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(54) Title: CANNABINOIDS IN THE TREATMENT OF AUTISM SPECTRUM DISORDER

(57) Abstract: A method of treating autism spectrum disorder (ASD) 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

# CANNABINOIDS IN THE TREATMENT OF AUTISM SPECTRUM DISORDER

## CROSS REFERENCE TO RELATED APPLICATIONS

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.

## BACKGROUND OF THE INVENTION

### TECHNICAL FIELD

The present disclosure relates to methods of treating symptoms of autism spectrum disorder (ASD) with a rapidly infusing composition formulated with cannabidiol (CBD), cannabinoids or a derivative/analog thereof as the active therapeutic ingredient (ATI), alone or in combination with other ATIs.

### 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.

Autism spectrum disorder (ASD) is a complex developmental condition that involves persistent challenges in social interaction, speech and nonverbal communication, and restricted/repetitive behaviors. Existing pharmacological interventions are able to attenuate some related symptoms but do not address the underlying etiologies associated with ASD. Recently, there has been interest, as well as anecdotal evidence of efficacy, in treating ASD symptoms using cannabinoids, and in particular cannabidiol (CBD). However, clinical trials for the treatment of ASD symptoms using cannabinoids have been generally disappointing to date. *See* Agrawal et al. "Current state of evidence of cannabis utilization for treatment of autism spectrum disorders" BMC Psychiatry, 2019, 19:328.

The present inventors believe that the problem in the above-mentioned trials is not with the active therapeutic ingredient(s), but with the dosage form. Indeed, the appropriateness of the trials of cannabinoids using oral administration has been questioned due to the variability in their gastrointestinal absorption. *See* Rog et al. "Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis" Neurology, 2005, 65, 812-819. Other cannabinoid dosage forms have also shown large variations in bioavailability. For example, Sativex®, an oromucosal spray containing $\Delta^9$ tetrahydrocannabinol (THC) and cannabidiol (CBD), showed high inter-subject variability in bioavailability. *See* Berman et al. "Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial" Pain, 2004, 112, 299-306.

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. Of children with treatment-resistant epilepsy (who also display other conditions such as mild to severe intellectual disability, sleep disturbances, mood disorders, and psychosis), an estimated 25% are comorbid with ASD. *See* Agrawal et al. "Current state of evidence of cannabis utilization for treatment of autism spectrum disorders" BMC Psychiatry, 2019, 19:328.

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 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 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 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 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 poor patient compliance when administered orally. The unpleasant oily and foul taste is a particular concern for autistic patients who have difficulty processing sensory information, for example those that experience a distorted hyper sensitivity to sensory inputs, and may respond poorly to new or unusual sensations.

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 ASD 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; 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 ASD symptoms in a bioavailable unit dosage form for accurate dosing, easy administration, and high levels of patient compliance.

CBD can be used alone in the RITe™ platform for treatment of ASD symptoms or combined in a single dose with other ASD treatments. For example, the FDA has approved the use of some antipsychotic drugs, such as risperidone (Risperdal®) and aripiprazole (Abilify®), for treating certain ASD symptoms in children between certain ages. As described below, CBD can be combined with either of those active ingredients in a single, convenient dosage form.

Thus, the present invention provides:

(1) A method of treating symptoms of autism spectrum disorder in a subject, comprising:

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.

(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.

(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.

(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 mammalian gelatin.

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

(8) The method of any one of (1) to (7), 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.

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

(10) The method of any one of (1) to (9), 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.

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

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

(13) The method of any one of (1) to (12), 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.

(14) The method of any one of (1) to (10), wherein the rapidly infusing composition is formulated with a CBD derivative/analog.

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

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

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

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

(19) The method of any one of (16) to (18), wherein the rapidly infusing composition comprises the sweetener, and the sweetener comprises a mixture of sucralose and acesulfame-K.

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

(21) The method of any one of (1) to (20), 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.

