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(54) Title: SUBLINGUAL SPRAY FORMULATIONS OF PSYCHEDELICS

(57) Abstract: The present disclosure relates in some aspects to sublingual spray formulations comprising therapeutic compounds, such as psychedelic compounds, and including psilocin, DMT, LSD, MDMA, and 2C-B. The disclosure further relates to methods of producing the formulations and methods of using the formulations, including methods of administering the formulations to subjects. In some aspects, the formulations modulate neurotransmission, such as serotonergic neurotransmission, as well as treat mental health disorders and other diseases and conditions.



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# SUBLINGUAL SPRAY FORMULATIONS OF PSYCHEDELICS

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## CROSS REFERENCE

[01] Priority is claimed under PCT Article 8(1) and Rule 4.10 to U.S. Provisional App. No. 63/465,797, filed May 11, 2023, and incorporated by reference for all purposes as if fully set forth herein.

## FIELD OF THE INVENTION

[02] Provided are sublingual formulations comprising therapeutic compounds, such as psychedelics. Also provided are methods of producing the formulations, devices comprising the formulations, and methods of their use. Further provided are uses of formulations to treat mental health disorders and other conditions.

## BACKGROUND OF THE INVENTION

[03] Certain drug compounds known as psychedelics induce altered states of consciousness associated with changes to perception, mood, thought processes, and creativity, by altering patterns of activity in neurotransmitter systems, neuronal firing patterns, and regional brain activity. The mystical and introspective nature of the subjective experience associated with the ingestion of psychedelics has been central to multiple ancient and modern cultural traditions. A variety of natural and synthetic psychedelic compounds have been used in these contexts, including psilocybin and psilocin, dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), methylenedioxymethamphetamine (MDMA), and various compounds in the "2C" family.

[04] The most common route of administration for most psychedelic compounds is oral ingestion. Compounds are passed through the digestive tract where they are absorbed into the bloodstream through the stomach lining or intestinal lining. As each lining has unique absorption properties, and the linings of different individuals vary widely, it is difficult to predict how much of a substance will be bioavailable to the brain. The contents of the gastrointestinal tract also can affect drug absorption and cause variability in drug pharmacokinetics. Additionally, oral ingestion leaves compounds vulnerable to first-pass (generally, liver) metabolism, which also can have substantial variability between individuals. Further, for various reasons, the variability of oral administration is especially high for certain psychedelics, such as psilocybin and psilocin.

[05] Although there is a need for delivery methods without these drawbacks, acceptable methods that are also convenient, including from the perspective of patient compliance and provider resources, are lacking. For example, prior art delivery methods for psilocin that avoid some drawbacks of oral administration involve intravenous administration, which presents its own set of significant downsides. Although oral mucosal (e.g., sublingual) administration may be advantageous, the solubility of psilocin is only 2.00 mg/mL in ethanol and 4.08 mg/mL in water, making it difficult to achieve a formulation with a sufficiently low administration volume.

[06] There is thus a need for innovative delivery methods that provide efficient, consistent, precise, and predictable dosing, and are convenient to use. Provided herein are formulations to meet these needs and others, having such advantages and improvements as will become apparent through the disclosure below.

## INCORPORATION BY REFERENCE

[07] Each cited patent, publication, and non-patent literature is incorporated by reference in its entirety, as if each was incorporated by reference individually, and as if each is fully set forth herein. However, no such citation should be construed as an admission that a cited reference is from an area that is analogous or directly applicable to the invention, nor should any citation be construed as an admission that a document or underlying information, in any jurisdiction, is prior art or part of the common general knowledge in the art.

## BRIEF SUMMARY OF THE INVENTION

[08] The following presents a simplified summary of some embodiments of the invention in order to provide a basic understanding thereof. This summary is not an extensive overview of the invention. It is not intended to identify key or critical elements of the invention or to delineate the full scope thereof. Its sole purpose is to present some embodiments in a simplified form as a prelude to the detailed description below.

[09] In aspects are provided sublingual spray formulations comprising: (a) psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof; (b) a solubilizing agent; and (c) a solvent system.

[10] In embodiments, the concentration of psilocin in the formulation is greater than about 0.4% (w/w). In embodiments, the concentration of psilocin in the formulation is greater than about 1.0% (w/w). In embodiments, the concentration of psilocin in the formulation is greater than about 1.5% (w/w). In embodiments, the concentration of psilocin in the formulation is greater than about 1.8% (w/w). In embodiments, the concentration of psilocin in the formulation is about 2.0% (w/w).

[11] In embodiments, the concentration of psilocin in the formulation is at least 2-fold higher than the solubility limit of psilocin in an identical formulation lacking the solubilizing agent. In embodiments, the concentration of psilocin in the formulation is at least 4-fold higher than the solubility limit of psilocin in an identical formulation lacking the solubilizing agent.

[12] In embodiments, the solubilizing agent is a cyclodextrin, a surfactant, or a phospholipid. In embodiments, the cyclodextrin is sulfobutylether- $\beta$ -cyclodextrin. In embodiments, a formulation comprises between about 1% and about 10% (w/w) of sulfobutylether- $\beta$ -cyclodextrin. In embodiments, a formulation comprises between about 5% and about 7% (w/w) of sulfobutylether- $\beta$ -cyclodextrin. In embodiments, a formulation comprises about 6% (w/w) of sulfobutylether- $\beta$ -cyclodextrin. In embodiments, the cyclodextrin is  $\beta$ -cyclodextrin. In embodiments, a formulation comprises between about 1% and about 10% (w/w) of  $\beta$ -cyclodextrin. In embodiments, a formulation comprises between about 5% and about 7% (w/w) of  $\beta$ -cyclodextrin. In embodiments, a formulation comprises about 6% (w/w) of  $\beta$ -cyclodextrin.

[13] In embodiments, the solvent system comprises water. In embodiments, the solvent system further comprises an alcohol. In embodiments, the alcohol is propylene glycol (PG). In embodiments, the solvent system comprises water and PG in a water:PG ratio of between about 5:1 and about 1:5. In embodiments, the solvent system comprises water and PG in a water:PG ratio of between about 3:1 and about 1:3. In embodiments, it comprises water and PG in a water:PG ratio of between about 1:2 and about 1:3.

[14] In embodiments, a formulation further comprises any of a penetration enhancer, an antioxidant, a taste-masking agent, a mucoadhesive polymer, and a flavoring agent. In embodiments, a formulation further comprises a mucoadhesive polymer. In embodiments, the mucoadhesive polymer is xanthan gum. In embodiments, a formulation comprises between about 0.1% and about 1.0% (w/w) of xanthan gum. In embodiments, a formulation comprises between about 0.1% and about 0.2% (w/w) of xanthan gum. In embodiments, the mucoadhesive polymer is carbomer homopolymer type B. In embodiments, a formulation comprises between about 0.01% and about 0.1% (w/w) of carbomer homopolymer type B. In embodiments, a formulation comprises between about 0.01% and about 0.05% (w/w) of carbomer homopolymer type B.

[15] In embodiments, a formulation further comprises a taste-masking agent. In embodiments, the taste-masking agent is xylitol. In embodiments, a formulation comprises between about 0.1% and about 1.0% (w/w) of xylitol. In embodiments, a formulation comprises between about 0.2% and about 0.3% (w/w) of xylitol. In embodiments, the taste-masking agent is menthol. In embodiments, a formulation comprises between about 0.01% and about 0.10% (w/w) of menthol. In embodiments, a formulation comprises about 0.04% (w/w) of menthol.

[16] In embodiments, a formulation further comprises an antioxidant. In embodiments, the antioxidant is rosmarinic acid. In embodiments, a formulation comprises between about 0.01% and about 0.10% (w/w) of rosmarinic acid. In embodiments, a formulation comprises about 0.05% (w/w) of rosmarinic acid. In embodiments, the antioxidant is vitamin E. In embodiments, a formulation comprises between about 0.01% and about 1.0% (w/w) of vitamin E. In embodiments a formulation comprises about 0.10% (w/w) of vitamin E.

[17] In embodiments, a formulation further comprises a polysorbate. In embodiments, the polysorbate is polysorbate 80. In embodiments, a formulation comprises between about 0.5% and about 2.0% (w/w) of polysorbate 80. In embodiments, a formulation comprises about 1.0% (w/w) of polysorbate 80.

[18] In embodiments is disclosed a sublingual spray formulation comprising: (a) about 1.8% to about 2.0% (w/w) of psilocin; (b) about 5% to about 7% (w/w) of sulfobutylether- $\beta$ -cyclodextrin; (c) about 0.1% to about 0.2% (w/w) of xanthan gum; (d) about 0.01% to about 1.0% (w/w) of a taste-masking agent; (e) about 0.01% to about 1.0% (w/w) of an antioxidant; and (f) about 0.5% to about 2.0% (w/w) of polysorbate 80.

[19] In embodiments is disclosed a sublingual spray formulation comprising: (a) about 1.8% to about 2.0% (w/w) of psilocin; (b) about 5% to about 7% (w/w) of sulfobutylether- $\beta$ -cyclodextrin; (c) about 0.01% to about 0.1% (w/w) of carbomer homopolymer type B; (d) about 0.01% to about 1.0% (w/w) of a taste-masking agent; (e) about 0.01% to about 1.0% (w/w) of an antioxidant; and (f) about 0.5% to about 2.0% (w/w) of polysorbate 80.

[20] In embodiments is disclosed a sublingual spray formulation comprising: (a) about 1.8% to about 2.0% (w/w) of psilocin; (b) about 5% to about 7% (w/w) of  $\beta$ -cyclodextrin; (c) about 0.1% to about 0.2% (w/w) of xanthan gum; (d) about 0.01% to about 1.0% (w/w) of a taste-masking agent; (e) about 0.01% to about 1.0% (w/w) of an antioxidant; and (f) about 0.5% to about 2.0% (w/w) of polysorbate 80.

[21] In embodiments is disclosed a sublingual spray formulation comprising: (a) about 1.8% to about 2.0% (w/w) of psilocin; (b) about 5% to about 7% (w/w) of  $\beta$ -cyclodextrin; (c) about 0.01% to about 0.1% (w/w) of carbomer homopolymer type B; (d) about 0.01% to about 1.0% (w/w) of a taste-masking agent; (e) about 0.01% to about 1.0% (w/w) of an antioxidant; and (f) about 0.5% to about 2.0% (w/w) of polysorbate 80.

[22] In embodiments, a formulation further comprises a therapeutically effective amount of an additional active compound, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, non-racemic mixture, isotopolog, prodrug, or derivative thereof. In embodiments, the additional active compound is selected from the group consisting of: amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathsogens, psychedelics, monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, and vitamins.

[23] In embodiments, the additional active compound acts to increase a therapeutic effect, provide an additional therapeutic effect, decrease an unwanted effect, increase stability or shelf-life, improve bioavailability, induce synergy, or alter pharmacokinetics or pharmacodynamics. In embodiments, the additional therapeutic effect is an antioxidant, anti-inflammatory, analgesic, antineuropathic, antinociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic, orexigenic, antiulcer, antihistamine, antihypertensive, anticonvulsant, antiepileptic, bronchodilator, neuroprotective, empathsogenic, psychedelic, sedative, or stimulant effect.

[24] In embodiments is disclosed a sublingual spray formulation comprising: (a) a psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof; (b) a pharmaceutically acceptable excipient; and (c) a solvent system.

[25] Also provided is a method of treating a medical condition in a subject in need of such treatment, the method comprising administering to the subject the formulation of any of the disclosed embodiments.

[26] In embodiments, the medical condition is a disorder linked to dysregulation or inadequate functioning of neurotransmission. In embodiments, the disorder linked to dysregulation or inadequate functioning of neurotransmission is that of monoaminergic neurotransmission. In embodiments, the disorder linked to dysregulation or inadequate functioning of neurotransmission is that of serotonergic, dopaminergic, or noradrenergic neurotransmission.

[27] In embodiments, the medical condition is a mental health disorder. In embodiments, the mental health disorder is selected from the group consisting of post-traumatic stress disorder (PTSD), adjustment disorder, affective disorder, depression, atypical depression, postpartum depression, catatonic depression, a depressive disorder due to a medical condition, premenstrual dysphoric disorder, seasonal affective disorder,

dysthymia, anxiety, phobia disorders, binge disorders, body dysmorphic disorder, alcohol or drug abuse or dependence disorders, a substance use disorder, substance-induced mood disorder, a mood disorder related to another health condition, disruptive behavior disorders, eating disorders, impulse control disorders, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), personality disorders, attachment disorders, and dissociative disorders.

[28] In embodiments, the medical condition is a neurodegenerative disease. In embodiments, the neurodegenerative disease is Alzheimer's disease, amyotrophic lateral sclerosis or Charcot's disease, chronic traumatic encephalopathy, corticobasal degeneration, dementias including vascular dementia, Huntington's disease, Lytico-Bodig disease, mild cognitive impairment, multiple sclerosis, a motor neuron disease, neuromyelitis optica spectrum disorder, Parkinson's disease or Parkinsonisms, prion diseases, progressive supranuclear palsy, and traumatic brain injury.

[29] In embodiments, the medical condition is pain or a pain disorder. In embodiments, the pain disorder is any of arthritis, allodynia, atypical trigeminal neuralgia, trigeminal neuralgia, somatoform disorder, hypoesthesia, hyperalgesia, neuralgia, neuritis, neurogenic pain, phantom limb pain, analgesia, anesthesia dolorosa, causalgia, sciatic nerve pain disorder, degenerative joint disorder, fibromyalgia, visceral disease, chronic pain disorders, headache disorders, migraine headaches, chronic cluster headaches, concussion headache, short-lasting unilateral neuralgiform headache attacks, chronic fatigue syndrome, complex regional pain syndrome, neurodystrophy, plantar fasciitis, or pain associated with cancer.

[30] In embodiments, the medical condition is inflammation or an inflammatory disorder. In embodiments, the inflammation is any of skin inflammation, muscle inflammation, tendon inflammation, ligament inflammation, bone inflammation, cartilage inflammation, lung inflammation, heart inflammation, liver inflammation, pancreatic inflammation, kidney inflammation, bladder inflammation, gastric inflammation, intestinal inflammation, neuroinflammation, and brain inflammation.

[31] In embodiments, the formulation is administered together with one or more sessions of psychotherapy, psychological support, or patient monitoring

[32] Also provided is a method of modulating neurotransmission in an individual, comprising administering to the mammal an effective amount of the formulation of any of the disclosed embodiments. In embodiments, the neurotransmission is monoaminergic neurotransmission. In embodiments, the monoaminergic neurotransmission is serotonergic, dopaminergic, or noradrenergic neurotransmission. In some embodiments of the disclosed methods, modulating neurotransmission treats a medical condition.

[33] Also provided is a method of increasing neuroplasticity in a subject, comprising administering to the subject the formulation of any of the disclosed embodiments.

[34] In another aspect, provided is the formulation of any of the disclosed embodiments for use in the treatment of a medical condition. In another aspect, provided is the formulation of any of the disclosed embodiments for use in modulating neurotransmission. In another aspect, provided is the formulation of any

of the disclosed embodiments for use in increasing neuroplasticity. In another aspect, provided is the use of the formulation of any of the disclosed embodiments for the manufacture of a medicament for the treatment of a medical condition.

[35] In another aspect, provided is a metered spray delivery device comprising the formulation of any of the disclosed embodiments. In embodiments, the device is a multi-dose, unit dose, or bi-dose device. In embodiments, the device is spray pump, a pre-compression sublingual spray pump, a metered valve device, an actuated spray device, a side actuated spray device, a syringe sublingual spray device, a mucosal atomization device, or an electromechanical pump device. In embodiments, the device is configured to administer between about 0.1 mL and about 1.0 mL of the formulation per actuation.

[36] The foregoing has outlined broadly and in summary certain pertinent features of the disclosure so that the detailed description of the invention that follows may be better understood, and so that the present contribution to the art can be more fully appreciated. Hence, this summary is to be considered as a brief and general synopsis of only some of the objects and embodiments disclosed herein, is provided solely for the benefit and convenience of the reader, and is not intended to limit in any manner the scope, or range of equivalents, to which the claims are lawfully entitled. Additional features of the invention are described hereinafter. It should be appreciated by those in the art that all disclosed specific compositions and methods are only exemplary, and may be readily utilized as a basis for modifying or designing other compositions and methods for carrying out the same purposes. Such equivalent compositions and methods will be appreciated to be also within the scope and spirit of the invention as set forth in the claims.

[37] The headings within this document are being utilized only to expedite its review by a reader. They should not be construed as limiting the invention in any manner.

## **DETAILED DESCRIPTION OF THE INVENTION**

[38] While various aspects and features of certain embodiments are summarized above, the following detailed description illustrates several exemplary embodiments in further detail to enable one of skill in the art to practice such embodiments, and to make and use the full scope of the invention claimed. The scope of the invention includes all embodiments and formulations thereof, not only those expressly described below. The described examples are provided for illustrative purposes and are not intended to limit the scope of the invention or its applications. It will be understood that many modifications, substitutions, changes, and variations in the described examples, embodiments, applications, and details of the invention can be made by those in the art without departing from the spirit of the invention, or the scope of the invention as claimed.

### **A. General Definitions and Terms**

[39] As used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" includes reference to a combination of two or more active agents, and reference to "an excipient" includes reference to a combination of two or more excipients. While the term "one or more" may be used, its

absence (or its replacement by the singular) does not signify the singular only, but simply underscores the possibility of multiple agents or ingredients in particular embodiments.

[40] The terms “comprising,” “including,” “such as,” and “having” are inclusive and not exclusive (i.e., there may be other elements in addition to the recited elements). Thus, the term “including” means, and is used interchangeably with, the phrase “including but not limited to.” The term “or” means, and is used interchangeably with, the term “and/or,” unless context clearly indicates otherwise.

[41] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as concentration, reaction conditions, and so forth, used to describe and claim certain embodiments of the invention are to be understood as being modified in some instances by the term “about,” even where not so stated explicitly. In alternative embodiments, such numbers will be understood as not being modified by the term “about.” In some embodiments (equivalently, and as shorthand, “in embodiments”), the numerical parameters set forth in the written description and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. In embodiments, “about” may refer to plus or minus five percent ( $\pm 5\%$ ) of the recited unit of measure. In other embodiments, “about” may refer to plus or minus ten percent ( $\pm 10\%$ ) of the recited unit of measure. Where “about” is used to modify one number in a series or range, it is understood to modify all numbers in the series or range, including, for a range, both the upper and lower bounds of the range; thus, the term “about 1, 2, or 3” is understood to mean “about 1, about 2, or about 3” and the term “about 1 to 10” means “about 1 to about 10.”

[42] The term “substantially,” where it is applied to modify a feature or limitation herein, will be read in the context of the invention and in light of the knowledge in the art to provide the appropriate certainty, e.g., by using a standard that is recognized in the art for measuring the meaning of “substantially” as a term of degree, or by ascertaining the scope as would one of skill in the art.

[43] In embodiments, the numerical parameters should be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of some embodiments of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as practicable. The numerical values presented in some embodiments may contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[44] Herein, “an effective amount” or “a pharmacologically effective amount” refers to an amount of a compound or formulation comprising a compound that is non-toxic and sufficient to provide the desired effect with performance at a reasonable benefit/risk ratio attending any similar use of a like compound or formulation, or more generally attending any like medical treatment. The effective amount will vary depending upon the subject and the effect sought, the disease condition being treated or health benefit sought, the weight and age of the subject, the severity of the disease condition or degree of health benefit sought, the manner of administration, and the like, all of which can readily be determined by one of skill.

[45] Herein, “effect” or “efficacy” (including “therapeutic effect” or “therapeutic efficacy”) means the responses(s) in a mammal, and especially a human, after administration of a disclosed compound or formulation, such as according to a disclosed method, that are judged to be desirable and beneficial. Depending on the effect or improvement sought, and depending on the particular compound(s) and/or formulation, such responses may differ, but would be understood by those of skill.

[46] Measures of therapeutic effect include any outcome measure, endpoint, effect measure, or measure of effect within clinical or medical practice or research which is used to assess the effect, both positive and negative, of an intervention or treatment, whether patient-reported (e.g., questionnaires), based on other patient data (e.g., patient monitoring), gathered through laboratory tests such as blood work, urine samples, etc., through medical examination by a doctor or other medical professional, or by digital tools or means, e.g., electronic tools such as online tools, smartphones, wireless devices, biosensors, or health apps.

[47] In embodiments, measures of therapeutic effect include an assessment. “Assessment” refers to any means or method used with a subject, whether before, during, after, or unrelated in time to administration of a disclosed formulation, to measure, estimate, or evaluate a nature, ability, symptom, disorder, or other characteristic of the subject, whether qualitatively or quantitatively, and whether performed by the therapist or other clinician (e.g., an interview), by the subject his or herself (e.g., a self-reported questionnaire), by a third-party, or by a computer, including a medical device (e.g., as such as defined by FDA or other regulatory body) or other device (e.g., a medical sensor, biosensor, a watch, fitness tracker, “wearable”), and whether graded by a human decision-maker or an artificial intelligence (AI), machine learning, or computer algorithm.

[48] Non-limiting examples of assessments, which include “questionnaires,” include the 36 item Short Form Health Survey (SF-36), the EQ-5D, the Beck Depression Inventory, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, the State-Trait Anxiety Inventory, the Daily Stress Inventory, the Perceived Stress Scale, the Profile of Mood States questionnaire, the Eating Disorder Examination Questionnaire, the Yale-Brown Obsessive-Compulsive Scale, the Relationship Patterns Questionnaire, the Clinician- Administered PTSD Scale, the Civilian Mississippi Post-Traumatic Stress Disorder (PTSD) Scale, the Wisconsin Card Sorting Test (WCST), the Parkinson’s Disease Questionnaire (PDQ-39), the Multiple Sclerosis Impact Scale (MSIS-29), the Delis-Kaplan Executive Function System (DKEFS-ST), the Columbia Suicide Severity Rating Scale (C-SSRS), the Patient Health Questionnaire (PHQ-9), the Generalized Anxiety Disorder 7 (GAD-7), the Pittsburgh Sleep Quality Index (PSQI), the Interpersonal Reactivity Index (IRI), the Visual Short-Term Memory Binding Test, the Short Form (36) Health Survey (SF-36), the Self-Compassion Scale (SCS), the Trauma History Questionnaire (THQ), the Generalized Anxiety Disorder Scale-7 (GAD-7), Montgomery-Asberg Depression Rating Scale (MADRS), the Global Assessment of Functioning (GAF) Scale, Clinical Global Impression (CGI), the Mini International Neuropsychiatric Interview 5 (MINI 5), and related subject- or observer-reported measures. Other exemplary assessments will be understood to one of skill in view of the teachings herein and knowledge in the art.

[49] An assessment may be computer-assisted, and other computer-assisted assessments may be performed besides the assessments above. The term “computer-assisted” in “computer-assisted assessment” means an assessment comprising the use of electronic tools such as online tools, smartphones, wireless devices, or health apps (in some such examples, also known as “digital phenotyping”). Computer-assisted assessment will include the use of an electronic psychiatric notes system, where relevant clinical information will be recorded for the duration of the therapy by a therapist interacting face-to-face with an individual, and will also include the use of computer systems where the therapist and subject interact virtually (either synchronously or asynchronously), as well as where an individual only interacts with a computer (“computer” broadly meaning any electronic tool suitable for such purposes, including desktop, laptop, and notebook computers; tablets, smartphones, and other mobile devices; watches, fitness trackers, and personal electronic devices; and the like).

[50] The nomenclature used and embodiments described herein are those known in fields relating to one or more aspects of the invention, such as pharmaceutical science, pharmaceuticals, drug product formulation and development, chemistry, biology, pharmacology, and medicine, and are those that will be well known and commonly employed in such fields. Standard techniques and procedures are those generally performed according to conventional methods in the art. Unless defined otherwise, all technical and scientific terms herein have the meaning as commonly understood by one having ordinary skill in the art to which the invention belongs, who as shorthand may be referred to as “one of skill.”

[51] Further definitions that may assist a reader in understanding disclosed embodiments follow; however, it will be appreciated that they should not limit the scope of the invention, which is properly interpreted and understood by reference to the full specification (as well as any plain meaning known to one of skill) in view of the specific language recited by the claims. The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

## **B. Formulations**

[52] In some aspects, provided herein are sublingual spray formulations of therapeutic compounds.

[53] Among the therapeutic compounds useful in the disclosed formulations are those commonly referred to and defined for purposes herein as “psychedelics” (e.g., psilocin, 2C-B, LSD, DMT, MDMA, and others).

[54] In some aspects, the disclosure further relates to methods of producing the formulations and methods of using the formulations, including methods of administering the formulations to subjects. In some aspects, disclosed formulations modulate neurotransmission, such as serotonergic neurotransmission.

[55] Research on psychedelic compounds has demonstrated beneficial effects for a variety of psychiatric indications including depression, anxiety, and PTSD, as well as other indications such as chronic pain, migraines, inflammation, and many more. For example, psilocybin, a naturally occurring tryptamine alkaloid found in fungi, including numerous species in the *Psilocybe* genus, and a prodrug of the active metabolite psilocin, is in clinical trials for various medical uses, owing to its psychedelic, anxiolytic, and antidepressant

effects. Psilocybin has received FDA “Breakthrough Therapy” designation for treatment-resistant depression (TRD) and major depressive disorder (MDD), in combination with psychotherapy or psychological support, meaning that preliminary clinic evidence indicates it may demonstrate substantial improvement on clinically significant endpoint(s) over available therapies, and is being investigated for numerous other disorders.

[56] Psychedelics are generally physiologically safe, yet can be relatively potent. With LSD, for example, in which a standard therapeutic dose is on the order of 100 micrograms, a very small dose relative to body weight is necessary for an individual to receive therapeutic benefit. Accidental over-administration can result in strong subjective effects that may be undesirable or unsafe to certain individuals in certain circumstances.

[57] The bioavailability of the active compound of a psychedelic pharmaceutical formulation to the brain depends on the location a compound enters the bloodstream, whether and how it interacts with metabolic enzymes (e.g., CYPs, MAOIs, etc), and the unique metabolism of the individual (e.g., variation in CYPs). A primary challenge to the medicalization of these compounds has therefore been to develop a delivery method that can provide efficient, consistent, precise, predictable, and convenient dosing.

[58] To meet these needs and others, provided herein are sublingual spray formulations, comprising: (i) a psychedelic compound; (ii) a pharmaceutically acceptable excipient; and (iii) a solvent system.

[59] Disclosed formulations may in some embodiments be referred to as “pharmaceutical” formulations or for “pharmaceutical” purpose or preparation; however, it will be appreciated that the term simply means that a formulation is contemplated or shown to possess therapeutic or beneficial effects when administered for its intended purpose to a mammal, such as a human. The disclosed formulations are useful regardless of the regulatory regime under which they are ultimately sold (e.g., as prescription pharmaceutical drug products or non-prescription over-the-counter (OTC) drug products, or as “functional” products which beneficially affect one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and wellbeing and/or reduction in risk of disease), and also if not sold under a specific regulatory regime at all, whether in the U.S. or any other country.

[60] The disclosed formulations may be considered to have or to provide therapeutic or beneficial effects whether or not they are marketed in any jurisdiction (or capable of being marketed in any jurisdiction, under any applicable regulatory regime) as having such effects. For example, a formulation may provide a therapeutic or beneficial effect even when not intended to diagnose, treat, cure, or prevent any disease, and when not marketed as being for purposes of diagnosing, treating, curing, or preventing any disease.

[61] “Pharmaceutical” formulations, and formulations for “pharmaceutical” purpose or preparation, may be intended for FDA or other regulatory approval or authorization and ultimate sale as a regulated medical product, for use in state-regulated access markets, such as that under Oregon’s 2020 Psilocybin Services Act (Measure 109) or Colorado’s 2022 Natural Medicine Health Act (Proposition 122), or for sale in other “regulated use,” “supervised use,” “adult use,” or “recreational” markets, and the like.

[62] In embodiments, one or more components (e.g., excipients or other active or inactive ingredients) in

a formulation are generally recognized as safe (GRAS). “GRAS” will mean that the component(s), if used as food additives, have been adequately shown to be safe under the conditions of their intended use.

[63] In embodiments, one or more components (e.g., excipients or other active or inactive ingredients) in a formulation may be pharmaceutically acceptable. “Pharmaceutically acceptable” as used in connection with a component means that the component is generally safe and, within the scope of sound medical judgment, suitable for use in contact with the cells of humans and other animals without undue toxicity, irritation, allergic response, or complication, and commensurate with a reasonable risk/benefit ratio.

[64] In preferred embodiments, the components (e.g., excipients or other active or inactive ingredients) in a formulation, whether GRAS, pharmaceutically acceptable, or as otherwise defined by regulation or their application, will be safe for human consumption when ingested according to their intended use.

#### **a. Compounds**

[65] In embodiments, a disclosed sublingual spray formulation (herein equivalently as shorthand, unless context clearly indicates otherwise, a “disclosed formulation”) comprises an active compound.

[66] In embodiments, the active compound is a psychedelic compound, such as a compound from a psychedelic, a compound having psychedelic effects, or a compound referred to in the art (or herein) as a “psychedelic.” Broadly, and without being limited by theory, “psychedelic” compounds include those that induce altered states of consciousness, characterized by perceptual and cognitive distortions, changes in mood, and often profound changes in thought and self-perception. Psychedelics are typically used for their psychoactive and “psychedelic” effects, which can have therapeutic, spiritual, or recreational applications. However, as noted below, other compounds may be considered “psychedelics” even without such effects.

[67] A “psychedelic” compound, as described herein, may include “empathogenic” or “entactogenic” compounds, such as MDMA and certain of its analogs, and compounds which are sometimes described as having both “psychedelic” and “entactogenic” effects, such as MDA and 2C-B. Although disputes about the appropriateness of the term “psychedelic” for some compounds (such as MDMA) is recognized, the term “psychedelic” should be given its broadest reasonable interpretation in view of its common use in the field.

[68] The term “psychedelic” herein also includes such “non-hallucinogenic” compounds that can induce plasticity (e.g., neural plasticity, such as brain structural plasticity), whether or not the compounds induce subjective “psychedelic” effects associated with classic psychedelics. Some such compounds are referred to as “psychoplastogens” or “neuroplastogens.” See, e.g., Ly et al. *Cell Rep.* 2018;23(11):3170-3182; Olson. *J Exp Neurosci.* 2018;12:1-4. These compounds also are within the definition of “psychedelic” herein.

[69] “Psychedelics” include naturally-occurring substances such as psilocybin, psilocin, and DMT, as well as synthetic compounds like LSD, MDMA, and 2C-B. “Psychedelics” include compounds obtained from natural sources (e.g., by extraction), produced by biosynthesis (e.g., from *E. coli* or yeast), or made (including in part) by chemical synthesis. In embodiments, a psychedelic may be obtained, isolated, and/or purified from a natural source, may be chemically synthesized, may be produced by biosynthesis, as well as

combinations thereof (e.g., semisynthesis or partial chemical synthesis from a natural isolate).

[70] For naturally-occurring substances, the term “psychedelic” may refer to the psychedelic compound itself (e.g., psilocin or DMT), any fungal or plant sources thereof (e.g., mushrooms of the *Psilocybe* genus, root bark of *Mimosa hostilis*), as well as fungal or plant extracts (e.g., aqueous extracts, alcoholic extracts), or any one or more of the above including combinations thereof, as will be understood depending on context.

[71] Other such compounds included within the meaning of a “psychedelic” compound as used herein will be appreciated based on the teachings of the full disclosure in view of the general knowledge in the art.

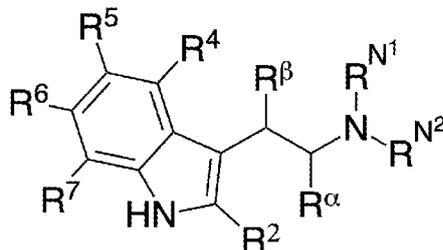
[72] In embodiments, the psychedelic compound is specifically a tryptamine, a phenethylamine, or a lysergamide. In embodiments, the psychedelic compound is a tryptamine. In embodiments, the psychedelic compound is a phenethylamine. In embodiments, the psychedelic compound is a lysergamide.

### 1. Tryptamines

[73] In embodiments, a disclosed sublingual spray formulation comprises a tryptamine. “Tryptamines” are as readily understood by those in the art. Non-limiting examples of tryptamines, useful in the practice of disclosed embodiments, include N,N-dibutyltryptamine (DBT), N,N-diethyltryptamine (DET), N,N-diisopropyltryptamine (DiPT), 5-methoxy- $\alpha$ -methyltryptamine ( $\alpha$ ,O-DMS), N,N-dimethyl-tryptamine (DMT), 2, $\alpha$ -dimethyltryptamine (2, $\alpha$ -DMT),  $\alpha$ ,N-dimethyltryptamine ( $\alpha$ ,N-DMT), N,N-dipropyltryptamine (DPT), N-ethyl-N-isopropyltryptamine (EiPT),  $\alpha$ -ethyltryptamine (AET), 3,4-dihydro-7-methoxy-1-methyl-carboline (Harmaline), 7-methoxy-1-methylcarboline (Harmine), N,N-dibutyl-4-hydroxytryptamine (4-HO-DBT), N,N-diethyl-4-hydroxytryptamine (4-HO-DET), N,N-diisopropyl-4-hydroxytryptamine (4-HO-DiPT), N,N-dimethyl-4-hydroxytryptamine (4-HO-DMT), N,N-dimethyl-5-hydroxytryptamine (5-HO-DMT, bufotenine), N,N-dipropyl-4-hydroxytryptamine (4-HO-DPT), N-ethyl-4-hydroxy-N-methyltryptamine (4-HO-MET), 4-hydroxy-N-isopropyl-N-methyltryptamine (4-HO-MiPT), 4-hydroxy-N-methyl-N-propyl-tryptamine (4-HO-MPT), 4-hydroxy-N,N-tetramethylenetryptamine (4-HO-pyr-T), 12-methoxyibogamine (Ibogaine), N-butyl-N-methyltryptamine (MBT), N,N-diisopropyl-4,5-methylenedioxytryptamine (4,5-MDO-DiPT), N,N-diisopropyl-5,6-methylenedioxytryptamine (5,6-MDO-DiPT), N,N-dimethyl-4,5-methylenedioxytryptamine (4,5-MDO-DMT), N,N-dimethyl-5,6-methylenedioxytryptamine (5,6-MDO-DMT), N-isopropyl-N-methyl-5,6-methylenedioxytryptamine (5,6-MDO-MiPT), N,N-diethyl-2-methyltryptamine (2-Me-DET), 2,N,N-trimethyl-tryptamine (2-Me-DMT), N-acetyl-5-methoxytryptamine (melatonin), N,N-diethyl-5-methoxytryptamine (5-MeO-DET), N,N-diisopropyl-5-methoxytryptamine (5-MeO-DiPT), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), N-isopropyl-4-methoxy-N-methyltryptamine (4-MeO-MiPT), N-isopropyl-5-methoxy-N-methyl-tryptamine (5-MeO-MiPT), 5,6-dimethoxy-N-isopropyl-N-methyltryptamine (5,6-MeO-MiPT), 5-methoxy-N-methyl-tryptamine (5-MeO-NMT), 5-methoxy-N,N-tetramethylenetryptamine (5-MeO-pyr-T), 6-methoxy-1-methyl-1,2,3,4-tetrahydrocarboline (6-MeO-THH), 5-methoxy-2,N,N-trimethyl-tryptamine (5-MeO-TMT), N,N-dimethyl-5-methylthiotryptamine (5-MeS-DMT), N-isopropyl-N-methyltryptamine (MiPT),  $\alpha$ -methyl-tryptamine ( $\alpha$ -MT), N-ethyltryptamine (NET), N-methyltryptamine (NMT), N,N-tetra-methylenetryptamine

(pyr-T), Tryptamine (T), 7-methoxy-1-methyl-1,2,3,4-tetrahydrocarboline (Tetrahydroharmine), or  $\alpha$ ,N-dimethyl-5-methoxytryptamine ( $\alpha$ ,N,O-TMS), as well as pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof, analogs, derivatives, metabolites, variants, and isotopologs (e.g., deuterated derivatives) thereof, and combinations of any of the foregoing thereof. See Shulgin and Shulgin, *TiHKAL: The Continuation*, Transform Press (1997) (“TiHKAL”), which is incorporated by reference as if fully set forth herein.

