as tablets taken with food or liquids, liquid dosage forms, as well as orodispersible dosage forms dissolved by mouth and then swallowed.

The rapidly infusing composition herein generally contains (a) a pharmaceutically acceptable binder and/or excipient system that includes gelatin and a sugar alcohol e.g., mannitol, and optionally one or more of a sweetener, a flavorant, and a colorant; and (b) a therapeutically effective amount of an active therapeutic ingredient such as cannabidiol (CBD) or a pharmaceutically acceptable derivative/analog, salt, or solvate thereof.

Pharmaceutically acceptable carrier and/or excipient system

Carriers and/or excipients are ingredients which do not provide a therapeutic effect themselves, but which are designed to interact with, and enhance the properties of, the active therapeutic ingredient. In particular, carriers and/or excipients may act as a vehicle for transporting the active therapeutic ingredient from one organ, or portion of the body, to another organ, or portion of the body. The selection of appropriate carrier/excipient ingredients may impact the solubility, distribution, release profile/kinetics, absorption, serum stability, therapeutic onset time, and ultimately the efficacy of the ATI, as well as the shelf-life, dosage forms, and processability of the drug product. Each ingredient in the

pharmaceutically acceptable carrier and/or excipient system must be “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of the rapidly infusing composition and not injurious to the patient.

In light of the above, particular preference is given herein to pharmaceutically acceptable carrier and/or excipient systems which include gelatin and a sugar alcohol (e.g., mannitol).

Gelatin is to be included in the pharmaceutically acceptable carrier and/or excipient system in order to effect matrix formation in the lyophilized product, i.e., gelatin may act primarily as a matrix former. During manufacture of the rapidly infusing composition, lyophilization from an aqueous suspension results in the removal of water thereby leaving behind a gelatin matrix/scaffolding upon which the ATI can be evenly dispersed or suspended. It has been found that gelatin has a propensity to establish a stable matrix in lyophilized form, yet allow for rapid disintegration when brought into contact with the aqueous oral environment, thereby providing efficient transfer of the ATI from the hydrophilic vehicle to the oral mucosa. In this regard, mammalian gelatins such as bovine gelatin and porcine gelatin are preferred, with bovine gelatin being particularly preferred. In some embodiments, the rapidly infusing composition does not contain fish gelatin.

The amount of gelatin used may be varied. Generally, gelatin may be present in the rapidly infusing composition in an amount of at least 10 wt.%, preferably at least 12 wt.%, preferably at least 14 wt.%, preferably at least 16 wt.%, preferably at least 18 wt.%, preferably at least 20 wt.%, preferably at least 22 wt.%, and up to 50 wt.%, preferably up to 45 wt.%, preferably up to 40 wt.%, preferably up to 35 wt.%, preferably up to 32 wt.%, preferably up to 30 wt.%, preferably up to 28 wt.%, preferably up to 26 wt.%, preferably up to 24 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

The pharmaceutically acceptable carrier and/or excipient system is also formulated with one or more sugar alcohols, which may act primarily as a bulking agent. Examples of sugar alcohols include, but are not limited to, erythritol, xylitol, sorbitol, maltitol, mannitol, lactitol, and glycerin, which may be used singly or in combinations. Advantage can also be taken of the effect of certain sugar alcohols in terms of taste (sweetness and coolness due to endothermal heat of solution), as well as their ability to aid/speed tablet disintegration. In this regard, particular preference is given to mannitol.

The sugar alcohol, preferably mannitol, may be present in the rapidly infusing composition in any amount which provides the desired bulking/taste/disintegration effects.

Generally, this amount will range from of at least 5 wt.%, preferably at least 10 wt.%, preferably at least 12 wt.%, preferably at least 14 wt.%, preferably at least 16 wt.%, preferably at least 18 wt.%, and up to 50 wt.%, preferably up to 45 wt.%, preferably up to 40 wt.%, preferably up to 35 wt.%, preferably up to 30 wt.%, preferably up to 28 wt.%, preferably up to 26 wt.%, preferably up to 24 wt.%, preferably up to 22 wt.%, preferably up to 20 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

In some embodiments, a weight ratio of gelatin to sugar alcohol ranges from 1:3, preferably from 1:2, preferably from 1:1, preferably from 1.1:1, and up to 3:1, preferably up to 2:1, preferably up to 1.5:1, preferably up to 1.2:1.

The pharmaceutically acceptable carrier and/or excipient system may also optionally include one or more of a sweetener, a flavorant, and a colorant.

The sweetener may be used in any amount which provides the desired sweetening effect, generally in amount of 0 to 10 wt.%, for example in an amount of up to 10 wt.%, preferably up to 8 wt.%, preferably up to 6 wt.%, preferably up to 5 wt.%, preferably up to 4 wt.%, preferably up to 3 wt.%, preferably up to 2 wt.%, preferably up to 1.5 wt.%, preferably up to 1 wt.%, preferably up to 0.5 wt.%, preferably up to 0.1 wt.%, based on a total weight of

the rapidly infusing composition on a dry basis. Suitable examples of sweeteners include, but are not limited to, aspartame, saccharin (as sodium, potassium or calcium saccharin), cyclamate (as a sodium, potassium or calcium salt), sucralose, acesulfame-K, thaumatin, neohesperidin, dihydrochalcone, ammoniated glycyrrhizin, dextrose, maltodextrin, fructose, levulose, sucrose, and glucose, which may be used singly or in combinations, with particular preference given to sucralose and acesulfame-K.

It is to be readily appreciated by those of ordinary skill in the art that one or more flavorants may be optionally included in the rapidly infusing composition to mask any unpleasant taste imparted by certain ingredients (e.g., an unpleasant tasting ATI) or to otherwise impart an acceptable taste profile to the composition, and the composition is not limited to any particular flavor. Suitable flavorants include, but are not limited to, oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, oil of clove, cinnamon, anethole, menthol, thymol, eugenol, eucalyptol, lemon, lime, lemon-lime, orange, and other such flavor compounds to add fruit notes (e.g., citrus, cherry etc.), spice notes, etc., to the composition. The flavorants may be constitutionally composed of aldehydes, ketones, esters, acids, alcohols (including both aliphatic and aromatic alcohols), as well as mixtures thereof. Specific mention is made to lemon-lime flavor powder, which works particularly well with CBD as the ATI. The flavorant may be used in any amount which provides the desired flavor, generally in an amount of 0 to 10 wt.%, for example in an amount of up to 10 wt.%, preferably up to 8 wt.%, preferably up to 6 wt.%, preferably up to 5 wt.%, preferably up to 4 wt.%, preferably up to 3 wt.%, preferably up to 2 wt.%, preferably up to 1.5 wt.%, preferably up to 1 wt.%, preferably up to 0.5 wt.%, preferably up to 0.1 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

Two main strategies contribute to the taste masking success of the present disclosure. First, any issues related to foul taste are fundamentally mitigated by the short oral residence

times provided by the rapid disintegration profile described heretofore. One “takes it and it’s gone.” Second, when formulated with a flavorant, a robust mixture of flavors will hit the tongue at essentially the same time—the flavor of the CBD still hits the tongue, but the perception of the flavor is canceled or mitigated by the simultaneous arrival of other flavors.

5 Even then, the robust mixture of flavors will quickly subside as the composition is rapidly absorbed through the oral mucosa.

Likewise, the rapidly infusing composition may be colored or tinted through the optional use of one or more colorants. Suitable colorants are those approved by appropriate regulatory bodies such as the FDA and those listed in the European Food and Pharmaceutical Directives and include both pigments and dyes such as FD&C and D&C dyes, with specific
10 mention being made to FD&C Yellow #5.