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

(23) The method of any one of (1) to (22), wherein the rapidly infusing composition further comprises a therapeutically effective amount of an antipsychotic agent.

(24) The method of (23), wherein the antipsychotic agent is risperidone.

(25) The method of (24), wherein the therapeutically effective amount of risperidone is from 0.25 mg to 20 mg per day.

(26) The method of (23), wherein the antipsychotic agent is aripiprazole.

(27) The method of (26), wherein the therapeutically effective amount of aripiprazole is from 1 mg to 30 mg per day.

(28) The method of any one of (1) to (27), wherein the subject presents with at least one symptom selected from the group consisting of stereotypic behavior, underdeveloped motor skills, atypical nonverbal behaviors, self-injurious behavior (SIB), restlessness, hyperactivity, sleep deprivation, lethargy, anxiety, psychosis, seizures, disruptive behaviors, irritability or severe mood dysregulation, aggression, agitation, challenges with social interaction, impaired communication, noncompliance, resistance to change in routine, and unusual sensory reactivity.

(29) The method of any one of (1) to (28), wherein the subject is comorbid with both ASD and epilepsy.

(30) The method of (29), wherein the epilepsy is one or more of childhood epilepsy, drug resistant epilepsy, and epilepsy that presents with atonic seizures.

(31) The method of (29) or (30), 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.

(32) The method of any one of (29) to (31), 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.

(33) The method of any one of (1) to (32), wherein the rapidly infusing composition is administered in combination with a second therapeutic agent.

(34) The method of (33), wherein the second therapeutic agent is an antidepressant, an anxiolytic, an antipsychotic, a stimulant, a cognition-enhancing medication, or an antiepileptic drug.

(35) A method of treating symptoms of Prader Willi Syndrome in a subject, comprising:

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.

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, ethanolates, methanolates, 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, pamoic, 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 Autism spectrum disorder.

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; improvement or remediation or amelioration of damage following a condition; and/or causing regression of symptoms of the condition. Thus, "treatment" may refer to therapeutic treatment and/or prophylactic or preventative measures for dealing with one or more symptoms associated with autism spectrum disorder or other conditions exhibiting similar symptoms.

The term "subject" and "patient" are used interchangeably. As used herein, they refer to any human subject for whom or which therapy is desired.

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 improving one or more symptoms associated with ASD. The result can be a reduction and/or alleviation of the signs or symptoms 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 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 ATIs in a solid dosage form directly into systemic circulation via the sublingual mucosa or the buccal mucosa and avoidance of first pass metabolism. Through a combination of rapid disintegration and direct systemic introduction, the rapidly infusing composition 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/analogs to be dosed in an amount of under 5 mg/kg/day for the treatment of autism spectrum disorder.

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 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 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 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 seconds or less, according to the United States Pharmacopeia (USP) <701> Disintegration Test performed in deionized water maintained at 37° C ± 2°. 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) <701> Disintegration Test performed in deionized water maintained at 37° C ± 2°. 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 over the cumbersome and generally unpleasant oral liquid dosage forms e.g., 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. In contrast, administration of the rapidly 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 in terms of maintaining a regimented dosing schedule, 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 oily or foul-tasting oral medications. 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." The short oral residency time 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. Second, when formulated with a flavorant, a robust mixture of flavors will hit the tongue at essentially the same time—the bitter flavor of the ATI still hits the tongue, but the perception of the flavor is canceled or mitigated by the simultaneous arrival of other flavors. Even then, the robust mixture of flavors will quickly subside as the composition is rapidly absorbed through the oral mucosa. The effective taste masking provided by the RITe™ platform is particularly advantageous when used to treat autistic patients who have difficulty processing sensory information, for example those that experience a distorted hyper sensitivity to sensory inputs, and may respond poorly to new or unusual sensations such as when administered an oily or foul-tasting oral medicament.