[74] In embodiments, the tryptamine is a substituted tryptamine having the structure below, wherein  $R^{N1}$ ,  $R^{N2}$ ,  $R^\alpha$ ,  $R^\beta$ ,  $R^2$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  will be as taught herein and as generally understood in the art:



[75] For example, in some embodiments,  $R^{N1}$ ,  $R^{N2}$ ,  $R^\alpha$ ,  $R^\beta$ ,  $R^2$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  are independently hydrogen, deuterium, halogen, hydroxy, methoxy, phosphoryloxy,  $C_1$ - $C_5$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl,  $C_3$ - $C_8$  cycloalkyl (independently or ring closed with the nitrogen),  $C_3$ - $C_8$  cycloalkenyl (independently or ring closed with the nitrogen), aryl, or heterocyclyl, any of which are optionally substituted at one or more positions by deuterium, halogen, alkyl, alkyl ester, hydroxy, alkoxy, carboxy, formyl, aryl, aryloxy, heterocyclyl, amino, alkylamino, arylamido, alkylamido, thiol, thioalkyl, thioaryl, alkylsulfonyl, alkylcarbamoyl, arylcarbamoyl, nitro, cyano, nitrate,  $-\text{OP}(\text{O})(\text{OH})_2$ ,  $-\text{OC}(\text{O})\text{H}$ ,  $-\text{OSO}_2\text{OH}$ ,  $-\text{OC}(\text{O})\text{NH}_2$ , and  $-\text{SONH}$ . In embodiments, the tryptamine comprises a quaternary ammonium cation wherein each of  $R^{N1}$ ,  $R^{N2}$ , and an additional  $R^{N3}$  are independently an alkyl group or an aryl group, and with all other substituents as above.

[76] In embodiments, a tryptamine will be a compound from a fungal source, such as a psychedelic fungus, e.g., a *Psilocybe* spp. fungus. For example, a tryptamine from a psychedelic fungus, such as a *Psilocybe* fungus is any of psilocybin, psilocin, norbaeocystin, baeocystin, aeruginascin, and norpsilocin.

[77] In embodiments, a tryptamine will be a “complex tryptamine” or other indolamine and including such examples as ergolines, ergot alkaloids, lysergamides, iboga alkaloids such as ibogaine, and their analogs, derivatives, metabolites, variants, and isotopologs, as well as pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof, and combinations of any of the foregoing thereof.

## 2. Phenethylamines

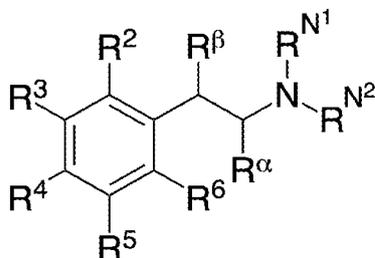
[78] In embodiments, a disclosed sublingual spray formulation comprises a phenethylamine. “Phenethylamines” are as readily understood by those in the art, and non-limiting examples of phenethylamines useful in the practice of the invention include  $\alpha$ -ethyl-3,4,5-trimethoxy-phenethylamine (AEM), 4-allyloxy-3,5-dimethoxyphenethylamine (AL), 2,5-dimethoxy-4-methylthioamphetamine (ALEPH), 2,5-dimethoxy-4-ethylthioamphetamine (ALEPH-2), 2,5-dimethoxy-4-isopropylthioamphetamine (ALEPH-4),

2,5-dimethoxy-4-phenylthio- amphetamine (ALEPH-6), 2,5-dimethoxy-4-propylthioamphetamine (ALEPH-7), 2,5-dimethoxy- $\alpha$ -ethyl-4-methylphenethylamine (ARIADNE), 3,4-diethoxy-5-methoxy- phenethylamine (ASB), 4-butoxy-3,5-dimethoxyphenethylamine (B), 2,5-dimethoxy-4,N-dimethylamphetamine (BEATRICE), 2,5-bismethylthio-4-methylamphetamine (BIS-TOM), 4-bromo-2,5, $\beta$ -trimethoxyphenethylamine (BOB), 2,5, $\beta$ -trimethoxy-4-methylphenethylamine (BOD),  $\beta$ -methoxy-3,4-methylenedioxyphenethylamine (BOH), 2,5-dimethoxy- $\beta$ -hydroxy-4-methylphenethylamine (BOHD), 3,4,5, $\beta$ -tetramethoxyphenethylamine (BOM), 4-bromo-3,5-dimethoxyamphetamine (4-Br-3,5-DMA), 2-bromo-4,5-methylenedioxyamphetamine (2-Br-4,5-MDA), 4-bromo-2,5-dimethoxyphenethylamine (2C-B), 4-benzyloxy-3,5-dimethoxy- amphetamine (3C-BZ), 4-chloro-2,5-dimethoxyphenethylamine (2C-C), 2,5-dimethoxy-4-methyl-phenethylamine (2C-D), 2,5-dimethoxy-4-ethyl-phenethylamine (2C-E), 3,5-dimethoxy-4-ethoxyamphetamine (3C-E), 2,5-dimethoxy-4-fluorophenethylamine (2C-F), 2,5-dimethoxy-3,4-dimethylphenethylamine (2C-G), 2,5-dimethoxy-3,4-trimethylene-phenethylamine (2C-G-3), 2,5-dimethoxy-3,4-tetramethylenephenethylamine (2C-G-4), 3,4-norbornyl-2,5-dimethoxyphenethylamine (2C-G-5), 1,4-dimethoxynaphthyl-2-ethylamine (2C-G-N), 2,5-dimethoxyphenethylamine (2C-H), 4-iodo-2,5-dimethoxyphenethylamine (2C-I), 2,5-dimethoxy-4-nitro-phenethylamine (2C-N), 2,5-dimethoxy-4-isopropoxyphenethylamine (2C-O-4), 2,5-dimethoxy-4-propylphenethylamine (2C-P), 4-cyclopropylmethoxy- 3,5-dimethoxyphenethylamine (CPM), 2,5-dimethoxy-4-methylselenophenethylamine (2C-SE), 2,5-dimethoxy-4-methylthiophenethylamine (2C-T), 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2), 2,5-dimethoxy-4-isopropylthiophenethylamine (2C-T-4), 2,6-dimethoxy-4- isopropylthiophenethylamine (psi-2C-T-4), 2,5-dimethoxy-4-propylthiophenethylamine (2C-T-7), 4-cyclopropylmethylthio-2,5-dimethoxyphenethylamine (2C-T-8), 4-(t)-butylthio-2,5-dimethoxy-phenethylamine (2C-T-9), 2,5-dimethoxy-4-(2-methoxyethylthio)phenethylamine (2C-T-13), 4-cyclopropylthio-2,5-dimethoxyphenethylamine (2C-T-15), 4-(s)-butylthio-2,5-dimethoxyphenethylamine (2C-T-17), 2,5-dimethoxy-4-(2-fluoroethylthio)phenethylamine (2C-T-21), 3,5-dimethoxy-4-trideuteromethylphenethylamine (4-D),  $\beta$ , $\beta$ -dideutero-3,4,5- trimethoxyphenethylamine ( $\beta$ -D), 3,5-dimethoxy-4-methyl-phenethylamine (DESOXY), 2,4-dimethoxyamphetamine (2,4-DMA), 2,5-dimethoxyamphetamine (2,5-DMA), 3,4-dimethoxyamphetamine (3,4-DMA), 2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine (DMCPA), 3,4-dimethoxy- $\beta$ -hydroxyphenethylamine (DME), 2,5-dimethoxy-3,4-methylenedioxyamphetamine (DMMDA), 2,3-dimethoxy-4,5-methylenedioxyamphetamine (DMMDA-2), 3,4-dimethoxyphenethylamine (DMPEA), 4-amyl-2,5-dimethoxyamphetamine (DOAM), 4-bromo-2,5-dimethoxyamphetamine (DOB), 4-butyl-2,5-dimethoxyamphetamine (DOBU), 4-chloro-2,5-dimethoxyamphetamine (DOC), 2,5-dimethoxy-4-(2-fluoroethyl) amphetamine (DOEF), 2,5-dimethoxy-4-ethylamphetamine (DOET), 4-iodo-2,5- dimethoxyamphetamine (DOI), 2,5-dimethoxy-4-methylamphetamine (DOM (STP)), 2,6-dimethoxy-4-methylamphetamine (psi-DOM), 2,5-dimethoxy-4-nitroamphetamine (DON),2,5-dimethoxy-4-propylamphetamine (DOPR), 3,5-dimethoxy-4-ethoxyphenethylamine (E), 2,4,5-triethoxyamphetamine (EEE), 2,4-diethoxy-5-methoxyamphetamine (EEM), 2,5-diethoxy-4-methoxyamphetamine (EME), 4,5-dimethoxy-2-ethoxyamphetamine (EMM), 2-ethylamino-

1-(3,4-methylenedioxyphenyl)butane (ETHYL-J), 2-ethylamino-1-(3,4-methylenedioxyphenyl)pentane (ETHYL-K), 6-(2-aminopropyl)-5-methoxy-2-methyl-2,3-dihydrobenzofuran (F-2), 6-(2-aminopropyl)-2,2-dimethyl-5-methoxy-2,3-dihydrobenzofuran (F-22), N-hydroxy-N-methyl-3,4-methylenedioxyamphetamine (FLEA), 2,5-dimethoxy-3,4-(trimethylene)amphetamine (G-3), 2,5-dimethoxy-3,4-(tetramethylene)amphetamine (G-4), 3,6-dimethoxy-4-(2-aminopropyl)benzonorbornane (G-5), 2,5-dimethoxy-3,4-dimethylamphetamine (GANESHA), 1,4-dimethoxynaphthyl-2-isopropylamine (G-N), 2,5-dimethoxy-4-ethylthio-N-hydroxyphenethylamine (HOT-2), 2,5-dimethoxy-N-hydroxy-4-(n)-propylthiophenethylamine (HOT-7), 4-(s)-butylthio-2,5-dimethoxy-N-hydroxyphenethylamine (HOT-17), 2,5-dimethoxy-N,N-dimethyl-4-iodoamphetamine (IDNNA), 2,3,4-trimethoxyphenethylamine (IM), 3,5-dimethoxy-4-isopropoxyphenethylamine (IP), 5-ethoxy-2-methoxy-4-methylamphetamine (IRIS), 2-amino-1-(3,4-methylenedioxyphenyl)butane (J, BDB), 3-methoxy-4,5-methylenedioxyphenethylamine (LOPHOPHINE), 3,4,5-trimethoxyphenethylamine (M), 4-methoxyamphetamine (4-MA, PMA), 2,N-dimethyl-4,5-methylenedioxyamphetamine (MADAM-6), 3,5-dimethoxy-4-methylallyloxyphenethylamine (MAL), 3,4-methylenedioxyamphetamine (MDA), N-allyl-3,4-methylenedioxyamphetamine (MDAL), N-butyl-3,4-methylenedioxyamphetamine (MDBU), N-benzyl-3,4-methylenedioxyamphetamine (MDBZ), N-cyclopropylmethyl-3,4-methylenedioxyamphetamine (MDCPM), N,N-dimethyl-3,4-methylenedioxyamphetamine (MDDM), N-ethyl-3,4-methylenedioxyamphetamine (MDE), N-(2-hydroxyethyl)-3,4-methylenedioxyamphetamine (MDHOET), N-isopropyl-3,4-methylenedioxyamphetamine (MDIP), N-methyl-3,4-methylenedioxyamphetamine (MDMA), 3,4-ethylenedioxy-N-methylamphetamine (MDMC), N-methoxy-3,4-methylenedioxyamphetamine (MDMEO), N-(2-methoxyethyl)-3,4-methylenedioxyamphetamine (MDMEOET), 3,4-methylenedioxy- $\alpha,\alpha$ ,N-trimethylphenethylamine (MDMP), N-hydroxy-3,4-methylenedioxyamphetamine (MDOH), 3,4-methylenedioxyphenethylamine (MDPEA),  $\alpha,\alpha$ -dimethyl-3,4-methylenedioxyphenethylamine (MDPH), 3,4-methylenedioxy-N-propargyl-amphetamine (MDPL), 3,4-methylenedioxy-N-propyl-amphetamine (MDPR), 3,4-dimethoxy-5-ethoxyphenethylamine (ME), 4,5-ethylenedioxy-3-methoxyamphetamine (MEDA), 4,5-diethoxy-2-methoxyamphetamine (MEE), 2,5-dimethoxy-4-ethoxyamphetamine (MEM), 4-ethoxy-3-methoxyphenethylamine (MEPEA), 5-bromo-2,4-dimethoxyamphetamine (META-DOB), 2,4-dimethoxy-5-methylthioamphetamine (META-DOT), 2,5-dimethoxy-N-methylamphetamine (METHYL-DMA), 4-bromo-2,5-dimethoxy-N-methylamphetamine (METHYL-DOB), 2-methylamino-1-(3,4-methylenedioxyphenyl)butane (METHYL-J, MBDB), 2-methylamino-1-(3,4-methylenedioxyphenyl)pentane (METHYL-K), 4-methoxy-N-methylamphetamine (METHYL-MA, PMMA), 2-methoxy-N-methyl-4,5-methylenedioxyamphetamine (METHYL-MMDA-2), 3-methoxy-4,5-methylenedioxyamphetamine (MMDA), 2-methoxy-4,5-methylenedioxyamphetamine (MMDA-2), 2-methoxy-3,4-methylenedioxyamphetamine (MMDA-3a), 4-methoxy-2,3-methylenedioxyamphetamine (MMDA-3b), 2,4-dimethoxy-5-ethoxyamphetamine (MME), 3,4-dimethoxy-5-(n)-propoxyphenethylamine (MP), 2,5-dimethoxy-4-(n)-propoxyamphetamine (MPM), 4,5-dimethoxy-2-methylthioamphetamine (ORTHO-DOT), 3,5-dimethoxy-4-propoxyphenethylamine (P), 3,5-dimethoxy-4-phenethyloxy-

phenethylamine (PE), phenethylamine (PEA), 3,5-dimethoxy-4-(2-propynyloxy)phenethylamine (PROPYNYL), 3,5-diethoxy-4-methoxyphenethylamine (SB), 2,3,4,5-tetra-methoxyamphetamine (TA), 4-ethoxy-3-ethylthio-5-methoxyphenethylamine (3-TASB), 3-ethoxy-4-ethylthio-5-methoxyphenethylamine (4-TASB), 3,4-diethoxy-5-methylthio-phenethylamine (5-TASB), 4-(n)-butylthio-3,5-dimethoxyphenethylamine (TB), 4-ethoxy-5-methoxy-3-methylthiophenethylamine (3-TE), 3,5-dimethoxy-4-ethylthiophenethylamine (TE, 4-TE), 3,4-dimethoxy-2-methylthiophenethylamine (2-TIM), 2,4-dimethoxy-3-methylthio-phenethylamine (3-TIM), 2,3-dimethoxy-4-methylthiophenethylamine (4-TIM), 3,4-dimethoxy-5-methylthiophenethylamine (3-TM), 3,5-dimethoxy-4-methylthiophenethylamine (4-TM), 3,4,5-trimethoxyamphetamine (TMA), 2,4,5-trimethoxyamphetamine (TMA-2), 2,3,4-trimethoxyamphetamine (TMA-3), 2,3,5-trimethoxyamphetamine (TMA-4), 2,3,6-trimethoxyamphetamine (TMA-5), 2,4,6-trimethoxyamphetamine (TMA-6), 4,5-dimethoxy-3-ethylthiophenethylamine (3-TME), 3-ethoxy-5-methoxy-4-methylthio-phenethylamine (4-TME), 3-ethoxy-4-methoxy-5-methylthiophenethylamine (5-TME), 3,4-methylenedioxy-2-methylthioamphetamine (2T-MMDA-3a), 2-methoxy-4,5-methylene-thiooxyamphetamine (4T-MMDA-2), 2,4,5-trimethoxyphenethylamine (TMPEA), 4-ethyl-5-methoxy-2-methylthioamphetamine (2-TOET), 4-ethyl-2-methoxy-5-methylthio-amphetamine (5-TOET), 5-methoxy-4-methyl-2-methylthioamphetamine (2-TOM), 2-methoxy-4-methyl-5-methylthioamphetamine (5-TOM), 2-methoxy-4-methyl-5-methyl-sulfinylamphetamine (TOMSO), 3,5-dimethoxy-4-propylthiophenethylamine (TP), 3,4,5-triethoxyphenethylamine (TRIS), 3-ethoxy-5-ethylthio-4-methoxyphenethylamine (3-TSB), 3,5-diethoxy-4-methylthiophenethylamine (4-TSB), 3,4-diethoxy-5-ethylthio-phenethylamine (3-T-TRIS), 3,5-diethoxy-4-ethylthiophenethylamine (4-T-TRIS), (R)-2,5-dimethoxy-4-iodoamphetamine (R-DOI), as well as pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, and tautomers thereof, analogs, derivatives, metabolites, variants, and isotopologs (e.g., deuterated derivatives) thereof, and combinations of any of the foregoing thereof. See Shulgin and Shulgin, PiHKAL: A Chemical Love Story, Transform Press (1991), which is incorporated by reference as if fully set forth herein. Phenethylamines in the meaning of the disclosure include cathinones, such as the beta-keto (cathinone) analogs of the above compounds, e.g., methylone ( $\beta$ k-MDMA) for MDMA.

[79] In embodiments, the phenethylamine is a substituted phenethylamine having the structure below, wherein  $R^{N1}$ ,  $R^{N2}$ ,  $R^\alpha$ ,  $R^\beta$ , and each of  $R^2$ - $R^6$  will be as taught herein and as generally understood in the art:

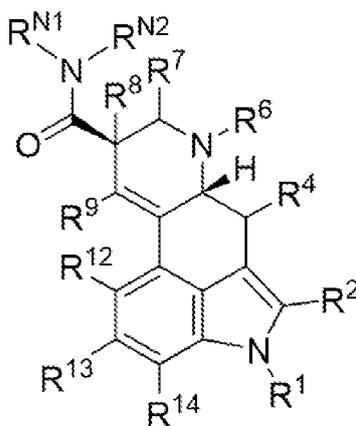


[80] For example, in some embodiments,  $R^{N1}$ ,  $R^{N2}$ ,  $R^\alpha$ ,  $R^\beta$ , and each of  $R^2$ - $R^6$  are independently hydrogen, deuterium, halogen,  $C_1$ - $C_5$  alkyl,  $C_2$ - $C_8$  alkenyl,  $C_2$ - $C_8$  alkynyl,  $C_3$ - $C_8$  cycloalkyl (independently or ring closed with the nitrogen, when  $R^N$ ),  $C_3$ - $C_8$  cycloalkenyl (independently or ring closed with the nitrogen, when  $R^N$ ),

aryl, or heterocyclyl; including where R<sup>3</sup> and R<sup>4</sup> may be joined together to form a dioxole (as with MDMA), a furan, a tetrahydrofuran, a thiophene, a pyrrole, a pyridine, a pyrrolidine, an ethylene oxide, an ethylenimine, a trimethylene oxide, a pyran, a piperidine, an imidazole, a thiazole, a dioxane, a morpholine, a pyrimidine, or otherwise so as to create a benzene heterocycle; and any of which are optionally substituted at one or more positions by deuterium, halogen, alkyl, alkyl ester, hydroxy, alkoxy, carboxy, formyl, aryl, aryloxy, heterocyclyl, amino, alkylamino, arylamido, alkylamido, thiol, thioalkyl, thioaryl, alkylsulfonyl, alkylcarbamoyl, arylcarbamoyl, nitro, cyano, nitrate, —OP(O)(OH)<sub>2</sub>, —OC(O)H, —OSO<sub>2</sub>OH, —OC(O)NH<sub>2</sub>, and —SONH. In embodiments, the phenethylamine comprises a quaternary ammonium cation wherein each of R<sup>N1</sup>, R<sup>N2</sup>, and an additional R<sup>N3</sup> are independently an alkyl group or an aryl group, and with all other substituents as above.

### 3. Lysergamides

[81] In embodiments, a disclosed sublingual spray formulation comprises an ergoline, an ergot alkaloid, or a lysergamide. In embodiments, a lysergamide is a compound having the general structure below, wherein R<sup>N1</sup>, R<sup>N2</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>12</sup>, R<sup>13</sup>, and R<sup>14</sup> are as taught herein and generally understood in the art:



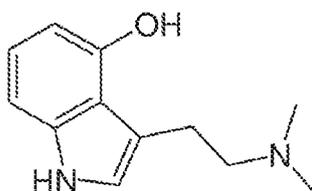
In embodiments, R<sup>N1</sup>, R<sup>N2</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>12</sup>, R<sup>13</sup>, and R<sup>14</sup> are each independently hydrogen, deuterium, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclyl. Additionally, any two of R<sup>N1</sup>, R<sup>N2</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>12</sup>, R<sup>13</sup>, and R<sup>14</sup> and the intervening atoms can be taken together to form an optionally substituted optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclyl. In embodiments, the lysergamide is a quaternary salt, in which an additional R<sup>6A</sup> is connected to the nitrogen to which R<sup>6</sup> is bound; wherein R<sup>6A</sup> is optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted aryl, or optionally substituted heterocyclyl. Non-limiting examples of ergolines useful in disclosed embodiments include lysergic acid diethylamide (i.e., LSD, LSD-25, LAD, Delysid), 6-ethyl-6-*nor*-lysergic acid diethylamide (ETH-LAD), 6-propynyl-6-*nor*-lysergic acid diethylamide (PARGY-LAD), 6-allyl-6-*nor*-lysergic acid diethylamide (AL-LAD), 6-propyl-6-*nor*-lysergic acid diethylamide (PRO-LAD), 6-isopropyl-6-*nor*-lysergic acid diethylamide (IP-LAD),

6-cyclopropyl-6-*nor*-lysergic acid diethylamide (CIP-LAD), 6-butyl-6-*nor*-lysergic acid diethylamide (BU-LAD), 6-(2-fluoroethyl)-6-*nor*-lysergic acid diethylamide (FLUOROETH-LAD), 1-acetyl-lysergic acid diethylamide (i.e., ALD, ALD-52, N-acetyl-LSD), 1-propionyl-lysergic acid diethylamide (1P-LSD), 1-butyryl-lysergic acid diethylamide (1B-LSD), 1-valeryl-lysergic acid diethylamide (1V-LSD), 1-(cyclopropylmethanoyl)-lysergic acid diethylamide (1cP-LSD), 1-(1,2-dimethylcyclobutane-1-carbonyl)-lysergic acid diethylamide (1D-LSD), 1-propionyl-6-allyl-6-*nor*-lysergic acid diethylamide (1P-AL-LAD), 1-(cyclopropylmethanoyl)-6-allyl-6-*nor*-lysergic acid diethylamide (1cP-AL-LAD), 1-propionyl-6-ethyl-6-*nor*-lysergic acid diethylamide (1P-ETH-LAD), lysergic acid 2,4-dimethylazetidide (i.e., LA-SS-Az, LSZ), lysergic acid piperidide (LSD-Pip), and lysergic acid methylisopropyl amide (MIPLA). Other ergolines useful in disclosed embodiments will be apparent to those of skill in the art in view of general references well-known in the art (see, e.g., TIHKAL; Nichols, D.E. Chemistry and Structure-Activity Relationship of Psychedelics. In: Halberstadt, A.L., Vollenweider, F.X., Nichols, D.E. (eds) Behavioral Neurobiology of Psychedelic Drugs. Current Topics in Behavioral Neurosciences, vol 36. Springer, Berlin, Heidelberg; Grob & Grigsby, Handbook of Medical Hallucinogens, 2021; Nichols. *Pharmacol Rev.* 2016; 68(2): 264-355; and references cited therein).

[82] Certain exemplary psychedelic compounds useful in disclosed sublingual spray formulations follow.

#### 4. Psilocin

[83] The psychedelic tryptamine psilocybin has received FDA Breakthrough Therapy designation and is on track for approval as a medicine, to be provided together with psychotherapy or psychological support. In vivo, psilocybin is rapidly dephosphorylated by endogenous phosphatase enzymes to produce psilocin (4-hydroxy-N,N-dimethyl-tryptamine; 4-OH-DMT), the active compound that agonizes serotonin 2A (5-HT<sub>2A</sub>) receptors in the brain and in other tissues. Psilocin itself is also naturally occurring at low concentrations in a variety of psychedelic mushroom species. Psilocin has the following chemical structure:



[84] In embodiments, a disclosed sublingual spray formulation comprises psilocin. In embodiments, a disclosed formulation comprises psilocin as a pharmaceutically acceptable salt, hydrate, or solvate.

[85] In embodiments, a disclosed formulation comprises a psilocin prodrug. Psilocin prodrugs include, for example, psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine; 4-OPO<sub>3</sub>H<sub>2</sub>-DMT) and psilacetin (4-acetoxy-N,N-dimethyltryptamine; 4-AcO-DMT). Numerous other psilocin prodrugs will be known in the art. In embodiments, a disclosed sublingual spray formulation comprises psilocybin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof. In embodiments, a disclosed formulation comprises psilacetin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof.

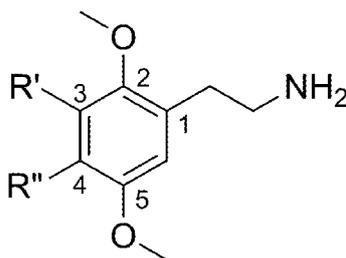
[86] In embodiments, a disclosed formulation comprises a psilocin metabolite. Psilocin is primarily

metabolized by enzymes such as liver monoamine oxidase (MAO), aldehyde dehydrogenase, UDP-glucuronosyltransferases, ceruloplasmin, cytochrome oxidase, and non-enzymatically by  $\text{Fe}^{3+}$ . Primary metabolites of psilocin include 4-hydroxy-indole-3-acetaldehyde, 4-hydroxy-indole-3-acetic acid (4-HIAA), 4-hydroxytryptophole (4-HTP), psilocin-O-glucuronide, psilocin iminoquinone, and psilocin o-quinone (Libânio Osório Marta. *Drug Metab Rev.* 2019; 51(3): 378-387).

[87] In embodiments, a disclosed sublingual spray formulation comprises no psilocybin. In embodiments, a disclosed sublingual spray formulation comprises no measurable psilocybin. In embodiments, a disclosed sublingual spray formulation comprises psilocybin below a defined threshold, such as by %w/w or %w/v of a disclosed formulation. In embodiments, a disclosed sublingual spray formulation comprises psilocybin below a defined molar ratio of psilocybin to psilocin, such as less than 1 mole psilocybin to every 10 moles of psilocin, less than 1:20, less than 1:30, less than 1:40, less than 1:50, less than 1:60, less than 1:70, less than 1:80, less than 1:90, or less than 1:100. In embodiments, a disclosed sublingual spray formulation comprises psilocybin and psilocin in a defined molar ratio of psilocybin to psilocin, such as about 1 mole psilocybin to every about 10 moles of psilocin, about 1:20, about 1:30, about 1:40, about 1:50, about 1:60, about 1:70, about 1:80, about 1:90, about 1:100, greater than 1:100, or less than 1:10.

## 5. 2C-X Compounds

[88] In embodiments, a disclosed sublingual spray formulation comprises a 2C-X compound. 2C-X compounds are psychedelic phenethylamines that contain methoxy substituents at the 2 and 5 positions of the core phenyl ring. 2C-X may be represented by the following general formula:



wherein, typically, R' and R'' are each independently hydrogen, halogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, cycloalkyl, cycloalkenyl, aryl, heterocyclyl; each optionally substituted by common substituents known to those of skill. Most commonly, R' is hydrogen and R'' is substituted. Exemplary 2C-X compounds include those in which R' is hydrogen and R'' is halogen, alkyl, substituted alkyl, alkoxy, or thioalkyl.

[89] A non-limiting list of 2C-X compounds includes, which will be known to those of skill by their common abbreviations, 2C-B, 2C-Bn, 2C-Bu, 2C-C, 2C-C-3, 2C-CN, 2C-CP, 2C-D, 2C-E, 2C-EF, 2C-F, 2C-G, 2C-G-1, 2C-G-2, 2C-G-3, 2C-G-4, 2C-G-5, 2C-G-6, 2C-G-N, 2C-H, 2C-I, 2C-iP, 2C-N, 2C-NH2, 2C-PYR, 2C-PIP, 2C-O, 2C-O-4, 2C-MOM, 2C-P, 2C-Ph, 2C-Se, 2C-T, 2C-T-2, 2C-T-3, 2C-T-4, 2C-T-5, 2C-T-6, 2C-T-7, 2C-T-8, 2C-T-9, 2C-T-10, 2C-T-11, 2C-T-12, 2C-T-13, 2C-T-14, 2C-T-15, 2C-T-16, 2C-T-17, 2C-T-18, 2C-T-19, 2C-T-21, 2C-T-21.5, 2C-T-22, 2C-T-23, 2C-T-24, 2C-T-25, 2C-T-27, 2C-T-28, 2C-T-30, 2C-T-31, 2C-T-32, 2C-T-33, 2C-DFM, 2C-TFM, 2C-TFE, 2C-PFE, 2C-PFS, 2C-YN, 2C-V, 2C-AL, or a

pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof.

[90] Some preferred 2C-X compounds of the disclosure are 2C-X compounds with a 4-halo substituent.

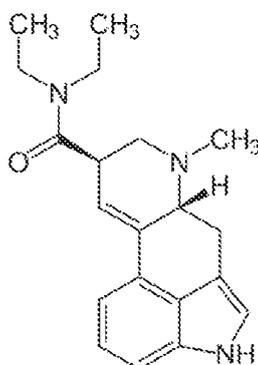
[91] In embodiments, a disclosed sublingual spray formulation comprises 2C-B, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof.

[92] In embodiments, a disclosed formulation comprises a prodrug of a 2C-X compound.

[93] In embodiments, a disclosed formulation comprises a metabolite of a 2C-X compound. 2C-X compounds are primarily metabolized by the MAO enzymes MAO-A and MAO-B, as well as the cytochrome P450 system. Studies on the metabolism of 2C-B have found that primary metabolites include an alcohol metabolite (4-bromo-2,5-dimethoxyphenylethylalcohol; i.e., 2C-B-ALC) and a carboxylated metabolite (4-bromo-2,5-dimethoxyphenylacetic acid; i.e., 2C-B-CBA) (Papaseit et al., Front. Pharmacol. 2018, 9, 206).

## 6. LSD

[94] In embodiments, a disclosed sublingual spray formulation comprises lysergic acid diethylamide (LSD), or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof. LSD has potent 5-HT<sub>2A</sub> agonist activity, and activity at other 5-HT and dopamine receptors. LSD has the structure:

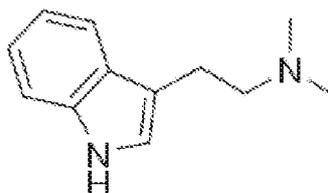


[95] In embodiments, a disclosed formulation comprises an LSD prodrug. Prodrugs of LSD will be known, and include N(1)-acyl prodrugs, such as 1-acetyl-LSD (i.e., ALD, ALD-52, N-acetyl-LSD), 1-propionyl-LSD (1P-LSD), 1-butyryl-LSD (1B-LSD), 1-valeryl-LSD (1V-LSD), and 1-(cyclopropylmethanoyl)-LSD (1cP-LSD).

[96] In embodiments, a disclosed formulation comprises an LSD metabolite. LSD is primarily metabolized in liver tissue by cytochrome P450 enzymes such as CYP3A4, CYP1A2, CYP2C19, CYP2D6, and CYP2E1, and possibly also peroxidase enzymes. LSD metabolism results in a variety of metabolites including N-demethyl-LSD, 13-OH-LSD, 14-OH-LSD, lysergic acid ethylamide, 2-oxo-LSD, and 2-oxo-3-hydroxy-LSD (Dinis-Oliveira, Drug Metab. Rev. 2017, 49(1), 84-91).

## 7. DMT

[97] In embodiments, a disclosed sublingual spray formulation comprises N,N-dimethyltryptamine (DMT). DMT occurs naturally in a range of plants and animals, occurring notably in plants native to South and Central America such as *Psychotria viridis*, *Mimosa tenuiflora*, and *Diplopterys cabrerana* (Dominguez-Clavé et al. *Brain Res Bull.* 2016; 126(1): 89-101). DMT has the following structure:



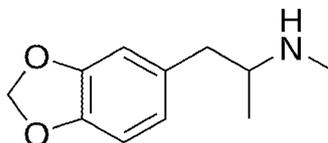
[98] In embodiments, a disclosed sublingual spray formulation comprises DMT as a pharmaceutically acceptable salt, hydrate, or solvate. In embodiments, the DMT is DMT freebase. In embodiments, the DMT is a pharmaceutically acceptable salt of DMT. In embodiments, the DMT is DMT fumarate.

[99] In embodiments, a disclosed formulation comprises a DMT prodrug.

[100] In embodiments, a disclosed formulation comprises a DMT metabolite. DMT is primarily metabolized by monoamine oxidase (MAO) and peroxidases. DMT can be metabolized into tryptamine, N-methyl-tryptamine, indoleacetic acid, DMT-N-oxide, 1,2,3,4-tetrahydro- $\beta$ -carboline, and 2-methyl-1,2,3,4-tetrahydro- $\beta$ -carboline (Cameron & Olson. *ACS Chem Neurosci*. 2018; 9: 2344-2357).