In addition to gelatin and a sugar alcohol (e.g., mannitol), and optionally one or more of a sweetener, a flavorant, and a colorant, the pharmaceutically acceptable carrier and/or excipient system may optionally include one or more other pharmaceutically acceptable
15 carriers and/or excipients known to those of ordinary skill in art, in art appropriate levels. Examples of which include, but are not limited to,

- fillers or extenders such as starches (e.g., corn starch and potato starch), sugars (e.g., lactose or milk sugar, maltose, fructose, glucose, trehalose, sucrose), dextrates, dextrin, polydextrose, high molecular weight polyethylene glycols,
20 silicic acid, potassium sulfate, aluminum monostearate, polyesters, polycarbonates, and polyanhydrides;
- binders, such as cellulose and its derivatives, (e.g., carboxymethyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose (hypromellose), hydroxyethyl methyl
25 cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate

phthalate, and microcrystalline cellulose), alginates (e.g., sodium alginate), polyvinyl pyrrolidone, polyvinyl acetate-vinylpyrrolidone, polyacrylic acid, methacrylate copolymers (e.g., methyl methacrylate copolymers and Eudragit® products available from Evonik), modified starch, powdered tragacanth, malt, acacia (gum arabic), carbomer/carboxyvinyl polymer, carrageenan, chitosan, copovidone, cyclodextrins and modified cyclodextrins, guar gum, inulin, pectin (e.g., low viscosity pectin), polycarbophil or a salt thereof, polyvinyl alcohol, pullulan, xanthan gum, casein, protein extracts (e.g., whey protein extract, soy protein extract), zein, levan, elsinan, gluten, locust bean gum, gellan gum, and agar;

- disintegrating agents, such as agar-agar, calcium carbonate, tapioca starch, alginic acid, certain silicates, sodium carbonate, sodium starch glycolate, and cross-linked sodium carboxymethyl cellulose (croscarmellose sodium);

- surfactants/absorption accelerators/wetting agents/emulsifying agents/solubilizers,

including any of the anionic, cationic, nonionic, zwitterionic, amphoteric and betaine variety, such as polyalkylene oxide copolymers (e.g., poloxamers, polyethylene oxide-polypropylene oxide copolymers), sodium lauryl sulfate, sodium dodecyl benzene sulfonate, sodium docusate, sodium lauryl sulfoacetate, alkali metal or ammonium salts of lauroyl sarcosinate, myristoyl sarcosinate, palmitoyl sarcosinate, stearyl sarcosinate and oleoyl sarcosinate, cetyl alcohol, glycerol monostearate, glycerol oleate, fatty acid mono- and di-esters of glycerol, fatty acid esters of polyethylene glycol, polyoxyethylene sorbitol, fatty acid esters of sorbitan, polysorbates (polyalkolyated fatty acid esters of sorbitan) (e.g., polyoxyethylene sorbitan monostearate, monoisostearate and monolaurate), polyethylene oxide condensates of alkyl phenols, cocoamidopropyl betaine,

lauramidopropyl betaine, palmityl betaine, glyceryl monooleate, glyceryl
 monostearate, fatty alcohols (e.g., cetostearyl and cetyl alcohol), medium chain
 triglycerides, medium chain fatty acids, polyethoxylated castor oil,
 polyethoxylated alkyl ethers (e.g., ethoxylated isostearyl alcohols), polyethylene
 glycols (Macrogols), polypropylene glycols, polyoxyethylene stearates, anionic
 5 and nonionic emulsifying waxes, propylene glycol alginates, alcohol-oil
 transesterification products, polyglycerized fatty acids, propylene glycol fatty acid
 esters, mixtures of propylene glycol fatty acid esters and glycerol fatty acid esters,
 sterol and sterol derivatives, sugar esters, lower alcohol fatty acid esters, fatty
 10 acids and bile acids and their corresponding salts, ricinoleic acid / sodium
 ricinoleate, linoleic acid/ sodium linoleate, lauric acid/sodium laurate, mono-, di-,
 and tri-hydroxy bile acids and their salts, sulfated bile salt derivatives,
 phospholipids, ether carboxylates, succinylated monoglycerides,
 mono/diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters
 15 of mono- and diglycerides, alginate salts, and lactic esters of fatty acids;
 - plasticizers such as glycerin fatty acid esters, sucrose fatty acid esters, lecithin
 (e.g., enzyme modified lecithin), polysorbates, sorbitan fatty acid esters,
 polyethylene glycol, propylene glycol, triacetin, glycerol oleate, medium chain
 fatty acids, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate, diethyl
 20 phthalate, castor oil, dibutyl sebacate, and acetylated monoglycerides;
 - absorbents, such as kaolin and bentonite clay;
 - lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene
 glycols, zinc stearate, sodium stearate, stearic acid, ethyl oleate, and ethyl laurate;
 - controlled release agents such as cross-linked polyvinyl pyrrolidone
 25 (crospovidone);

- opacifying agents such as titanium dioxide;
- buffering agents, including alkaline buffering agents, such as sodium hydroxide, sodium citrate, magnesium hydroxide, aluminum hydroxide, sodium carbonate, sodium bicarbonate, potassium phosphate, potassium carbonate, potassium bicarbonate, calcium phosphate, potassium hydroxide, calcium hydroxide, magnesium oxide, potassium dihydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, calcium carbonate, magnesium carbonate;
- osmotic agents such as sodium chloride, calcium chloride, potassium chloride
- diluents/tableting agents such as dicalcium phosphate and colloidal silicon dioxide;
- antioxidants, including (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, and sodium sulphite, (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, and alpha-tocopherol; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), tartaric acid, and phosphoric acid;
- antibacterial and antifungal agents, such as paraben, chlorobutanol, phenol, sorbic acid;
- mucosal adhesion enhancers such as starch graft copolymers (e.g., starch/acrylic acid copolymers) and other water-swellaable polymers that adhere to wet surfaces of the oral mucosa such as carbomers, hydrolysed polyvinyl alcohol, polyethylene oxides, and polyacrylates;
- as well as other non-toxic compatible substances employed in pharmaceutical formulations, such as liposomes and micelle forming agents;
- including mixtures thereof.

Preferred rapidly infusing compositions are those which contain less than 1 wt.%, preferably less than 0.5 wt.%, preferably less than 0.1 wt.%, preferably less than 0.05 wt.%, preferably less than 0.001 wt.%, preferably 0 wt.%, of other pharmaceutically acceptable carriers and/or excipients, such as those listed above, in particular alkaline buffering agents and/or surfactants.

Also preferred are rapidly infusing compositions which do not contain inert diluents, aqueous carriers, or non-aqueous carriers commonly used in the art for manufacture of liquid dosage forms for oral administration, such as emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. Examples of inert diluents, aqueous or non-aqueous carriers, etc. which are preferably excluded herein may include, but are not limited to, water or other solvents, solubilizing agents, and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, glycerol, polyethylene glycol, propylene glycol, 1,3-butylene glycol, oils (whether synthetic, semi-synthetic, or naturally occurring, such as long chain triglycerides, mixed glycerides, and free fatty acids, in particular, cottonseed oil, groundnut oil, corn oil, germ, olive oil, castor oil, sesame oil, borage oil, coconut oil, soybean oil, safflower oil, sunflower oil, palm oil, peanut oil, peppermint oil, poppy seed oil, canola oil, hydrogenated soybean oil, hydrogenated vegetable oils, glyceryl distearate, behenic acid, caprylic/capric glycerides, lauric acid, linoleic acid, linolenic acid, myristic acid, palmitic acid, palmitoleic acid, palmitostearic acid, ricinoleic acid, stearic acid, soy fatty acids, oleic acid, glyceryl esters of fatty acids such as glyceryl behenate, glyceryl isostearate, glyceryl laurate, glyceryl palmitate, glyceryl palmitostearate, glyceryl ricinoleate, glyceryl oleate, glyceryl stearate), tetrahydrofuryl alcohol, fatty acid esters of sorbitan, organic esters such as ethyl oleate, and mixtures thereof, with specific mention being made to ethyl alcohol and sesame oil.