The rapid disintegration profile disclosed herein, coupled with the direct introduction 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 one or more ASD symptoms (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 one or more active therapeutic ingredient(s) such as cannabidiol (CBD) or a pharmaceutically acceptable derivative/analog, salt, or solvate thereof, or a combination of cannabidiol (CBD) or a pharmaceutically acceptable derivative/analog, salt, or solvate thereof and an antipsychotic agent.

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, neohisperidin, 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.

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 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

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, 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 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, stearoyl 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 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 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 of mono- and diglycerides, alginate salts, and lactylic 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 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 (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-swellable 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, caprylyic/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 (e.g., CBD or derivative/analog thereof or a combination of CBD or derivative/analog thereof and an antipsychotic agent), 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 0.5 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 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. 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 an antipsychotic agent for the treatment of ASD.

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 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 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.%, 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. 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 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 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 (Δ9-THC) and related THC-cannabinoids such as Δ8-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, spiroxamine, and thiacloprid;
- 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, geranul 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, guaiol, 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 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 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 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 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 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 autism spectrum disorder.

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 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.

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. 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 or a combination of CBD or derivative/analog thereof and an antipsychotic agent.

The derivatives/analogs of CBD contemplated for use herein are those that retain the desired activity for relief of one or more symptoms associated with ASD. Derivatives/analogs 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/analogs may exhibit a lesser degree of activity than CBD, so long as they retain sufficient activity to be therapeutically effective. Derivatives/analogs 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 ($H_2$-CBD) and tetrahydrocannabidiol ($H_4$-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 ASD 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. In some embodiments, CBD or derivative/analogs thereof may be combined with an antipsychotic agent useful in the treatment of ASD. Examples of antipsychotic agents include, but are not limited to, risperidone (Risperdal®) and aripiprazole (Abilify®). Specific dosages and dosing regimens would be based on physicians' evolving knowledge and the general skill in the art. For example, rapidly infusing compositions formulated with risperidone may contain an amount which will provide the subject with at least 0.25 mg, preferably at least 0.5 mg, preferably at least 1 mg of risperidone per day, and up to 20 mg, preferably up to 10 mg, preferably up to 3 mg of risperidone per day. In another example, rapidly infusing compositions formulated with aripiprazole may contain an amount which will provide the subject with at least 1 mg, preferably at least 2 mg, preferably at least 3 mg, preferably at least 5 mg of aripiprazole per day, and up to 30 mg, preferably up to 20 mg, preferably up to 15 mg, preferably up to 10 mg of aripiprazole per day.

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 or a combination of CBD and antipsychotic agent) 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(s) (e.g., CBD or a combination of CBD and antipsychotic agent) may be subsequently charged and dispersed using the homogenizer, with preferable micronization of the ATI, to form a drug product suspension. When a combination of CBD and antipsychotic agent are used, the ATIs are charged sequentially and dispersed using the homogenizer. 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 autism spectrum disorder (ASD) by administering to a subject in need thereof the disclosed rapidly infusing composition, in one or more of its embodiments.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by impairments in social interaction and communication, restricted interests, and repetitive behavior. Individuals on the autism spectrum experience widely varying degrees and types of impairments, from mild to severe. Although early detection and interventions are encouraged to maximize the benefits and reduce the severity of the symptoms, individuals of any age can benefit from interventions and therapies that can reduce symptoms and increase skills and abilities. Appropriate subjects for the methods described herein include, without limitation, humans diagnosed as having or suspected of having autism spectrum disorder, such as those diagnosed as having or suspected of having autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), or Asperger syndrome, as well as humans diagnosed with other conditions that exhibit certain ASD-like symptoms, such as Prader Willi Syndrome (PWS).

Subjects with ASD may present with many different types of symptoms, any of which may be treated herein. Symptoms associated with ASD that may be treated herein include, but are not limited to, stereotypic behavior (stimming) such as rocking and vocal stereotypy, underdeveloped motor skills, atypical nonverbal behaviors, self-injurious behavior (SIB),

restlessness, hyperactivity, sleep deprivation, lethargy, anxiety, psychosis, seizures, disruptive behaviors, irritability or severe mood dysregulation, aggression, agitation, challenges with social interaction including social withdrawal, impaired communication including inappropriate speech, noncompliance, resistance to change in routine, and unusual sensory reactivity.