## 8. MDMA

[101] In embodiments, a disclosed sublingual spray formulation comprises 3,4-methylenedioxymethamphetamine (MDMA). MDMA is a member of a pharmacological class called empathogens, or entactogens, that have demonstrated antidepressant, anxiolytic, and prosocial effects. MDMA has the following structure:



[102] In embodiments, MDMA is formulated as a pharmaceutically acceptable salt, hydrate, or solvate.

[103] In embodiments, a disclosed formulation comprises an MDMA prodrug.

[104] In embodiments, the disclosed formulation comprises an MDMA metabolite. Metabolites of MDMA include 3,4-methylenedioxyamphetamine (MDA), 3,4-dihydroxymethamphetamine (HHMA), 3,4-dihydroxyamphetamine (HHA), 4-hydroxy-3-methoxymethamphetamine (HMMA) and 4-hydroxy-3-methoxyamphetamine (HMA) (de la Torre et al. *Ther Drug Monit*. 2004; 26: 137–144).

[105] In embodiments, a disclosed sublingual spray formulation comprises another empathogen or entactogen, which terms will be used interchangeably herein. In embodiments, the entactogen is any of 1-(1,3-benzodioxol-5-yl)-2-butanamine (BDB); 1-(1,3-benzodioxol-5-yl)-N-methyl-2-butanamine (MBDB); 3,4-methylenedioxyamphetamine (MDA); 3,4-methylenedioxy-N-ethyl-amphetamine (MDEA), 3-methylmethcathinone (3-MMC), mephedrone (4-MMC), methylone, ethylone, butylone,  $\alpha$ -ethyltryptamine ( $\alpha$ ET),  $\alpha$ -methyltryptamine ( $\alpha$ MT), 5-iodo-2-aminoindane (5-IAI), methylenedioxyaminoindane, 5,6-di-methoxy-2-aminoindane (MDAI), 5-(2-Aminopropyl)-2,3-dihydro-1H-indene (5-APDI, IAP), 6-(2-aminopropyl) benzofuran (6-APB, benzofury), 5-(2-aminopropyl)benzofuran (5-APB), 1-(benzofuran-5-yl)-N-methylpropan-2-amine (5-MAPB), 3,4-methylenedioxy-N-hydroxyamphetamine (MDOH), 4-fluoroamphetamine (4-FA), 5-methoxy-2-aminoindane (MEAI), N-allyl-3,4-methylenedioxyamphetamine (MDAL), N-butyl-3,4-methylenedioxy-

amphetamine (MDBU), N-benzyl-3,4-methylenedioxyamphetamine (MDBZ), N-cyclopropylmethyl-3,4-methylenedioxyamphetamine (MDCPM), N,N-dimethyl-3,4-methylenedioxyamphetamine (MDDM), N-(2-hydroxyethyl)-3,4-methylenedioxyamphetamine (MDHOET), N-isopropyl-3,4-methylenedioxyamphetamine (MDIP); N-methyl-3,4-ethylenedioxyamphetamine (MDMC), N-methoxy-3,4-methylenedioxyamphetamine (MDMEO), N-(2-methoxyethyl)-3,4-methylenedioxyamphetamine (MDMEOET),  $\alpha,\alpha$ -N-trimethyl-3,4-methylenedioxyphenethylamine, 3,4-methylenedioxy-N-methylphentermine (MDMP), 3,4-methylenedioxyphenethylamine (MDPEA),  $\alpha,\alpha$ -dimethyl-3,4-methylenedioxyphenethylamine, 3,4-methylenedioxyphentermine (MDPH;), N-propargyl-3,4-methylenedioxyamphetamine (MDPL), and N-propyl-3,4-methylenedioxyamphetamine (MDPR). In embodiments, the entactogen is a substituted amphetamine, phenethylamine, or benzofuran, such as any of 3-chloromethamphetamine (3-CMA), 4-fluoromethamphetamine (4-FMA), 4-methylamphetamine (4-MA), 4-methylmethamphetamine (4-MMA), 4-methylthioamphetamine (4-MTA), 5-(2-aminopropyl)-2,3-dihydro-benzofuran (5-APDB), 1-(benzofuran-5-yl)-N-ethylpropan-2-amine (5-EAPB), 5-(2-aminopropyl)indole (5-IT), 1-(2,3-dihydrobenzofuran-5-yl)-N-methylpropan-2-amine (5-MAPDB), 6-(2-aminopropyl)-2,3-dihydro-benzofuran (6-APDB), 1-(benzofuran-6-yl)-N-ethylpropan-2-amine (6-EAPB), 5-(2-aminopropyl)indole (6-IT), 1-(2,3-dihydrobenzofuran-6-yl)-N-methylpropan-2-amine (6-MAPDB), 3,4-ethylidenedioxyamphetamine (EDA), 2,3-methylenedioxyamphetamine (2,3-MDA), tenamfetamine (3,4-MDA), tetralinylaminopropane (TAP), and naphthylaminopropane (PAL-287). In embodiments, the entactogen is a serotonin releasing agent.

### 9. Salts, Isomers, Isotopologs, Prodrugs, and Derivatives

[106] A compound in any disclosed formulation will be understood to also include a pharmaceutically acceptable salt of the compound. A "pharmaceutically acceptable salt" refers to a salt prepared from pharmaceutically acceptable non-toxic acids or bases, which may be synthesized by conventional chemical methods. Generally, such salts are prepared by reacting the free acid or base forms of a compound 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, nonaqueous media (e.g., ether, ethyl acetate, ethanol, isopropanol, acetonitrile) are preferred. For therapeutic use, salts of a compound are those wherein the counter-ion is pharmaceutically acceptable.

[107] Exemplary salts include 2-hydroxyethanesulfonate, 2-naphthalenesulfonate, 2-napsylate, 3-hydroxy-2-naphthoate, 3-phenylpropionate, 4-acetamidobenzoate, acefyllinate, acetate, aceturate, adipate, alginate, aminosalicylate, ammonium, amsonate, ascorbate, aspartate, benzenesulfonate, benzoate, besylate, bicarbonate, bisulfate, bitartrate, borate, butyrate, calcium edetate, calcium, camphocarbonate, camphorate, camphorsulfonate, camsylate, carbonate, cholate, citrate, clavulariate, cyclopentanepropionate, cypionate, d-aspartate, d-camsylate, d-lactate, decanoate, dichloroacetate, digluconate, dodecylsulfate, edentate, edetate, edisylate, estolate, esylate, ethanesulfonate, ethyl sulfate, fumarate, furate, fusidate, galactarate (mucate), galacturonate, gallate, gentisate, gluceptate, glucoheptanoate, gluconate, glucuronate, glutamate, glutarate, glycerophosphate, glycolate, glycolylarsanilate, hemisulfate, heptanoate (enanthate),

heptanoate, hexafluorophosphate, hexanoate, hexylresorcinate, hippurate, hybenzate, hydrabamine, hydrobromide, hydrobromide/bromide, hydrochloride, hydroiodide, hydroxide, hydroxybenzoate, hydroxynaphthoate, iodide, isethionate, isothionate, l-aspartate, l-camsylate, l-lactate, lactate, lactobionate, laurate, laurylsulphonate, lithium, magnesium, malate, maleate, malonate, mandelate, meso-tartrate, mesylate, methanesulfonate, methylbromide, methylnitrate, methylsulfate, mucate, myristate, N-methylglucamine ammonium salt, napadisilate, naphthylate, napsylate, nicotinate, nitrate, octanoate, oleate, orotate, oxalate, p-toluenesulfonate, palmitate, pamoate, pantothenate, pectinate, persulfate, phenylpropionate, phosphate, phosphateldiphosphate, picrate, pivalate, polygalacturonate, potassium, propionate, pyrophosphate, saccharate, salicylate, salicylsulfate, sodium, stearate, subacetate, succinate, sulfate, sulfosalicylate, sulfosalicylate, suramate, tannate, tartrate, teoate, terephthalate, thiocyanate, thiosalicylate, tosylate, tribrophenate, triethiodide, undecanoate, undecylenate, valerate, valproate, xinafoate, zinc and the like (see Berge et al. *J Pharm Sci.* 1977; 66(1): 1-19).

[108] Disclosed pharmaceutical agents may contain one or more asymmetric centers and give rise to enantiomers, diastereomers, and other stereoisomeric forms. Each chiral center may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The invention includes all such possible isomers, as well as mixtures thereof, including racemic and optically pure forms. Optically active (R)- and (S)-, (-)- and (+)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Various methods are known in the art for preparing optically active forms and determining activity. Such methods include standard tests which are well known in the art. Examples of methods that can be used to obtain optical isomers of the compounds according to the disclosure include selective crystallization, enzymatic resolution, asymmetric synthesis (including asymmetric chemical synthesis and asymmetric enzymatic synthesis), kinetic resolution, and chiral chromatography (including chiral liquid chromatography, gas chromatography, and high-performance liquid chromatography). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, tautomeric forms are included. Disclosed compounds include all possible isomers, and mixtures thereof, such as non-racemic mixtures in any proportions, as well as racemic and optically pure forms.

[109] Where a disclosed compound is provided in a composition that is enantiomerically enriched, such as a mixture of enantiomers in which one enantiomer is present in excess, the enantiomeric excess may be in any amount greater than 0%. In embodiments, one enantiomer is in excess of at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, at least about 99.5%, at least about 99.9%, up to (and including) 100%. In embodiments, one enantiomer is in excess of less than 50%, such as less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, including less than 1%, less than 0.5%,

and up to 0%. In embodiments where a disclosed formulation comprises a non-racemic mixture of two isomers (e.g., R- and S-enantiomers), the isomers may be in a defined molar ratio, in any proportions (e.g., greater than 100:1, 100:1, 50:1, 40:1, 30:1, 20:1, 15:1, 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1.5:1, 1.2:1, 1:1, 1:1.2, 1:1.5, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, 1:30, 1:40, 1:50, 1:100, or less than 1:100, as well as any ratios in between).

[110] The disclosure also includes compounds with at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, i.e., isotopically enriched. Such compounds may be referred to as “isotopologs” herein. Isotopes are atoms having the same atomic number but different mass numbers, i.e., the same number of protons but a different number of neutrons. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, and chlorine such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{17}\text{O}$ ,  $^{18}\text{O}$ , and  $^{36}\text{Cl}$  respectively. In one non-limiting embodiment, isotopically labeled compounds can be used in metabolic studies (with  $^{14}\text{C}$ ), reaction kinetic studies (with, for example  $^2\text{H}$  or  $^3\text{H}$ ), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an  $^{18}\text{F}$ -labeled compound may be particularly desirable for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium, i.e.,  $^2\text{H}$ , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[111] In embodiments, the isotopolog is a deuterated compound. A “deuterated” compound includes any compound otherwise within the disclosure (e.g., a “psychedelic” compound), wherein at least one hydrogen, at any position, is replaced by a deuterium (including, in embodiments, at levels greater than would be expected from the natural abundance of deuterium on earth). In embodiments, a disclosed formulation comprises a deuterated psychedelic compound in place of the (non-deuterated) psychedelic compound.

[112] In embodiments, a disclosed formulation comprises deuterated psilocybin, deuterated psilocin, deuterated DMT, deuterated 5-MeO-DMT, or another deuterated tryptamine. In embodiments, a disclosed formulation comprises deuterated MDMA, deuterated 2-CB, or another deuterated phenethylamine. In embodiments, a disclosed formulation comprises deuterated LSD or another deuterated lysergamide. Deuterated compounds, such as deuterated psilocin and other psychedelics, will be readily appreciated in the art; they have been, e.g., disclosed in numerous patent applications published as of the time of this filing.

[113] In embodiments, a formulation comprises a deuterated compound together with a (non-deuterated) compound, such as in a defined molar ratio, in any proportions (e.g., greater than 100:1, 100:1, 50:1, 40:1, 30:1, 20:1, 15:1, 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, 1.5:1, 1.2:1, 1:1, 1:1.2, 1:1.5, 1:2, 1:3, 1:4, 1:5, 1:6,

1:7, 1:8, 1:9, 1:10, 1:15, 1:20, 1:30, 1:40, 1:50, 1:100, or less than 1:100, as well as any ratios in between).

[114] Prodrugs of disclosed compounds, e.g., of psychedelic compounds, also are within the scope of the invention. The term “prodrug” refers to a precursor of a biologically active pharmaceutical agent. Prodrugs undergo a chemical or a metabolic conversion to become a biologically active pharmaceutical agent. A prodrug can be converted *ex vivo* to the biologically active pharmaceutical agent by chemical transformative processes. *In vivo*, a prodrug is converted to the biologically active pharmaceutical agent by the action of a metabolic process, an enzymatic process or a degradative process that removes the prodrug moiety, such as a glycoside or acetyl group, to form the biologically active pharmaceutical agent. Other examples include addition of hydroxyl groups (TsujiKawa et al. *Xenobiotica*. 2011; 41(7): 578-584; Yamamoto et al. *Xenobiotica*. 1984; 14(11): 867-875), acyloxy alkyl carbonyl derivatives, amino acids (such as lysine), or peptides (Vig et al. *Adv Drug Delivery Rev.* 2013; 65(10): 1370-1385), which are generally added to the amine, and can be removed within the body by chemical reactions or enzymes, but other prodrugs and precursors, at the amine and other sites, should be understood to be within the scope of the invention (Simplicio et al. *Molecules*. 2008; 13(3): 519-547; Shah, Chauhan, Chauhan, & Mishra (Eds.). 2020. *Recent Advancement in Prodrugs*. CRC Press).

[115] Typical examples of prodrugs include compounds with biologically labile or cleavable (protecting) groups on a functional moiety of the active compound. In embodiments, disclosed compounds may be modified to increase or to decrease their blood-brain barrier (BBB) permeability. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. Examples of prodrugs using ester or phosphoramidate as biologically labile or cleavable (protecting) groups are disclosed in U.S. Pat. Nos. 6,875,751, 7,585,851, and 7,964,580; conventional procedures for the selection and preparation of suitable prodrugs are also described, for example, in Bundgaard (Ed). 1985. *Design of Prodrugs*. Elsevier; the disclosures of which are incorporated herein by reference. Disclosed prodrugs are metabolized to produce a disclosed compound.

[116] Derivatives of disclosed compounds, e.g., of psychedelic compounds, also are within the scope of the invention. Among derivatives of a compound are included its “physiologically functional derivatives,” which refer to physiologically tolerated chemical derivatives of the compound having the same physiological function, e.g., by being convertible in the body thereto, and which upon administration are able to form (directly or indirectly) the compound or an active metabolite thereof (and thus may also act like a prodrug), or by otherwise having the same physiological function, despite one or more structural differences. Examples of physiologically functional derivatives include esters, amides, carbamates, ureas, and heterocycles.

### **10. Combinations of Compounds; Additional Active Compounds**

[117] In embodiments, a disclosed sublingual spray formulation comprises more than one psychedelic compound. In embodiments, a disclosed formulation comprises two psychedelic compounds. As one

non-limiting example, in embodiments, a disclosed formulation comprises a combination of psilocin and LSD. In another example, in embodiments, a disclosed formulation comprises a combination of psilocin and DMT. In embodiments, a formulation comprises psilocin and MDMA. In embodiments, a formulation comprises psilocin and 2C-B. In embodiments, a formulation comprises psilocin and a psychedelic. In embodiments, a formulation comprises psilocin and a psychedelic tryptamine. In embodiments, a formulation comprises psilocin and a psychedelic phenethylamine. In embodiments, a formulation comprises psilocin and a psychedelic lysergamide. In embodiments, a formulation comprises LSD and DMT. In embodiments, a formulation comprises LSD and MDMA. In embodiments, a formulation comprises LSD and 2C-B. In embodiments, a formulation comprises DMT and MDMA. In embodiments, a formulation comprises DMT and 2C-B. In embodiments, a formulation comprises MDMA and 2C-B. In embodiments, a formulation comprises two or more psychedelic compounds. In embodiments, a disclosed formulation comprises three or more psychedelic compounds. In embodiments, a disclosed formulation comprises four or more psychedelic compounds. In embodiments, a disclosed formulation comprises five or more psychedelic compounds. In embodiments, a disclosed formulation comprises two or more psychedelic compounds at a synergistic ratio.

[118] In embodiments, a formulation comprises psilocin and another active compound. In embodiments, a formulation comprises psilocin and another tryptamine. In embodiments, a formulation comprises psilocin and a phenethylamine. In embodiments, a formulation comprises psilocin and a lysergamide. In embodiments, a formulation comprises psilocin and an MAOI. In embodiments, a formulation comprises psilocin and an additional active compound, such as any additional active compound disclosed herein.

[119] In embodiments, a disclosed formulation comprises an additional active compound.

[120] In embodiments, the additional active compound is any of: amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathsogens, psychedelics, plasticity-inducing agents (e.g., psychoplastogens), monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, and vitamins. In embodiments, the additional active compound acts to increase a therapeutic effect, provide an additional therapeutic effect, decrease an unwanted effect, increase stability or shelf-life, improve bioavailability, induce synergy, increase plasticity (e.g., neural plasticity), or alter pharmacokinetics or pharmacodynamics.

[121] In embodiments, the additional active compound is a serotonergic agent. In embodiments, a "serotonergic agent" will be an agent that binds to, blocks, or otherwise influences (e.g., via an allosteric reaction) activity at one or more serotonin receptors, including any one or more serotonin receptor subtypes. In embodiments, a serotonergic agent is not a psychedelic. In embodiments, a serotonergic agent binds to a serotonin receptor. In embodiments, a serotonergic agent indirectly affects a serotonin receptor, e.g., via

interactions affecting the reactivity of other molecules at the serotonin receptor. In embodiments, a serotonergic agent is an agonist, e.g., an agent activating a serotonin receptor. In embodiments, a serotonergic agent is an antagonist, e.g., an agent binding but not activating a serotonin receptor, e.g., blocking a receptor. In embodiments, a serotonergic agent is an effector molecule, e.g., an agent binding to an enzyme for allosteric regulation. In embodiments, a serotonergic agent acts (either directly or indirectly) at more than one type of receptor, including receptors other than serotonergic or other monoaminergic receptors. In embodiments, a serotonergic agent blocks the serotonin transporter (SERT) and results in an elevation of the synaptic concentration of serotonin, and an increase of neurotransmission. In embodiments, a serotonergic agent acts as a reuptake modulator and inhibits the plasmalemmal transporter-mediated reuptake of serotonin from the synapse into the presynaptic neuron, leading to an increase in extracellular concentrations of serotonin and an increase in neurotransmission. In embodiments, a serotonergic agent inhibits the activity of one or both monoamine oxidase enzymes, resulting in an increase in concentrations of serotonin and an increase in neurotransmission. In embodiments, a serotonergic agent is an antidepressant or anxiolytic, such as an SSRI, serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), or atypical antidepressant. In embodiments, a serotonergic agent is selected from the group consisting of: (1) serotonin transport inhibitors; (2) serotonin receptor modulators; (3) serotonin reuptake inhibitors; (4) serotonin and norepinephrine reuptake inhibitors; (5) serotonin dopamine antagonists; (6) monoamine reuptake inhibitors; (7) pyridazinone aldose reductase inhibitors; (8) stimulants of serotonin receptors; (9) stimulants of serotonin synthesis; (10) serotonin receptor agonists; (11) serotonin receptor antagonists; and (12) serotonin metabolites. Additional serotonergic agents will be known to those in the art, and can be found, for example, on DrugBank (<https://go.drugbank.com>).

[122] In embodiments, the additional active compound is a cannabinoid. In embodiments, the cannabinoid is any of a  $\Delta^9$ -THC-type cannabinoid, a  $\Delta^8$ -THC-type cannabinoid, a CBG-type cannabinoid, a CBD-type cannabinoid, a CBND-type cannabinoid, a CBE-type cannabinoid, a CBL-type cannabinoid, a CBC-type cannabinoid, a CBN-type cannabinoid, a CBT-type cannabinoid, or a miscellaneous-type cannabinoid. In embodiments, the cannabinoid is any of  $\Delta^9$ -THC- $C_5$ ,  $\Delta^9$ -THCAA- $C_5$ ,  $\Delta^9$ -THCAB- $C_5$ ,  $\Delta^9$ -THC- $C_4$ ,  $\Delta^9$ -THCAA- $C_4$ ,  $\Delta^9$ -THCV,  $\Delta^9$ -THCVAA,  $\Delta^9$ -THCO,  $\Delta^9$ -THCOAA,  $\Delta^9$ -THC-aldehyde,  $\beta$ -fenchyl (-)- $\Delta^9$ -trans-tetrahydrocannabinolate,  $\alpha$ -fenchyl (-)- $\Delta^9$ -trans-tetrahydrocannabinolate, epi-bornyl (-)- $\Delta^9$ -trans-tetrahydrocannabinolate, bornyl (-)- $\Delta^9$ -trans-tetrahydrocannabinolate,  $\alpha$ -terpenyl (-)- $\Delta^9$ -trans-tetrahydrocannabinolate, 4-terpenyl (-)- $\Delta^9$ -trans-tetrahydrocannabinolate,  $\alpha$ -cadinyl (-)- $\Delta^9$ -trans-tetrahydrocannabinolate,  $\gamma$ -eudesmyl (-)- $\Delta^9$ -trans-tetrahydrocannabinolate, 8 $\alpha$ -hydroxy-(-)- $\Delta^9$ -trans-tetrahydrocannabinol, 8 $\beta$ -hydroxy-(-)- $\Delta^9$ -trans-tetrahydrocannabinol, 11-acetoxy-(-)- $\Delta^9$ -trans-tetrahydrocannabinolic acid A, 8-oxo-(-)- $\Delta^9$ -trans-tetrahydrocannabinol, cannabisol, (-)- $\Delta^9$ -trans-tetrahydrocannabinol, (-)- $\Delta^9$ -trans-tetrahydrocannabinol,  $\Delta^8$ -THC,  $\Delta^8$ -THCA, 10 $\alpha$ -OH- $\Delta^8$ -THC, 10 $\beta$ -OH- $\Delta^8$ -THC, 10 $\alpha$ -hydroxy-10-oxo- $\Delta^8$ -THC, (E)CBG, (E)CBGA, (E)CBGG, (E)CBGAM, (E)CBGV, (E)CBGVA, (Z)CBGA,

5-acetyl-4-hydroxy-cannabigerol, ( $\pm$ )-6,7-*trans*- epoxycannabigerolic acid, ( $\pm$ )-6,7-*cis*-epoxycannabigerolic acid, ( $\pm$ )-6,7-*cis*- epoxycannabigerol, ( $\pm$ )-6,7-*trans*-epoxycannabigerol, camagerol, sesquicannabigerol, CBD-C<sub>5</sub>, CBDA-C<sub>5</sub>, CBDM-C<sub>5</sub>, CBD-C<sub>4</sub>, CBDV, CBDVA, CBD-C<sub>1</sub>, CBDH, CBDP, CBDD, CBND-C<sub>3</sub>, CBND-C<sub>5</sub>, CBE-C<sub>5</sub>, CBEAA-C<sub>5</sub>, CBEAB-C<sub>5</sub>, CBE-C<sub>3</sub>, CBEAB-C<sub>3</sub>, CBL, CBLA, CBLV, CBC, CBCA,  $\pm$ CBCV, +CBCV, CBCVA, 4-acetoxy-CBC, ( $\pm$ )-3<sup>n</sup>-hydroxy- $\Delta^7$ -cannabichromene, (-)-7-hydroxy- cannabichromane, CBC-C<sub>3</sub>, CBN-C<sub>5</sub>, CBNA-C<sub>5</sub>, CBN-C<sub>4</sub>, CBN-C<sub>3</sub>, CBN-C<sub>2</sub>, CBN-C<sub>1</sub>, CBNM-C<sub>5</sub>, 8-OH-CBN, 8-OH-CBNA, 1'S-OH-CBN, 4-terpenyl-cannabinolate, (-)-*trans*-CBT-C<sub>5</sub>, (+)-*trans*-CBT-C<sub>5</sub>, ( $\pm$ )-*cis*-CBT-C<sub>5</sub>, ( $\pm$ )-*trans*-CBT-C<sub>3</sub>, CBT-C<sub>3</sub>-homologue, (-)-*trans*-CBT-OEt-C<sub>5</sub>, (-)-*trans*-CBT-OEt-C<sub>3</sub>, 8,9-Di-OH-CBT-C<sub>5</sub>, CBDA-C<sub>5</sub>, 9-OH-CBT-C<sub>5</sub> ester, DCBF-C<sub>5</sub>, CBF-C<sub>5</sub>, OH-iso-HHCV-C<sub>3</sub> OTHC, cannabicitran, *cis*- $\Delta^9$ -THC, CBCON-C<sub>5</sub>, CBR, CBTT, CBCN-C<sub>5</sub>, CBCN-C<sub>3</sub>, *cis*-iso- $\Delta^7$ -THCV, *trans*-iso- $\Delta^7$ -THCV, *trans*-iso- $\Delta^7$ -THC, CBCNB, CBCNC, CBCND, (-)-(7*R*)-cannabicoumarononic acid, 4-acetoxy-2-geranyl-5-hydroxy-3-*n*-pentylphenol, 2-geranyl-5-hydroxy-3-*n*-pentyl-1,4-benzo- quinone, 5-acetoxy-6-geranyl-3-*n*-pentyl-1,4- benzoquinone, CBM, CBX, 10 $\alpha$ -hydroxy- $\Delta^{9,11}$ -hexahydrocannabinol, 9 $\beta$ ,10 $\beta$ -epoxyhexahydrocannabinol, 9 $\alpha$ -hydroxyhexahydrocannabinol, 7-oxo-9 $\alpha$ -hydroxyhexahydrocannabinol, 10 $\alpha$ -hydroxyhexahydrocannabinol, 10 $\alpha$ R-hydroxyhexahydrocannabinol, or 9 $\alpha$ -hydroxy-10-oxo- $\Delta^{6a,10a}$ -THC (see Radwan et al. *Molecules*. 2021; 26(9): 2774 ("Radwan et al. 2021"), incorporated by reference as if fully set forth herein).

[123] In embodiments, the additional active compound is a terpene. In embodiments, the terpene is a monoterpene, a sesquiterpene, a diterpene, a triterpene, or a miscellaneous terpene. In embodiments, the monoterpene is any of myrcene, *cis*- $\beta$ -ocimene, *trans*- $\beta$ -ocimene, *p*-cymene,  $\alpha$ -terpinene,  $\beta$ -phellandrene,  $\gamma$ -terpinene,  $\alpha$ -terpinolene,  $\alpha$ -phellandrene, 3-phenyl-2-methyl-prop-1-ene,  $\alpha$ -pinene,  $\beta$ -pinene, camphene,  $\Delta^3$ -carene,  $\Delta^4$ -carene, sabinene,  $\alpha$ -thujene, linalool, citral B, nerol, geraniol, ipsienol, citronellol, 2-methyl-2-heptene-6-on, geranyl acetone, *m*-mentha-1,8-(9)-dien-5-ol, carvacrol, carvone,  $\alpha$ -terpineol, terpinene-4-ol, pulegone, dihydrocarvone,  $\beta$ -terpineol, dihydrocarveyl acetate, *p*-cymene-8-ol,  $\beta$ -cyclocitral, safranal, *cis*-linalool oxide, perillene, sabinol, thujyl alcohol, linalool oxide, *cis*-carveol, *cis*-sabinene hydrate, sabinene hydrate, 8-cineol, 1,4-cineol, piperitone oxide, piperitenone oxide, fenchyl alcohol, fenchone, borneol, bornyl acetate, camphor, camphene hydrate,  $\alpha$ -pinene oxide, pinocarveol, and pinocarvone. In embodiments, the sesquiterpene is any of  $\alpha$ -caryophyllene,  $\beta$ -caryophyllene, caryophyllene oxide, curcumene,  $\alpha$ -*trans*-bergamotene,  $\alpha$ -selinene,  $\beta$ -farnesene, longifolene, humulene epoxide I, humulene epoxide II, caryophyllene alcohol (caryophyllenol),  $\beta$ -bisabolene, allo-aromadendrene, calamenene,  $\alpha$ -copaene, nerolidol,  $\alpha$ -gurjunene, iso-caryophyllene,  $\beta$ -selinene, selina-3,7(11)-diene, selina-4(14),7(11)-diene,  $\alpha$ -bisabolol,  $\alpha$ -cedrene,  $\alpha$ -cubebene,  $\delta$ -cadinene, epi- $\beta$ -santalene, farnesol,  $\gamma$ -cadinene,  $\gamma$ -elemene,  $\gamma$ -eudesmol, guaiol, ledol, *trans*-*trans*- $\alpha$ -farnesene, (*Z*)- $\beta$ -farnesene, farnesyl acetone,  $\alpha$ -cadinene,  $\alpha$ -*cis*-bergamotene,  $\alpha$ -eudesmol,  $\alpha$ -guaiene,  $\alpha$ -longipinene,  $\alpha$ -ylangene,  $\beta$ -elemene,  $\beta$ -eudesmol, epi- $\alpha$ -bisabolol,  $\gamma$ -*cis*-bisabolene,  $\gamma$ -curcumene,  $\gamma$ -muurolene,  $\gamma$ -*trans*-bisabolene, viridiflorene, germacrene-B, and clovandiol. In embodiments, the diterpene is either of phytol and neophytadiene. In embodiments, the

triterpene is either of friedeline and epifriedelanol. In embodiments, the miscellaneous terpene is any of vomifoliol, dihydrovomifoliol,  $\beta$ -ionone, and dihydroactinidiolide. (See Radwan et al. 2021)

[124] A therapeutic effect may, e.g., be synergistically increased or provided by an additional active compound. Such a “therapeutic effect” includes but is not limited to an antioxidant, anti-inflammatory, analgesic, antineuropathic, anti-nociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic, orexigenic, antiulcer, antihistamine, antihypertensive, anticonvulsant, antiepileptic, bronchodilator, neuroprotective, nootropic, empathogenic, psychedelic, plasticity-inducing, sedative, or stimulant effect.

[125] In one example, an additional active compound is a bioactive molecule that modulates neurotransmission and may induce synergy when co-administered with a psychedelic compound of the disclosure. For example, in some embodiments, the additional active compound is a 5-HT<sub>2A</sub> antagonist. In embodiments, the 5-HT<sub>2A</sub> antagonist is ketanserin. Ketanserin is used clinically as an antihypertensive agent, but it is also a high-affinity non-selective antagonist of 5-HT<sub>2</sub> receptors (van Nueten et al. *J Pharmacol Exp Ther.* 1981; 218(1): 217-230). In embodiments, inclusion of ketanserin (or another 5-HT<sub>2A</sub> receptor antagonist) in a disclosed formulation, alongside a psychedelic compound of the disclosure, modulates neurotransmission so as to increase a therapeutic effect, provide an additional therapeutic effect, or decrease an unwanted effect. In other embodiments, a 5-HT<sub>2A</sub> receptor antagonist is any of methiothepin, ritanserin, flibanserin, methysergide, trazodone, nefazodone, cinitapride, cyproheptadine, brexpiprazole, cariprazine, agomelatine, pimavanserin, eplivanserin, volinanserin, altanserin, setoperone, LY-367,265, 1-(1-Naphthyl)piperazine, SB 206553, pirenperone, SB-215505, metergoline, deramoiclone, amperozide, glemanserin, 5-MeO-NBpBrT, adatanserin, AMOA, cinanserin, fananserin, iferanserin, AC-90179, LY86057, GSK-215083, cyamemazine, mesulergine, BF-1, LY215840, sergolexole, spiramide, LYS3857, amesergide, LY108742, pipamperone, LY314228 and 5-I-R91150, and combinations thereof. In embodiments, the 5-HT<sub>2A</sub> receptor antagonist is selected from MDL-11,939, eplivanserin (SR-46,349), ketanserin, ritanserin, altanserin, acepromazine, mianserin, mirtazapine, quetiapine, SB204741, SB206553, SB242084, LY272015, SB243213, blonanserin, SB200646, RS 102221, nefazodone, MDL-100,907, pimavanserin, nelotanserin and lorcaserin. In embodiments, the 5-HT<sub>2A</sub> antagonist is volinanserin. In embodiments, the 5-HT<sub>2A</sub> antagonist is deuterated volinanserin. In other aspects are disclosed methods of administering a 5-HT<sub>2A</sub> antagonist before, at the same time as, or after the administration of a disclosed formulation, such as to reduce, prevent, shorten, or extinguish one or more subjective or psychedelic effects of the formulation.

[126] In embodiments, the additional active compound compound is a monoamine oxidase inhibitor. Herein, “monoamine oxidase inhibitor” or “MAOI” refers to any compound, whether natural or synthetic, that exhibits the ability to inhibit the enzymatic activity of MAO, including MAO-A and MAO-B. It encompasses all chemical structures, including organic molecules, peptides, proteins, nucleic acids, derivatives, analogs, and combinations thereof, capable of interfering with the catalytic function of monoamine oxidase enzymes,

thereby preventing or reducing the metabolism or breakdown of monoamine neurotransmitters. MAOIs useful in the practice of the disclosure, such as in a disclosed formulation in combination with DMT, include reversible, irreversible, competitive, non-competitive, selective, and non-selective inhibitors, as well as any substance that indirectly modulates or regulates MAO activity through allosteric, regulatory, or indirect mechanisms. In embodiments, the MAOI is a reversible inhibitor. In embodiments, the MAOI is an irreversible inhibitor. In embodiments, the MAOI is a competitive inhibitor. In embodiments, the MAOI is a non-competitive inhibitor. In embodiments, the MAOI is a selective inhibitor. In embodiments, the selective inhibitor is a MAO-A-selective inhibitor. In embodiments, the selective inhibitor is a MAO-B-selective inhibitor. In embodiments, the MAOI is a non-selective inhibitor.