Active therapeutic ingredient (ATI)

The amount of active therapeutic ingredient (ATI) which can be combined with the pharmaceutically acceptable carrier and/or excipient system to produce the rapidly infusing composition may vary depending upon the subject being treated, and other factors. The amount of ATI which can be combined with the pharmaceutically acceptable carrier and/or excipient system to produce a single dosage form will generally be that amount which produces a therapeutic effect. Generally, this amount will range from 0.1 to 90 wt.% of ATI, for example, at least 20 wt.%, preferably at least 22 wt.%, preferably at least 24 wt.%, preferably at least 26 wt.%, preferably at least 28 wt.%, preferably at least 30 wt.%, preferably at least 32 wt.%, preferably at least 34 wt.%, preferably at least 36 wt.%, preferably at least 38 wt.%, preferably at least 40 wt.%, preferably at least 42 wt.%, preferably at least 44 wt.%, preferably at least 46 wt.%, preferably at least 48 wt.%, preferably at least 50 wt.%, preferably at least 52 wt.%, preferably at least 54 wt.%, and up to 70 wt.%, preferably up to 68 wt.%, preferably up to 66 wt.%, preferably up to 64 wt.%, preferably up to 62 wt.%, preferably up to 60 wt.%, preferably up to 58 wt.%, preferably up to 56 wt.% of the ATI, based on a total weight of the rapidly infusing composition on a dry basis.

In terms of unit dose, the rapidly infusing composition is generally formulated with 2 to 100 mg of ATI per unit (e.g. tablet), for example at least 2 mg, preferably at least 4 mg, preferably at least 6 mg, preferably at least 8 mg, preferably at least 10 mg, preferably at least 12 mg, preferably at least 14 mg, preferably at least 16 mg, preferably at least 18 mg, preferably at least 20 mg, preferably at least 22 mg, preferably at least 24 mg, and up to 100 mg, preferably up to 75 mg, preferably up to 70 mg, preferably up to 65 mg, preferably up to 60 mg, preferably up to 55 mg, preferably up to 50 mg, preferably up to 45 mg, preferably up

to 40 mg, preferably up to 35 mg, preferably up to 30 mg, preferably up to 25 mg of ATI per unit (e.g., tablet).

In preferred embodiments, the rapidly infusing composition is formulated with, as the active therapeutic ingredient, cannabidiol (CBD), or any pharmaceutically acceptable

5 derivative/analog, salt, solvate, or stereoisomer thereof. In some preferred embodiments, CBD or a derivative/analog thereof is the only active therapeutic ingredient in the rapidly infusing composition. In some preferred embodiments, CBD is the only active therapeutic ingredient in the rapidly infusing composition. In some preferred embodiments, a CBD derivative/analog is the only active therapeutic ingredient in the rapidly infusing composition.

10 In other embodiments, CBD or derivative/analog thereof may be combined with other active therapeutic ingredients. For example, CBD or derivative/analog thereof, formulated as described below may be combined with a water-soluble ATI such as melatonin, as a sleep aid.

Preferred rapidly infusing compositions are those which are formulated with CBD, preferably a solid form of CBD. That is, the rapidly infusing composition is prepared through
15 lyophilization from a drug product suspension in which the CBD is in the form of a solid. In particular, micronized particles of CBD are preferred. In some embodiments, the rapidly infusing composition is formulated with solid CBD in the form of micronized particles having a D50 particle size in the range of 1 μm to 50 μm , for example, those having a D50
20 particle size of at least 1 μm , preferably at least 10 μm , preferably at least 20 μm , preferably at least 30 μm , preferably at least 40 μm , and up to 50 μm , preferably up to 40 μm , preferably up to 30 μm , preferably up to 20 μm , preferably up to 10 μm .

Even more preferred are those rapidly infusing compositions which are formulated with a solid form of CBD having a purity of at least 95 wt.%, preferably at least 96 wt.%,
25 preferably at least 97 wt.%, preferably at least 98 wt.%, preferably at least 99 wt.%. While

- CBD having a purity of 100 wt.% is likely not achievable, preferably rapidly infusing compositions are formulated with a solid form of CBD having a purity up to 99.1 wt.%, preferably up to 99.2 wt.%, preferably up to 99.3 wt.%, preferably up to 99.4 wt.%, preferably up to 99.5 wt.%, preferably up to 99.6 wt.%, preferably up to 99.7 wt.%, preferably up to 99.8 wt.%, preferably up to 99.9 wt.%. The percent purity of CBD refers to the percent of CBD by mass relative to a total weight of CBD containing material—the CBD containing material being the sum of CBD plus any additional impurities which may be present, such as those impurities originating from the biomass from which the CBD is obtained (e.g., *Cannabis sativa* L./“Industrial Hemp”) or encountered during manufacture.
- 10 The purity may be determined by methods known to those of ordinary skill in the art, for example, one or more of liquid chromatography such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LCMS), and liquid chromatography with tandem mass spectrometry (LCMSMS); gas chromatography such as headspace gas chromatography with flame ionization detection (HS-GC-FID), gas
- 15 chromatography mass spectrometry (GC/MS), and headspace gas chromatography-mass spectrometry (HSGCMS); inductively coupled plasma-mass spectrometry (ICP-MS); and polymerase chain reaction (PCR).

Examples of potential impurities, such as those originating from the biomass from which the CBD is obtained (e.g., *Cannabis sativa* L./“Industrial Hemp”) or encountered

20 during manufacture, include, but are not limited to,

- cannabinoids (other than CBD) including, but not limited to, cannabidivarin (CBDV), cannabichromene (CBC), cannabidiolic acid (CBDA), cannabigerol (CBG), cannabigerolic acid (CBGa), cannabinol (CBN), tetrahydrocannabinolic acid (THCa), tetrahydrocannabivarin (THCV), tetrahydrocannabivarin acid

(THCVa), and tetrahydrocannabinol (Δ^9 -THC) and related THC-cannabinoids such as Δ^8 -THC;

- pesticides including, but not limited to, aldicarb, carbofuran, chlordane, chlorfenapyr, chlorpyrifos, coumaphos, daminozide, dichlorvos (DDVP), dimethoate, ethoprophos, etofenprox, fenoxycarb, fipronil, imazalil, methiocarb, methyl parathion, paclobutrazol, propoxur, spiromamine, and thiocloprid;
- residual solvents including, but not limited to, 1,4-dioxane, 2-butanol, 2-ethoxyethanol, 1,2-dichloroethane, acetone, acetonitrile, benzene, butane, cumene, cyclohexane, chloroform, ethanol, ethyl acetate, ethyl benzene, ethylene oxide, ethylene glycol, ethyl ether, heptane, isopropanol, methanol, methylene chloride, hexanes, isopropyl acetate, pentanes, propane, toluene, tetrahydrofuran, trichloroethene, and xylenes;
- microbials including, but not limited to, *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terreus*, *Salmonella*, and Shiga toxin-producing *E. coli*;
- mycotoxins including, but not limited to, aflatoxins (e.g., aflatoxin B1, aflatoxin B2, aflatoxin G1, and aflatoxin G2) and ochratoxin A;
- heavy metals including, but not limited to, arsenic, cadmium, lead, and mercury;
- terpenes including, but not limited to, (1) monoterpenes such as camphene, camphor, 3-carene, α -cedrene, cedrol, endo-fenchyl alcohol, eucalyptol, fenchone, geraniol, geranyl acetate, hexahydrothymol, isoborneol, isopulegol, limonene, linalool, p-mentha-1,5-diene, β -myrcene, α - and β -pinene, pulegone, sabinene and hydrate, α - and γ -terpinene, terpineol, terpinolene, α -, β -, and γ -terpineol, nerol, borneol, and ocimene isomers I and II, and (2) sesquiterpenes such as α -bisabolol,

β -caryophyllene, caryophyllene oxide, guaiaol, α -humulene, cis- and trans-nerolidol, and valencene;

- as well as mixtures thereof.