Subjects may be screened/evaluated for ASD and their response to treatment and general progress (e.g., improvement of symptom(s)) may be determined, quantified, monitored, and/or tracked using various observation/charting tools and measurements known by those of ordinary skill in the art, examples of which may include, *inter alia*, the Clinical Global Impression (CGI), the Children Autism Rating Scale (CARS), the Children Autism Rating Scale (second edition) (CARS2), the Children Autism Rating Scale (second edition)-High Functioning (CARS2-HF), the Autism Parenting Stress Index (APSI), the Aberrant Behavior Checklist (ABC), Home Situations Questionnaire-Modified for autism spectrum disorder (HSQ-ASD), eye tracking (e.g., infrared light-based eye test), magnetic resonance spectroscopy (MRS), etc.

For example, the subject treated herein may exhibit at least a 10% reduction in severity of symptoms, preferably at least a 15% reduction, preferably at least a 20% reduction, preferably at least a 25% reduction, preferably at least a 30% reduction, preferably at least a 35% reduction, preferably at least a 40% reduction, preferably at least a 45% reduction, preferably at least a 50% reduction, preferably at least a 55% reduction, preferably at least a 60% reduction, preferably at least a 65% reduction, preferably at least a 70% reduction, preferably at least a 75% reduction, preferably at least a 80% reduction, preferably at least a 85% reduction, preferably at least a 90% reduction in severity of symptoms as a result of the treating relative to severity as assessed prior to initiating the treatment, as assessed by one or more of CARS, CARS2, CARS2-HF, or ABC.

One of ordinary skill in the art understands that the foregoing assessment systems are only exemplary tools for evaluating ASD-related social and cognitive symptoms. Other similar tools can be used or designed to evaluate core ASD-related symptoms. For example, subjects may be screened/evaluated for ASD and their response to treatment and general progress may be determined, quantified, monitored, and/or tracked using one or more of Autism Diagnosis Interview-Revised (ADI-R), the Autism Diagnostic Observation Schedule second edition (ADOS-2), the Social Responsiveness Scale second edition (SRS-2), the Vineland Adaptive Behavior Scale II (VABS-II), the Leiter International Performance Scale, the Autism Treatment Evaluation Checklist (ATEC), the Pervasive Developmental Disorders Behavior Inventory (PDD-BI), among others.

An estimated 25% of children with treatment resistant epilepsy (TRE) are comorbid with ASD. Accordingly, particularly preferred methods of the present disclosure involve the co-treatment of patients suffering from both ASD and epilepsy. The types of epilepsy that can be co-treated with ASD and dosing regimens for epilepsy treatments are as set forth in U.S. provisional application 63/180,193—incorporated herein by reference in its entirety.

For example, the epilepsy treated 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-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.

In another example, the epilepsy treated may be drug resistant epilepsy (DRE). Examples of types of epilepsy which frequently fall into the drug resistant epilepsy category include, but are not 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.

In yet another example, the epilepsy treated may be those epileptic disorder etiologies that present in the form of atonic seizures, which involve the loss of muscle tone, causing the person to 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 to subjects suffering from both ASD and epilepsy may thus treat one or more symptoms associated with ASD, such as those described heretofore, while also reducing the total convulsive seizure frequency or eliminating epileptic episodes altogether, for example, 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 70%, preferably at least 75%, preferably at least 80%, preferably at least 85%, preferably at least 90%, preferably at least 95%, preferably at least 99%, preferably 100%, relative to the seizure frequency prior to administration of the rapidly infusing composition. In some embodiments, the subject suffers from 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 seizure 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, the therapeutically effective amount of CBD or a derivative/analog thereof is 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 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.