[127] In embodiments, the MAOI is any of isocarboxazid, pargyline, selegiline, furazolidone, phenelzine, amiflamine, iproniazid, nialamide, tranylcypromine, octamoxin, phenoxypropazine, pivhydrazine, iproclozide, bifemelane, prodipine, benmoxin, etryptamine, fenoxypipazine, mebanazine, pheniprazine, safrazine, hypericine, methylene blue, moclobemide, brofaromine, eprobemide, metralindole, befloxatone, toloxatone, clorgyline, caroxazone, CX157, CX009, cimoxatone, bazinaprine, harmine, harmaline, serclorephine, minaprine, esuprone, pirlindole, tetrindole, and rosiridin. In embodiments, the MAOI is isocarboxazid. In embodiments, the MAOI is pargyline. In embodiments, the MAOI is selegiline. In embodiments, the MAOI is furazolidone. In embodiments, the MAOI is phenelzine. In embodiments, the MAOI is amiflamine. In embodiments, the MAOI is iproniazid. In embodiments, the MAOI is nialamide. In embodiments, the MAOI is tranylcypromine. In embodiments, the MAOI is octamoxin. In embodiments, the MAOI is phenoxypropazine. In embodiments, the MAOI is pivhydrazine. In embodiments, the MAOI is iproclozide. In embodiments, the MAOI is bifemelane. In embodiments, the MAOI is prodipine. In embodiments, the MAOI is benmoxin. In embodiments, the MAOI is etryptamine. In embodiments, the MAOI is fenoxypipazine. In embodiments, the MAOI is mebanazine. In embodiments, the MAOI is pheniprazine. In embodiments, the MAOI is safrazine. In embodiments, the MAOI is hypericine. In embodiments, the MAOI is methylene blue. In embodiments, the MAOI is moclobemide. In embodiments, the MAOI is brofaromine. In embodiments, the MAOI is eprobemide. In embodiments, the MAOI is metralindole. In embodiments, the MAOI is befloxatone. In embodiments, the MAOI is toloxatone. In embodiments, the MAOI is clorgyline. In embodiments, the MAOI is caroxazone. In embodiments, the MAOI is CX157. In embodiments, the MAOI is CX009. In embodiments, the MAOI is cimoxatone. In embodiments, the MAOI is bazinaprine. In embodiments, the MAOI is harmine. In embodiments, the MAOI is harmaline. In embodiments, the MAOI is serclorephine. In embodiments, the MAOI is minaprine. In embodiments, the MAOI is esuprone. In embodiments, the MAOI is pirlindole. In embodiments, the MAOI is tetrindole. In embodiments, the MAOI is rosiridin.

[128] In embodiments, a disclosed formulation comprises DMT and a monoamine oxidase inhibitor (MAOI). Combining DMT with a MAOI can prolong the duration and increase the intensity of the subjective and psychedelic effects of DMT (Halberstadt. *Pharmacol Biochem Behav.* 2016; 143: 1-10), similar to the

effects of the psychedelic brew made from natural plant sources known as ayahuasca, or when combined as extracted, isolated, purified, or synthetic drug compounds or drug products often known as “pharmahuasca.” Accordingly, in some disclosed embodiments is a “pharmahuasca” sublingual spray formulation comprising DMT and an MAOI. In other embodiments, a disclosed formulation may comprise an MAOI and another psychedelic compound, such as psilocybin or psilocin (“psilohuasca”), or any other disclosed compound.

[129] In other aspects are disclosed methods of administering an MAOI before, at the same time as, or after the administration of a disclosed formulation, such as one comprising DMT, psilocybin, or psilocin, such as to prolong the duration of and/or increase the intensity of the subjective and psychedelic effects thereof.

[130] In embodiments, a disclosed formulation comprises an enzyme inhibitor. A major function of saliva is to initiate digestion in advance of the gastrointestinal tract, and saliva accordingly contains various enzymes, including amylases, lipases, proteases, and phosphatases (Valdez et al. *Dig Dis.* 1991; 9(3): 125–132). Salivary enzymes may reduce the absorption of a psychedelic compound by degrading the compound prior to absorption. Accordingly, in some embodiments, a disclosed formulation comprises an additional active compound that inhibits the activity of one or more salivary enzymes. Salivary enzyme inhibitors are known to those of skill in the art, and include various naturally occurring and synthetic compounds (Zhang et al. *Caries Res.* 1998; 32(3): 233-238; Kandra et al. *Biochem Biophys Res Commun.* 2004; 319(4): 1265-1271).

[131] In embodiments, two or more compounds or ingredients in a disclosed formulation are selected to provide, are able to provide, or do provide, a synergistic effect. The two or more compounds or ingredients may be active agents or ingredients or inactive agents or ingredients, or a mixture thereof.

[132] Numerous methods are known to those of skill to determine a synergistic effect, i.e., whether, when two or more components are mixed together, the effect is greater than the sum of the effects of the individual components applied alone, thereby producing “1+1 > 2.” Suitable methods include isobologram (or contour) analysis (Huang. *Front Pharmacol.* 2019; 10: 1222), or the equation of Loewe additivity (Loewe & Muischnek. *Arch Exp Pathol Pharmacol.* 1926; 114: 313-326). A synergistic effect also may be calculated using methods such as the Sigmoid-Emax equation (Holford & Scheiner. *Clin Pharmacokinet.* 1981; 6: 429-453) and the median-effect equation (Chou & Talalay. *Adv Enzyme Regul.* 1984; 22: 27-55). The corresponding graphs associated with the equations referred to above are the concentration-effect curve and combination index curve, respectively. Each equation referred to above may be applied to experimental data to generate a corresponding graph to aid in assessing the effects of, e.g., a disclosed sublingual spray formulation comprising two (or more) psychedelic compounds.

[133] Non-limiting examples of synergistic effects of a disclosed formulation include increased and/or prolonged receptor (e.g., serotonin receptor) activation, enhanced pharmacological and/or therapeutic efficacy, reduced side effects, increased and/or modulated signaling pathway activation, effects resulting from the simultaneous activation of different receptor systems and/or subtypes, and effects resulting from a combination of such factors. In embodiments, the synergistic effect is a pharmacokinetic effect. In

embodiments, the synergistic effect is a pharmacodynamic effect. Other synergistic effects include increasing an existing therapeutic effect, providing an additional therapeutic effect, decreasing an unwanted effect or property (e.g., nausea, vomiting), altering a property in a desirable way (such as pharmacokinetics or pharmacodynamics), modulating a desired system or pathway (e.g., a neurotransmitter system), and increasing a desired property relating to drug formulation such as solubility, stability, or shelf-life.

[134] Generally, the compounds in a disclosed formulation are isolated or purified compounds. The terms “isolated,” “purified,” or “substantially pure,” as used herein, refer to material that is substantially or essentially free from components that normally accompany the material when the material is synthesized, manufactured, or otherwise produced. An “isolated,” “purified,” or “substantially pure” compound or preparation of a compound is accordingly defined as a compound or preparation thereof having a chromatographic purity of greater than 90%, more preferably greater than 95%, more preferably greater than 96%, more preferably greater than 97%, more preferably greater than 98%, more preferably greater than 99%, more preferably greater than 99.5%, and most preferably greater than 99.9%, as determined by area normalization of an HPLC profile or other similar detection method. Preferably the pure or substantially pure compound is substantially free of any other active compounds which are not intended to be administered to a subject. In this context “substantially free” can be taken to mean that no active compound(s) other than the active compound intended to be administered to a subject are detectable by HPLC or other similar detection method, or are below a desired threshold of detection such as defined above.

#### **b. Excipients**

[135] In embodiments, a disclosed sublingual spray formulation comprises a pharmaceutically acceptable excipient. In embodiments, the excipient is a solubilizing agent, an antioxidant, a penetration enhancer, a taste-masking agent, a mucoadhesive polymer, or a combination thereof.

[136] The exemplary functions of disclosed excipients are merely illustrative of some properties of excipients, and should not be construed as limiting upon the classification or function of any specific disclosed excipients. It will be appreciated by those in the art based on the teachings of the disclosure in view of the general knowledge in the art that excipients can have multiple functions depending on how they are used in a formulation, and the other components of that formulation, and that an excipient used for one function in one formulation need not mean that the same excipient used in another formulation must be serving that same function; rather, despite some functions being typical or more common than others, one may only fully understand the function of an excipient by its use in the context of a specific formulation, together with knowledge of the other components of the formulation. Hence, reference to any function of an excipient (or agent, compound, or other ingredient), or the inclusion of any excipient or other ingredient in a list herein will be understood to be non-limiting, as the disclosed excipients and other ingredients may have one or more other functions and/or classifications that will be appreciated by those in the art. As one example, cyclodextrin may, in a formulation, be any one or more of a solubilizing agent, a penetration

enhancer, an antioxidant, and/or a taste-masking agent. As other examples, chitosan may be a penetration enhancer and/or a mucoadhesive polymer; L-menthol may be a penetration enhancer and/or a taste-masking agent; lecithin (phosphatidylcholine) may be a solubilizing agent and/or a penetration enhancer; and xanthan gum may be a solubilizing agent and/or a muco-adhesive polymer; all depending on the specific formulation. In embodiments, a disclosed excipient can function as any one or more of a solubilizing agent, an antioxidant, a penetration enhancer, a taste-masking agent, and a mucoadhesive polymer. An excipient may have multiple functions when incorporated into a disclosed formulation.

[137] Exemplary and non-limiting concentrations for certain disclosed excipients herein include the following. D- $\alpha$ -tocopherol:  $\leq 5$ ; Chitosan:  $\leq 5$ ; Hydroxymethylcellulose:  $\leq 25$ ; L-Menthol:  $\leq 0.5$ ; Lecithin (Phosphatidylcholine):  $\leq 10$ ; Propylene Glycol:  $\leq 50$ ; Polysorbate 80:  $\leq 10$ ; Rosmarinic acid:  $\leq 5$ ; Xanthan gum:  $\leq 10$ ; Xylitol:  $\leq 20$ . Exemplary and non-limiting concentrations for other disclosed excipients will be appreciated by one of skill from the teachings of the disclosure in view of the general knowledge in the art.

### **1. Solubilizing Agents**

[138] In embodiments, a disclosed sublingual spray formulation comprises a solubilizing agent. Without being bound by theory, solubilizing agents may form complexes with drug molecules which can have different physicochemical properties than the drug molecule alone. The properties of the complexes can increase the solubility of the drug molecules.

[139] In embodiments, a suitable solubilizing agent or combination of solubilizing agents may be determined by conducting excipient compatibility and screening studies. Certain psychedelic compounds may exhibit synergies with specific solubilizing agents (e.g., certain cyclodextrins).

[140] In embodiments, the inclusion of a solubilizing agent in a disclosed formulation increases the solubility of a psychedelic compound in the formulation, which can in some embodiments increase the solubility of the psychedelic compound in the formulation to a point beyond the compound's natural solubility limit in the solvent system. In embodiments, the solubility of the psychedelic compound is increased by about 1.1-fold, 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or at least 100-fold compared to the solubility limit of the psychedelic compound in the same solvent system, in the absence of any solubilizing agent. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 1.1-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 1.2-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 1.3-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 1.4-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 1.5-fold. In embodiments, the solubility of the psychedelic

compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 1.6-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 1.7-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 1.8-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 1.9-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 2-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 5-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 10-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 20-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 50-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by 100-fold. In embodiments, the solubility of the psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug, is increased by at least 100-fold.

[141] In embodiments, the solubilizing agent is a water-soluble enhancing agent, a surfactant, a water insoluble lipid, an organic liquid, a cyclodextrin, or a phospholipid. In embodiments, the solubilizing agent is a cyclodextrin, surfactant, or phospholipid.

[142] In embodiments, the solubilizing agent is a phospholipid. In embodiments, the phospholipid is hydrogenated soy phosphatidylcholine, distearoylphosphatidylglycerol, L-alpha-dimyristoylphosphatidylcholine, or L-alpha-dimyristoylphosphatidylglycerol.

[143] In embodiments, the solubilizing agent is a water-soluble enhancing agent. In embodiments, the water-soluble enhancing agent is any of polyethylene glycol 300, polyethylene glycol 400, and propylene glycol, or a combination thereof. In embodiments, the water-soluble enhancing agent is polyethylene glycol 300. In embodiments, the water-soluble enhancing agent is polyethylene glycol 400. In embodiments, the water-soluble enhancing agent is propylene glycol.

[144] In embodiments, the solubilizing agent is a surfactant. In embodiments, the surfactant is an anionic surfactant. Anionic surfactants include, for example, sodium alkyl sulfate, sodium alkyl sulfonate, sodium alkyl aryl sulfonate, sodium stearate, dioctyl sodium sulfosuccinate, sodium cholate, and any combination thereof. Additional suitable examples of anionic surfactants are higher alkyl sulfates such as potassium or sodium lauryl sulfate, higher fatty acid monoglyceride monosulfates, such as the salt of the monosulfated monoglyceride of hydrogenated coconut oil fatty acids, alkyl sulfonates such as sodium dodecyl benzene sulfonate, higher fatty sulfoacetates, higher fatty acid esters of 1,2 dihydroxypropane sulfonate. In

embodiments, the surfactant is a nonionic surfactant. Nonionic surfactants include, for example, organosilicone surfactants (e.g., alkyl- and alkoxy-dimethicone copolyol, such as cetyl dimethicone copolyol) and nonionic organic surfactants (e.g., polysorbate, glyceryl stearate, polyoxyethylene (POE) fatty acid ester, poly(oxyethylene)alkyl ether, polyethoxylene castor oil derivative, PEG-6 octanoic/decanoic glycerides, polyoxyethylene glycerol trioleate, decaglycerol mono/dioleate). In embodiments, the non-ionic surfactant is Cremophor EL, Cremophor RH 40, Cremophor RH 60, d-tocopherol polyethylene glycol 1000 succinate, polysorbate 20, polysorbate 80, Solutol HS 15, sorbitan monooleate, poloxamer 407, Labrafil M-1944CS, Labrafil M-2125CS, Labrasol, Gellucire 44/14, Softigen 767, mono- and di-fatty acid esters of PEG 300, 400, or 1750, or a combination thereof. In embodiments, the non-ionic surfactant is polysorbate 80. In embodiments, the surfactant is polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan monopalmitate (Tween 40), polyoxyethylene sorbitan monostearate (Tween 60), or polyoxyethylene sorbitan monooleate (Tween 80). Additional examples of water soluble nonionic surfactants are condensation products of ethylene oxide with various hydrogen-containing compounds that are reactive therewith and have long hydrophobic chains (e.g., aliphatic chains of about 12 to 20 carbon atoms), which condensation products contain hydrophilic polyoxyethylene moieties, such as condensation products of poly (ethylene oxide) with fatty acids, fatty alcohols, fatty amides and other fatty moieties, and with propylene oxide and polypropylene oxides, e.g., Pluronic® materials such as Pluronic® F127. Exemplary suitable alkyl polyglycoside (APG) surfactant(s) that may be used in the formulation may comprise APG C8-C10, APG C10-C16, decyl glucoside, coco-glucoside, anionic APG carboxylate, sodium lauryl glucose carboxylate, lauryl glucoside, D-glucopyranose (oligomeric, C10-16 glycosides, carboxymethyl ethers, sodium salts), C12-C16 fatty alcohol glycoside, and combinations thereof. Exemplary APG surfactant(s) that may be used may have an industry designation of Plantaren® 2000 N UP/MB, Plantapon® LGC Sorb, Plantaren® 1200 N UP/MB, and Plantaren® 818 UP/MB. In embodiments, the surfactant is a cationic surfactant, an amphoteric surfactant, or a combination thereof.

[145] In embodiments, a disclosed formulation comprises a surfactant in an amount between about 0.01% and 60% of the total weight of the formulation (expressed herein as “w/w” as shorthand). In embodiments, a disclosed formulation comprises between about 0.1% and 10% (w/w) of a surfactant. In embodiments, a disclosed formulation comprises between about 0.1% and 5% (w/w) of a surfactant. In embodiments, a disclosed formulation comprises between about 0.1% and 2% (w/w) of a surfactant. In embodiments, a disclosed formulation comprises between about 0.5% and 2% (w/w) of a surfactant. In embodiments, a disclosed formulation comprises between about 0.5% and 1.5% (w/w) of a surfactant. In embodiments, a disclosed formulation comprises between about 1% and 10% (w/w) of a surfactant. In embodiments, a disclosed formulation comprises between about 1% and 5% (w/w) of a surfactant. In embodiments, a disclosed formulation comprises between about 5% and 20% (w/w) of a surfactant. In embodiments, a disclosed formulation comprises between about 30% and 60% (w/w) of a surfactant. In embodiments, a

disclosed formulation comprises between about 30% and 40% (w/w) of a surfactant. In embodiments, a disclosed formulation comprises at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, or at least 60%, of a surfactant.

[146] In embodiments, a disclosed formulation comprises polysorbate 80 in an amount between about 0.01% and 10% of the total weight of the formulation (expressed herein as “w/w” as shorthand). In embodiments, a disclosed formulation comprises between about 0.1% and 10% (w/w) of polysorbate 80. In embodiments, a disclosed formulation comprises between about 0.1% and 5% (w/w) of polysorbate 80. In embodiments, a disclosed formulation comprises between about 0.1% and 2% (w/w) of polysorbate 80. In embodiments, a disclosed formulation comprises between about 0.5% and 2% (w/w) of polysorbate 80. In embodiments, a disclosed formulation comprises between about 0.5% and 5% (w/w) of polysorbate 80. In embodiments, a disclosed formulation comprises between about 0.5% and 1.5% (w/w) of polysorbate 80. In embodiments, a disclosed formulation comprises about 1% (w/w) of polysorbate 80.

[147] In embodiments, the solubilizing agent is an organic liquid. In embodiments, the organic liquid is beeswax, vitamin E, e.g., D- $\alpha$ -tocopherol, oleic acid, or a medium-chain mono- or diglyceride.

[148] In embodiments, a disclosed formulation comprises a solubilizing agent in an amount between about 1% and 70% of the total weight of the formulation (expressed herein as “w/w” as shorthand). In embodiments, a disclosed formulation comprises between about 2% and 10% (w/w), between about 10% and 60% (w/w), between about 15% and 50% (w/w), between about 20% and 40% (w/w), between about 25% to 30% (w/w), or between about 25% and 35% (w/w) of a solubilizing agent. In embodiments, a disclosed formulation comprises about 20% (w/w) of a solubilizing agent. In embodiments, a disclosed formulation comprises about 25% (w/w) of a solubilizing agent. In embodiments, a disclosed formulation comprises about 30% (w/w) of a solubilizing agent. In embodiments, a disclosed formulation comprises about 35% (w/w) of a solubilizing agent. In embodiments, a disclosed formulation comprises at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, or at least 70%, of a solubilizing agent.

[149] In embodiments, the solubilizing agent is a cyclodextrin. In embodiments, the cyclodextrin is any of alpha-cyclodextrin,  $\beta$ -cyclodextrin, gamma-cyclodextrin, hydroxypropyl- $\beta$ -cyclodextrin, sulfobutylether- $\beta$ -cyclodextrin, a modified cyclodextrin, an O-alkylated cyclodextrin, a fully O-alkylated cyclodextrin, a partially O-alkylated cyclodextrin, a randomly O-alkylated cyclodextrin, an O-methylated cyclodextrin, a fully O-methylated cyclodextrin, partially O-methylated cyclodextrin, a randomly O-methylated cyclodextrin, a hydroxyalkyl cyclodextrin, a hydroxymethyl cyclodextrin, a hydroxyethyl cyclodextrin, a hydroxypropyl cyclodextrin, a sulfonated cyclodextrin, a sulfobutyl-cyclodextrin, an acylated cyclodextrin, an acetylated cyclodextrin, a cyclodextrin that is conjugated to an organic acid, a cyclodextrin that is conjugated to succinic acid, a cyclodextrin that is conjugated to malic acid, and a cyclodextrin that is conjugated to citric acid.

[150] In embodiments, the cyclodextrin is alpha-cyclodextrin. In embodiments, the cyclodextrin is beta-cyclodextrin ( $\beta$ -cyclodextrin,  $\beta$ -CD). In embodiments, the cyclodextrin is gamma-cyclodextrin. In embodiments, the cyclodextrin is hydroxypropyl- $\beta$ -cyclodextrin. In embodiments, the cyclodextrin is sulfobutylether- $\beta$ -cyclodextrin. In embodiments, the sulfobutylether- $\beta$ -cyclodextrin is CAPTISOL®.

[151] In embodiments, the cyclodextrin is a modified cyclodextrin. In embodiments, the modified cyclodextrin is a modified  $\beta$ -cyclodextrin. In embodiments, the modified  $\beta$ -cyclodextrin is sulfobutylether  $\beta$ -cyclodextrin (SBE- $\beta$ -CD). In embodiments, the sulfobutylether  $\beta$ -cyclodextrin possesses higher aqueous solubility, lower toxicity, and improved binding capacity of compounds for complexation compared to the parent  $\beta$ -cyclodextrin (see Pardeshi et al. *Carbohydr Polym.* 2023; 301(Pt B): 120347).

[152] In embodiments, the cyclodextrin is an *O*-alkylated cyclodextrin. In embodiments, the cyclodextrin is a fully *O*-alkylated cyclodextrin. In embodiments, the cyclodextrin is a partially *O*-alkylated cyclodextrin. In embodiments, the cyclodextrin is a randomly *O*-alkylated cyclodextrin. In embodiments, the cyclodextrin is an *O*-methylated cyclodextrin. In embodiments, the cyclodextrin is a fully *O*-methylated cyclodextrin. In embodiments, the cyclodextrin is a partially *O*-methylated cyclodextrin. In embodiments, the cyclodextrin is a randomly *O*-methylated cyclodextrin. In embodiments, the cyclodextrin is a hydroxyalkyl cyclodextrin. In embodiments, the cyclodextrin is a hydroxymethyl cyclodextrin. In embodiments, the cyclodextrin is a hydroxyethyl cyclodextrin. In embodiments, the cyclodextrin is a hydroxypropyl cyclodextrin. In embodiments, the cyclodextrin is a sulfonated cyclodextrin. In embodiments, the cyclodextrin is a sulfobutyl-cyclodextrin. In embodiments, the cyclodextrin is an acylated cyclodextrin. In embodiments, the cyclodextrin is an acetylated cyclodextrin. In embodiments, the cyclodextrin is a cyclodextrin that is conjugated to an organic acid. In embodiments, the cyclodextrin is conjugated to succinic acid. In embodiments, the cyclodextrin is conjugated to malic acid. In embodiments, the cyclodextrin is conjugated to citric acid.

[153] In embodiments, a disclosed formulation comprises between about 1% and 70% (w/w) of a cyclodextrin. In embodiments, a disclosed formulation comprises between about 1% and 10% (w/w) of cyclodextrin. In embodiments, a disclosed formulation comprises between about 5% and 7% (w/w) of cyclodextrin. In embodiments, a disclosed formulation comprises about 6% (w/w) of a cyclodextrin. In embodiments, a disclosed formulation comprises between about 10% and 60% (w/w), between about 15% and 50% (w/w), between about 20% and 40% (w/w), or between about 25% and 35% (w/w) of a cyclodextrin. In embodiments, a disclosed formulation comprises at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, or at least 70%, of a cyclodextrin.

[154] In embodiments, a disclosed formulation comprises between about 1% and 70% (w/w) of  $\beta$ -cyclodextrin. In embodiments, a disclosed formulation comprises between about 1% and 10% (w/w) of  $\beta$ -cyclodextrin. In embodiments, a disclosed formulation comprises between about 5% and 7% (w/w) of  $\beta$ -cyclodextrin. In embodiments, a disclosed formulation comprises about 6% (w/w) of  $\beta$ -cyclodextrin. In

embodiments, a disclosed formulation comprises between about 10% and 60% (w/w), between about 15% and 50% (w/w), between about 20% and 40% (w/w), or between about 25% and 35% (w/w) of  $\beta$ -cyclodextrin.

[155] In embodiments, a disclosed formulation comprises between about 1% and 70% (w/w) of a modified  $\beta$ -cyclodextrin. In embodiments, a disclosed formulation comprises between about 1% and 10% (w/w) of a modified  $\beta$ -cyclodextrin. In embodiments, a disclosed formulation comprises between about 5% and 7% (w/w) of a modified  $\beta$ -cyclodextrin. In embodiments, a disclosed formulation comprises about 6% (w/w) of a modified  $\beta$ -cyclodextrin. In embodiments, a disclosed formulation comprises between about 10% and 60% (w/w), between about 15% and 50% (w/w), between about 20% and 40% (w/w), or between about 25% and 35% (w/w) of a modified  $\beta$ -cyclodextrin.

[156] In embodiments, a disclosed formulation comprises between about 1% and 70% (w/w) of SBE- $\beta$ -CD. In embodiments, a disclosed formulation comprises between about 1% and 10% (w/w) of SBE- $\beta$ -CD. In embodiments, a disclosed formulation comprises between about 5% and 7% (w/w) of SBE- $\beta$ -CD. In embodiments, a disclosed formulation comprises about 6% (w/w) of SBE- $\beta$ -CD. In embodiments, a disclosed formulation comprises between about 10% and 60% (w/w), between about 15% and 50% (w/w), between about 20% and 40% (w/w), or between about 25% and 35% (w/w) of SBE- $\beta$ -CD.

## 2. Antioxidants

[157] In embodiments, a disclosed sublingual spray formulation comprises an antioxidant. Without being bound by theory, antioxidants generally can delay or inhibit the oxidative decomposition of components of disclosed formulations (e.g., psychedelic compounds), which may thereby improve the solution stability and extend the shelf-life of disclosed formulations.

[158] In embodiments, the antioxidant is vitamin E, retinol (vitamin A), lycopene, alpha-carotene, beta-carotene, coenzyme Q10, lutein, zeaxanthin, beta-cryptoxanthin, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, uric acid, glutathione, methionine, citric acid, ascorbic acid (vitamin C), sodium ascorbate, sodium thiosulfate, sodium sulfite, sodium bisulfite, sodium metabisulfite, sodium pyrosulfite, thioglycerol, propyl gallate, N-acetyl-cysteine (NAC), allicin, melatonin, deoxyribose, trolox, nuphlutine, hermidin, rosmarinic acid, or a combination thereof. In embodiments, the antioxidant is a water-soluble antioxidant. In embodiments, the antioxidant is uric acid, glutathione, methionine, citric acid, ascorbic acid), sodium ascorbate, sodium thiosulfate, sodium sulfite, sodium bisulfite, sodium metabisulfite, sodium pyrosulfite, thioglycerol, propyl gallate, NAC, allicin, melatonin, deoxyribose, trolox, nuphlutine, hermidin, rosmarinic acid, or a combination thereof. In embodiments, the antioxidant is rosmarinic acid.

[159] In embodiments, the antioxidant is vitamin E. In embodiments, vitamin E is a tocopherol or a tocotrienol, or any mixture thereof. In embodiments, vitamin E is a tocopherol. In embodiments, vitamin E is any of alpha-tocopherol, beta-tocopherol, gamma-tocopherol, or delta-tocopherol, including all mixtures thereof, and including either D- or L-isomers thereof, including all mixtures thereof. In embodiments, vitamin E is a tocotrienol. In embodiments, vitamin E is any of alpha-tocotrienol, beta-tocotrienol, gamma-tocotrienol,

or delta-tocotrienol, including all mixtures thereof, and including either D- or L-isomers thereof, including all mixtures thereof. In some preferred embodiments, vitamin E comprises, comprises substantially, or is alpha-tocopherol ( $\alpha$ -Tocopherol, "E307"). In some preferred embodiments, vitamin E comprises, comprises substantially, or is D- $\alpha$ -Tocopherol (RRR- $\alpha$ -tocopherol).

[160] In embodiments, a disclosed formulation comprises an antioxidant in an amount between about 0.01% and 5% of the total weight of the formulation (expressed herein as "w/w" as shorthand). In embodiments, a disclosed formulation comprises between about 0.1% and 5% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises between about 0.01% and 0.10% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises between about 0.1% and 2% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises between about 0.01% and 1% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises between about 0.1% and 0.5% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises about 0.1% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises about 0.2% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises about 0.3% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises about 0.4% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises about 0.05% (w/w) of an antioxidant. In embodiments, a disclosed formulation comprises at least 0.01%, at least 0.02%, at least 0.03%, at least 0.04%, at least 0.05%, at least 0.06%, at least 0.07%, at least 0.08%, at least 0.09%, at least 0.1%, at least 0.2%, at least 0.3%, at least 0.4%, at least 0.5%, at least 0.6%, at least 0.7%, at least 0.8%, at least 0.9%, or at least 1% of an antioxidant.

[161] In embodiments, a disclosed formulation comprises between about 0.01% and 5% (w/w) of rosmarinic acid. In embodiments, a disclosed formulation comprises between about 0.1% and 5% (w/w) of rosmarinic acid. In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of rosmarinic acid. In embodiments, a disclosed formulation comprises between about 0.01% and 0.10% (w/w) of rosmarinic acid. In embodiments, a disclosed formulation comprises between about 0.1% and 2% (w/w) of rosmarinic acid. In embodiments, a disclosed formulation comprises between about 0.01% and 1% (w/w) of rosmarinic acid. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of rosmarinic acid. In embodiments, a disclosed formulation comprises between about 0.1% and 0.5% (w/w) of rosmarinic acid. In embodiments, a disclosed formulation comprises about 0.04% (w/w) of rosmarinic acid. In embodiments, a disclosed formulation comprises about 0.05% (w/w) of rosmarinic acid.

[162] In embodiments, a disclosed formulation comprises between about 0.01% and 5% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises between about 0.1% and 5% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises between about 0.1% and 2% (w/w) of

D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises between about 0.01% and 1% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises between about 0.1% and 0.5% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises about 0.1% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises about 0.2% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises about 0.3% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises about 0.4% (w/w) of D- $\alpha$ -tocopherol. In embodiments, a disclosed formulation comprises about 0.5% (w/w) of D- $\alpha$ -tocopherol.

### 3. Penetration Enhancers

[163] In embodiments, a disclosed sublingual spray formulation comprises a penetration enhancer. Without being bound by theory, penetration enhancers are generally characterized by their ability to unidirectionally and reversibly increase the permeability of biological barriers, such as the sublingual mucous surface. In embodiments, including a penetration enhancer in disclosed sublingual spray formulation increases the bioavailability of a psychedelic compound by improving the ability of the compound to diffuse into sublingual tissue. In embodiments, the penetration enhancer further enhances bioavailability by reducing or eliminating diffusion of the psychedelic compound in the reverse direction (i.e., from the sublingual tissue, back into the oral cavity).

[164] In embodiments, the penetration enhancer is 1,2-lauryl ether, aprotinin, azone, benzalkonium chloride, benzalkonium bromide, cetylpyridinium chloride, cetyltrimethyl ammonium, cyclodextrin, dextran sulfate, glycol, lauric acid, lauric acid, propylene, lysophosphatidylcholine, menthol, lecithin (phosphatidylcholine), polyoxyethylene, polysorbate 80, sodium EDTA, chitosan, sodium glycocholate (SGC, NaGC), sodium deoxyglycocholate (SDGC, NaDGC), sodium taurocholate (STC, NaTC), sodium lauryl sulfate (SLS), sulfoxide, dimethyl sulfoxide, or a combination thereof. In embodiments, the penetration enhancer is menthol. In embodiments, the penetration enhancer is polysorbate 80.

[165] In embodiments, the penetration enhancer is selected from a group comprising lower chain alcohol with a carbon chain length of 1 to 5, sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate, oleic acid, capric acid, lauric acid, lecithin, myristic acid, palmitic acid, lysophosphatidylcholine, phosphatidylcholine, azone, cyclodextrin, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether, benzalkonium chloride, cetylpyridinium chloride, vitamin E TPGS, a caprylocaproyl polyoxylglyceride, stearyl macrogolglycerides, propylene glycol dicaprylocaprate, or mixtures thereof.

[166] In embodiments, a disclosed formulation comprises a penetration enhancer in an amount between about 0.01% and 10% of the total weight of the formulation (expressed herein as "w/w" as shorthand). In embodiments, a disclosed formulation comprises between about 0.1% and 10% (w/w) of a penetration enhancer. In embodiments, a disclosed formulation comprises between about 0.1% and 5% (w/w) of a

penetration enhancer. In embodiments, a disclosed formulation comprises between about 0.1% and 2% (w/w) of a penetration enhancer. In embodiments, a disclosed formulation comprises between about 0.5% and 2% (w/w) of a penetration enhancer. In embodiments, a disclosed formulation comprises between about 0.5% and 1.5% (w/w) of a penetration enhancer. In embodiments, a disclosed formulation comprises between about 0.01% and 1% of a penetration enhancer. In embodiments, a disclosed formulation comprises about 1% (w/w) of a penetration enhancer. In embodiments, a disclosed formulation comprises at least 0.01%, at least 0.02%, at least 0.03%, at least 0.04%, at least 0.05%, at least 0.06%, at least 0.07%, at least 0.08%, at least 0.09%, at least 0.1%, at least 0.2%, at least 0.3%, at least 0.4%, at least 0.5%, at least 0.6%, at least 0.7%, at least 0.8%, at least 0.9%, or at least 1% of a penetration enhancer.

[167] In embodiments, a disclosed formulation comprises between about 0.01% and 10% (w/w) of chitosan. In embodiments, a disclosed formulation comprises between about 0.1% and 10% (w/w) of chitosan. In embodiments, a disclosed formulation comprises between about 0.1% and 5% (w/w) of chitosan. In embodiments, a disclosed formulation comprises between about 0.5% and 5% (w/w) of chitosan. In embodiments, a disclosed formulation comprises between about 1% and 5% (w/w) of chitosan. In embodiments, a disclosed formulation comprises between about 0.1% and 2% (w/w) of chitosan. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of chitosan.

[168] In embodiments, a disclosed formulation comprises between about 0.01% and 10% (w/w) of lecithin. In embodiments, a disclosed formulation comprises between about 0.1% and 10% (w/w) of lecithin. In embodiments, a disclosed formulation comprises between about 0.1% and 5% (w/w) of lecithin. In embodiments, a disclosed formulation comprises between about 0.5% and 5% (w/w) of lecithin. In embodiments, a disclosed formulation comprises between about 1% and 5% (w/w) of lecithin. In embodiments, a disclosed formulation comprises between about 0.1% and 2% (w/w) of lecithin. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of lecithin.

#### **4. Taste-Masking Agents**

[169] In embodiments, a disclosed sublingual spray formulation comprises a taste-masking agent. Without being bound by theory, taste-masking agents are generally characterized by an ability to hide or minimize undesirable tastes arising from the psychedelic compound or other excipients in a formulation. In embodiments, this is particularly important, as disclosed sublingual formulations may come into contact with the taste buds.

[170] In embodiments, the taste-masking agent is a sweetener or a flavoring agent. In other embodiments, the taste-masking agent is an agent that creates a nanocarrier system or inclusion complex to prevent direct contact between taste buds and compounds with unpalatable flavors.