In some embodiments, the rapidly infusing composition is formulated with a form of
5 CBD which contains less than 1 wt.%, preferably less than 0.5 wt.%, preferably less than 0.1 wt.%, preferably less than 0.05 wt.%, preferably less than 0.001 wt.%, preferably 0 wt.% of the above listed impurities, based on a total weight of the CBD material, with specific mention being made to THC. In some embodiments, the rapidly infusing composition is formulated with a form of CBD which contains no impurity, such as those listed above, in an
10 amount above the limits of detection (LOD) and/or limits of quantification (LOQ) for the technique/instrumentation being used to make such a determination. For example, preferred rapidly infusing compositions are those formulated with a pure form of CBD which has a THC content of less than 0.1577 wt.%, preferably less than 0.1 wt.%, preferably less than 0.01 wt.%, preferably less than 0.001 wt.%, based on a total weight of the CBD material. In
15 preferred embodiments, the rapidly infusing composition is formulated with a pure form of CBD which consists of, or consists essentially of, CBD.

The full effects of the present disclosure may not be realized when the rapidly infusing composition is formulated with an impure form of CBD or when the composition is formulated with CBD in oil/liquid form. Without being bound by theory, it is believed that
20 during the manufacture of the rapidly infusing composition, when the CBD is in solid form with sufficiently high purity, lyophilization from a drug product suspension generates a structured and robust matrix of gelatin as the water is removed via sublimation, and an even distribution of the CBD throughout the gelatin matrix. Such a structured assembly of CBD suspended within a gelatin matrix is believed to afford the rapidly infusing composition with
25 rapid disintegration properties and efficient transfer of CBD from the hydrophilic vehicle to

the mucous membrane of the buccal cavity, or the ventral surface under the tongue, upon administration.

On the contrary, when the composition is formulated with an impure (oil) form of CBD during manufacture, lyophilization is instead performed from an o/w emulsion of CBD, which may produce an unstable, disordered matrix of gelatin more prone to collapse back into an oil or semi-solid state. The resulting composition tends to suffer from poor shelf-life, increased disintegration times, and inferior delivery/uptake of the CBD into systemic circulation reflected in longer onset times and overall less efficacy against epilepsy conditions.

Accordingly, any CBD manufacturing method known by those of ordinary skill in the art which provides CBD in solid form, and of sufficient purity, may be utilized herein for preparation of the CBD ATI. For illustration purposes, one exemplary CBD manufacturing method is described below, although it should be understood that numerous modifications and variations are possible, and the CBD may be produced using methods or techniques otherwise than as specifically described.

CBD may be extracted/isolated from biomass, for example, a cured flower of *Cannabis sativa* L. The biomass may contain, for example, at least 1 mg/g, preferably at least 2 mg/g, preferably at least 3 mg/g, and up to 10 mg/g, preferably up to 8 mg/g, preferably up to 6 mg/g, preferably up to 4 mg/g of CBD; at least 50 mg/g, preferably at least 60 mg/g, preferably at least 70 mg/g, preferably at least 80 mg/g, preferably at least 90 mg/g, and up to 150 mg/g, preferably up to 140 mg/g, preferably up to 130 mg/g, preferably up to 120 mg/g, preferably up to 110 mg/g, preferably up to 100 mg/g of cannabidiolic acid (CBDa); and no detectable amount of THC. Extraction of the biomass with an alcoholic solvent (e.g., ethanol) and cooling may form a tincture. The tincture may be filtered to remove sediment and particulates, and concentrated, for example, using a rotary evaporator.

An aluminum phyllosilicate clay (e.g., bentonite) may then be mixed with the concentrated product at a weight ratio of at least 2:1, preferably at least 3:1, preferably at least 4:1, and up to 6:1, preferably up to 5:1, and the resulting mix filtered to remove fats, waxes, and lipids. The product may then be frozen/winterized, after which the frozen product
5 may be again filtered and taken through another solvent removal/recovery cycle to form a winterized crude.

Decarboxylation of the winterized crude by heating, for example in an induction oven centrifugal reactor, may be performed to remove the carboxylic acid functionality from the cannabinoids. Distillation of the decarboxylated material may then provide a distillate.

10 The distillate may then be precipitated in a high-pressure reactor using an alkane solvent (e.g., pentane), and a cryochamber may be used to subject the precipitate to cryo temperatures (e.g., -20 °F to -40 °F) to promote the growth of crystalline CBD. The CBD crystals may be washed with an alkane solvent (e.g., pentane), filtered, and ground to a finer particle size, prior to being purged in a vacuum oven for removal of solvents and impurities.

15 The obtained solid CBD may then be analyzed for purity, as appropriate.

In preferred embodiments, the rapidly infusing composition comprises, consists essentially of, or consists of gelatin, mannitol, sweetener, flavorant, colorant, and as the ATI, CBD or derivative/analog thereof.

Also contemplated for use as an active therapeutic ingredient are derivatives/analog
20 of CBD that retain the desired activity for the treatment of epilepsy. Derivatives/analog that retain substantially the same activity as CBD, or more preferably exhibit improved activity, may be produced according to standard principles of medicinal chemistry, which are well known in the art. Such derivatives/analog may exhibit a lesser degree of activity than CBD, so long as they retain sufficient activity to be therapeutically effective. Derivatives/analog
25 may exhibit improvements in other properties that are desirable in active therapeutic agents

such as, for example, improved solubility, reduced toxicity, enhanced uptake, increased bioavailability, etc. Contemplated CBD derivatives/analogs include, but are not limited to, cannabidiolic acid compounds and variants thereof, such as cannabidiolic acid and esters of cannabidiolic acid, in particular alkyl esters of cannabidiolic acid (e.g., cannabidiolic acid methyl ester); 5' side chain modified CBD compounds such as cannabidivarin (CBDV), cannabidiol-dimethylheptyl (CBD-DMH), and 1,2-cannabidiol-dimethylheptyl (1,2-CBD-DMH); 7-methyl modified CBD compounds such as 7-carboxy cannabidiol (7-COOH-CBD) and 7-hydroxy cannabidiol (7-OH-CBD); hydrogenated CBD compounds such as 8,9-dihydrocannabidiol (H₂-CBD) and tetrahydrocannabidiol (H₄-CBD); halogenated CBD compounds such as 3'-chloro-CBD, 3',5'-dichloro-CBD, 3'-bromo-CBD, 3',5'-dibromo-CBD, 3'-iodo-CBD, and 3',5'-diiodo-CBD; hydroxyl group modified CBD compounds such as desoxy-CBD and dimethylether CBD; cannabielsoin (CBE); machaeridiols A, B, and C; as well as any pharmaceutically acceptable salts, solvates, and/or stereoisomers of such compounds. When a CBD derivative/analog is used as the ATI in the disclosed rapidly infusing composition, particular preference is given to cannabidiolic acid methyl ester.

It is contemplated that CBD or derivatives/analogs of CBD may be useful in combination. It is also contemplated that CBD or derivatives/analogs of CBD may be useful in combination with current Standards of Care for the treatment of epilepsy as well as any that evolve over the foreseeable future. Specific dosages and dosing regimens would be based on physicians' evolving knowledge and the general skill in the art.

Process for manufacturing the rapidly infusing composition

Manufacturing of the rapidly infusing compositions are preferably pharmaceutical-GMP compliant and may be accomplished generally by bringing into association the ATI (e.g., CBD) with the gelatin and sugar alcohol (e.g., mannitol), and, optionally, one or more

accessory pharmaceutically acceptable carrier and/or excipient ingredients, in water to form a drug product suspension which is then lyophilized.

One exemplary method for manufacturing the rapidly infusing composition is presented below, although it should be understood that numerous modifications and variations are possible, and the rapidly infusing composition may be produced using methods or techniques otherwise than as specifically described.