In addition to CBD or derivatives/analogs thereof, rapidly infusing compositions may also be formulated with an antipsychotic agent for treatment of ASD. The dosing of the antipsychotic can be determined by a physician having ordinary skill in the art using sound medical judgment based on a variety of factors such as those described previously. In one example, the antipsychotic agent is risperidone and the subject is administered at least 0.25 mg, preferably at least 0.5 mg, preferably at least 1 mg of risperidone per day, and up to 20 mg, preferably up to 10 mg, preferably up to 3 mg of risperidone per day. In another example, the antipsychotic agent is aripiprazole and the subject is administered at least 1 mg, preferably at least 2 mg, preferably at least 3 mg, preferably at least 5 mg of aripiprazole per day, and up to 30 mg, preferably up to 20 mg, preferably up to 15 mg, preferably up to 10 mg of aripiprazole per 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, 4 times, or more 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 ASD related symptoms, 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 (Tmax) 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 autism spectrum disorder or may be used in combination therapy—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 ASD, or a combination of ASD and a different condition.

Combination therapy may involve administering the rapidly infusing composition and a second therapeutic agent, such as antidepressants, anxiolytics, antipsychotics, stimulants, cognition-enhancing medications (non-stimulant), and antiepileptic drugs (AEDs).

Antidepressants and anxiolytics suitable for use in combination therapy may include, but are not limited to, selective serotonin reuptake inhibitors such as citalopram, escitalopram, fluoxetine, paroxetine, sertraline; serotonin and norepinephrine reuptake inhibitors such as duloxetine and venlafaxine; norepinephrine and dopamine reuptake inhibitors such as bupropion; tetracyclic antidepressants such as mirtazapine; combined

reuptake inhibitors and receptor blockers such as trazodone, nefazodone, maprotiline; tricyclic antidepressants such as amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline and trimipramine; monoamine oxidase inhibitors such as phenelzine, tranylcypromine, isocarboxazid, selegiline; benzodiazepines such as lorazepam, clonazepam, alprazolam, and diazepam; serotonin 1A receptor agonists such as buspirone, aripiprazole, quetiapine, tandospirone, and bifeprunox; and beta-adrenergic receptor blockers such as propranolol.

Antipsychotics suitable for use in combination therapy may include, but are not limited to, risperidone and aripiprazole.

Stimulants suitable for use in combination therapy may include, but are not limited to, methylphenidate, dextroamphetamine, and amphetamine.

Cognition-enhancing medications (non-stimulant) suitable for use in combination therapy may include, but are not limited to, atomoxetine, guanfacine, and clonidine.

Antiepileptic drugs (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 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, vigabatrin, gabapentin, lamotrigine, pregabalin, baclofen, phenytoin, valproic acid or its salts such as sodium valproate, topiramate, zonisamide, levetiracetam, clonazepam, rufinamide, stiripentol, perampanel, and fosphenytoin.

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 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 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 composition in further combination with other biologically active ingredients and non-drug therapies. 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 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 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”, “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 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

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.

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).

Table 2. Example rapidly infusing composition formulation

| | Drug product suspension | Rapidly Infusing Composition | |
|---|---|---|---|
| **Ingredient** | **% 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 |

Table 3. Example rapidly infusing composition formulation

| | Drug product suspension | Rapidly Infusing Composition | |
|---|---|---|---|
| **Ingredient** | **% 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 | 5.0 | 15 mg | 32.4 |
| Aripiprazole | 3.4 | 10 mg | 21.6 |
| 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 compositions

- 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.
- The solution was cooled to 30 °C, moved to an overhead homogenizer, and then the requisite amount of active therapeutic ingredient(s) was charged and dispersed using the homogenizer to micronize the ATI(s) 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.
- 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 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 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
    - Visual inspection was performed
    - Dry weight testing was performed

Placebo

A placebo product was also formulated in the same manner as the rapidly infusing 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. 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 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.