[171] In embodiments, the taste-masking agent is a sweetener. Disclosed formulations may include a sweetener capable of providing a palatable and pleasurable factor to the user, and/or capable of masking undesirable flavors present in the dosage form. Exemplary sweeteners that may be included in disclosed

formulations may include, but not be limited to, one or more artificial sweeteners, one or more natural sweeteners, one or more soluble fibers (e.g., for a sugar-free formulation), or a combination thereof. Artificial sweeteners include, e.g., acesulfame and its various salts such as the potassium salt (available as Sunett®), alitame, aspartame (available as NutraSweet® and Equal®), salt of aspartame-acesulfame (available as Twinsweet®), neohesperidin dihydrochalcone, naringin dihydrochalcone, dihydrochalcone compounds, neotame, sodium cyclamate, saccharin and its various salts such as the sodium salt (available as Sweet'N Low®), stevia, chloro derivatives of sucrose such as sucralose (available as Kaltame® and Splenda®), and mogrosides. Natural sweeteners include, e.g., glucose, dextrose, invert sugar, fructose, sucrose, glycyrrhizin; monoammonium glycyrrhizinate (sold under the trade name MagnaSweet®); Stevia rebaudiana (Stevioside), natural intensive sweeteners, such as Lo Han Kuo, polyols such as sorbitol, mannitol, xylitol, erythritol, and the like. Examples of soluble fibers that can be incorporated into the formulations, alone or in combination with other sweeteners, may include, but not be limited to, soluble fibers from tapioca, fruit (e.g., pears, nectarines, apples, and the like), starch, nuts (such as oats, hazelnuts, barley and the like), and legume sources. Sweeteners may be present, individually or in total (if more than one sweetener is included), in the formulation in an amount ranging from about 0.1 wt% to about 20 wt% (calculated as the total weight of sweeteners in the formulation divided by the total weight of the formulation). In embodiments, a disclosed formulation does not comprise a sweetener. In embodiments, a disclosed formulation does not comprise a sugar. In embodiments, the sweetener is sucralose, sucrose, fructose, acesulfame K, aspartame, sodium saccharin, stevia, xylitol, sorbitol, or a combination thereof. In embodiments, the sweetener is xylitol.

[172] In embodiments, the taste-masking agent is a flavoring agent. In embodiments, disclosed formulations may include a flavoring agent or a mixture of flavoring agents including natural or synthetic flavorants, such as flavoring oils, flavoring aldehydes, esters, alcohols, similar materials, and combinations thereof. Flavorants may include vanillin, spearmint oil, cinnamon oil, oil of wintergreen (methylsalicylate), peppermint oil, clove oil, anise oil, eucalyptus oil, citrus oils, fruit oils, essences, limonene, menthone, carvone, menthol, anethole, eucalyptol, anethole, eugenol, cassia, oxanone, a-irisone, propenyl guaiethol, thymol, linalool, benzaldehyde, 3-l-menthoxypropane-1,2-diol, cineole, cinnamaldehyde, cinnamaldehyde glycerol acetal (CGA), methone glycerol acetal (MGA), N-ethyl-p-menthan-3-carboxamine, N,2,3-trimethyl-2-isopropylbutanamide, and combinations thereof.

[173] In embodiments a formulation comprises a flavoring agent, which may be a flavor. A flavor may be any of a liquid flavor, a powder flavor, a powdered encapsulated flavor, a spray-dried flavor, an emulsion flavor, a plant, fruit, vegetable, or other extraction-based flavor, a seasoning, an organic flavor, a natural flavor, a non-GMP flavor, a clean label flavor, a concentrated flavor, a savory flavor, a sweet flavor, a masking flavor, and the like, including combinations thereof. Flavors may be produced using methods known to those in the art, or obtained from flavor suppliers as known in the art, for example from Gold Coast Ingredients, Inc. (GCI) (Commerce, California). In embodiments, the flavoring agent is menthol.

[174] In embodiments, a nanocarrier is used to mask the taste of an undesirable compound. In embodiments, the nanocarrier is a liposome, a polymeric nanoparticle, a solid lipid nanoparticle, a nanostructured lipid carrier, a polymeric micelle, a reverse micelle, a submicron lipid emulsion, a nanosphere, a nanocapsule, an inclusion complex, a pH-responsive polymer-coated mesoporous silica nanoparticle, a nanosponge, or a combination thereof.

[175] In embodiments, an inclusion complex is used to mask the taste of an undesirable compound. In embodiments, the inclusion complex is formed between the psychedelic compound and a taste-masking complexing agent. In embodiments, the taste-masking complexing agent is alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin, or a combination thereof. In embodiments, the taste-masking complexing agent is beta-cyclodextrin. In embodiments, the taste-masking complexing agent is a modified beta-cyclodextrin. In embodiments, the taste-masking complexing agent is SBE-beta-CD.

[176] In embodiments, a disclosed formulation comprises between about 0.01% and 20% (w/w) of a taste-masking agent. In embodiments, a disclosed formulation comprises between about 0.01% and 10% (w/w) of a taste-masking agent. In embodiments, a disclosed formulation comprises between about 0.01% and 5% (w/w) of a taste-masking agent. In embodiments, a disclosed formulation comprises between about 0.01% and 0.10% (w/w) of a taste-masking agent. In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of a taste-masking agent. In embodiments, a disclosed formulation comprises between about 0.01% and 1% (w/w) of a taste-masking agent. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of a taste-masking agent. In embodiments, a disclosed formulation comprises between about 0.2% and 0.3% (w/w) of a taste-masking agent. In embodiments, a disclosed formulation comprises at least 0.01%, at least 0.02%, at least 0.03%, at least 0.04%, at least 0.05%, at least 0.06%, at least 0.07%, at least 0.08%, at least 0.09%, at least 0.1%, at least 0.2%, at least 0.3%, at least 0.4%, at least 0.5%, at least 0.6%, at least 0.7%, at least 0.8%, at least 0.9%, or at least 1% of a taste-masking agent.

[177] In embodiments, a disclosed formulation comprises between about 0.01% and 20% (w/w) of xylitol. In embodiments, a disclosed formulation comprises between about 0.01% and 10% (w/w) of xylitol. In embodiments, a disclosed formulation comprises between about 0.01% and 5% (w/w) of xylitol. In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of xylitol. In embodiments, a disclosed formulation comprises between about 0.01% and 1% (w/w) of xylitol. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of xylitol. In embodiments, a disclosed formulation comprises between about 0.1% and 1.0% (w/w) of xylitol. In embodiments, a disclosed formulation comprises between about 0.2% and 0.3% (w/w) of xylitol. In embodiments, a disclosed formulation comprises about 0.1% (w/w) of xylitol. In embodiments, a disclosed formulation comprises about 0.2% (w/w) of xylitol. In embodiments, a disclosed formulation comprises about 0.3% (w/w) of xylitol. In embodiments, a disclosed formulation comprises about 0.4% (w/w) of xylitol. In

embodiments, a disclosed formulation comprises about 0.5% (w/w) of xylitol.

[178] In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of menthol. In embodiments, a disclosed formulation comprises between about 0.01% and 1.0% (w/w) of menthol. In embodiments, a disclosed formulation comprises between about 0.01% and 0.5% (w/w) of menthol. In embodiments, a disclosed formulation comprises between about 0.01% and 0.1% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.01% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.02% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.03% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.04% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.05% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.06% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.07% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.08% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.09% (w/w) of menthol. In embodiments, a disclosed formulation comprises about 0.1% (w/w) of menthol.

## 5. Mucoadhesive Polymers

[179] In embodiments, a disclosed sublingual spray formulation comprises a mucoadhesive polymer. Mucoadhesive polymers have physicochemical properties that allow prolonged binding to mucosal surfaces. In embodiments, inclusion of a mucoadhesive polymer in a disclosed sublingual spray formulation increases the amount of time that a psychedelic compound is in contact with, and can diffuse across, a mucosal barrier (e.g., the sublingual mucosa).

[180] In embodiments, the mucoadhesive polymer is chitosan, gelatin, guar gum, lectins, sodium alginate, soluble starch, tragacanth, xanthan gum, carbomer homopolymer type B, deacetylated gum, polyacrylic acid, polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, a thiomers, polycarbophil, hyaluronic acid, dermatan sulfate, or a combination thereof. In embodiments, the mucoadhesive polymer is xanthan gum. In embodiments, the mucoadhesive polymer is carbomer homopolymer type B. In embodiments, the mucoadhesive polymer is CARBOPOL® 974P NF polymer (Lubrizol; Wickliffe, OH) or XANTURAL® 75 (CP Kelco; Atlanta, GA). In embodiments, the mucoadhesive polymer is CARBOPOL® 974P NF polymer (i.e., a polymer of acrylic acid crosslinked with allyl sucrose or allyl pentaerythritol, also referred to as carbomer homopolymer type B, carbomer, or carboxypolymethylene; a homopolymer having a viscosity of 29,400-39,400 cP (0.5 wt% at pH 7.5), using ethyl acetate as the polymerization solvent). In embodiments, the mucoadhesive polymer is CARBOPOL® 934P NF (carbomer, carboxypolymethylene), 940 NF, or another CARBOPOL® polymer. In embodiments, the mucoadhesive polymer is XANTURAL® 75 (i.e., xanthan gum, dehydroxanthan gum, xanthan, xanthan biopolymer, or xanthomonas gum).

[181] In embodiments, a disclosed formulation comprises between about 0.01% and 30% (w/w) of a mucoadhesive polymer. In embodiments, a disclosed formulation comprises between about 0.01% and 10%

(w/w) of a mucoadhesive polymer. In embodiments, a disclosed formulation comprises between about 0.01% and 5% (w/w) of a mucoadhesive polymer. In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of a mucoadhesive polymer. In embodiments, a disclosed formulation comprises between about 0.01% and 1% (w/w) of a mucoadhesive polymer. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of a mucoadhesive polymer. In embodiments, a disclosed formulation comprises at least 0.01%, at least 0.02%, at least 0.03%, at least 0.04%, at least 0.05%, at least 0.06%, at least 0.07%, at least 0.08%, at least 0.09%, at least 0.1%, at least 0.2%, at least 0.3%, at least 0.4%, at least 0.5%, at least 0.6%, at least 0.7%, at least 0.8%, at least 0.9%, or at least 1% of a mucoadhesive polymer.

[182] In embodiments, a disclosed formulation comprises between about 0.01% and 10% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises between about 0.01% and 5% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises between about 0.01% and 1% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises between about 0.1% and 0.2% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises about 0.05% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises about 0.1% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises about 0.15% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises about 0.2% (w/w) of xanthan gum. In embodiments, a disclosed formulation comprises about 0.3% (w/w) of xanthan gum.

[183] In embodiments, a disclosed formulation comprises between about 0.01% and 10% (w/w) of hydroxypropylcellulose (HPC). In embodiments, a disclosed formulation comprises between about 0.01% and 10% (w/w) of HPC. In embodiments, a disclosed formulation comprises between about 0.01% and 5% (w/w) of HPC. In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of HPC. In embodiments, a disclosed formulation comprises between about 0.01% and 1% (w/w) of HPC. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of HPC. In embodiments, a disclosed formulation comprises about 0.05% (w/w) of HPC. In embodiments, a disclosed formulation comprises about 0.1% (w/w) of HPC. In embodiments, a disclosed formulation comprises about 0.15% (w/w) of HPC. In embodiments, a disclosed formulation comprises about 0.2% (w/w) of HPC. In embodiments, a disclosed formulation comprises about 0.3% (w/w) of HPC.

[184] In embodiments, a disclosed formulation comprises between about 0.01% and 10% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises between about 0.01% and 10% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises between about 0.01% and 0.1% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises between about 0.01% and 0.05% (w/w) of CARBOPOL® 974P NF polymer. In

embodiments, a disclosed formulation comprises between about 0.01% and 5% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises between about 0.01% and 2% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises between about 0.01% and 1% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises between about 0.1% and 1% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises about 0.05% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises about 0.1% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises about 0.15% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises about 0.2% (w/w) of CARBOPOL® 974P NF polymer. In embodiments, a disclosed formulation comprises about 0.3% (w/w) of CARBOPOL® 974P NF polymer.

## 6. Additional Excipients and Ingredients

[185] In embodiments, disclosed formulations comprise an additional excipient. In embodiments, suitable additional excipients to be incorporated in disclosed formulations may include a colorant, a dye, a pigment, a binder, a solvent, a humectant, a viscosity modifier, a complexing agent, a preservative, a pH adjusting agent, an opacifier, a surfactant, a gelling agent, an effervescence material, and combinations thereof.

[186] Colorants and/or dyes and/or pigments may be added to disclosed formulations in some embodiments. Suitable colorants and/or dyes and/or pigments may include, but not be limited to, colors such as e.g., white, black, yellow, blue, green, pink, red, orange, violet, indigo, brown, and combinations thereof, pigments such as, e.g., Timica Extra Large Sparkles, titanium dioxide and chromium oxide greens, ultramarine blues and pinks and ferric oxides. Colorants and/or dyes and/or pigments may be present, individually or in total (if more than one colorant and/or dye and/or pigment is included), in disclosed formulations in an amount ranging from about 0.01 wt% to about 5 wt% (calculated as the total weight of colorants and/or dyes and/or pigments in the formulation divided by the total weight of the formulation). In embodiments, a disclosed formulation does not comprise a colorant. In embodiments, a disclosed formulation does not comprise a dye. In embodiments, a disclosed formulation does not comprise a pigment.

[187] The formulations of the disclosure may contain a binder that could contribute to the rheology of the formulation and to the feel of the formulation in the oral cavity. Suitable binders include, without limitations, polyvinylpyrrolidone (PVP), marine colloids, carboxyvinyl polymers, starches, cellulosic polymers such as hydroxyethylcellulose, carboxymethylcellulose (carmellose), hydroxypropylmethylcellulose, hydroxyethylpropylcellulose, hydroxybutyl methyl cellulose, and salts thereof (e.g., carmellose sodium), natural gums such as karaya, xanthan, carrageenans, gellan gum, locust bean gum, gum arabic and tragacanth, chitosan, colloidal magnesium aluminum silicate, and colloidal silica. Binders may be present, individually or in total (if more than one binder is included), in disclosed formulations in an amount ranging from about 0.01 wt% to about 5 wt% (calculated as the total weight of binders in the formulation divided by the total weight of the formulation). In embodiments, a disclosed formulation does not comprise a binder.

[188] Humectant(s), such as low molecular weight polyethylene glycol (e.g., PEG6-PEG12), may be present, individually or in total (if more than one humectant is included), in the formulation in an amount of up to about 10 wt%, up to about 5 wt%, up to about 3 wt%, up to about 1 wt%, or up to about 0.1 wt% (calculated as the total weight of humectants in the formulation divided by the total weight of the formulation). In embodiments, a disclosed formulation does not comprise a humectant.

[189] Exemplary gelling agent(s) that may be issued in disclosed formulations may comprise pectins, starches, and gelatin forms derived from animals or from plants (e.g., pork gelatin) or a different gelling agent that would be suitable for consumption by individuals who do not consume meat products (e.g., vegetarians, vegans). The pectin in the formulation may include, e.g., high methoxyl pectin, low methoxyl pectin, or a combination thereof. In embodiments, the pectin is amidated pectin. In other embodiments, the pectin is non-amidated pectin. In certain embodiments, the pectin is a combination of amidated pectin and non-amidated pectin. The gelatin in the formulation may include Type A gelatin, Type B gelatin, a hide or skin gelatin (e.g., calf skin, pig skin) and/or a bone gelatin (e.g., calf bone, pig bone) used alone or in combination. Gelling agent(s) may be present, individually or in total (if more than one gelling agent is included) in the formulation in an amount ranging from about 0.1 wt% to about 20 wt% (calculated as the total weight of gelling agents in the formulation divided by the total weight of the formulation). In embodiments, a disclosed formulation does not comprise a gelling agent.

[190] In embodiments, disclosed formulations may comprise a preservative. Preservatives can be used to inhibit microbial growth or increase stability of the formulation, thereby prolonging the shelf life of the formulation. Suitable preservatives are known in the art and include EDTA, EGTA, benzalkonium chloride or benzoic acid or benzoates (e.g., sodium benzoate), vitamin A, vitamin C (ascorbic acid), citric acid, vitamin E, and tocopherol. In embodiments, a disclosed formulation does not comprise a preservative.

[191] In embodiments, disclosed formulations may comprise a pH adjusting agent. Without being bound by theory, the pH of aqueous formulations can influence the relative concentration of ionized and unionized forms of an active compound present in solution. Suitable pH adjusting agents are known in the art and include triethanolamine, diethanolamine, lactic acid, citric acid, dilute sulfuric acid, dipotassium hydrogen phosphate, disodium hydrogen phosphate, DL-tartaric acid, sodium carbonate, sodium citrate, tannic acid, and tricalcium phosphate. In embodiments, the pH adjusting agent is triethanolamine. In embodiments, the pH adjusting agent is 0.5 N HCl. In embodiments, the pH adjusting agent is 0.2 N NaOH.

[192] In embodiments, the pH of a disclosed formulation is about 5 to 9. In embodiments, the pH of a disclosed formulation is about 5 to 6. In embodiments, the pH of a disclosed formulation is about 6 to 7. In embodiments, the pH of a disclosed formulation is about 7 to 8. In embodiments, the pH of a disclosed formulation is about 8 to 9. In embodiments, the pH of a disclosed formulation is about 6 to 7. In embodiments, the pH of a disclosed formulation is about 6 to 6.5. In embodiments, the pH of a disclosed formulation is about 6. In embodiments, the pH of a disclosed formulation is about 6.3. In embodiments, the

pH of a disclosed formulation is about 6.5 to 7. In embodiments, the pH of a disclosed formulation is about 6.5. In embodiments, the pH of a disclosed formulation is about 7.

[193] In embodiments, the pH of a disclosed formulation is adjusted using a disclosed pH adjusting agent to about 5 to 9. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 5 to 6. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 6 to 7. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 7 to 8. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 8 to 9. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 6 to 7. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 6 to 6.5. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 6. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 6.3. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 6.5 to 7. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 6.5. In embodiments, the pH of a disclosed formulation is adjusted using a pH adjusting agent to about 7.

[194] In embodiments, a disclosed formulation is formulated for controlled release, including sustained (i.e., extended release). Controlled release formulations alter the delivery kinetics of the psychedelic compound and can be used to manipulate (e.g., extend) the half-life or duration of effects of an active compound. In one example, the absorption of a psychedelic compound through the sublingual mucosa may be dependent on the time that a disclosed sublingual spray is in contact with the tissue. As such, a controlled release formulation may contain excipients, such as a mucoadhesive agent, that prolongs the time that the formulation remains in contact with the mucosal tissue, thereby increasing the time for absorption of the psychedelic compound. In this example, a permeation enhancer can also be used to increase the absorption of the psychedelic compound and/or reduce the adhesion time necessary for sufficient absorption. A non-limiting list of additional excipients that can be included in controlled release formulations includes nanostructured formulations (e.g., polymeric micelles, liposomes, polymersomes), mucoadhesive polymers (*vide supra*), penetration enhancers (*vide supra*), drug delivery vectors (including surface-functionalization of particles or nanoparticles), and enzyme inhibitors.

[195] In embodiments, the formulations disclosed herein are prepared for administration as a nanostructured formulation such as a nanoemulsion, a nanocapsule, a nanoparticle conjugate, a liposome, a polymersome, or a polymer micelle. Preparations of the disclosed compositions as certain nanostructured formulations may be done by reference to the general knowledge of the art (see, e.g., Jaiswal et al. *Biotech.* 2015; 3(5): 123-27; Discher et al. *Science.* 1999; 284: 1143–1146; Duncan. *Nat Rev Drug Discov.* 2003; 2: 347–360; Hua. *Front Pharmacol.* 2019; 10: 1328).

[196] The prefix “nano” as used in the terms describing various embodiments of a nanostructured formulation denotes a size range in the nanometer (“nm”) scale. Accordingly, sizes of such nanoparticle

delivery vehicles include those in the about 1 to about 100 nm, about 100 to about 200 nm, about 200 to about 400 nm, about 400 to about 600 nm, about 600 to about 800 nm, and about 800 to about 1000 nm, as well as “microparticles” in the about 1000 to about 2000 nm (1-2 micrometer (“ $\mu\text{m}$ ”) scale). Particles of certain sizes may be particularly advantageous depending on the method of administration (e.g., for oral liquid emulsion versus for transdermal or topical application). Regardless of method of administration, one will appreciate that smaller particles provide for increased surface area over larger particles such that a higher concentration of agent may be applied per volume of particles. A nanoparticle may be metal, lipid, polymer or other materials, or a combination of materials, and nanoparticles may be functionalized such that another moiety also may be attached thereto. Surface functionalization may involve the use of a moiety comprising an anchor group, a spacer and/or a functional group.

[197] In embodiments, a disclosed formulation is a lipid-based nanoparticle (LBNP) formulation. LBNP formulations include liposomes, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC), which can be used to transport both hydrophobic and hydrophilic molecules, and can be formulated to display very low or no toxicity. Lipid nanosystems also can include chemical modifications to avoid immune system detection (e.g., gangliosides or PEG) or to improve solubility of active agents.

[198] The primary components of nanoparticles are phospholipids, which are organized in a bilayer structure due to their amphipathic properties. In presence of water, they form vesicles, improving the solubility and stability of the active agents once they are loaded into their structure. Besides phospholipids, other compounds can be added to the formulations, such as cholesterol, which decreases the fluidity of the nanoparticle and increases the permeability of hydrophobic drugs through the bilayer membrane, improving stability of nanoparticles in blood. Cholesterol-modified liposomes may present a multiple bilayer with sizes from 0.5-10 nm, as multilaminar vesicles (MLVs); a single bilayer with sizes above 100 nm, as large unilamellar vesicles (LUVs); and intermediate sizes (10-100 nm), as small unilamellar vesicles (SUVs).

[199] In embodiments, a disclosed formulation is a polymer micelle formulation. Amphiphilic polymers with hydrophilic and hydrophobic units may self-assemble into a micelle when the concentration is raised to above the critical micelle concentration. Micelles are spherical particles that comprise monolayers of amphiphilic polymers. In embodiments, the micelles have an internal core used to encapsulate small molecules, and are used as drug delivery vehicles for oral mucosal administration (Montazeri Aliabadi et al. *Expert Opin Drug Deliv.* 2006; 3(1): 139-162).

[200] In embodiments, a disclosed formulation comprises a drug carrier. Drug carriers can be designed to give controlled release profiles, improved circulation times and better penetration across the epithelium. In embodiments, the drug carrier is a hydrophobic drug carrier. Hydrophobic drug carriers can have the advantage of exhibiting slow sustained release and may adhere well to biological surfaces. Hydrophobic drug carriers can have slow (i.e., extended) release kinetics, or may also be constructed to have a rapid or immediate release profile. New techniques include the development of hydrophilic coatings on hydrophobic

nanoparticles to improve their transport across mucosal surfaces while retaining the slow-release profiles. These include polyethylene glycol and chitosan coatings. (de la Fuente et al. *Nanomed.* 2008; 3: 845–857.)

### c. Solvent Systems

[201] In embodiments, a disclosed sublingual spray formulation comprises a solvent system. Solvent systems can be used to dissolve or solubilize the psychedelic compound, and any included excipients. The solvent system chosen can affect the stability, bioavailability, and overall efficacy of the psychedelic compound and the formulation as a whole. Preferred solvent systems are those capable of dissolving or solubilizing the psychedelic compound and any included excipients at the desired concentration(s), and should be stable and compatible with components (e.g., psychedelic compound, excipients) included in the formulation. In embodiments, wherein the solvent system comprises more than one solvent, the ratio of cosolvents can be selected to increase the bioavailability of the specific psychedelic compound for sublingual administration. Preferred solvent systems are also safe and non-toxic for human consumption. In embodiments, potential adverse effects, such as irritation or allergic reactions, are considered and minimized during selection of solvents included in a solvent system of the disclosure.

[202] Solvents used in disclosed formulations may include, without limitations, water, ethanol, polyhydric alcohols (e.g., glycerin), 1,3-butylene glycol, glycerin, N-methyl-2-pyrrolidone, dimethylacetamide, dimethylsulfoxide, propylene glycol, hexylene glycol, propane diol, ethylene glycol, diethylene glycol, dipropylene glycol, lecithin, diglycerin, sorbitol, other sugars which are liquid at room temperature, water-soluble alkoxyated nonionic polymers such as polyethylene glycol, and combinations thereof. Solvents may be present, individually or in total (if more than one solvent is included), in the formulation in an amount ranging from about 0.1 wt% to about 95 wt% (calculated as the total weight of solvents in the formulation divided by the total weight of the formulation). In embodiments, a disclosed formulation does not comprise a solvent. In embodiments, the solvent is lecithin. In embodiments, the solvent is not lecithin.

[203] In embodiments, the solvent system is an aqueous solvent system. In embodiments, the solvent system comprises water. In embodiments, the solvent system comprises greater than or equal to about 50% water, on a weight basis (i.e., w/w) or volume basis (i.e., v/v). In embodiments, the solvent system comprises about 50% water, about 60% water, about 70% water, about 80% water, about 90% water, about 95% water, about 99% water, or 100% water, including amounts and ranges in between these values.

[204] In embodiments, the solvent system comprises an alcohol. In embodiments, the solvent system comprises less than or equal to about 50% an alcohol, on a weight or volume basis. For example, in some embodiments, the solvent system comprises about 50% alcohol, about 40% alcohol, about 30% alcohol, about 20% alcohol, about 10% alcohol, about 5% alcohol, or about 1% alcohol, including amounts and ranges in between these values.

[205] In embodiments, the solvent system comprises a glycol. In embodiments, the solvent system comprises less than or equal to about 50% glycol, on a weight or volume basis. For example, in some

embodiments, the solvent system comprises about 50% glycol, about 40% glycol, about 30% glycol, about 20% glycol, about 10% glycol, about 5% glycol, or about 1% glycol, including amounts and ranges in between these values.

[206] In embodiments, the solvent system comprises propylene glycol. In embodiments, the solvent system comprises less than or equal to about 50% propylene glycol, on a weight or volume basis. For example, in some embodiments, the solvent system comprises about 50% propylene glycol, about 40% propylene glycol, about 30% propylene glycol, about 20% propylene glycol, about 10% propylene glycol, about 5% propylene glycol, or about 1% propylene glycol, including amounts and ranges in between these values.

[207] In embodiments, the solvent system comprises water and a second solvent. In embodiments, the solvent system comprises water and an alcohol. In embodiments, the solvent system comprises water and a glycol. In embodiments, the glycol is propylene glycol.

[208] In embodiments, the solvent system comprises about 50% water and about 50% of an alcohol, on a weight or volume basis. In embodiments, the solvent system comprises about 60% water and about 40% of an alcohol. In embodiments, the solvent system comprises about 70% water and about 30% of an alcohol. In embodiments, the solvent system comprises about 80% water and about 20% of an alcohol. In embodiments, the solvent system comprises about 90% water and about 10% of an alcohol. In embodiments, the solvent system comprises about 95% water and about 5% of an alcohol. In embodiments, the solvent system comprises about 99% water and about 1% of an alcohol.

[209] In embodiments, the solvent system comprises about 50% water and about 50% of a glycol, on a weight or volume basis. In embodiments, the solvent system comprises about 60% water and about 40% of a glycol. In embodiments, the solvent system comprises about 70% water and about 30% of a glycol. In embodiments, the solvent system comprises about 80% water and about 20% of a glycol. In embodiments, the solvent system comprises about 90% water and about 10% of a glycol. In embodiments, the solvent system comprises about 95% water and about 5% of a glycol. In embodiments, the solvent system comprises about 99% water and about 1% of a glycol.

[210] In embodiments, the solvent system comprises about 50% water and about 50% propylene glycol, on a weight or volume basis. In embodiments, the solvent system comprises about 60% water and about 40% propylene glycol. In embodiments, the solvent system comprises about 70% water and about 30% propylene glycol. In embodiments, the solvent system comprises about 80% water and about 20% propylene glycol. In embodiments, the solvent system comprises about 90% water and about 10% propylene glycol. In embodiments, the solvent system comprises about 95% water and about 5% propylene glycol. In embodiments, the solvent system comprises about 99% water and about 1% propylene glycol.

[211] It will be readily appreciated that values for the solvents in a solvent system expressed as a % on a weight or volume basis can be alternatively and equivalently expressed as ratios. As one example, a solvent

system comprising 25% water and 75% PG can be alternatively expressed as comprising water and PG in a 1:3 ratio of water:PG. Likewise for all of the other embodiments expressed herein as such percentages. Additional exemplary and non-limiting solvent systems, wherein the solvents are expressed as a ratio follow.

[212] In embodiments, the solvent system comprises water and a second solvent in a ratio from 5:1 to 1:5, from 3:1 to 1:3, or from 2:1 to 1:2, water:second solvent. In embodiments, the ratio of water to second solvent is between about 1:2 and 1:3. In embodiments, the ratio of water to second solvent is about 1:2. In embodiments, the ratio of water to second solvent is about 1:2.5.

[213] In embodiments, the solvent system comprises water and an alcohol in a ratio from 5:1 to 1:5, from 3:1 to 1:3, or from 2:1 to 1:2, water:alcohol. In embodiments, the ratio of water to alcohol is between about 1:2 and 1:3. In embodiments, the ratio of water to alcohol is about 1:2. In embodiments, the ratio of water to alcohol is about 1:2.5.

[214] In embodiments, the solvent system comprises water and a glycol in a ratio from 5:1 to 1:5, from 3:1 to 1:3, or from 2:1 to 1:2, water:glycol. In embodiments, the ratio of water to glycol is between about 1:2 and 1:3. In embodiments, the ratio of water to glycol is about 1:2. In embodiments, the ratio of water to glycol is about 1:2.5.

[215] In embodiments, the solvent system comprises water and propylene glycol (PG), in a ratio from 5:1 to 1:5, from 3:1 to 1:3, or from 2:1 to 1:2, water:PG. In embodiments, the ratio of water to PG is between about 1:2 and 1:3. In embodiments, the ratio of water to PG is about 1:2. In embodiments, the ratio of water to PG is about 1:2.5.

#### d. Exemplary Excipient/Solvent Combinations

[216] In some embodiments, the excipient(s) and solvent system of a disclosed sublingual spray formulation are selected to provide a formulation that (partially, substantially, or preferably fully) dissolves a disclosed compound at a concentration sufficient to provide a desired dose, which may depend on the potency of the compound, bioavailability of the compound when administered in a disclosed formulation, and design of the delivery device (including, e.g., spray volume, spray dose, plume geometry, etc.). In embodiments, a disclosed sublingual spray formulation comprises the excipients and solvents described below in Exemplary Formulations I-XV; and further comprises a compound at a concentration according to embodiments disclosed herein (see, e.g., the *Dose and Dosage* section below).

[217] *Exemplary Formulation I.*

<b>Solvent system: water:propylene glycol (1:1)</b>	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
β-cyclodextrin	30
Xanthan gum	0.5
Xylitol	0.2

Rosmarinic acid	0.02
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[218] *Exemplary Formulation II.*

<b>Solvent system:</b> water:propylene glycol (2:1)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
$\beta$ -cyclodextrin	30
Xanthan gum	2.5
Xylitol	1
Rosmarinic acid	0.2

[219] *Exemplary Formulation III.*

<b>Solvent system:</b> water:propylene glycol (2:1)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
SBE- $\beta$ -cyclodextrin	25
Xanthan gum	5
Xylitol	5
Rosmarinic acid	2

[220] *Exemplary Formulation IV.*

<b>Solvent system:</b> water:propylene glycol (2:1)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
SBE- $\beta$ -cyclodextrin	40
Carbomer homopolymer type B	1
Menthol	0.2
Polysorbate 80	2
Triethanolamine	q.s. to pH 6.3
Rosmarinic acid	0.5

[221] *Exemplary Formulation V.*

<b>Solvent system:</b> water:propylene glycol (1:5)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
SBE- $\beta$ -cyclodextrin	15
Menthol	0.5

Chitosan	2.5
$\alpha$ -tocopherol	0.1

[222] *Exemplary Formulation VI.*

<b>Solvent system:</b> ethanol:propylene glycol (2:1)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
$\beta$ -cyclodextrin	25
Xanthan gum	0.5
Xylitol	0.1
$\alpha$ -tocopherol	0.5

[223] *Exemplary Formulation VII.*

<b>Solvent system:</b> water:ethanol (2:1)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
$\beta$ -cyclodextrin	25
Xanthan gum	0.1
Menthol	0.05
Rosmarinic acid	0.05

[224] *Exemplary Formulation VIII.*

<b>Solvent system:</b> water:propylene glycol (2:1)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
SBE- $\beta$ -cyclodextrin	55
Xanthan gum	3
Xylitol	3
Rosmarinic acid	1
Vitamin E - TPGS	0.1
0.5 N HCl solution	q.s. to pH of 6.5-7.0

[225] *Exemplary Formulation IX.*

<b>Solvent system:</b> water:propylene glycol (2:1)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
SBE- $\beta$ -cyclodextrin	35

Xanthan gum	2
Xylitol	13
Rosmarinic acid	3
Polysorbate-80	9
Menthol	0.2
Vitamin E - TPGS	0.1
0.5 N HCl solution	q.s. to pH of 6.5-7.0

[226] *Exemplary Formulation X.*

<b>Solvent system:</b> water:propylene glycol (5:1)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
$\beta$ -cyclodextrin	10
Xanthan gum	3
Xylitol	3
Rosmarinic acid	1
Vitamin E - TPGS	0.1
0.5 N HCl solution	q.s. to pH of 6.5-7.0
0.2 N NaOH solution	q.s. to pH of 6.5-7.0

[227] *Exemplary Formulation XI.*

<b>Solvent system:</b> water:propylene glycol (5:1)	
<b>Ingredient</b>	<b>Weight Concentration in Solution (%w/w)</b>
$\beta$ -cyclodextrin	5
Xanthan gum	9
Xylitol	10
Rosmarinic acid	3
Menthol	0.1
Polysorbate-80	7
Vitamin E - TPGS	0.1
0.2 N NaOH solution	q.s. to pH of 6.5-7.0

[228] *Exemplary Formulation XII.*

<b>Solvent system:</b> water:propylene glycol (1:1)
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Ingredient	Weight Concentration in Solution (%w/w)
SBE- $\beta$ -cyclodextrin	5
CARBOPOL® 974P	2
Xylitol	13
Rosmarinic acid	4
Vitamin E - TPGS	0.09
0.5 N HCl solution	q.s. to pH of 6.5-7.0

[229] *Exemplary Formulation XIII.*

Solvent system: water:propylene glycol (1:1)	
Ingredient	Weight Concentration in Solution (%w/w)
SBE- $\beta$ -cyclodextrin	40
CARBOPOL® 974P	3
Xylitol	5
Rosmarinic acid	0.5
Menthol	0.05
Polysorbate-80	5.5
Vitamin E - TPGS	0.09
0.5 N HCl solution	q.s. to pH of 6.5-7.0

[230] *Exemplary Formulation XIV.*

Solvent system: water:propylene glycol (2:1)	
Ingredient	Weight Concentration in Solution (%w/w)
$\beta$ -cyclodextrin	6
CARBOPOL® 974P	5
Xylitol	13
Rosmarinic acid	3.5
Vitamin E - TPGS	0.09
0.5 N HCl solution	q.s. to pH of 6.5-7.0

[231] *Exemplary Formulation XV.*

Solvent system: water:propylene glycol (2:1)	
Ingredient	Weight Concentration in Solution (%w/w)

$\beta$ -cyclodextrin	40
CARBOPOL® 974P	3
Xylitol	15
Rosmarinic acid	3
Menthol	0.02
Polysorbate-80	5
Vitamin E - TPGS	0.09
0.5 N HCl solution	<i>q.s.</i> to pH of 6.5-7.0

### C. Dose and Dosage

[232] In embodiments where a disclosed formulation is administered to create a desired effect, it will be readily appreciated that dose and dosage may vary depending upon the general health, age, gender, and race of the individual, bioavailability, potential adverse systemic, regional, or local side effects, the presence of any (including comorbid) disorders or diseases in the individual, and other factors that will be appreciated by those in the art (e.g., medical or familial history). Those in the art will appreciate the factors that may influence the dosage, frequency, and timing required to provide an amount sufficient or effective for providing a desired effect, and to do so depending on the type of desired effect and to avoid or minimize adverse effects. While dosage may differ from patient to patient, for individual patients across time, and for different disclosed formulations, it can be determined by a medical professional such as a physician or a pharmacist or a clinician based, as examples, any of the subject's: height, weight, age, gender, severity of condition, side effects of drug administration, other concurrently administered agents, inherited enzymes affecting metabolism, diet, lifestyle, and physical condition, and will be within ordinary skill in view of the disclosure and general knowledge. Determination of appropriate dosing shall include not only that of single dosage amounts, but also that of the number and timing of doses, and the time(s) of day or time(s) preferable for administration. Dose amount, frequency, and/or duration therefore may be increased or reduced, as indicated by the therapeutic outcome(s) or effect(s) desired, the beneficial outcome(s) or effect(s) desired, and/or by the specific subjective outcome(s) or effect(s) desired, as will be known in view of this disclosure.