Purified water, gelatin, and sugar alcohol (e.g., mannitol) may be charged to a mixer, for example a pot equipped with an overhead stirrer, and heated (e.g., 40 to 80 °C) with agitation until complete solvation. Any desired sweetener (e.g., a mixture of sucralose and acesulfame-K) may then be added and allowed to dissolve.

Upon cooling, for example to 20 to 35 °C, the solution may next be transferred to a homogenizer, and the ATI (e.g., CBD) may be subsequently charged and dispersed using the homogenizer, with preferable micronization of the ATI, to form a drug product suspension. Any desired flavorant and colorant may be added at this point with continued mixing. The drug product suspension may be transferred to a second mixer whilst maintaining a cooled temperature (e.g., 20 to 35 °C).

In a blistering machine equipped with a dosing system, blister pockets may next be filled with the drug product suspension until achieving a target dose weight, followed by freezing in a suitable cryochamber. The blister trays may be transferred from the cryochamber to a suitable refrigerated storage cabinet (e.g., at a temperature below 0 °C) to keep the product frozen prior to lyophilization. Then, the frozen blisters may be loaded into a lyophilizer and subject to lyophilization to sublimate the water and form the rapidly infusing compositions. Finally, when the lyophilization cycle is deemed complete, final sealing (e.g., heat sealing of blister lidding) may be performed to provide the rapidly infusing compositions in single dose units in individual blister units.

Therapeutic applications and methods

The present disclosure provides a method of treating epilepsy by administering to a subject in need thereof the disclosed rapidly infusing composition, in one or more of its
5 embodiments.

Epileptic syndromes often present with many different types of seizures, any of which may be treated herein. Epileptic seizures are generally categorized as: 1) focal onset seizures, where the seizure originates within networks limited to only one hemisphere, such as aura, motor, autonomic, and awareness/responsiveness seizures (e.g., focal impaired awareness
10 seizure and focal awareness seizure), including ictal atonia seizures; 2) generalized onset seizures, where the seizure arises within and rapidly engages bilaterally distributed networks, such as generalized tonic-clonic seizures, absence seizures, clonic seizures, tonic seizures, atonic seizures, and myoclonic seizures; and 3) unknown onset seizures where the origination site of the seizure cannot be determined. Subjects with epilepsy can also present with “mixed
15 seizures,” which are those defined by the existence of both generalized and focal onset seizures in the same subject.

The epilepsy treated herein may be childhood epilepsy, which refers to the many different syndromes and genetic mutations that can occur to cause epilepsy in childhood. Examples of childhood epilepsy include, but are not limited to, Dravet Syndrome, myoclonic-
20 absence epilepsy, Lennox-Gastaut syndrome, generalized epilepsy of unknown origin, CDKL5 deficiency disease, PCDH19-epilepsy, continuous spikes and waves during sleep (CSWS), electrical status epilepticus during slow-wave sleep (ESES) epilepsy, Aicardi syndrome, Ohtahara syndrome, bilateral polymicrogyria, Dup15q syndrome, SNAP25-associated epilepsy, febrile infection related epilepsy syndrome (FIRES), benign rolandic

epilepsy, juvenile myoclonic epilepsy, myoclonic astatic epilepsy (Doose syndrome), infantile spasm (West syndrome), and Landau-Kleffner syndrome.

The epilepsy treated herein may be drug resistant epilepsy (DRE). Examples of types of epilepsy which frequently fall into the drug resistant epilepsy category include, but are not
5 limited to, Dravet syndrome, Lennox-Gastaut syndrome, myoclonic absence seizures, febrile infection related epilepsy syndrome (FIRES), treatment-resistant adult focal epilepsy (TRAFE), and PCDH19-epilepsy.

The epilepsy treated herein may also be those epileptic disorder etiologies that present in the form of atonic seizures, which involve the loss of muscle tone, causing the person to
10 fall to the ground. Atonic seizures are often associated with Lennox-Gastaut syndrome, but are also associated with tuberous sclerosis complex, Dravet syndrome, Doose syndrome, Aicardi syndrome, CDKL5 deficiency, and Dup15q syndrome.

Administration of the rapidly infusing composition may result in the reduction of total convulsive seizure frequency or elimination of epileptic episodes altogether, for example,
15 where the subject attains seizure freedom, preferably where the subjects epilepsy is eventually considered to be resolved. In some embodiments, treatment with the rapidly infusing composition herein reduces the total convulsive frequency by at least 50%, preferably at least 60%, preferably at least 70%, preferably at least 75%, preferably at least 80%, preferably at least 85%, preferably at least 90%, preferably at least 95%, preferably at
20 least 99%, preferably 100%, relative to the total convulsive frequency observed prior to administration of the rapidly infusing composition. In some embodiments, the epilepsy is drug resistant epilepsy, and treatment herein reduces the total convulsive frequency by at least 50%, preferably at least 60%, preferably at least 70%, preferably at least 80%, preferably at least 90%, preferably at least 95%, preferably at least 99%, preferably 100%,

relative to the total convulsive frequency achieved from taking one or more antiepileptic drugs (AED) and prior to administration of the rapidly infusing composition.

With respect to administration, the rapidly infusing composition is preferably administered to the subject via one or more of the oral mucosae, preferably via the buccal mucosa (buccally) or the sublingual mucosa (sublingually). Advantages of oral mucosal delivery include the ease of administration, the ability to bypass first pass metabolic processes thereby enabling higher bioavailability than through enteral delivery via the gastrointestinal tract (which in turn allows the dosage amount of ATI to be reduced whilst maintaining the same pharmacological effect), less variability between patients, sustained drug delivery, and extensive drug absorption and rapid onset of therapeutic action due to either a large surface area in the case of sublingual administration or high-levels of vascularization in the case of buccal administration. Administration may be carried out by simply placing the rapidly infusing composition directly in the buccal cavity (between the cheek and gum) or over the sublingual mucous gland (under the ventral surface of the tongue). While the sublingual mucosa has a large surface area and extremely good permeability, the blood supply (blood flow) is lesser than that of the buccal cavity. Furthermore, sublingual administration tends to stimulate the flow of saliva more than buccal administration, and the increased saliva production may make it more difficult for patients to avoid swallowing. Any amount of ATI that is swallowed would be subject to first pass metabolism and thus overall lower bioavailability. Swallowing further results in greater variability in the effective amount of dosing, as a result of, including but not limited to, the variability in the amount swallowed and the greater patient variability of bioavailability through first-pass metabolism for the amount swallowed. Therefore, in preferred embodiments, the rapidly infusing composition is administered buccally (through the buccal mucosa). The rapid disintegration of the rapidly infusing composition, approximately in 1-5

seconds in preferred embodiments, and buccal administration together combine to provide optimal dosing control by limiting the time for potential swallowing and ensuring that the vast majority of the ATI is absorbed through the buccal mucosa. Administration may be performed by the subject (self-administered) or by someone other than the subject, for example, a healthcare provider, care-taker, family member, etc.

The actual amount of ATI administered to the subject may be varied so as to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, without being toxic to the subject. The selected amount of ATI administered to the subject will depend upon a variety of factors including the condition being treated, the activity of the ATI employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds, and/or materials used in combination with the rapidly infusing composition, the age, sex, weight, condition, general health, and prior medical history of the subject being treated, and like factors well known in the medical arts.