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-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.

CLAIMS

1. A method of treating symptoms of autism spectrum disorder in a subject, comprising:

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.

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

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.

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.

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 mammalian gelatin.

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

8. 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.

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

10. 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.

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

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

13. 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.

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

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

16. 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.

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

18. The method of claim 16, wherein the rapidly infusing composition comprises the colorant, and the colorant comprises FD&C Yellow #5.

19. The method of claim 16, wherein the rapidly infusing composition comprises the sweetener, and the sweetener comprises a mixture of sucralose and acesulfame-K.

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

21. 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.

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

23. The method of claim 1, wherein the rapidly infusing composition further comprises a therapeutically effective amount of an antipsychotic agent.

24. The method of claim 23, wherein the antipsychotic agent is risperidone.

25. The method of claim 24, wherein the therapeutically effective amount of risperidone is from 0.25 mg to 20 mg per day.

26. The method of claim 23, wherein the antipsychotic agent is aripiprazole.

27. The method of claim 26, wherein the therapeutically effective amount of aripiprazole is from 1 mg to 30 mg per day.

28. The method of claim 1, wherein the subject presents with at least one symptom selected from the group consisting of stereotypic behavior, underdeveloped motor skills, atypical nonverbal behaviors, self-injurious behavior (SIB), restlessness, hyperactivity, sleep deprivation, lethargy, anxiety, psychosis, seizures, disruptive behaviors, irritability or severe mood dysregulation, aggression, agitation, challenges with social interaction, impaired communication, noncompliance, resistance to change in routine, and unusual sensory reactivity.

29. The method of claim 1, wherein the subject is comorbid with both ASD and epilepsy.

30. The method of claim 29, wherein the epilepsy is one or more of childhood epilepsy, drug resistant epilepsy, and epilepsy that presents with atonic seizures.

31. The method of claim 29, 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.

32. The method of claim 29, 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.

33. The method of claim 1, wherein the rapidly infusing composition is administered in combination with a second therapeutic agent.

34. The method of claim 33, wherein the second therapeutic agent is an antidepressant, an anxiolytic, an antipsychotic, a stimulant, a cognition-enhancing medication, or an antiepileptic drug.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/57931

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/352; A61K 36/185; A61P 25/18 (2021.01)

CPC - A61K 31/05; A61K 31/192; A61K 31/352

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) - entire document especially abstract and para [0003], [00164], [0165], [0052], [0192], [0069], [0048], [0049], [0213], [0357], [0176], [0178], [0260], [0378], [0375], [0234], [0232], [0305] | 1, 3-5, 8-14, 16-17, 19-22, 28-32 |
| Y | | 2, 6-7, 15, 18, 23-27, 33-34 |
| Y | WO 2018/222923 A1 (PHYTECS, INC.) 6 December 2018 (06.12.2018) - entire document especially para [0084], [0269], [0274] | 2 |
| Y | US 9,408,879 B2 (GUGLIELMETTI ET AL.) 9 August 2016 (09.08.2016) - entire document especially col 11, 12 | 6-7 |
| Y | WO 2020/186010 A1 (EPM GROUP, INC) 17 September 2020 (17.09.2020) - entire document especially abstract and para [00192], [0015] | 15 |
| Y | WO 2018/082814 A1 (METRIOPHARM AG) 11 May 2018 (11.05.2018) - entire document especially abstract and pg 17 | 18 |
| Y | WO 2020/188568 A1 (BOL PHARMA LTD.) 24 September 2020 (24.09.2020) - entire document especially abstract and para [093], [096], [098] | 23-27, 33-34 |
| A | US 2018/0311205 A1 (KOTZKER CONSULTING LLC) 1 November 2018 (01.11.2018) - entire document | 1-34 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"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
"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
"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
"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
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 4 January 2022 | JAN 31 2022 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Kari Rodriquez<br>Telephone No. PCT Helpdesk: 571-272-4300 |