[233] In embodiments, a disclosed formulation comprises a disclosed compound, such as a disclosed psychedelic compound, such as any of a tryptamine, a phenethylamine, or a lysergamide, and including as examples psilocin, 2C-X compounds, LSD, DMT, and MDMA, in an amount so that a single administration volume comprises a sufficient dose of the compound to achieve a therapeutic effect. The standard dose amounts and dose ranges to achieve a therapeutic effect, including for sublingual administration (i.e., adjusted based on greater bioavailability by bypassing first-pass metabolism) will be known to those of skill, or be able to be readily ascertained by those of skill. It will be understood that standard dose amounts and

dose ranges include both the dose amounts and ranges used to achieve a “full” or “psychedelic” experience (e.g., “macrodoses”), such as about 20-25 mg of psilocin, as well as those dose amounts and dose ranges used for what is known as “microdosing” (generally, without psychedelic effect, and often considered to be about 1/10th of a “macro” dose), and further including such dose amounts and dose ranges in between these amounts, as well as above these amounts (up to and until dose amounts present an unwarranted risk of adverse or harmful psychological or physiological effects). Accordingly, the dose amounts and dose ranges provided in this section will be understood to be exemplary only, and it will be readily appreciated that dose amounts, dose ranges, dosages, and dosing regimens including frequencies of administration, disclosed herein are not intended to limit the full scope of the disclosure.

[234] A “single dose” may refer to the amount of the disclosed compound in a single administration volume, whether or not the single administration volume is achieved by, with a disclosed sublingual spray formulation for example, one spray, two sprays, three sprays, or more than three sprays of the formulation.

[235] In some embodiments of disclosed formulations, including, e.g., formulations comprising psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, a single dose of the active compound such as psilocin is between about 0.1 mg and 50 mg. In embodiments, a single dose is between about 0.1 mg and 10 mg. In embodiments, a single dose is between about 0.1 mg and 1 mg. In embodiments, a single dose is between about 1 mg and 5 mg. In embodiments, a single dose is between about 5 mg and 10 mg. In embodiments, a single dose is between about 10 mg and 50 mg. In embodiments, a single dose is between about 15 mg and 30 mg. In embodiments, a single dose is between about 20 mg and 30 mg. In embodiments, a single dose is between about 0.1 mg and 20 mg. In embodiments, a single dose is between about 1 mg and 10 mg. In embodiments, a single dose is between about 3 mg and 6 mg. In embodiments, a single dose is about 5 mg. In embodiments, a single dose is between about 0.5 mg and 3 mg. In embodiments, a single dose is about 1 mg. In embodiments, a single dose is between about 5 mg and 15 mg. In embodiments, a single dose is between about 8 mg and 12 mg. In embodiments, a single dose is about 10 mg. In embodiments, a single dose is any of about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, including amounts in between.

[236] In some embodiments of disclosed formulations, a single dose amount of a disclosed compound, including, e.g., 2C-B or a 2C-X compound, is between about 0.5 mg and 20 mg, 1 mg and 10 mg, 2 mg and 8 mg, 3 mg and 6 mg, or about 5 mg. In embodiments, a single dose is between about 0.5 mg and 20 mg. In embodiments, a single dose is between about 1 mg and 10 mg. In embodiments, a single dose is between about 2 mg and 8 mg. In embodiments, a single dose is between about 3 mg and 6 mg. In embodiments, a single dose is about 3 mg. In embodiments, a single dose is about 5 mg. In embodiments, a single dose is about 10 mg. In embodiments, a single dose is about 15 mg. In embodiments, a single dose is about 20 mg.

[237] In some embodiments of disclosed formulations, a single dose amount of a disclosed compound, including, e.g., DMT, is between about 10 mg and 100 mg, 20 mg and 80 mg, 30 mg and 60 mg, or about 50

mg. In embodiments, a single dose is between about 10 mg and 100 mg. In embodiments, a single dose is between about 20 mg and 80 mg. In embodiments, a single dose is between about 30 mg and 60 mg. In embodiments, a single dose is about 30 mg. In embodiments, a single dose is about 50 mg. In embodiments, a single dose is about 100 mg.

[238] In some embodiments of disclosed formulations, a single dose amount of a disclosed compound is between about 15 mg and 300 mg, 25 mg and 200 mg, 20 mg and 50 mg, or 50 mg and 100 mg. In embodiments, a single dose is between about 15 mg and 300 mg. In embodiments, a single dose is between about 25 mg and 200 mg. In embodiments, a single dose is between about 20 mg and 50 mg. In embodiments, a single dose is between about 50 mg and 100 mg. In embodiments, a single dose is about 50 mg. In embodiments, a single dose is about 75 mg. In embodiments, a single dose is about 100 mg.

[239] In some embodiments of disclosed formulations, a single dose amount of a disclosed compound, including, e.g., MDMA, is between about 50 mg and 300 mg, between about 75 mg and 200 mg, or between about 100 and 150 mg. In embodiments, a single dose is between about 50 mg and 300 mg. In embodiments, a single dose is between about 75 mg and 200 mg. In embodiments, a single dose is between about 100 mg and 150 mg. In embodiments, a single dose is about 125 mg. In embodiments, a single dose is about 175 mg. In embodiments, a single dose is about 200 mg.

[240] In some embodiments of disclosed formulations, a single dose amount of a disclosed compound, including, e.g., an additional active compound, is about 25 mg or less (including 10 mg or less, 5 mg or less, 1 mg or less, and 0.5 mg or less), at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least 100 mg, at least 105 mg, at least 110 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, at least 145 mg, at least 150 mg, at least 155 mg, at least 160 mg, at least 165 mg, at least 170 mg, at least 175 mg, at least 180 mg, at least 185 mg, at least 190 mg, at least 195 mg, at least 200 mg, at least 225 mg, or at least 250 mg (including a dose of 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, and greater than 1 g), and amounts within these ranges.

[241] In some embodiments of disclosed formulations, a single dose amount of a disclosed compound, including, e.g., LSD, is about 25  $\mu$ g or less (including 10  $\mu$ g or less, 5  $\mu$ g or less, 1  $\mu$ g or less, and 0.5  $\mu$ g or less), at least 25  $\mu$ g, at least 30  $\mu$ g, at least 35  $\mu$ g, at least 40  $\mu$ g, at least 45  $\mu$ g, at least 50  $\mu$ g, at least 55  $\mu$ g, at least 60  $\mu$ g, at least 65  $\mu$ g, at least 70  $\mu$ g, at least 75  $\mu$ g, at least 80  $\mu$ g, at least 85  $\mu$ g, at least 90  $\mu$ g, at least 95  $\mu$ g, at least 100  $\mu$ g, at least 105  $\mu$ g, at least 110  $\mu$ g, at least 115  $\mu$ g, at least 120  $\mu$ g, at least 125  $\mu$ g, at least 130  $\mu$ g, at least 135  $\mu$ g, at least 140  $\mu$ g, at least 145  $\mu$ g, at least 150  $\mu$ g, at least 155  $\mu$ g, at least 160  $\mu$ g, at least 165  $\mu$ g, at least 170  $\mu$ g, at least 175  $\mu$ g, at least 180  $\mu$ g, at least 185  $\mu$ g, at least 190  $\mu$ g, at least 195  $\mu$ g, at least 200  $\mu$ g, at least 225  $\mu$ g, or at least 250  $\mu$ g, and amounts within these ranges.

[242] In embodiments, where a disclosed formulation is administered based on patient weight, it may be

administered so that a single dose of the active compound is (in a milligram dosage amount calculated based on the kilogram weight of the patient), e.g., 0.25 mg/kg or less (including a dose of 0.10 mg/kg or less, 0.05 mg/kg or less, 0.01 mg/kg or less, and 0.005 mg/kg or less), at least 0.50 mg/kg, at least 0.55 mg/kg, at least 0.60 mg/kg, at least 0.65 mg/kg, at least 0.70 mg/kg, at least 0.75 mg/kg, at least 0.80 mg/kg, at least 0.85 mg/kg, at least 0.90 mg/kg, at least 0.95 mg/kg, at least 1.0 mg/kg, at least 1.1 mg/kg, at least 1.2 mg/kg, at least 1.3 mg/kg, or at least 1.4 mg/kg, at least 1.5 mg/kg, at least 1.6 mg/kg, at least 1.7 mg/kg, at least 1.8 mg/kg, at least 1.9 mg/kg, at least 2.0 mg/kg, at least 2.1 mg/kg, at least 2.2 mg/kg, at least 2.3 mg/kg, at least 2.4 mg/kg, at least 2.5 mg/kg, at least 2.6 mg/kg, at least 2.7 mg/kg, at least 2.8 mg/kg, at least 2.9 mg/kg, or at least 3.0 mg/kg, as well as amounts within these ranges. In embodiments, a single dose of the compound is administered in an amount between about 0.20 mg/kg and 1.0 mg/kg, 0.20 mg/kg and 0.80 mg/kg, 0.20 mg/kg and 0.60 mg/kg, 0.30 mg/kg and 0.80 mg/kg, or 0.30 mg/kg and 0.60 mg/kg. In embodiments, a single dose is administered in an amount between about 0.02 mg/kg and 0.20 mg/kg, 0.03 mg/kg and 0.13 mg/kg, 0.03 mg/kg and 0.07 mg/kg, 0.05 mg/kg and 0.10 mg/kg, or about 0.08 mg/kg.

[243] Where a microgram amount of a disclosed compound is administered (such as with LSD or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof), one will readily appreciate that when the compound is administered based on patient weight, it may be administered so that a single dose of the compound is (in a microgram dosage amount calculated based on the kilogram weight of the patient), e.g., 0.25  $\mu\text{g}/\text{kg}$  or less (including a dose of 0.10  $\mu\text{g}/\text{kg}$  or less, 0.05  $\mu\text{g}/\text{kg}$  or less, 0.01  $\mu\text{g}/\text{kg}$  or less, and 0.005  $\mu\text{g}/\text{kg}$  or less), at least 0.50  $\mu\text{g}/\text{kg}$ , at least 0.55  $\mu\text{g}/\text{kg}$ , at least 0.60  $\mu\text{g}/\text{kg}$ , at least 0.65  $\mu\text{g}/\text{kg}$ , at least 0.70  $\mu\text{g}/\text{kg}$ , at least 0.75  $\mu\text{g}/\text{kg}$ , at least 0.80  $\mu\text{g}/\text{kg}$ , at least 0.85  $\mu\text{g}/\text{kg}$ , at least 0.90  $\mu\text{g}/\text{kg}$ , at least 0.95  $\mu\text{g}/\text{kg}$ , at least 1.0  $\mu\text{g}/\text{kg}$ , at least 1.1  $\mu\text{g}/\text{kg}$ , at least 1.2  $\mu\text{g}/\text{kg}$ , at least 1.3  $\mu\text{g}/\text{kg}$ , or at least 1.4  $\mu\text{g}/\text{kg}$ , at least 1.5  $\mu\text{g}/\text{kg}$ , at least 1.6  $\mu\text{g}/\text{kg}$ , at least 1.7  $\mu\text{g}/\text{kg}$ , at least 1.8  $\mu\text{g}/\text{kg}$ , at least 1.9  $\mu\text{g}/\text{kg}$ , at least 2.0  $\mu\text{g}/\text{kg}$ , at least 2.1  $\mu\text{g}/\text{kg}$ , at least 2.2  $\mu\text{g}/\text{kg}$ , at least 2.3  $\mu\text{g}/\text{kg}$ , at least 2.4  $\mu\text{g}/\text{kg}$ , at least 2.5  $\mu\text{g}/\text{kg}$ , at least 2.6  $\mu\text{g}/\text{kg}$ , at least 2.7  $\mu\text{g}/\text{kg}$ , at least 2.8  $\mu\text{g}/\text{kg}$ , at least 2.9  $\mu\text{g}/\text{kg}$ , or at least 3.0  $\mu\text{g}/\text{kg}$ , as well as amounts within these ranges. In embodiments, a single dose of the compound is administered in an amount between about 0.20  $\mu\text{g}/\text{kg}$  and 1.0  $\mu\text{g}/\text{kg}$ , 0.20  $\mu\text{g}/\text{kg}$  and 0.80  $\mu\text{g}/\text{kg}$ , 0.20  $\mu\text{g}/\text{kg}$  and 0.60  $\mu\text{g}/\text{kg}$ , 0.30  $\mu\text{g}/\text{kg}$  and 0.80  $\mu\text{g}/\text{kg}$ , or 0.30  $\mu\text{g}/\text{kg}$  and 0.60  $\mu\text{g}/\text{kg}$ . In embodiments, a single dose is administered in an amount between about 0.02  $\mu\text{g}/\text{kg}$  and 0.20  $\mu\text{g}/\text{kg}$ , 0.03  $\mu\text{g}/\text{kg}$  and 0.13  $\mu\text{g}/\text{kg}$ , 0.03  $\mu\text{g}/\text{kg}$  and 0.07  $\mu\text{g}/\text{kg}$ , 0.05  $\mu\text{g}/\text{kg}$  and 0.10  $\mu\text{g}/\text{kg}$ , or about 0.08  $\mu\text{g}/\text{kg}$ .

[244] In embodiments, the administration volume of a disclosed formulation (i.e., the volume of the formulation that is administered to achieve a specific dose of the psychedelic compound) is between about 0.1 and 10 mL, between about 0.2 and 9 mL, between about 0.3 and 8 mL, between about 0.4 and 7 mL, between about 0.5 and 6 mL, between about 0.6 and 5 mL, between about 0.7 and 4 mL, between about 0.8 and 3 mL, or between about 0.9 and 2 mL. In embodiments, the administration volume is less than 1.0 mL (e.g., about 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL, 0.6 mL, 0.7 mL, 0.8 mL, and 0.9 mm), about 1.0 mL,

about 1.1 mL, about 1.2 mL, about 1.3 mL, about 1.4 mL, about 1.5 mL, about 1.6 mL, about 1.7 mL, about 1.8 mL, about 1.9 mL, about 2 mL, about 2.1 mL, about 2.2 mL, about 2.3 mL, about 2.4 mL, about 2.5 mL, about 2.6 mL, about 2.7 mL, about 2.8 mL, about 2.9 mL, about 3.0 mL, about 3.1 mL, about 3.2 mL, about 3.3 mL, about 3.4 mL, about 3.5 mL, about 3.6 mL, about 3.7 mL, about 3.8 mL, about 3.9 mL, about 4.0 mL, about 4.1 mL, about 4.2 mL, about 4.3 mL, about 4.4 mL, about 4.5 mL, about 4.6 mL, about 4.7 mL, about 4.8 mL, about 4.9 mL, about 5.0 mL, or greater than 5.0 mL (including, e.g., about 5.5 mL, about 6.0 mL, about 6.5 mL, about 7.0 mL, about 7.5 mL, about 8.0 mL, about 8.5 mL, about 9.0 mL, about 9.5 mL, about 9.5 mL, and about 10.0 mL. In embodiments, the administration volume is greater than 0.1 mL, 0.5 mL, 1.0 mL, 1.5 mL, 2.0 mL, 2.5 mL, 3.0 mL, 3.5 mL, 4.0 mL, 4.5 mL, 5.0 mL, 5.5 mL, 6.0 mL, 6.5 mL, 7.0 mL, 7.5 mL, 8.0 mL, 8.5 mL, 9.0 mL, 9.5 mL, or greater than 10 mL. In embodiments, the administration volume is less than 1.0 mL, 0.9 mL, 0.8 mL, 0.7 mL, 0.6 mL, 0.5 mL, 0.4 mL, 0.3 mL, 0.2 mL, or 0.1 mL. In embodiments of disclosed formulations, total administration volume is about 0.1 mL. In embodiments of disclosed formulations, total administration volume is about 0.2 mL. In embodiments of disclosed formulations, total administration volume is about 0.3 mL. In embodiments of disclosed formulations, total administration volume is about 0.4 mL. In embodiments of disclosed formulations, total administration volume is about 0.5 mL. In embodiments of disclosed formulations, total administration volume is about 0.6 mL. In embodiments of disclosed formulations, total administration volume is about 0.7 mL. In embodiments of disclosed formulations, total administration volume is about 0.8 mL. In embodiments of disclosed formulations, total administration volume is about 0.9 mL. In embodiments of disclosed formulations, total administration volume is about 1 mL.

[245] In embodiments, the administration volume of a disclosed formulation comprising psilocin or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof (i.e., the volume of the formulation that is administered to achieve a specific dose of the psychedelic compound) is between about 0.1 and 5 mL, between about 0.2 and 4.5 mL, between about 0.3 and 4.0 mL, between about 0.4 and 3.5 mL, between about 0.5 and 3.0 mL, between about 0.6 and 2.5 mL, between about 0.7 and 2.0 mL, between about 0.8 and 1.5 mL, and between about 0.9 and 1.25 mL. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a total administration volume between about 0.5 and 2.0 mL and between about 1.0 and 1.5 mL. In embodiments, the administration volume of a disclosed formulation comprising psilocin or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof is less than 1.0 mL (e.g., about 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL, 0.6 mL, 0.7 mL, 0.8 mL, or less than 0.9 mL), about 1.1 mL, about 1.2 mL, about 1.3 mL, about 1.4 mL, about 1.5 mL, about 1.6 mL, about 1.7 mL, about 1.8 mL, about 1.9 mL, about 2 mL, about 2.5 mL, about 3.0 mL, about 3.5 mL, about 4.0 mL, about 4.5 mL, and about 5.0 mL. In embodiments, the administration volume of a disclosed formulation comprising psilocin or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof is greater than 0.1 mL, 0.2

mL, 0.3 mL, 0.4 mL, 0.5 mL, 0.6 mL, 0.7 mL, 0.8 mL, 0.9 mL, or 1.0 mL (including e.g., greater than 1.1 mL, 1.2 mL, 1.3 mL, 1.4 mL, 1.5 mL, 1.6 mL, 1.7 mL, 1.8 mL, 1.9 mL, or 2.0 mL). In embodiments, the administration volume of a disclosed formulation comprising psilocin or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof is about 1.0 mL, 1.1 mL, 1.2 mL, 1.3 mL, 1.4 mL, and 1.5 mL. In embodiments, the administration volume of a disclosed formulation comprising psilocin or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof is about 1.1 mL. In embodiments, the administration volume of a disclosed formulation comprising psilocin or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof is less than 1.0 mL, 0.9 mL, 0.8 mL, 0.7 mL, 0.6 mL, 0.5 mL, 0.4 mL, 0.3 mL, 0.2 mL, or 0.1 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 0.1 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 0.2 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 0.3 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 0.4 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 0.5 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 0.6 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 0.7 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 0.8 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 0.9 mL. In embodiments of disclosed psilocin formulations, total administration volume is about 1.0 mL.

[246] In embodiments, a disclosed sublingual spray formulation comprises a disclosed compound at a concentration between about 0.1 and 2,000 mg/g, between about 0.1 and 1,500 mg/g, between about 0.1 and 1,000 mg/g, between about 0.1 and 500 mg/g, between about 0.1 and 250 mg/g, between about 0.1 and 100 mg/g, between about 0.1 and 50 mg/g, between about 0.1 and 25 mg/g, between about 0.1 and 10 mg/g, between about 0.1 and 5 mg/g, between about 0.1 and 4 mg/g, between about 0.1 and 3 mg/g, between about 0.1 and 2 mg/g, or between about 0.1 and 1 mg/g. In embodiments, a disclosed sublingual spray formulation comprises a disclosed compound at a concentration of about 0.1 mg/g, about 0.2 mg/g, about 0.3 mg/g, about 0.4 mg/g, about 0.5 mg/g, about 0.6 mg/g, about 0.7 mg/g, about 0.8 mg/g, about 0.9 mg/g, or about 1.0 mg/g. In embodiments, a disclosed formulation comprises a disclosed compound at a concentration of greater than 0.1 mg/g, 0.2 mg/g, 0.3 mg/g, 0.4 mg/g, 0.5 mg/g, 0.6 mg/g, 0.7 mg/g, 0.8 mg/g, 0.9 mg/g, or greater than 1.0 mg/g (including greater than e.g., 1.5 mg/g, 2.0 mg/g, 3.0 mg/g, 4.0 mg/g, 5.0 mg/g, 6.0 mg/g, 7.0 mg/g, 8.0 mg/g, 9.0 mg/g, and 10.0 mg/g). In embodiments, a disclosed formulation comprises a disclosed compound at a concentration of greater than 15 mg/g, 20 mg/g, 30 mg/g, 40 mg/g, 50 mg/g, 60 mg/g, 70 mg/g, 80 mg/g, 90 mg/g, and 100 mg/g. In embodiments, a disclosed formulation comprises a disclosed compound at a concentration of greater than 110 mg/g, 120 mg/g, 130 mg/g, 140 mg/g, 150 mg/g, 160 mg/g, 170 mg/g, 180 mg/g, 190 mg/g, and 200 mg/g.

[247] In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration between about 4 and 200 mg/g, between about 5 and 175 mg/g, between about 6 and 150 mg/g, between about 7 and 125 mg/g, between about 8 and 100 mg/g, between about 9 and 75 mg/g, between about 10 and 50 mg/g, and between about 15 and 25 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 4 mg/g, about 5 mg/g, about 6 mg/g, about 7 mg/g, about 8 mg/g, about 9 mg/g, about 10 mg/g, about 15 mg/g, about 20 mg/g, about 25 mg/g, about 30 mg/g, about 35 mg/g, about 40 mg/g, about 45 mg/g, about 50 mg/g, about 55 mg/g, about 60 mg/g, about 65 mg/g, about 70 mg/g, about 75 mg/g, about 80 mg/g, about 85 mg/g, about 90 mg/g, about 95 mg/g, about 100 mg/g, and greater than 100 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of greater than 4 mg/g, 5 mg/g, 6 mg/g, 7 mg/g, 8 mg/g, 9 mg/g, 10 mg/g, 15 mg/g, 20 mg/g, 25 mg/g, 30 mg/g, 35 mg/g, 40 mg/g, 45 mg/g, 50 mg/g, 60 mg/g, 70 mg/g, 80 mg/g, 90 mg/g, 100 mg/g, 110 mg/g, 120 mg/g, 130 mg/g, 140 mg/g, 150 mg/g, 160 mg/g, 170 mg/g, 180 mg/g, or greater than 190 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 200 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of greater than 200 mg/g.

[248] In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of between about 4.0 and 20.0 mg/g, including about 4.0 mg/g, 5.0 mg/g, 6.0 mg/g, 7.0 mg/g, 8.0 mg/g, 9.0 mg/g, 10.0 mg/g, 11.0 mg/g, 12.0 mg/g, 13.0 mg/g, 14.0 mg/g, 15.0 mg/g, 16.0 mg/g, 17.0 mg/g, 18.0 mg/g, 19.0 mg/g, and 20.0 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of between about 4.0 mg/g and 10.0 mg/g, between about 5.0 mg/g and 10.0 mg/g, between about 5.0 mg/g and 15.0 mg/g, between about 5.0 mg/g and 20.0 mg/g, between about 10.0 mg/g and 20.0 mg/g, and between about 15.0 mg/g and 20.0 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of between about 15.0 and 25.0 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of between about 16.0 and 22.0 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of between about 17.0 mg/g and 20.0 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate,

metabolite, or prodrug thereof, at a concentration of about 17.0 mg/g, 18.0 mg/g, 19 mg/g, and 20 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 17.0 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 17.1 mg/g, 17.2 mg/g, 17.3 mg/g, 17.4 mg/g, 17.5 mg/g, 17.6 mg/g, 17.7 mg/g, 17.8 mg/g, or 17.9 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 18.0 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 18.1 mg/g, 18.2 mg/g, 18.3 mg/g, 18.4 mg/g, 18.5 mg/g, 18.6 mg/g, 18.7 mg/g, 18.8 mg/g, or 18.9 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 19.0 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 19.1 mg/g, 19.2 mg/g, 19.3 mg/g, 19.4 mg/g, 19.5 mg/g, 19.6 mg/g, 19.7 mg/g, 19.8 mg/g, or 19.9 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 20.0 mg/g. In embodiments, a disclosed sublingual spray formulation comprises psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, at a concentration of about 20.1 mg/g, 20.2 mg/g, 20.3 mg/g, 20.4 mg/g, 20.5 mg/g, 20.6 mg/g, 20.7 mg/g, 20.8 mg/g, or 20.9 mg/g.

[249] In embodiments, a subject is administered (including is directed to self-administer) a therapeutically effective dose of a disclosed formulation as part of a drug-assisted therapy (drug-AT) or drug-assisted psychotherapy (drug-AP) protocol, wherein a disclosed formulation comprising the drug is administered at least once during a session where a subject is provided with therapy or psychotherapy. In embodiments, a subject is administered a disclosed formulation and then monitored or supervised, which may be in person or remote. In embodiments, a subject is administered a disclosed formulation and provided with psychological support. In embodiments, a subject receives one drug-AT, drug-AP, or other monitored, supervised, or supported drug administration session (i.e., where a subject is administered a disclosed formulation).

[250] In embodiments, a subject receives two or more drug-AT, drug-AP, or other monitored, supervised, or supported drug administration sessions (i.e., where a subject is administered a disclosed formulation). In embodiments, a subject receives three or more drug-AT, drug-AP, or other monitored, supervised, or supported drug administration sessions (i.e., where a subject is administered a disclosed formulation).

[251] Together with (including before, after, and in between) such sessions, a subject also may receive other non-drug-assisted sessions, such as “preparation” (generally, referring to taking place before at least one drug-assisted session) and “integration” (generally, referring to taking place after at least one

drug-assisted session) sessions. Such drug administration protocols will be appreciated in the art, and have been described, e.g., in Grof. *LSD Psychotherapy*. 4th ed. MAPS; 2008; Passie. *Healing with Enactogens*. 1st ed. MAPS; 2012; Johnson et al. *J Psychopharmacol*. 2008; 22(6): 603-620; Sessa & Fischer. *Drug Science, Policy and Law*. 2015; 2: 2050324515578080.; Schmid et al. *J Psychopharmacol*. 2021; 35(4): 362-374; Greer & Tolbert. *J Psychoactive Drugs*. 1998; 30(4): 371-379; Mithoefer et al. *Psychopharmacol (Berl)*. 2019; 236(9): 2735-2745; Mithoefer et al. *J Psychopharmacol*. 2013; 27(1): 28-39; and U.S. App. No. 2020/0360311; all incorporated by reference.

[252] In embodiments, a subject is administered (including is directed to self-administer) a therapeutically effective dose of a disclosed formulation on a regular or chronic basis, which may include the subject being administered the disclosed formulation daily or several times per day; on a set, repeating schedule, wherein the subject is administered the disclosed formulation every other day, every three days, every four days, every five days, every six days, every seven days, or more than every seven days; or, in embodiments, a varying schedule comprised of one or more days "on" (where the disclosed formulation is administered), alternating with one or more days "off" (where no administration occurs), such as one day on two days off, two days on three days off, three days on four days off, or other such schedules as are apparent to those of skill (for example, with "microdosing," what are known as the Paul Stamets and James Fadiman protocols).

[253] In some aspects are disclosed methods wherein an additional active compound or other agent is administered before, at the same time as, or after the administration of a disclosed formulation. In embodiments, an MAOI is administered before, at the same time as, or after the administration of a disclosed formulation. In embodiments, a 5-HT<sub>2A</sub> antagonist is administered before, at the same time as, or after the administration of a disclosed formulation. In embodiments, the additional active compound is as defined herein.

[254] In embodiments, where an agent is administered before a disclosed formulation, the agent is administered at least 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, or 24 hours before administration of the disclosed formulation. In embodiments, an agent is administered between about 1 hour and 12 hours before administration of the disclosed formulation. In embodiments, an agent is administered between about 2 hours and 8 hours before administration of the disclosed formulation. In embodiments, an agent is administered between about 3 hours and 6 hours before administration of the disclosed formulation. In embodiments, an agent is administered about 2 hours before administration of the disclosed formulation. In embodiments, an agent is administered about 4 hours before administration of the disclosed formulation.

[255] In embodiments, where an agent is administered "at the same time as" a disclosed formulation, such administration may refer to administration at substantially the same time as administration of the disclosed formulation. In embodiments, it may refer to administration of the agent within not more than 15 minutes, 10 minutes, preferably 5 minutes, or more preferably 1 minute of administration of the disclosed formulation. In embodiments, the agent is administered less than 15 minutes before administration of the disclosed formulation. In embodiments, the agent is administered less than 10 minutes before administration of the

disclosed formulation. In embodiments, the agent is administered less than 5 minutes before administration of the disclosed formulation. In embodiments, the agent is administered less than 1 minute before administration of the disclosed formulation.

[256] In embodiments, where an agent is administered after a disclosed formulation, the agent is administered at least 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, or 24 hours after administration of the disclosed formulation. In embodiments, the agent is administered between about 1 hour and 12 hours after administration of the disclosed formulation. In embodiments, the agent is administered between about 2 hours and 8 hours after administration of the disclosed formulation. In embodiments, the agent is administered between about 3 hours and 6 hours after administration of the disclosed formulation. In embodiments, the agent is administered about 2 hours after administration of the disclosed formulation. In embodiments, the agent is administered about 4 hours after administration of the disclosed formulation.

[257] As will be appreciated by one of skill, the timing of administration of an agent may be selected based on the properties (including pharmacokinetic and pharmacodynamic) of the agent and the release profile of the drug product or composition comprising the agent, as well as the properties of the psychedelic or other compound in the disclosed formulation that the agent is administered before, at the same time as, or after.

#### **D. Pharmaceutical Kits**

[258] The present disclosure further provides kits comprising the disclosed formulations. Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any formulation described herein. For example, a kit may comprise one or more containers comprising a sublingual spray formulation, such as a sublingual spray formulation comprising a disclosed compound, such as a sublingual spray formulation comprising psilocin. Each component can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

[259] Disclosed kits, for example, may contain sufficient dosages of a disclosed formulation for an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may be packaged in quantities sufficient for storage at home or a retail location. The kits may optionally include a set of instructions, generally written instructions, although electronic storage media containing instructions are also acceptable, relating to the use of component(s) of the methods of the present disclosure. The instructions included with the kit generally include information as to the components and their administration to an individual.

#### **E. Exemplary Features and Advantages of Disclosed Formulations**

[260] The sublingual mucosa is the membrane of the ventral surface of the tongue, and is the most permeable region in the oral mucosa due to its highly vascularized tissue structure (Şenel. *Int J Mol Sci.* 2021; 22(15): 7821). The buccal and sublingual mucosal structure (non-keratinized oral epithelium) consists of a top mucus layer, found atop the stratified squamous epithelium, supported by a layer of tissue called the basal lamina, with *Lamina propria* lying underneath (*id*). The thickness of the sublingual mucosa is

approximately 100–200  $\mu\text{m}$ , compared with 500–800  $\mu\text{m}$  for the buccal mucosa (Harris et al. *J Pharm Sci.* 1992; 81(1): 1–10; Shojaei. *J Pharm Pharm Sci.* 1998; 1(1): 15–30).

[261] The sublingual gland is the smallest, most diffuse, and the only unencapsulated major salivary gland. It is responsible for only 3-5% of the total salivary volume. As such, psychedelic compounds administered according to disclosed sublingual spray formulations offer advantages over the same compounds administered by conventional routes of administration (e.g., by oral administration or inhalation.)

[262] In embodiments, compounds administered in disclosed formulations are absorbed primarily via the sublingual mucosa, therefore bypassing the gastrointestinal (GI) tract. Consequently, first-pass metabolism may be avoided, and compounds administered in disclosed formulations may exhibit improved bioavailability, as compared to the same compounds administered via a different route of administration.

[263] In embodiments, the bioavailability of a compound administered in a disclosed sublingual spray formulation or according to a disclosed method is increased by about 1.1-fold, 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2-fold, 5-fold, 10-fold, 20-fold, 50-fold, or about 100-fold, including all amounts in between. In embodiments, the bioavailability of a compound administered in a disclosed sublingual spray formulation or according to a disclosed method is increased by at least 1.1-fold, 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2-fold, 5-fold, 10-fold, 20-fold, 50-fold, or at least 100-fold, including all amounts in between.