A physician having ordinary skill in the art can readily determine and prescribe the effective amount of the ATI required. For example, the physician could start doses of the ATI at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, a suitable dose of the ATI will be that amount which is the lowest dose effective to produce a therapeutic effect, which will generally depend upon the factors described above. Typically, when the ATI is CBD or a derivative/analog thereof, the therapeutically effective amount of CBD or a derivative/analog thereof will be under 5 mg/kg/day, for example in a range of from at least 0.1 mg/kg/day, preferably at least 0.15 mg/kg/day, preferably at least 0.2 mg/kg/day, preferably at least 0.25 mg/kg/day, preferably at least 0.3 mg/kg/day, preferably at least 0.35

mg/kg/day, preferably at least 0.4 mg/kg/day, preferably at least 0.45 mg/kg/day, preferably at least 0.5 mg/kg/day, preferably at least 0.55 mg/kg/day, preferably at least 0.6 mg/kg/day, and up to 4.9 mg/kg/day, preferably up to 4.8 mg/kg/day, preferably up to 4.6 mg/kg/day, preferably up to 4.4 mg/kg/day, preferably up to 4.2 mg/kg/day, preferably up to 4

5 mg/kg/day, preferably up to 3.5 mg/kg/day, preferably up to 3 mg/kg/day, preferably up to 2.5 mg/kg/day, preferably up to 2 mg/kg/day, preferably up to 1.5 mg/kg/day, preferably up to 1.25 mg/kg/day, preferably up to 1 mg/kg/day, preferably up to 0.9 mg/kg/day, preferably up to 0.8 mg/kg/day, preferably up to 0.7 mg/kg/day, preferably up to 0.65 mg/kg/day.

The methods herein may involve administering one, or more than one, unit of the rapidly infusing composition per dose (dosing event). For example, in circumstances where each unit of the rapidly infusing composition contains 20 mg of ATI (e.g., CBD), and it has been determined that a subject weighing 20 kg requires a therapeutically effective amount of 2 mg/kg/day of ATI, then the subject may be given one (1) unit (e.g., tablet) twice a day (b.i.d.) to achieve the desired therapeutically effective amount of 2 mg/kg/day. In another example, in circumstances where each unit of the rapidly infusing composition contains 10 mg of ATI (e.g., CBD), and it has been determined that a subject weighing 20 kg requires a therapeutically effective amount of 2 mg/kg/day of ATI, then the subject may be given two (2) units (e.g., tablets) twice a day (b.i.d.) to achieve the desired therapeutically effective amount of 2 mg/kg/day. Accordingly, depending on the unit dose of ATI in each unit of the rapidly infusing composition, the therapeutically effective amount of ATI prescribed, etc., 1, 2, 3, 4, 5, or more units (e.g., tablets) may be administered to the subject per dose.

Accordingly, the phrases “administering to the subject in need thereof a rapidly infusing composition”, “the rapidly infusing composition is administered”, etc., are intended herein to include administration of a single unit (e.g., tablet), or multiple units (e.g., tablets), to the subject in order to provide the therapeutically effective amount of ATI, e.g., CBD. While it

may be possible to administer partial (e.g., half) tablets to the subject, for practical reasons, it is preferred that one or more whole tablets are administered to the subject.

In preferred embodiments, the subject may be prescribed a dosage regimen that involves a single dosing event per day (QD), or multiple, separate dosing events at appropriate time intervals throughout the day. The subject may be administered a therapeutically effective amount of ATI 1 time, 2 times, 3 times, or 4 times, at appropriate intervals, throughout the day. Preferred dosing regimens involve administration at the same time each day, for example, at meal times every morning and/or evening. Particularly preferred dosing schedules involve administration of the rapidly infusing composition once (QD), two times (b.i.d.), or three times (t.i.d.) per day. The rapidly infusing composition may also be administered on an hourly dosing schedule (q), for example, administration may take place every 8 to 12 hours, as appropriate. Regardless of dosing schedule, when the ATI is CBD or a derivative/analog thereof, the maximum daily dosage of CBD or derivative/analog thereof is preferably less than 5 mg/kg/day. Treatment may involve administration until desired effects are achieved, for example for weeks, months, or even years, or throughout the subjects life-span.

Preferred dosing regimens are those involving a consistent dosing amount and schedule. One non-limiting example of a dosing regimen may involve the subject taking one unit of the rapidly infusing composition (e.g., 25 mg CBD)—therapeutically effective amount of 25 mg CBD per dose—once per day (QD). Another non-limiting example of a dosing regimen may involve the subject taking one unit of the rapidly infusing composition (e.g., 25 mg CBD)—therapeutically effective amount of 25 mg CBD per dose—two times per day (b.i.d.). Another non-limiting example of a dosing regimen may involve the subject taking two units of the rapidly infusing composition (e.g., 10 mg CBD each)—therapeutically effective amount of 20 mg CBD per dose—two times per day (b.i.d.).

Upon being administered buccally (between the cheek and gum) or sublingually (under the ventral surface of the tongue), the rapidly infusing composition preferably disintegrates in 5 seconds or less, preferably 4 seconds or less, preferably 3 seconds or less, preferably 2 seconds or less, preferably about 1 second. Further, this route of administration may provide a single dose bioavailability of at least 50%, preferably at least 55%, preferably at least 60%, preferably at least 65%, preferably at least 70%, preferably at least 75%, preferably at least 80%, preferably at least 85%, preferably at least 90%, and up to 99%, preferably up to 98%, preferably up to 96%, preferably up to 95%, preferably up to 92%.

Besides efficacy of treatment and general relief from seizures, pharmacokinetic outcomes may provide another useful measure of *in vivo* performance. In this regard, the rapidly infusing composition formulated with CBD and administered according to the methods described herein may provide a time to maximum plasma concentration (T_{max}) of less than 5 hours, preferably less than 4 hours, preferably less than 3 hours, preferably less than 2 hours, preferably less than 1 hour, preferably less than 45 minutes, preferably less than 30 minutes, preferably less than 15 minutes; an area under the plasma concentration versus time curve (AUC) of at least 1 h x ng/mL, preferably at least 3 h x ng/mL, preferably at least 5 h x ng/mL, preferably at least 10 h x ng/mL, preferably at least 15 h x ng/mL, preferably at least 20 h x ng/mL, preferably at least 25 h x ng/mL, preferably at least 30 h x ng/mL, and up to 80 h x ng/mL, preferably up to 70 h x ng/mL, preferably up to 60 h x ng/mL, preferably up to 50 h x ng/mL, preferably up to 40 h x ng/mL, from a single (1) unit of rapidly infusing composition formulated with 25 mg CBD; and a mean plasma half-life ($t_{1/2}$) of CBD of at least 1 hour, preferably at least 2 hours, preferably at least 3 hours, preferably at least 4 hours, preferably at least 5 hours, preferably at least 6 hours, and up to 12 hours, preferably up to 11 hours, preferably up to 10 hours, preferably up to 9 hours, preferably up to 8 hours, preferably up to 7 hours, for a single dose, but may provide a significantly higher mean

plasma half-life ($t_{1/2}$) after prolonged buccal or sublingual administration (e.g., $t_{1/2}$ of 2 to 5 days).

Using the platform, the rapidly infusing composition may be used as a stand-alone therapeutic agent for the treatment of epilepsy or may be used in combination therapy—

5 wherein the rapidly infusing composition is used in combination with one or more other forms of therapy such as one or more second therapeutic agents. The combination therapy may be applied to treat epileptic seizures, or a combination of epileptic seizures and a different condition.

Combination therapy may involve administering the rapidly infusing composition
10 formulated with CBD or derivative/analog thereof and a second therapeutic agent, such as one or more antiepileptic drugs (AEDs) (other than CBD or its derivatives/analog) for the treatment of epilepsy. In particular, when co-administered with one or more AEDs, the rapidly infusing compositions formulated with CBD or a derivative/analog thereof may advantageously function to reduce traditional AED usage, for example by reducing the
15 number of AEDs dosed, reducing the overall dosage of the AED(s) needed, or shortening the AED dosage period, without sacrificing antiepileptic efficacy.

AEDs suitable for use in combination therapy may function as voltage-gated ion channel blockers, ligand-gated ion channel blockers, antagonists of the excitatory receptors for glutamate and N-methyl-D-aspartate, or enhancers of the γ -aminobutyric acid, and may be
20 categorized as narrow-spectrum (typically used to treat focal seizures) or broad-spectrum (treats a variety of seizure varieties). Examples of AEDs include, but are not limited to, phenobarbital, eslicarbazepine, ethosuximide, everolimus, tiagabine, acetazolamide, brivaracetam, cenobamate, clobazam, clorazepate, lorazepam, methsuximide, primidone, diazepam, divalproex, felbamate, fenfluramine, carbamazepine, oxcarbazepine, lacosamide,
25 vigabatrin, gabapentin, lamotrigine, pregabalin, baclofen, phenytoin, valproic acid or its salts

such as sodium valproate, topiramate, zonisamide, levetiracetam, clonazepam, rufinamide, stiripentol, perampanel, and fosphenytoin. When the rapidly infusing composition is co-administered with an AED, it is preferred that the AED is not clobazam, i.e., the rapidly infusing composition is not co-administered with clobazam.

5 Combination therapy is intended to embrace administration of these therapies in a sequential manner, that is, wherein the rapidly infusing composition and one or more other therapies are administered at a different time, as well as administration of these therapies, or at least two of the therapies, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the
10 subject multiple, single dosage forms for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, the rapidly infusing
15 composition formulated with CBD or derivative/analog thereof may be administered via buccal administration while a second therapeutic agent of the combination may be administered intravenously. Alternatively, for example, all therapeutic agents may be administered buccally.

 Combination therapy also can embrace the administration of the rapidly infusing
20 composition in further combination with other biologically active ingredients and non-drug therapies. Examples of non-drug therapies may include, but are not limited to, surgery to remove a localized resectable section of brain tissue identified to cause seizures such as anterior temporal lobe resection to remove the hippocampus, removal of tumors, removing parts of the neocortex, and corpus callosotomy; and neurostimulation such as vagus nerve
25 stimulation, anterior thalamic stimulation (deep brain stimulation), and closed-loop

responsive stimulation. Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agent(s) and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still
5 achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

The examples below are intended to further illustrate the materials and methods of the present disclosure, and are not intended to limit the scope of the claims.

Where a numerical limit or range is stated herein, the endpoints are included. Also, all
10 values and subranges within a numerical limit or range are specifically included as if explicitly written out.

As used herein the words “a” and “an” and the like carry the meaning of “one or more.”

The present disclosure also contemplates other embodiments “comprising”,
15 “consisting of” and “consisting essentially of”, the embodiments or elements presented herein, whether explicitly set forth or not.

All patents and other references mentioned above are incorporated in full herein by this reference, the same as if set forth at length.

Obviously, numerous modifications and variations of the present invention are
20 possible in light of the above teachings. It is therefore to be understood that, within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

EXAMPLES

25 Rapidly Infusing Composition

Ingredients

The ingredients that were used to make the rapidly infusing composition and the placebo are given in Table 1. USP = United States Pharmacopeia. EP = European Pharmacopoeia. NF = National Formulary.

5

Table 1. Ingredients

Ingredient	Primary Function	Specification
Gelatin	Matrix former	USP/EP/NF
Mannitol	Bulking agent	USP/EP
Lemon-lime flavor powder	Flavorant	Non-compendial
CBD isolate	ATI	Non-compendial
Sucralose	Sweetener	USP/NF
Acesulfame-K	Sweetener	USP/NF
FD&C Yellow #5	Colorant	Non-compendial
Purified water	Vehicle	USP/EP

An example rapidly infusing composition was made using the formulation given in Table 2. The amount of each component is expressed in terms of weight percentage relative to a total weight (100%). The weight percentage of each component in the drug product suspension is on a wet basis (prior to removal of water). The weight percentage of each component in the rapidly infusing composition is on a dry basis (after removal of water).

10

Table 2. Example rapidly infusing composition formulation

Ingredient	Drug product suspension	Rapidly Infusing Composition	
	% wt./wt. (wet)	wt./unit (dry)	% wt./wt. (dry)
Gelatin	3.5	10.5 mg	22.7
Mannitol	3.0	9 mg	19.4
Lemon-lime flavor powder	0.2	0.6 mg	1.3
CBD isolate	8.4	25 mg	54.0
Sucralose	0.2	0.6 mg	1.3
Acesulfame-K	0.2	0.6 mg	1.3
FD&C Yellow #5	Trace	Trace	Trace
Purified water	84.5	Removed during manufacture	Removed during manufacture
Total	100.0	--	100.0

Methods of making the rapidly infusing composition

- 5 • Purified water was charged to a pot and mixed using an overhead stirrer as an agitating device.
- With agitation, the requisite amount of gelatin and mannitol were dispersed, and the mixture was heated until the excipients were dissolved.
- Once dissolved, the sweeteners sucralose and acesulfame-K were added and allowed to dissolve.
- 10 • The solution was cooled to 30 °C, moved to an overhead homogenizer, and then the requisite amount of cannabidiol (CBD) isolate was charged and dispersed using the homogenizer to micronize the CBD and create a drug product suspension.
- The requisite amount of Lemon-Lime flavor was charged and mixed for 10 minutes, then the FD&C Yellow #5 colorant was added.

- The resulting drug product suspension was transferred to a second overhead mixer and maintained at a temperature of 30 °C for the ensuing dosing operation.
- In a blistering machine equipped with a dosing system, blister pockets were filled with a target dose weight of 300.0 mg of the drug product suspension.
- 5 • The product was frozen in a suitable cryochamber and then the blister trays were transferred from the cryochamber to a suitable refrigerated storage cabinet (temperature below 0 °C) prior to lyophilizing to keep the product frozen.
- The frozen blisters were loaded from the refrigerated storage cabinet into lyophilizers and the product was lyophilized (water was sublimated) to form the rapidly infusing
10 compositions.
- When the lyophilizing cycle was completed, the rapidly infusing compositions were transferred from the lyophilizers to the blistering machine where the blister trays were heat sealed with lidding material. The resulting tablets are flat-topped circular units approximately 15 mm in diameter with a convex bottom packaged in individual
15 blister units (*see* also U.S. Provisional Application 63/114,181— incorporated herein by reference in its entirety).
- The following tests were performed:
 - A seal integrity test was performed at -0.5 Bar for 30 seconds, 1-minute soak time
 - 20 ○ Visual inspection was performed
 - Dry weight testing was performed

Placebo

A placebo product was also formulated in the same manner as the rapidly infusing
25 composition, with the exception that the placebo product was formulated without CBD.

Interim Clinical Trial Results

Interim results from a clinical trial addressing post-surgical pain following shoulder arthroscopy, the methodology for which is described in U.S. Patent Application No.

5 17/225,738 filed April 08, 2021, which is incorporated herein by reference, show that the rapidly infusing dosage form of the instant invention has superior safety compared to all known CBD dosage forms.

So far, 87 patients have completed the study, with 47 completed subjects in the active-treatment cohort receiving the ATI. In the completed subjects in the active-treatment cohort
10 there were no serious adverse events, and only three (3) mild adverse events total potentially related to treatment. No single subject in the active-treatment cohort had more than one adverse event and no two subjects had the same type of adverse event. This extremely low rate of adverse events, 6.4%, is basically unheard of in CBD trials and will likely make a tremendous difference in adherence to the therapy by future patients.

15 By contrast, clinical trial data for Epidiolex®, the only currently FDA-approved drug containing CBD, showed a far higher incidence of adverse events. For example, in epilepsy-related trials, adverse event rates varied from 45% (NCT02224703 at “mid dose” of 20 mg/kg/day) to 94% (NCT02564952 at 20-30 mg/kg/day) and a Parkinson’s disease related trial (NCT02818777) experienced adverse events in 100% of the subjects. Results for pain-
20 related clinical trials of Sativex®, an oromucosal spray containing both THC and CBD (which is not approved for any indication in the United States), also showed far more adverse events, with serious adverse events occurring in as high as 45.6% of patients (NCT01337089) and other adverse events (not including serious adverse events) occurring in as high as 97% of patients (NCT01606176) in certain trials.