[264] In embodiments, the bioavailability of a disclosed compound (herein and elsewhere, understood to also include, for the compound, a pharmaceutically acceptable salt, hydrate, solvate, isotopolog, derivative, metabolite, isomer, single enantiomer, non-racemic mixture, or prodrug thereof, including combinations thereof), is increased by 1.1-fold. In embodiments, the bioavailability of the compound is increased by 1.2-fold. In embodiments, the bioavailability of the compound is increased by 1.3-fold. In embodiments, the bioavailability of the compound is increased by 1.4-fold. In embodiments, the bioavailability of the compound is increased by 1.5-fold. In embodiments, the bioavailability of the compound is increased by 1.6-fold. In embodiments, the bioavailability of the compound is increased by 1.7-fold. In embodiments, the bioavailability of the compound is increased by 1.8-fold. In embodiments, the bioavailability of the compound is increased by 1.9-fold. In embodiments, the bioavailability of the compound is increased by 2-fold. In embodiments, the bioavailability of the compound is increased by 5-fold. In embodiments, the bioavailability of the compound is increased by 10-fold. In embodiments, the bioavailability of the compound is increased by 20-fold. In embodiments, the bioavailability of the compound is increased by 50-fold. In embodiments, the bioavailability of the compound is increased by 100-fold. In embodiments, the bioavailability of the compound is increased by at least 100-fold.

[265] Certain compounds are unstable and have a short shelf-life. Psilocin and (to a lesser extent) psilocybin are notoriously unstable in solution. It is relatively unstable in solution due to the reactivity of the phenolic hydroxy group, of which oxidation leads to blue and black colored quinoids. Although this instability

has long been recognized, the exact chemistry of the mechanisms and products of decomposition is a matter of ongoing research. Studies of *Psilocybe* mushrooms that have been damaged, thus exposing the tryptamine alkaloids therein to environmental oxygen, have revealed that psilocybin is dephosphorylated to psilocin, whose hydroxy group is subsequently oxidized to produce 4-oxo degradation products (Lenz et al. *Angew Chem Int Ed.* 2020; 59: 1450-1454). For example, phosphatase PsiP removes the 4-O-phosphate group from psilocybin to yield psilocin, while laccase PsiL oxidizes its 4-hydroxy group to prepare for instant oligomerization into a mixture of quinoid psilocyl oligomers, primarily coupled via carbon 5, that account for blueing, triggered by damage to *Psilocybe* mushrooms (*id*).

[266] In embodiments, compounds formulated in disclosed formulations exhibit improved solution stability relative to a comparator solution that does not comprise the excipient(s) and/or solvent system of the disclosed formulations. Solution stability can be assessed according to methods known in the art. For example, in embodiments wherein the compound is psilocybin or psilocin, the decomposition products, such as oxidation products, or oligomers formed by oxidative coupling (such as oxidative dimerization) can be characterized according to methods such as disclosed in Lenz et al. *Chem Eur J.* 2021; 27: 12166-12171).

[267] In embodiments, the solution stability of a disclosed compound in a disclosed sublingual spray formulation is increased by about 1.1-fold, 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, or at least 100-fold. In embodiments, the solution stability of the compound is increased by 1.1-fold. In embodiments, the solution stability of the compound is increased by 1.2-fold. In embodiments, the solution stability of the compound is increased by 1.3-fold. In embodiments, the solution stability of the compound is increased by 1.4-fold. In embodiments, the solution stability of the compound is increased by 1.5-fold. In embodiments, the solution stability of the compound is increased by 1.6-fold. In embodiments, the solution stability of the compound is increased by 1.7-fold. In embodiments, the solution stability of the compound is increased by 1.8-fold. In embodiments, the solution stability of the compound is increased by 1.9-fold. In embodiments, the solution stability of the compound is increased by 2-fold. In embodiments, the solution stability of the compound is increased by 5-fold. In embodiments, the solution stability of the compound is increased by 10-fold. In embodiments, the solution stability of the compound is increased by 20-fold. In embodiments, the solution stability of the compound is increased by 50-fold. In embodiments, the solution stability of the compound is increased by 100-fold. In embodiments, the solution stability of the compound is increased by at least 100-fold.

[268] In embodiments, where a disclosed compound in a disclosed formulation exhibits improved solution stability, the increase in solution stability translates into an increased shelf-life for the formulation. Shelf life can be determined by methods known to those of skill in the art. In embodiments, the shelf life of the formulation is at least 1 month. In embodiments, the shelf life of the formulation is about 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or at least 12 months. In preferred embodiments, the shelf life of disclosed formulations is at least 6 months.

[269] Other advantages of administering disclosed spray formulations sublingually can include reducing or eliminating an adverse event, such as an undesirable side effect. For example, nausea is a commonly reported side effect that can adversely affect the subjective character and potential therapeutic value of a psychedelic experience. Nausea is an especially common side effect of psilocin and psilocybin (see, e.g., Barrett et al. *British Assoc Psychopharmacol.* 2016; 41(12): 1163-1164; Dinis-Oliveira. *Drug Metab Rev.* 2006; 49(1): 84-91). In embodiments, nausea caused by psychedelic compounds administered in disclosed formulations is reduced or eliminated compared to when the same compound is administered conventionally (e.g., orally). Drugs can also be conventionally administered in nasal spray formulations. Advantages of disclosed sublingual spray formulations over nasal sprays include avoiding drawbacks of delivery to the mucosal area of the nasal cavity, which can be susceptible to irritation and difficult to access. Other limitations of nasal delivery, which are obviated by the disclosed sublingual spray formulations, include rapid clearance of administered substances and potential disruption of physiological functions of the nasal cavity (Ugwoke et al. *J Pharm Pharmacol.* 2001; 53: 3-22). Furthermore, administration of drugs across the nasal mucosa can cause irreversible damage to the nasal cilia (Sankar et al. *Oral Dis.* 2011; 17(Suppl. 1): 73-84). In contrast, the oral mucosa can be more readily accessible and acceptable as a site for drug delivery. The sublingual gland is the smallest, most diffuse, and the only unencapsulated major salivary gland. It can be more permeable than the skin, have better properties of self-repair, is generally more vascular, is typically less responsive to allergenic and irritant materials, and can provide a more hydrated environment for solubilization of drugs. Despite such recognized advantages, sublingual formulations of the disclosed compounds, such as psilocin, that are acceptable for therapeutic and especially clinical development and use, have remained out of reach until the work of the inventors.

[270] In embodiments, a disclosed formulation reduces the risk of swallowing the API compared to an alternative sublingual, buccal, or transmucosal formulation, and having the API enter the GI tract, e.g., leading to reduced drug absorption or increased side effects. In embodiments, a disclosed formulation reduces the risk of swallowing the API due to the relatively low administration volume. In embodiments, a disclosed formulation reduces the risk of swallowing the API due to the mucoadhesive polymer.

[271] In embodiments, a disclosed formulation does not comprise alcohol or another organic solvent.

[272] In embodiments, a disclosed sublingual spray formulation is packaged as a metered spray. Devices for metered spray administration are known to those of skill. In a non-limiting example, a disclosed sublingual spray formulation is packaged in a 10 mL amber plastic-coated glass container, fitted with a metering pump, a polypropylene dip tube, and elastomer neck covered with a polypropylene cap. This and other similar devices allow for precise administration of a specified volume of a disclosed formulation to an individual.

[273] In embodiments, the metered spray device is a multi-dose, unit dose, or bi-dose device. Examples of metered spray devices include pump devices, mechanical devices, pressurized devices, and electromechanical devices. In embodiments, the metered spray device is a spray pump, a pre-compression

sublingual spray pump, a metered valve device, an actuated spray device, a side actuated spray device, a syringe sublingual spray device (e.g. a syringe that has an atomizer to deliver a spray to the oral cavity), a mucosal atomization device, or an electromechanical pump device (with or without a counter). Examples of metered spray devices also include commercially available devices, such as UDS (Aptar Pharma), BDS (Aptar Pharma), eDevices (Aptar Pharma), Equadel (Aptar Pharma), Latitude (Aptar Pharma), DF30 (Aptar Pharma), VP7 (Aptar Pharma), 10 Classic Nasal Device (Aptar Pharma), MAD Nasal Drug Device (Wolf Tory Medical, Inc.), BD Accuspray SCF™ (Becton Dickinson), and the like.

[274] Disclosed formulations can be administered in metered spray dosages so that a predetermined amount of the compound is administered to the subject in a pharmaceutically or therapeutically effective amount. For example, the sublingual spray formulation may be packaged as a bulk liquid containing multiple doses in a pump spray system comprising a sealed container fitted with a metering pump. In embodiments, a subject is treated by sublingual self-administration, such as by one or more actuations from a spray pump. An advantage of disclosed sublingual spray formulations is the ability to titrate subjects by single doses as supplied by single, discrete actuations. This advantage may be absent from other comparator forms of drug delivery (e.g., patches, lozenges, tablets, and suppositories) in which a single dosage is administered in a standard regimen. Additional advantages of disclosed sublingual spray formulations include ease of use, especially when self-administered absent an attending health care professional.

[275] A metered spray device may be pre-metered or, alternately, a device may be device-metered. Pre-metered spray devices may contain previously measured doses or a dose fraction in some type of units (e.g., single unit dose amount of solution, single or multiple blisters or other cavities) that may be included in the device during manufacture or by the subject before use. Typical device-metered units have a reservoir containing a formulation sufficient for multiple doses that are delivered as metered sprays by the device itself when activated by the subject. The device may be metered both in the amount of drug substance delivered (i.e., the dosage per actuation), as well as the length of time between each dosage. Limiting the time between each dosage can prevent over-use by limiting how often a dosage can be delivered to the subject.

[276] In embodiments, the spray volume (i.e., the volume of a disclosed sublingual spray formulation that is delivered in a single spray of the delivery device) is between about 0.1 mL and 1.0 mL, including about 0.1 mL, about 0.2 mL, about 0.3 mL, about 0.4 mL, about 0.5 mL, about 0.6 mL, about 0.7 mL, about 0.8 mL, about 0.9 mL, about 0.9 mL, about 1.0 mL, and ranges between these values. In embodiments, the spray volume is about 0.1 mL. In embodiments, the spray volume is about 0.2 mL. In embodiments, the spray volume is about 0.3 mL. In embodiments, the spray volume is about 0.4 mL. In embodiments, the spray volume is about 0.5 mL. In embodiments, the spray volume is about 0.6 mL. In embodiments, the spray volume is about 0.7 mL. In embodiments, the spray volume is about 0.8 mL. In embodiments, the spray volume is about 0.9 mL. In embodiments, the spray volume is about 1.0 mL.

[277] In embodiments, the spray dose (i.e., the amount of the compound in a disclosed sublingual spray

formulation that is delivered in a single spray of the delivery device) can depend on the selection of the specific compound, the potency of the compound, and the concentration of the formulation. For example, for a sublingual spray formulation comprising psilocin, the spray dose is in embodiments between about 1 mg and 40 mg, including about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg, and 50 mg of psilocin, and ranges between these values. In embodiments, the spray dose is about 1 mg of psilocin. In embodiments, the spray dose is about 5 mg of psilocin. In embodiments, the spray dose is about 10 mg of psilocin. In embodiments, the spray dose is about 15 mg of psilocin. In embodiments, the spray dose is about 20 mg of psilocin. In embodiments, the spray dose is about 25 mg of psilocin. In embodiments, the spray dose is about 30 mg of psilocin. In embodiments, the spray dose is between about 1 mg and 5 mg of psilocin. In embodiments, the spray dose is between about 1 mg and 10 mg of psilocin. In embodiments, the spray dose is between about 1 mg and 15 mg of psilocin. In embodiments, the spray dose is between about 1 mg and 20 mg of psilocin. In embodiments, the spray dose is between about 1 mg and 25 mg of psilocin. In embodiments, the spray dose is between about 1 mg and 30 mg of psilocin. In embodiments, the spray dose is between about 5 mg and 10 mg of psilocin. In embodiments, the spray dose is between about 5 mg and 15 mg of psilocin. In embodiments, the spray dose is between about 5 mg and 20 mg of psilocin. In embodiments, the spray dose is between about 5 mg and 25 mg of psilocin. In embodiments, the spray dose is between about 5 mg and 30 mg of psilocin. In embodiments, the spray dose is between about 10 mg and 15 mg of psilocin. In embodiments, the spray dose is between about 10 mg and 20 mg of psilocin. In embodiments, the spray dose is between about 10 mg and 25 mg of psilocin. In embodiments, the spray dose is between about 10 mg and 30 mg of psilocin. In embodiments, the spray dose is between about 15 mg and 20 mg of psilocin. In embodiments, the spray dose is between about 15 mg and 25 mg of psilocin. In embodiments, the spray dose is between about 15 mg and 30 mg of psilocin. In embodiments, the spray dose is between about 20 mg and 25 mg of psilocin. In embodiments, the spray dose is between about 20 mg and 30 mg of psilocin. In embodiments, the spray dose is between about 25 mg and 30 mg of psilocin.

[278] In embodiments, the plume geometry of a disclosed sublingual spray formulation is controlled by the delivery device. Plume geometry includes the shape and density of the spray pump plume, and can be measured by techniques known to those of skill in the art. In embodiments, measuring the plume geometry comprises determining the plume width. In embodiments, the plume width is about 1 mm to about 100 mm, including about 5 mm to 80 mm, about 10 mm to 60 mm, and about 20 mm to 50 mm. In embodiments, the plume width is about 1 mm. In embodiments, the plume width is about 5. In embodiments, the plume width is about 10 mm. In embodiments, the plume width is about 15 mm. In embodiments, the plume width is about 20 mm. In embodiments, the plume width is about 25 mm. In embodiments, the plume width is about 30 mm. In embodiments, the plume width is about 35 mm. In embodiments, the plume width is about 40 mm. In embodiments, the plume width is about 45 mm. In embodiments, the plume width is about 50 mm. In embodiments, the plume width is about 55 mm. In embodiments, the plume width is about 60 mm. In

embodiments, the plume width is about 65 mm. In embodiments, the plume width is about 70 mm. In embodiments, the plume width is about 75 mm. In embodiments, the plume width is about 80 mm. In embodiments, the plume width is about 85 mm. In embodiments, the plume width is about 90 mm. In embodiments, the plume width is about 95 mm. In embodiments, the plume width is about 100 mm.

[279] In embodiments, measuring the plume geometry comprises determining the spray span. Spray span is defined as the maximum droplet volume ( $D_{V90}$ ) subtracted by the minimum droplet volume ( $D_{V10}$ ) divided by the median droplet volume ( $D_{V50}$ ) and can be determined according to methods known in the art (e.g., as described in WO 2015/038327). In embodiments, the spray span is about 1.0 to 10.0, including about 1.1 to 8.0, about 1.1 to 2.0, about 1.1 to 3.0, about 1.1 to 4.0, about 1.5 to 6.0, about 1.8 to 4.0, about 2.0 to 3.0, about 2.0 to 4.0, and about 3.0 to 5.0. In embodiments, the spray span is about 1.0. In embodiments, the spray span is about 1.1. In embodiments, the spray span is about 1.2. In embodiments, the spray span is about 1.3. In embodiments, the spray span is about 1.4. In embodiments, the spray span is about 1.5. In embodiments, the spray span is about 1.6. In embodiments, the spray span is about 1.7. In embodiments, the spray span is about 1.8. In embodiments, the spray span is about 1.9. In embodiments, the spray span is about 2.0. In embodiments, the spray span is about 2.5. In embodiments, the spray span is about 3.0. In embodiments, the spray span is about 3.5. In embodiments, the spray span is about 4.0. In embodiments, the spray span is about 4.5. In embodiments, the spray span is about 5.0. In embodiments, the spray span is about 5.5. In embodiments, the spray span is about 6.0. In embodiments, the spray span is about 6.5. In embodiments, the spray span is about 7.0. In embodiments, the spray span is about 7.5. In embodiments, the spray span is about 8.0. In embodiments, the spray span is about 8.5. In embodiments, the spray span is about 9.0. In embodiments, the spray span is about 9.5. In embodiments, the spray span is about 10.0.

[280] In embodiments, measuring the plume geometry comprises determining the ovality ratio. Ovality ratio is defined as the maximum droplet diameter ( $D_{max}$ ) divided by the minimum droplet diameter ( $D_{min}$ ), and can be determined according to methods known in the art (e.g., as described in WO 2015/038327). In embodiments, the ovality ratio is about 1.0 to 10.0, including about 1.1 to 8.0, about 1.1 to 2.0, about 1.1 to 3.0, about 1.1 to 4.0, about 1.5 to 6.0, about 1.8 to 4.0, about 2.0 to 3.0, about 2.0 to 4.0, and about 3.0 to 5.0. In embodiments, the ovality ratio is about 1.0. In embodiments, the ovality ratio is about 1.1. In embodiments, the ovality ratio is about 1.2. In embodiments, the ovality ratio is about 1.3. In embodiments, the ovality ratio is about 1.4. In embodiments, the ovality ratio is about 1.5. In embodiments, the ovality ratio is about 1.6. In embodiments, the ovality ratio is about 1.7. In embodiments, the ovality ratio is about 1.8. In embodiments, the ovality ratio is about 1.9. In embodiments, the ovality ratio is about 2.0. In embodiments, the ovality ratio is about 2.5. In embodiments, the ovality ratio is about 3.0. In embodiments, the ovality ratio is about 3.5. In embodiments, the ovality ratio is about 4.0. In embodiments, the ovality ratio is about 4.5. In embodiments, the ovality ratio is about 5.0. In embodiments, the ovality ratio is about 5.5. In embodiments, the ovality ratio is about 6.0. In embodiments, the ovality ratio is about 6.5. In embodiments, the ovality ratio

is about 7.0. In embodiments, the ovality ratio is about 7.5. In embodiments, the ovality ratio is about 8.0. In embodiments, the ovality ratio is about 8.5. In embodiments, the ovality ratio is about 9.0. In embodiments, the ovality ratio is about 9.5. In embodiments, the ovality ratio is about 10.0.

[281] In embodiments, measuring the plume geometry comprises determining the plume angle. The plume angle is defined as the width of spray distribution from the spray source. The plume angle (C) can be defined by the formula  $C = 2D \tan(\theta/2)$  and can be determined according to methods known in the art (e.g., as described in WO 2015/038327). In embodiments, the plume angle is about 10 degrees to 180 degrees, including about 20 degrees to 160 degrees, about 30 degrees to 140 degrees, about 40 degrees to 120 degrees, about 50 degrees to 100 degrees, about 60 degrees to 80 degrees, about 25 degrees to 75 degrees, about 30 degrees to 60 degrees, and about 35 degrees to 50 degrees. In embodiments, the plume angle is about 10 degrees. In embodiments, the plume angle is about 20 degrees. In embodiments, the plume angle is about 30 degrees. In embodiments, the plume angle is about 40 degrees. In embodiments, the plume angle is about 50 degrees. In embodiments, the plume angle is about 60 degrees. In embodiments, the plume angle is about 70 degrees. In embodiments, the plume angle is about 80 degrees. In embodiments, the plume angle is about 90 degrees. In embodiments, the plume angle is about 100 degrees. In embodiments, the plume angle is about 110 degrees. In embodiments, the plume angle is about 120 degrees. In embodiments, the plume angle is about 130 degrees. In embodiments, the plume angle is about 140 degrees. In embodiments, the plume angle is about 150 degrees. In embodiments, the plume angle is about 160 degrees. In embodiments, the plume angle is about 170 degrees. In embodiments, the plume angle is about 180 degrees.

[282] In embodiments, the droplet size of a disclosed sublingual spray formulation is controlled by the delivery device. Droplet size analysis can be conducted using standard laser analysis procedures known by those of skill. In embodiments, the average droplet size is between about 5 microns and 500 microns, including about 10 microns to 200 microns, and about 20 microns to 100 microns. In embodiments, the droplet size is about 5 microns. In embodiments, the droplet size is about 10 microns. In embodiments, the droplet size is about 15 microns. In embodiments, the droplet size is about 20 microns. In embodiments, the droplet size is about 30 microns. In embodiments, the droplet size is about 40 microns. In embodiments, the droplet size is about 50 microns. In embodiments, the droplet size is about 60 microns. In embodiments, the droplet size is about 70 microns. In embodiments, the droplet size is about 80 microns. In embodiments, the droplet size is about 90 microns. In embodiments, the droplet size is about 100 microns. In embodiments, the droplet size is about 125 microns. In embodiments, the droplet size is about 150 microns. In embodiments, the droplet size is about 5 microns. In embodiments, the droplet size is about 175 microns. In embodiments, the droplet size is about 200 microns. In embodiments, the droplet size is about 300 microns. In embodiments, the droplet size is about 400 microns. In embodiments, the droplet size is about 500 microns.

[283] In embodiments, the droplet size distribution of a disclosed sublingual spray formulation is controlled

by the delivery device. Droplet size distribution analysis can be conducted using standard laser analysis procedures known by those of skill in the art. Droplet size distribution can be defined by 90% (D90) of the sample having a size equal to or less than the defined values. In embodiments, the D90 is between about 5 microns and 2000 microns, including about 10 microns to 1800 microns, about 20 microns to 1500 microns, about 30 microns to 1250 microns, about 50 microns to 1000 microns, about 75 microns to 800 microns, about 90 microns to 600 microns, about 100 microns to 600 microns, and about 200 microns to 400 microns. In embodiments, the D90 is about 5 microns. In embodiments, the D90 is about 10 microns. In embodiments, the D90 is about 15 microns. In embodiments, the D90 is about 20 microns. In embodiments, the D90 is about 30 microns. In embodiments, the D90 is about 40 microns. In embodiments, the D90 is about 50 microns. In embodiments, the D90 is about 60 microns. In embodiments, the D90 is about 70 microns. In embodiments, the D90 is about 80 microns. In embodiments, the D90 is about 90 microns. In embodiments, the D90 is about 100 microns. In embodiments, the D90 is about 125 microns. In embodiments, the D90 is about 150 microns. In embodiments, the D90 is about 5 microns. In embodiments, the D90 is about 175 microns. In embodiments, the D90 is about 200 microns. In embodiments, the D90 is about 300 microns. In embodiments, the D90 is about 400 microns. In embodiments, the D90 is about 500 microns. In embodiments, the D90 is about 600 microns. In embodiments, the D90 is about 700 microns. In embodiments, the D90 is about 800 microns. In embodiments, the D90 is about 900 microns. In embodiments, the D90 is about 1000 microns. In embodiments, the D90 is about 1200 microns. In embodiments, the D90 is about 1400 microns. In embodiments, the D90 is about 1600 microns. In embodiments, the D90 is about 1800 microns. In embodiments, the D90 is about 2000 microns.

[284] In embodiments, droplet size distribution is alternatively defined by 50% (D50) of the sample having a size equal to or less than the defined values. In embodiments, the D50 is between about 5 microns and 2000 microns, including about 10 microns to 1800 microns, about 20 microns to 1500 microns, about 30 microns to 1250 microns, about 50 microns to 1000 microns, about 75 microns to 800 microns, about 90 microns to 600 microns, about 100 microns to 600 microns, and about 200 microns to 400 microns. In embodiments, the D50 is about 5 microns. In embodiments, the D50 is about 10 microns. In embodiments, the D50 is about 15 microns. In embodiments, the D50 is about 20 microns. In embodiments, the D50 is about 30 microns. In embodiments, the D50 is about 40 microns. In embodiments, the D50 is about 50 microns. In embodiments, the D50 is about 60 microns. In embodiments, the D50 is about 70 microns. In embodiments, the D50 is about 80 microns. In embodiments, the D50 is about 90 microns. In embodiments, the D50 is about 100 microns. In embodiments, the D50 is about 125 microns. In embodiments, the D50 is about 150 microns. In embodiments, the D50 is about 5 microns. In embodiments, the D50 is about 175 microns. In embodiments, the D50 is about 200 microns. In embodiments, the D50 is about 300 microns. In embodiments, the D50 is about 400 microns. In embodiments, the D50 is about 500 microns. In embodiments, the D50 is about 600 microns. In embodiments, the D50 is about 700 microns. In

embodiments, the D50 is about 800 microns. In embodiments, the D50 is about 900 microns. In embodiments, the D50 is about 1000 microns. In embodiments, the D50 is about 1200 microns. In embodiments, the D50 is about 1400 microns. In embodiments, the D50 is about 1600 microns. In embodiments, the D50 is about 1800 microns. In embodiments, the D50 is about 2000 microns.

[285] In embodiments, droplet size distribution is alternatively defined by 10% (D10) of the sample having a size equal to or less than the defined values. In embodiments, the D10 is between about 5 microns and 2000 microns, including about 10 microns to 1800 microns, about 20 microns to 1500 microns, about 30 microns to 1250 microns, about 50 microns to 1000 microns, about 75 microns to 800 microns, about 90 microns to 600 microns, about 100 microns to 600 microns, and about 200 microns to 400 microns. In embodiments, the D10 is about 5 microns. In embodiments, the D10 is about 10 microns. In embodiments, the D10 is about 15 microns. In embodiments, the D10 is about 20 microns. In embodiments, the D10 is about 30 microns. In embodiments, the D10 is about 40 microns. In embodiments, the D10 is about 50 microns. In embodiments, the D10 is about 60 microns. In embodiments, the D10 is about 70 microns. In embodiments, the D10 is about 80 microns. In embodiments, the D10 is about 90 microns. In embodiments, the D10 is about 100 microns. In embodiments, the D10 is about 125 microns. In embodiments, the D10 is about 150 microns. In embodiments, the D10 is about 5 microns. In embodiments, the D10 is about 175 microns. In embodiments, the D10 is about 200 microns. In embodiments, the D10 is about 300 microns. In embodiments, the D10 is about 400 microns. In embodiments, the D10 is about 500 microns. In embodiments, the D10 is about 600 microns. In embodiments, the D10 is about 700 microns. In embodiments, the D10 is about 800 microns. In embodiments, the D10 is about 900 microns. In embodiments, the D10 is about 1000 microns. In embodiments, the D10 is about 1200 microns. In embodiments, the D10 is about 1400 microns. In embodiments, the D10 is about 1600 microns. In embodiments, the D10 is about 1800 microns. In embodiments, the D10 is about 2000 microns.

#### **F. Methods of Use**

[286] In some aspects, provided herein are methods of using the disclosed formulations. In embodiments, disclosed formulations are used to modulate neurotransmission. In embodiments, disclosed formulations are used to treat a condition, such as a disease or a disorder. In embodiments, disclosed formulations are used in the manufacture of a medicament for the therapeutic and/or the prophylactic treatment of a condition, such as a disease or a disorder. In embodiments, disclosed formulations are administered in a therapeutically effective amount to a subject having a condition, such as a disease or a disorder. In embodiments, the condition is a mental health disorder. In embodiments, the condition is a neurodegenerative disorder. In embodiments, the condition is an inflammatory disorder. In embodiments, the condition is pain and/or inflammation. In embodiments, disclosed formulations are administered to a subject that is healthy.

[287] In embodiments, disclosed formulations are administered as part of drug-assisted therapy, drug-assisted psychotherapy, or other monitored, supervised, or supported drug administration sessions.

[288] As used herein, the terms “subject,” “user,” “patient,” and “individual” are used interchangeably, and refer to any mammal, including murines, simians, mammalian farm animals, mammalian sport animals, and mammalian pets, such as canines and felines, although preferably humans. Such terms will be understood to include one who has an indication for which a compound, formulation, or method described herein may be efficacious, or who otherwise may benefit by the invention. In general, all of the disclosed formulations and methods will be appreciated to work for all individuals, although individual variation is to be expected, and will be understood. The disclosed methods of treatment also can be modified to treat multiple subjects at once, including couples or families. Hence, these terms will be understood to also mean two or more individuals.

**a. Modulating Neurotransmission**

[289] In embodiments, the disclosed formulations are used to modulate neurotransmission in an individual, following administration of a pharmacologically effective amount to said subject. In embodiments, modulating neurotransmission comprises regulating levels of monoamines in, for example, the CNS and peripheral tissues. In embodiments, modulating neurotransmission comprises increasing levels of monoamines in, for example, the CNS and peripheral tissues of an individual to whom a disclosed formulation has been administered. In embodiments, modulating neurotransmission comprises decreasing levels of monoamines in, for example, the CNS and peripheral tissues of an individual to whom a disclosed formulation has been administered. In embodiments, modulating neurotransmission by administering a disclosed formulation to an individual treats a disease or disorder in the individual.

[290] In embodiments, modulating neurotransmission comprises inhibiting the reuptake of one or more neurotransmitters. In embodiments, modulating neurotransmission comprises increasing the extracellular concentration of one or more neurotransmitters, including the amount of extracellular serotonin (5-HT), dopamine (DA), or norepinephrine (NE).

[291] In some methods herein, the disclosed formulations, when administered to an individual in a pharmacologically effective amount, affect monoaminergic neurotransmission, including serotonergic, dopaminergic, and noradrenergic neurotransmission. Accordingly, in some embodiments, the disclosed formulations, when administered to an individual in a pharmacologically effective amount, are used to treat a medical condition linked to dysregulation or inadequate functioning of neurotransmission, and in specific embodiments, are used to treat a medical condition linked to monoaminergic neurotransmission.

[292] In embodiments, disclosed formulations, when administered in a pharmacologically effective amount, act on or modulate one or more monoamine receptors, such as a serotonin receptor, a dopamine receptor, or a norepinephrine receptor. In embodiments, the compositions are agonists or partial agonists of a monoamine receptor, including any one or more of a 5-HT receptor, a DA receptor, and a NE receptor.

[293] In embodiments, disclosed formulations comprise a compound that activates serotonin receptors. In some such embodiments, disclosed formulations, when administered to an individual in a pharmacologically effective amount, are used to agonize 5-HT receptors, such as a 5-HT<sub>1</sub> and/or 5-HT<sub>2</sub> receptor, including a

5-HT<sub>2A</sub> receptor. In embodiments, administration of a disclosed formulation agonizes 5-HT<sub>2A</sub> receptors.

[294] In embodiments disclosed formulations comprise a compound that modulates the activity of a dopamine receptor (DR). In some such embodiments, disclosed formulations, when administered in a pharmacologically effective amount, are used to modulate the activity of a DR, such as to agonize or partially agonize any one or more of DRD1, DRD2, DRD3, DRD4, and DRD5.

[295] In embodiments, a disclosed formulation comprises a compound that acts on or modulates one or more membrane monoamine transporters, including any one or more of a serotonin membrane transporter (SERT), a dopamine membrane transporter (DAT), a norepinephrine membrane transporter (NET), and a vesicular monoamine transporter. Thus, in some embodiments, disclosed formulations are used to block the uptake activity of monoamine transporters. In embodiments, disclosed formulations are used to block the uptake activity of one or more of a serotonin transporter (SERT), dopamine transporter (DAT), and norepinephrine transporter (NET).

[296] In embodiments, a disclosed formulation comprises a compound that acts as a serotonin (5-HT) releaser (i.e., as a serotonin releasing agent (SRA), and that, e.g., induces the release of serotonin into the neuronal synaptic cleft), a dopamine (DA) releaser, and/or a norepinephrine (NE) releaser. In embodiments, a formulation comprises a compound that is a 5-HT releaser (i.e., a SRA). In embodiments, a formulation comprises a compound that is a selective 5-HT releaser, with less or no activity as to one or more other monoamine neurotransmitters (e.g., DA and/or NE), i.e., is a selective serotonin releasing agent (SSRA).

#### **b. Modulating Neuroplasticity**

[297] In embodiments, a disclosed formulation is used to increase neuroplasticity. Neuroplasticity (also, “neural plasticity” or “brain plasticity”), refers to the brain's ability to change and adapt in response to experiences, learning, and environmental factors. Neuroplasticity occurs through several mechanisms, including synaptic plasticity, involving the strengthening or weakening of connections (synapses) between neurons. Synaptic plasticity is often associated with learning and memory processes. Neuroplasticity also includes structural plasticity, involving changes in the physical structure of neurons, such as the growth of new dendritic branches or the formation of new synapses. In embodiments, increasing neuroplasticity contributes to the therapeutic effects of a disclosed formulation in a subject. In embodiments, increasing neuroplasticity by administering a formulation to a subject treats a disease or disorder in the subject.

[298] Neuroplasticity can be defined in terms of neuritogenesis, spinogenesis, and synaptogenesis in neurons. Neuritogenesis refers to the process by which neurons generate and extend their neurites (i.e., to form axons and dendrites). Neuritogenesis is a critical step in neural development and the formation of neuronal circuits. Spinogenesis refers to the formation of dendritic spines, which are small protrusions on the dendrites of neurons. Dendritic spines are crucial for synaptic connections and play a vital role in synaptic transmission and plasticity. Synaptogenesis refers to the formation of synapses, which is crucial for the establishment and refinement of neural circuits, and is a fundamental process underlying learning, memory,

and information processing in the brain.

[299] In embodiments, administration of a disclosed formulation increases neuritogenesis. Neuritogenesis can be measured in terms of total neurite length, maximum neurite length, number of neurite nodes, and/or number of neurite extremities. In embodiments, administration of a disclosed formulation increases total neurite length. In embodiments, administration of a disclosed formulation increases maximum neurite length. In embodiments, administration of a disclosed formulation increases the number of neurite nodes. In embodiments, administration of a disclosed formulation increases the number of neurite extremities.

[300] In embodiments, administration of a disclosed formulation to a subject results in an increase in the number of dendritic branches, the number of dendritic crossings, the density of dendritic spines, the density of synapses (i.e., number of synapses per neuron), or total dendritic length. These factors can be measured using a Sholl analysis and other techniques known to those of skill in the art (Ly et al. *ACS Pharmacol Transl Sci.* 2020;4(2):452-460).

### c. Treatment

[301] In embodiments, a disclosed formulation is used to treat a medical condition, such as a disease or a disorder. In embodiments, a disclosed formulation is used in the manufacture of a medicament to treat a condition, such as a disease or disorder. Also provided are methods of administering disclosed formulations to a subject having a condition, such as a disease or disorder, thereby treating said condition.

[302] In general, all of the disclosed formulations and methods will be appreciated to work for all individuals, although individual variation is to be expected, and will be readily appreciated. Where there is variation between individuals, modification to the disclosed methods will be understood based on the teachings herein in combination with general knowledge in the art. In embodiments, certain personalized approaches (i.e., "personalized" or "precision" medicine) may be utilized, based on individual characteristics, such as drug metabolism, further disclosure of which is provided elsewhere and also will be known in the art.

[303] In embodiments, a disclosed formulation is used to treat mental health disorders. In embodiments, disclosed formulations are administered, such as in a pharmacologically effective amount, to a subject having a mental health disorder, thereby treating said mental health disorder. In some methods herein, the disclosed formulations, when administered in a pharmacologically effective amount, provide beneficial therapeutic effects for the treatment of mental health disorders.

[304] In embodiments, a disclosed formulation is used to treat a central nervous system (CNS) disorder. Broadly, CNS disorders include diseases of the nervous system (e.g., movement disorders, neurodegenerative disorders) as well as mental, behavioral, and neurodevelopmental disorders, such as those in the DSM-5, Merck Manual, ICD-11, or other such diagnostic resources known to one of skill.