25

CLAIMS

1. A method of treating epilepsy in a subject, comprising:

administering to the subject in need thereof, via the oral mucosa, a rapidly infusing

5 composition comprising (a) a pharmaceutically acceptable binder and/or excipient system comprising gelatin and a sugar alcohol, and (b) a therapeutically effective amount of cannabidiol (CBD) or a derivative/analog thereof.

2. The method of claim 1, wherein the rapidly infusing composition is lyophilized.

10

3. The method of claim 1, wherein the rapidly infusing composition has a disintegration time of approximately 1 to 30 seconds in deionized water maintained at 37° C ± 2° C.

15

4. The method of claim 1, wherein the rapidly infusing composition has a disintegration time of approximately 1 to 5 seconds in deionized water maintained at 37° C ± 2° C.

20

5. The method of claim 1, wherein the gelatin is present in the rapidly infusing composition in an amount of 10 to 35 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

6. The method of claim 1, wherein the gelatin is bovine gelatin.

7. The method of claim 1, wherein the sugar alcohol is present in the rapidly infusing composition in an amount of 5 to 35 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

5 8. The method of claim 1, wherein the sugar alcohol comprises mannitol.

9. The method of claim 1, wherein the CBD or derivative/analog thereof is present in the rapidly infusing composition in an amount of 20 to 70 wt.%, based on a total weight of the rapidly infusing composition on a dry basis.

10

10. The method of claim 1, wherein the rapidly infusing composition is formulated with a solid form of the CBD.

11. The method of claim 1, wherein the rapidly infusing composition is formulated
15 with a solid form of the CBD having a purity between 95 and 99.9 wt.%.

12. The method of claim 1, wherein the rapidly infusing composition is formulated with a solid form of the CBD that has been micronized to have a D50 diameter between 1 and 50 μm .

20

13. The method of claim 1, wherein the rapidly infusing composition is formulated with a CBD derivative/analog.

14. The method of claim 13, wherein the CBD derivative/analog is cannabidiolic acid
25 methyl ester.

15. The method of claim 1, wherein the rapidly infusing composition further comprises at least one selected from the group consisting of a sweetener, a flavorant, and a colorant.

5 16. The method of claim 15, wherein the rapidly infusing composition comprises the flavorant, and the flavorant comprises lemon-lime flavor.

17. The method of claim 15, wherein the rapidly infusing composition comprises the colorant, and the colorant comprises FD&C Yellow #5.

10

18. The method of claim 15, wherein the rapidly infusing composition comprises the sweetener, and the sweetener comprises a mixture of sucralose and acesulfame-K.

15

19. The method of claim 1, wherein the rapidly infusing composition is administered to the subject via the buccal mucosa.

20. The method of claim 1, wherein the therapeutically effective amount of CBD or derivative/analog thereof is from 0.1 mg/kg/day to less than 5 mg/kg/day.

20

21. The method of claim 1, wherein the rapidly infusing composition is administered to the subject 1 to 3 times per day.

22. The method of claim 1, wherein the subject presents with focal onset seizures.

23. The method of claim 1, wherein the subject presents with generalized onset seizures.

24. The method of claim 1, wherein the subject presents with both generalized onset
5 and focal onset seizures.

25. The method of claim 1, wherein the epilepsy is childhood epilepsy.

26. The method of claim 25, wherein the subject has Dravet Syndrome, myoclonic-
10 absence epilepsy, Lennox-Gastaut syndrome, generalized epilepsy of unknown origin, CDKL5 deficiency disease, PCDH19-epilepsy, continuous spikes and waves during sleep (CSWS), electrical status epilepticus during slow-wave sleep (ESES) epilepsy, Aicardi syndrome, Ohtahara syndrome, bilateral polymicrogyria, Dup15q syndrome, SNAP25-associated epilepsy, febrile infection related epilepsy syndrome (FIRES), benign rolandic
15 epilepsy, juvenile myoclonic epilepsy, Doose syndrome, infantile spasm (West syndrome), or Landau-Kleffner syndrome.

27. The method of claim 1, wherein the epilepsy is drug resistant epilepsy.

20 28. The method of claim 27, wherein the subject has Dravet syndrome, Lennox-Gastaut syndrome, myoclonic absence seizures, febrile infection related epilepsy syndrome (FIRES), treatment-resistant adult focal epilepsy (TRAFF), or PCDH19-epilepsy.

29. The method of claim 1, wherein the subject presents with atonic seizures.

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30. The method of claim 29, wherein the subject has Lennox-Gastaut syndrome, tuberous sclerosis complex, Dravet syndrome, Doose syndrome, Aicardi syndrome, CDKL5 deficiency, or Dup15q syndrome.

5 31. The method of claim 1, wherein the subject has Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex.

32. The method of claim 1, wherein a total convulsive frequency of the subject is reduced by at least 50%, relative to the total convulsive frequency observed prior to
10 administration of the rapidly infusing composition.

33. The method of claim 1, wherein a total convulsive frequency of the subject is reduced by at least 70%, relative to the total convulsive frequency observed prior to administration of the rapidly infusing composition.

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34. The method of claim 1, wherein the rapidly infusing composition is administered in combination with an antiepileptic drug.

35. The method of claim 34, wherein the antiepileptic drug is at least one selected
20 from the group consisting of phenobarbital, eslicarbazepine, ethosuximide, everolimus, tiagabine, acetazolamide, brivaracetam, cenobamate, clorazepate, lorazepam, methsuximide, primidone, diazepam, divalproex, felbamate, fenfluramine, carbamazepine, oxcarbazepine, lacosamide, vigabatrin, gabapentin, lamotrigine, pregabalin, baclofen, phenytoin, valproic acid or its salts such as sodium valproate, topiramate, zonisamide, levetiracetam, clonazepam,
25 rufinamide, stiripentol, perampanel, and fosphenytoin.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/57901

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/05; A61K 31/352 (2021.01)

CPC - A61K 31/05; A61K 31/352; A61K 36/185; A61K 9/0019

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)

See Search History document

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

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2020/0330423 A1 (MedCan Pharma A/S) 22 October 2020 (22.10.2020), abstract, para[0213], para[0378], para[0232], para[0270], para[0486], para[0165], para[0192], para[0056], para[0020], para[0077], Table 8, para[0059], para[0052], para[0174]-para[0175], para[0181]para[0049]	1, 3-5, 7-13, 15, 18-33
Y		2, 6, 14, 16-17, 34-35
Y	WO 2016/014454 A1 (Pharmaceutical Productions, Inc.) 28 January 2016 (28.01.2016), entire document especially para[0047], para[0042]	2
Y	MILLÉ "Gelatin vs. Veggie Capsules & C&B" 9 October 2020 (09.10.2020), entire document especially pg 1, para 3, pg 2, para 1	6
Y	US 2020/0115317 A1 (Yissum Research Development Company of the Hebrew University of Jerusalem Ltd. et al.) 16 April 2020 (16.04.2020), entire document especially abstract, para[0065]	14
Y	WO 2020/146753 A1 (Columbia Care LLC) 16 July 2020 (16.07.2020), entire document especially abstract, para[0026], para[0078]	16-17
Y	US 10,799,467 B2 (GW Pharma Limited et al.) 13 October 2020 (13.10.2020), entire document especially abstract	34-35
A	US 2016/0058866 A1 (Sekura et al.) 3 March 2016 (03.03.2016), entire document	1-35



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

4 January 2022

Date of mailing of the international search report

JAN 31 2022

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/57901

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2020/0138730 A1 (Intelgenx Corp.) 7 May 2020 (07.05.2020), entire document	1-35
A	WO 2020/024011 A1 (Auscann Group Holdings LTD) 6 February 2020 (06.02.2020), entire document	1-35