[305] In embodiments, a disclosed formulation is administered together with psychotherapy, such as psychosocial or behavioral therapy, including any of (or adapted from any of) cognitive behavioral therapy (e.g., as described in Crits-Christoph et al. *Arch Gen Psychiatry.* 1999; 56(6): 493-502), interpersonal

therapy (e.g., as described in Barry et al. *Psychol Addict Behav.* 2009; 23(1): 168-174), contingency management based therapy (e.g., as described in *id.*; in Petry et al. *J Consult Clin Psychol.* 2005; 73(2): 354-359; or in Adams et al. *Case Reports in Psychiatry.* 2012: 731638), motivational interviewing based therapy (e.g., as described in Stotts et al. *J Consult Clin Psychol.* 2001; 69(5): 858-862), meditation based therapy, such as transcendental meditation based therapy (e.g., as described in Rohsenow et al. *J Consult Clin Psychol.* 2000; 68(3): 515-520), or the therapeutic approach used by MAPS to treat subjects with PTSD (e.g., as in Mithoefer. *Manual for MDMA-Assisted Psychotherapy in the Treatment of Post-traumatic Stress Disorder.* 8th ed. MAPS; 2017 (“Mithoefer, 2017”).

[306] In embodiments, a disclosed formulation may be administered in conjunction with or as an adjunct to psychotherapy. In other embodiments, psychotherapy is neither necessitated nor desired, or no specific type of psychotherapy is necessitated or desired, however any of the disclosed methods can be used in combination with one or more psychotherapy sessions. The flexibility to participate in specific therapies, as well as to choose between any such therapies (or to decide to forgo any specific therapy), while still receiving clinically significant therapeutic effects, is among the advantages of the invention. Furthermore, a subject can participate in numerous other therapeutically beneficial activities, where such participation follows or is in conjunction with the administration of the composition, including breathing exercises, meditation and concentration practices, focusing on an object or mantra, listening to music, physical exercise, stretching or bodywork, journaling, grounding techniques, positive self-talk, or engaging with a pet or animal, and it should be understood that such participation can occur with or without the participation or guidance of a therapist.

[307] In embodiments, “psychotherapy” is specifically “psychedelic-assisted psychotherapy.” Psychedelic-assisted psychotherapy, broadly, includes a range of related approaches involving at least one session where the subject ingests a psychedelic and is monitored, supported, or otherwise engaged by one or more trained mental health professionals while under the effects of the psychedelic (see, e.g., Schenberg 2018). Protocols have been developed for the standardization of procedures which emphasize a high degree of care (see, e.g., Johnson et al. *J Psychopharmacol.* 2008; 22(6): 603-620), such as the therapeutic approach used by MAPS to treat subjects with PTSD using MDMA (e.g., as described in Mithoefer, 2017).

[308] In embodiments, the psychotherapy conducted with a disclosed formulation is conducted in widely spaced sessions. These sessions can be as frequently as weekly but are more often approximately monthly or less frequently. In most cases, a small number of sessions, on the order of one to three, is needed for a subject to experience significant clinical progress, as indicated, for example, by a reduction in the symptoms of the mental health disorder being treated. In embodiments, psychotherapy comprises multiple sessions, during some of which a disclosed formulation is administered (“drug-assisted psychotherapy”); in others, the subject participates in psychosocial or behavioral therapy without concomitant administration of a drug, or without administration of a disclosed formulation.

[309] In embodiments, a formulation is administered together with standardized psychological treatment or

support, which refers to any accepted modality of standard psychotherapy or counseling sessions, whether once a week, twice a week, or as needed; whether in person or virtual (e.g., over telemedicine or by means of a web program or mobile app); and whether with a human therapist or a virtual or AI “therapist.” Herein, “therapist” refers to a person who treats a subject using a disclosed formulation, whether that person is a psychiatrist, clinical psychologist, clinical therapist, registered therapist, psychotherapist, or other trained clinician, counselor, facilitator, or guide, although it is understood that certain requirements are appropriate to certain aspects of drug-assisted therapy (e.g., prescribing, dispensing, or administering a drug, offering psychotherapeutic support). In embodiments, a “person” may also include an AI.

[310] In embodiments, a disclosed formulation is administered together with psychotherapy, psychological support, or patient monitoring. In other embodiments, including where a disclosed formulation has a reduced risk of adverse events that would require clinician or other supervision, a formulation is administered without the need for such supervision, including without the requirement of psychotherapy, support, or monitoring.

[311] In some instances, certain personalized approaches (i.e., “personalized” or “precision” medicine) may be utilized, based on individual characteristics, including drug metabolism (e.g., CYP2D6 or CYP3A4) or individual genetic variation. “Genetic variation” refers to a change in a gene sequence relative to a reference sequence (e.g., a commonly-found and/or wild-type sequence). Genetic variation may be recombination events or mutations such as substitution/deletion/insertion events like point and splice site mutations.

[312] In embodiments, the genetic variation is a genetic variation in one or more cytochrome P450 (CYP or CYP450) enzymes that affects drug metabolism, including metabolism of a disclosed composition, and including CYP1A2, CYP2C9, CYP2D6, CYP2C19, CYP3A4 and CYP3A5. Other examples of CYP enzymes include CYP1A1, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, and CYP51.

[313] In embodiments, a disclosed composition is taken together with a compound that is metabolized by the same CYP enzyme(s) as the disclosed composition, so as to permit a lower dose to be taken, increase the effective bioavailability of one or both, or otherwise affect drug metabolism or pharmacokinetics. In embodiments, the dose of a disclosed composition is adjusted, such as reduced, when administered to a subject known to be a poor metabolizer of an active compound in the composition (e.g., having a genetic variation in CYP2D6 and/or CYP3A4), or increased when administered to a subject known to be a rapid metabolizer. In embodiments, a subject is tested using ordinary means known to those of skill to determine if the subject is a poor or rapid metabolizer for one or more such CYP enzymes.

[314] In embodiments, the genetic variation is a genetic variation in metabotropic glutamate receptor type 5 (mGluR5), which has been implicated in mood and anxiety symptoms in humans. In another embodiment,

the genetic variation is one or more single nucleotide polymorphisms (SNPs) in the FKBP5 gene that are associated with elevated levels of FKBP51 protein relative to persons lacking such SNPs. The FKBP5 gene has been implicated in responses to stress and trauma, and such SNPs are correlated with susceptibility to certain depression, PTSD, and anxiety disorders. In embodiments, a genetic variation is an inclusion criteria for the administration of a disclosed formulation. In embodiments, a genetic variation is an exclusion criteria for the administration of a disclosed formulation.

[315] In embodiments, the mammal being treated has altered epigenetic regulation of a gene, the expression of which is associated with a mental health condition or susceptibility to a mental health treatment, such as the SIGMAR1 gene for the non-opioid sigma-1 receptor.

**i. Mental, Behavioral, or Neurodevelopmental Disorders**

[316] In embodiments, a disclosed formulation is used to treat a mental, behavioral, or neurodevelopmental disorder. In embodiments, disclosed formulations are administered, such as in a therapeutically effective amount, to a subject having a mental, behavioral, or neurodevelopmental disorder, thereby treating said mental, behavioral, or neurodevelopmental disorder. In some methods herein, a disclosed composition, when administered in a therapeutically effective amount, provides beneficial therapeutic effects for the treatment of a mental, behavioral, or neurodevelopmental disorder.

[317] The ICD-11, which is incorporated by reference herein in its entirety, defines “mental, behavioral, or neurodevelopmental disorders” as syndromes characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes that underlie mental and behavioral functioning. Such disorders include, but are not limited to, neurodevelopmental disorders, schizophrenia or other primary psychotic disorders, catatonia, mood disorders, anxiety or fear-related disorders, obsessive-compulsive or related disorders, disorders specifically associated with stress, dissociative disorders, feeding (or eating) disorders, elimination disorders, disorders of bodily distress or bodily experience, disorders due to substance use or addictive behaviors, impulse control disorders, disruptive behavior or dissocial disorders, personality disorders (and related traits), paraphilic disorders, factitious disorders, neurocognitive disorders, mental or behavioral disorders associated with pregnancy, childbirth or the puerperium, sleep-wake disorders, sexual dysfunctions, and gender incongruence.

[318] A mental, behavioral, or neurodevelopmental disorder where otherwise undefined, will be understood to refer to the disorder as defined in the ICD-11. Within the category of mental, behavioral, or neurodevelopmental disorders, the term mental disorder (or “mental health disorder”) generally refers to a disease condition that involves negative changes in emotion, mood, thinking, and/or behavior. In general, mental health disorders are characterized by clinically significant disturbances in an individual's cognition, emotion, behavior, or a combination thereof, resulting in impaired functioning, distress, or increased risk of suffering. Although the terms “mental disorder” and “mental health disorder,” as well as terms that define

specific diseases and disorders, generally shall refer to the criteria in the ICD-11, or a subject with a diagnosis based thereon, it will be appreciated that methods are equally applicable to subjects having an equivalent underlying disorder, whether the disorder is diagnosed based on the criteria in ICD-11, ICD-10, DSM-5, or DSM-IV (each of which is incorporated by reference herein in its entirety) whether a diagnosis is based on other clinically acceptable criteria, or whether a subject has not yet had a formal clinical diagnosis.

[319] In embodiments, a disclosed formulation is used to treat a mental health disorder. In embodiments, disclosed formulations are administered, such as in a therapeutically effective amount, to a subject having a mental health disorder, thereby treating said mental health disorder. In some methods herein, a disclosed composition, when administered in a therapeutically effective amount, provides beneficial therapeutic effects for the treatment of a mental health disorder. In embodiments, a disclosed formulation is used to reduce the symptoms of a mental health disorder. The symptoms of the mental health disorder to be treated shall be able to be determined by one of skill, by reference to the general knowledge in the art regarding the disorder.

[320] In embodiments, measures of therapeutic efficacy include reports by a subject or an observer. In embodiments, measures of therapeutic efficacy include responses to a questionnaire. Non-limiting representative examples of applicable measures of symptom improvement include the Generalized Anxiety Disorder Scale-7 (GAD-7), Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment of Functioning (GAF) Scale, Clinical Global Impression (CGI), Substance Abuse Questionnaire (SAQ), Mini International Neuropsychiatric Interview 5 (MINI 5), Columbia Suicide Severity Rating Scale (C-SSRS), Patient Health Questionnaire (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), Interpersonal Reactivity Index (IRI), Short Form (36) Health Survey (SF-36), Self-Compassion Scale (SCS), Trauma History Questionnaire (THQ), Beck Depression Index (BDI), and related subject- or observer-reported measures.

[321] In embodiments, a disclosed formulation is used to treat a neurodevelopmental disorder. In embodiments, a “neurodevelopmental disorder” is a neurological and/or cognitive disorder that arises during the developmental period that involves significant difficulties in the acquisition and execution of specific neurological functions (e.g., intellectual, motor, language, or social functions). In embodiments, the neurodevelopmental disorder is a disorder of intellectual development, a developmental speech or language disorder, autism spectrum disorder, a developmental learning disorder, a developmental motor coordination disorder, attention deficit hyperactivity disorder, or stereotypic movement disorder.

[322] In embodiments, a disclosed formulation is used to treat schizophrenia or another primary psychotic disorder. In general, these disorders are characterized by significant impairments in reality and alterations in behavior manifest in positive symptoms like persistent delusions, persistent hallucinations, disorganized thinking and speech, grossly disorganized behavior, as well as experience of negative symptoms such as blunted or flat affect and avolition and psychomotor disturbances. In embodiments, a disclosed formulation is used to treat schizophrenia, schizoaffective disorder, schizotypal disorder, acute and transient psychotic disorder, delusional disorder, or a substance-induced psychotic disorder.

[323] In embodiments, a disclosed formulation is used to treat catatonia. In embodiments, “catatonia” refers to a category of syndromes characterized by the co-occurrence of several symptoms of decreased, increased, or abnormal psychomotor activity. In embodiments, the catatonia is associated with another mental disorder. In embodiments, the catatonia is induced by substances or medications.

[324] In embodiments, a disclosed formulation is used to treat a mood disorder. As defined in the ICD-11, mood disorders are categorized according to the specific type(s) of mood episodes, and their pattern over time. The primary types of mood episodes are depressive episodes, manic episodes, mixed episodes, and hypomanic episodes. In embodiments, the mood disorder is a bipolar or related disorder (e.g., bipolar type I disorder, bipolar type II disorder, cyclothymic disorder), a depressive disorder, or a substance-induced mood disorder. In embodiments, the mood disorder is a depressive disorder. In embodiments, the depressive disorder is single-episode depressive disorder, major depressive episode disorder, persistent depressive disorder (formally known as dysthymia), disruptive mood dysregulation disorder, premenstrual dysphoric disorder, postpartum depression, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, seasonal affective disorder, mixed depressive and anxiety disorder, or an unspecified depressive disorder. In embodiments, depression is assessed through the Patient Health Questionnaire-9 (PHQ-9) screening tool, Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale, Beck Depression Inventory (BDI-II), Zung Self-Rating Depression Scales (SDS), Major Depression Inventory (MDI), Center for Epidemiologic Studies Depression Scale (CED-D), Rome Depression Inventory (RDI), Hamilton Rating Scale for Depression (HRSD), and Carroll Rating Scale (CRS).

[325] In embodiments, a disclosed formulation is used to treat an anxiety or fear-related disorder. An “anxiety disorder” refers to a class of mental disorders that induce excessive or abnormal fear, dread, or worry. In embodiments, the anxiety disorder is selected from the group consisting of generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, social anxiety disorder, separation anxiety disorder, selective mutism, or a substance-induced anxiety disorder.

[326] In embodiments, a disclosed formulation is used to treat an obsessive-compulsive or related disorder. In general, these disorders are characterized by repetitive thoughts and behaviors, such as cognitive phenomena (obsessions, intrusive thoughts and preoccupations). In embodiments, the disorder is characterized by a compulsive need to accumulate possessions and distress related to discarding them (i.e., hoarding disorder). In embodiments, the disorder is body-focused and can be characterized by recurrent and habitual actions (hair-pulling, skin-picking). In embodiments, the disorder is obsessive-compulsive disorder, body dysmorphic disorder, olfactory reference disorder, hypochondriasis, hoarding disorder, a body-focused repetitive behavior disorder, or a substance-induced obsessive-compulsive disorder.

[327] In embodiments, a disclosed formulation is used to treat a disorder associated with stress. In embodiments, the disorder associated with stress has an identifiable stressor that is a causal factor, like exposure to a stressful or traumatic event, or a series of such events or adverse experiences. Stressors may

be within the normal range of life experiences (e.g., divorce, socioeconomic problems), or from a threatening or traumatizing experience. In general, the nature and duration of the symptoms that arise in response to the stressor can distinguish the disorder from everyday stress. In embodiments, a disclosed formulation is used to treat post-traumatic stress disorder, complex post-traumatic stress disorder, prolonged grief disorder, adjustment disorder, reactive attachment disorder, or disinhibited social engagement disorder.

[328] In embodiments, a disclosed formulation is used to treat a dissociative disorder. Dissociative disorders can be characterized by involuntary disruption or discontinuity in the normal integration of one or more of the following: identity, sensations, perceptions, affects, thoughts, memories, control over body movements, or behavior. In some subjects, dissociative disorder symptoms can be severe, and may result in impairment in personal, social, educational, occupational or other areas of functioning. In embodiments, a disclosed formulation is used to treat dissociative neurological symptom disorder, dissociative amnesia (including amnesia with dissociative fugue and without dissociative fugue), trance disorder, possession trance disorder, dissociative identity disorder, partial dissociative identity disorder, or depersonalization-derealization disorder.

[329] In embodiments, a disclosed formulation is used to treat a feeding or eating disorder. Feeding or eating disorders generally involve abnormal eating or feeding behaviors that are not explained by another health condition, and are not developmentally appropriate or culturally sanctioned. These disorders can involve preoccupation with food as well as body weight and shape concerns. In embodiments, a disclosed formulation is used to treat anorexia nervosa (including anorexia with significantly low body weight, anorexia with dangerously low body weight, or anorexia in recovery with normal body weight), bulimia nervosa, binge eating disorder, avoidant-restrictive food intake disorder, pica, or rumination-regurgitation disorder.

[330] In embodiments, a disclosed formulation is used to treat an elimination disorder. Elimination disorders include, for example, the repeated voiding of urine into clothes or bed, and the repeated passage of feces in inappropriate places once the individual has reached a developmental age when continence is ordinarily expected. In embodiments, a disclosed formulation is used to treat enuresis (including nocturnal enuresis, diurnal enuresis, and nocturnal and diurnal enuresis) or encopresis (including both with encopresis constipation or overflow incontinence, and encopresis without constipation or overflow incontinence).

[331] In embodiments, a disclosed formulation is used to treat a disorder of bodily distress or bodily experience. Disorders of bodily stress typically involve bodily symptoms that the subject finds distressing and to which the subject devotes excessive attention. Bodily integrity dysphoria typically involves a disturbance in the person's experience of the body manifested by persistent discomfort or intense feelings of body configuration. In embodiments, a disclosed formulation is used to treat a bodily distress disorder (including mild, moderate, and severe bodily distress disorder) or body integrity dysphoria.

[332] In embodiments, a disclosed formulation is used to treat a disorder due to substance use or addictive behaviors. Disorders due to substance use or addictive behaviors are mental and/or behavioral

disorders that develop predominantly as a result of the use of psychoactive substances (including medications and illegal or illicit substances), or specific repetitive rewarding and reinforcing behaviors. In embodiments, a disclosed formulation is used to treat disorders due to substance use (i.e., a substance use disorder, or SUD). In embodiments, the substance use disorder is associated with alcohol, cannabis, synthetic cannabinoids, opioids, sedatives, hypnotics or anxiolytics, cocaine, stimulants (e.g., amphetamines, methamphetamines, methcathinone, synthetic cathinones, caffeine), hallucinogens, nicotine, volatile inhalants, MDMA or MDA, dissociative drugs like ketamine and phencyclidine, or another substance (including medications and non-psychoactive substances). In embodiments, the substance use disorder is selected from alcohol use disorder, cannabis use disorder, caffeine use disorder, phencyclidine use disorder, inhalants use disorder, opioids use disorder, sedatives use disorder, hypnotics use disorder, anxiolytics use disorder, stimulants use disorder, and tobacco use disorder. In embodiments, the substance use disorder is alcohol use disorder (AUD). In embodiments, the substance use disorder is cannabis use disorder. In embodiments, the substance use disorder is caffeine use disorder. In embodiments, the substance use disorder is phencyclidine use disorder. In embodiments, the substance use disorder is inhalant use disorder. In embodiments, the substance use disorder is opioids use disorder. In embodiments, the substance use disorder is sedatives use disorder. In embodiments, the substance use disorder is hypnotics use disorder. In embodiments, the substance use disorder is anxiolytics use disorder. In embodiments, the substance use disorder is stimulants use disorder. In embodiments, the substance use disorder is tobacco use disorder. In embodiments, the substance use disorder is alcohol use disorder, wherein said alcohol use disorder is selected from alcohol abuse, alcohol dependence, and alcoholism. In embodiments, the disorder is associated with another addictive behavior (e.g., gambling disorders, gaming disorder).

[333] In embodiments, a substance use disorder can be screened using a Screening to Brief Intervention (S2BI), Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), Brief Screener for Alcohol, Tobacco, and other Drugs (BSTAD), Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS), the Opioid Risk Tool - OUD (ORT-OUD) Chart, Drug Abuse Screen Test (DAST-10), and Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS).

[334] In embodiments, a disclosed formulation is used to treat an impulse control disorder. In general, impulse control disorders are characterized by the repeated failure to resist an impulse, drive, or urge to perform an act that is rewarding to the subject despite negative long-term consequences, such as harm to the subject or a significant impairment in important areas of the subject's functioning. In embodiments, impulse control behaviors include fire-setting, stealing, inappropriate sexual behavior, and explosive outbursts. In embodiments, a disclosed formulation is used to treat pyromania, kleptomania, compulsive sexual behavior disorder, or intermittent explosive disorder.

[335] In embodiments, a disclosed formulation is used to treat a disruptive behavior disorder or a dissocial disorder. Such disorders may be broadly characterized by persistent behavior problems that range from

persistently defiant, disobedient, provocative or spiteful behaviors to behaviors that violate the rights of others or norms, rules, or laws. In embodiments, a disclosed formulation is used to treat oppositional defiant disorder (including oppositional defiant disorder with chronic irritability-anger and oppositional defiant disorder without chronic irritability-anger) or conduct-dissocial disorder (including childhood-onset conduct-dissocial disorder and adolescent-onset conduct-dissocial disorder).

[336] In embodiments, a disclosed formulation is used to treat a personality disorder. Personality disorders may be generally characterized by problems in perceiving one's identity, self-worth, accuracy of self-view, and self-discretion that is manifest in patterns of cognition, emotional experience, emotional expression, and maladaptive behavior. In embodiments, a disclosed formulation is used to treat a mild, moderate, or severe personality disorder. In embodiments, a disclosed formulation is used to treat a prominent personality trait or patterns (e.g., negative affectivity, detachment, dissociation, disinhibition, anankastia, borderline pattern).

[337] In embodiments, the personality disorder is antisocial personality disorder, avoidant personality disorder, borderline personality disorder, dependent personality disorder, histrionic personality disorder, masochistic or sadistic behavior, narcissistic personality disorder, obsessive-compulsive personality disorder, paranoid personality disorder, psychopathy, sociopathy, schizoid personality disorder, or schizotypal personality disorder.

[338] In embodiments, a disclosed formulation is used to treat a paraphilic disorder. Paraphilic disorders can be characterized by persistent and intense patterns of atypical sexual arousal, the focus of which involves others whose age or status renders them unwilling or unable to consent. In embodiments, a disclosed formulation is used to treat exhibitionistic disorder, voyeuristic disorder, pedophilic disorder, coercive sexual sadism disorder, frotteuristic disorder, other paraphilic disorders involving non-consenting individuals, or paraphilic disorders involving solitary behavior or consenting individuals.

[339] In embodiments, a disclosed formulation is used to treat a factitious disorder. In general, factitious disorders may be characterized by intentionally feigning, falsifying, inducing or aggravating medical, psychological, or behavior signs and symptoms or injury to oneself or another person. Subjects with factitious disorders may seek treatment or otherwise present themselves or another person as ill, injured, or impaired. In embodiments, a disclosed formulation is used to treat factitious disorder imposed on self or a factitious disorder imposed on another.

[340] In embodiments, a disclosed formulation is used to treat a neurocognitive disorder. Neurocognitive disorders may be characterized by primary clinical defects in cognitive functioning that are acquired (rather than developmental), and therefore the subject experiences a decline from a previously attained level of functioning. In embodiments, a disclosed formulation is used to treat delirium. In embodiments, the delirium is associated with another disease or disorder. In embodiments, the delirium is associated with a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed formulation is used to treat mild neurocognitive disorder. In embodiments, a disclosed formulation is used to

treat an amnestic disorder. In embodiments, the amnestic disorder is associated with another disease or disorder. In embodiments, the delirium is associated with a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed formulation is used to treat dementia. In embodiments, the dementia is associated with Alzheimer's disease, Parkinson's disease, cerebrovascular disease, Lewy body disease, a psychoactive substance (including medications and illicit or illegal substances). In embodiments, a disclosed formulation is used to treat a behavioral or psychological disturbance associated with dementia. In embodiments, dementia is assessed using a Functional Activities Questionnaire (FAQ), Ascertain Dementia 8 (AD8), Mini-Cog, Mini-Mental State Exam (MMSE), the Montreal Cognitive Assessment (MoCA), and the Neuropsychiatric Inventory Questionnaire (NPI-Q).

[341] In embodiments, a disclosed formulation is used to treat a mental or behavioral disorder associated with pregnancy, childbirth, or the puerperium. In embodiments, the syndrome associated with pregnancy or the puerperium involves significant mental and behavioral features, including a depressive symptom. In embodiments, the disorder includes psychotic symptoms. In embodiments, a disclosed formulation is used to treat mental or behavioral disorders associated with pregnancy, childbirth or the puerperium, with psychotic symptoms. In embodiments, a disclosed formulation is used to treat mental or behavioral disorders associated with pregnancy, childbirth or the puerperium, without psychotic symptoms.

[342] In embodiments, a disclosed formulation is used to treat a sleep-wake disorder. In general, sleep-wake disorders are associated with difficulty initiating or maintaining sleep (e.g., insomnia), excessive sleepiness (e.g., hypersomnolence disorders), respiratory disturbance during sleep (e.g., sleep-related breathing disorders (SRBDs), such as obstructive sleep apnea (OSA), central sleep apnea (CSA), sleep-related hypoventilation disorders, sleep-related hypoxemia disorder, snoring, catathrenia, Cheyne-Stokes breathing, and sleep-disordered breathing), disorders of the sleep-wake schedule (e.g., circadian rhythm sleep-wake disorders), abnormal movements during sleep, or problematic behavioral or psychological events that occur while falling asleep, during sleep, or upon arousal from sleep (e.g., parasomnia disorders). In embodiments, a disclosed formulation is used to treat an insomnia disorder, a hypersomnolence disorder, a sleep-related breathing disorder, a circadian rhythm sleep-wake disorder, or a parasomnia disorder.

[343] In embodiments, a disclosed formulation is used to treat sexual dysfunction. Sexual dysfunctions can be defined as syndromes wherein a subject may have difficulty experiencing personally satisfying, non-coercive sexual activities. In embodiments, a disclosed formulation is used to treat hypoactive sexual desire dysfunction, sexual arousal dysfunction, orgasmic dysfunction, ejaculatory dysfunction, or sexual dysfunction associated with pelvic organ prolapse.

## ii. Neurodegenerative Disorders

[344] In embodiments, a disclosed formulation is used to treat a neurodegenerative disorder. In embodiments, disclosed formulations are administered, such as in a therapeutically effective amount, to a subject having a neurodegenerative disorder. In some methods herein, a disclosed composition, when

administered in a therapeutically effective amount, provides beneficial therapeutic effects for the treatment of a neurodegenerative disorder.

[345] The term “neurodegenerative disorder” refers to a class of progressive, chronic, and debilitating conditions characterized by the gradual loss of structure and function of neurons within the central nervous system (CNS) or peripheral nervous system (PNS). These disorders involve the degeneration, impairment, or death of neuronal cells, leading to a decline in cognitive, motor, and/or sensory abilities.

[346] Neurodegenerative disorders can be classified according to primary clinical features, e.g., dementia, parkinsonism, or motor neuron disease, anatomic distribution of neurodegeneration, e.g., frontotemporal degenerations, extrapyramidal disorders, or spinocerebellar degenerations, or principal molecular abnormality (Dugger & Dickson. *Cold Spring Harb Perspect Biol.* 2017; 9(7): a028035). These disorders may involve various etiologies, including but not limited to, presence of pathogenic proteins, age, environmental stressors, and genetic predisposition (Armstrong. *Folia Neuropathol.* 2020; 58(2): 93-112).

[347] In embodiments, the neurodegenerative disorder is selected from the group consisting of Alzheimer’s disease, amyotrophic lateral sclerosis or Charcot’s disease, chronic traumatic encephalopathy, corticobasal degeneration, dementias including vascular dementia, Huntington’s disease, Lytico-Bodig disease, mild cognitive impairment, multiple sclerosis, a motor neuron disease, neuromyelitis optica spectrum disorder, Parkinson’s disease or Parkinsonisms, prion diseases, progressive supranuclear palsy, and traumatic brain injury.

### iii. Pain and Inflammatory Disorders

[348] In embodiments, a disclosed formulation is used to treat pain and/or inflammation, such as a pain disorder and/or an inflammatory disorder. In embodiments, a disclosed formulation is administered, such as in a pharmacologically effective amount, to a subject having pain and/or inflammation, thereby treating said pain and/or inflammation. In some methods, a disclosed composition, when administered in a pharmacologically effective amount, provides beneficial therapeutic effects for the treatment of pain and/or inflammation.

[349] In embodiments, a disclosed formulation is used to treat a pain disorder. In embodiments, the pain disorder is any of arthritis, allodynia, atypical trigeminal neuralgia, trigeminal neuralgia, somatoform disorder, hypoesthesia, hyperalgesia, neuralgia, neuritis, neurogenic pain, phantom limb pain, analgesia, anesthesia dolorosa, causalgia, sciatic nerve pain disorder, degenerative joint disorder, fibromyalgia, visceral disease, chronic pain disorders, headache disorders, migraine headaches, chronic cluster headaches, concussion headache, short-lasting unilateral neuralgiform headache attacks, chronic fatigue syndrome, complex regional pain syndrome, neurodystrophy, plantar fasciitis, or pain associated with cancer.

[350] In embodiments, a disclosed formulation is used to treat an inflammatory disorder. In embodiments, the inflammatory disorder is characterized by inflammation of an organ or tissue. In embodiments, the inflammatory disorder comprises any one or more of skin inflammation, muscle inflammation, tendon

inflammation, ligament inflammation, bone inflammation, cartilage inflammation, lung inflammation, heart inflammation, liver inflammation, pancreatic inflammation, kidney inflammation, bladder inflammation, gastric inflammation, intestinal inflammation, neuroinflammation, and brain inflammation. In embodiments, the inflammatory disorder is a disorder that causes acute inflammation, or that exhibits chronic inflammation as a symptom. In embodiments, the inflammatory disorder comprises chronic inflammation.

[351] In embodiments, a disclosed formulation is used to reduce inflammation. In embodiments, a disclosed formulation is used in the manufacture of a medicament to reduce inflammation. In embodiments, a disclosed formulation, e.g., in a therapeutically effective amount, is administered to a subject to reduce inflammation.

[352] The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Although the mechanism for serotonin modulators, such as 5-HT<sub>2A</sub> agonists and 5-HT<sub>2A</sub> antagonists, to ameliorate pain remains unclear, the synaptic plasticity associated with such compounds may alter pathologic changes in neural connections seen in chronic pain states, potentially resulting in a reduced pain intensity and duration (Castellanos et al. *Reg Anesth Pain Med*. 2020; 45(7): 486-494). Additionally, 5-HT<sub>2A</sub> activation has been shown to promote anti-inflammatory effects, e.g., a reduction of TNF- $\alpha$ -induced inflammation. See, e.g., Pelletier & Siegel. *Mol Interv*. 2009; 9(6): 299-301, Flanagan et al. *Sci Rep*. 2019; 9(1): 13444, Nichols et al. *Clin Pharmacol Ther*. 2017; 101(2): 209-219; Flanagan et al. *Int Rev Psychiatry*. 2018; 30(4): 363-375, Okamoto et al. *Neurosci*. 2005; 130(2): 465-74.

[353] Pain, such as chronic pain, and improvements thereof, such as a reduction of symptoms, may be measured according to known methods, e.g., by subject reporting, pain diaries, pain scales, applicable questionnaires (assessments of chronic pain and its impact on physical, emotional and social functions), ecological momentary assessments and computerized versions thereof. See, e.g., Salaffi et al. *Best Practice & Research Clinic Rheumatol*. 2015; 29(1): 164-186 and Hawker et al. *Arthritis Care Res (Hoboken)*. 2011; 63 Suppl 11: S240-52. Exemplary questionnaires include the Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP), Migraine Diagnosis Questionnaire, the Migraine-Screen Questionnaire (MS-Q), the Fibromyalgia Survey Questionnaire (FSQ).

[354] A reduction in inflammation, such as chronic systemic inflammation, may be measured according to various methods available to one of skill. Inflammatory biomarkers may be detected from biological specimens, for example, a subject's blood, such as plasma or serum, or saliva. In one example, inflammation may be detected by measuring high-sensitivity C-reactive protein (CRP) and white blood cell count from a blood test. CRP may also be detected in a saliva sample. Salivary CRP is not synthesized locally in the mouth and may reflect more systemic levels of inflammation compared to other inflammatory biomarkers,

such as cytokines (Szabo & Slavish. *Psychoneuroendocrinology*. 202; 124: 105069). Additionally clinical pathology data, e.g., hematology data on erythrocyte parameters, platelet count, total number of leukocytes, and leukocyte differentials and morphology, coagulation data on clotting times and fibrinogen, and clinical chemistry data on total protein, albumin and globulin, liver enzymes, renal parameters, electrolytes, and bilirubin can provide an initial indication of the presence and potentially the location of inflammation, in the absence of specific data on immune tissues. See, e.g., Germolec et al. *Methods Mol Biol*. 2018; 1803: 57-79 and Luo et al. *Clin Lab*. 2019;65(3):10.7754/Clin.Lab.2018.180715.

### G. Examples

[355] The following examples are included for illustrative purposes only and are not intended to limit the scope of the disclosure.

#### Example 1: Preparation of Exemplary Sublingual Spray Formulations

[356] Sublingual spray formulations are prepared by mixing the indicated components until, for example, a clear solution is formed, indicating complete dissolution of the formulation constituents. All amounts for ingredients in exemplary formulations below are per 1.0 mL. CD = cyclodextrin; PG = propylene glycol.

[357] Formulation 1: 100 mg psilocin, 555 mg  $\beta$ -CD, and water q.s. to 1.0 mL.

[358] Formulation 2: 100 mg psilocin, 555 mg  $\beta$ -CD, 0.3 mL PG, and water q.s. to 1.0 mL.

[359] Formulation 3: 50 mg psilocin, 278 mg  $\beta$ -CD, 100 mg flavoring agent(s), 0.3 mL PG, and water q.s. to 1.0 mL.

[360] Formulation 4: 100 mg psilocin, 315 mg lecithin, 10 mg D- $\alpha$ -tocopherol, 50 mg L-menthol, and water q.s. to 1.0 mL.

[361] Formulation 5: 100 mg MDMA, 670 mg gamma-CD, and water q.s. to 1.0 mL.

[362] Formulation 6: 1 mg LSD, 21 mg alpha-CD, 0.3 mL PG, and water q.s. to 1.0 mL.

[363] Formulation 7: 150 mg DMT, 150 mg xylitol, 100 mg HMC, 0.3 mL PG, and water q.s. to 1.0 mL.

[364] It will be appreciated that the above formulation examples are illustrative only. Other formulation examples follow, which also shall be understood to be non-limiting of the formulations of the disclosure.

[365] In embodiments, a sublingual spray formulation comprises any of psilocin,  $\beta$ -cyclodextrin USP, a modified  $\beta$ -cyclodextrin USP, propylene glycol USP, xanthan gum NF (e.g., XANTURAL® 75), xylitol BP, rosmarinic acid, polysorbate 80 USP/NF, menthol USP, and purified water, or a combination thereof.

[366] In embodiments, a sublingual spray formulation comprises any of psilocin,  $\beta$ -cyclodextrin USP, a modified  $\beta$ -cyclodextrin USP, propylene glycol USP, carbomer homopolymer type B USP NF (e.g., CARBOPOL® 974P NF), triethanolamine, xylitol BP, rosmarinic acid, polysorbate 80 USP/NF, menthol USP, and purified water, or a combination thereof.

[367] In embodiments, a sublingual spray formulation comprises psilocin,  $\beta$ -cyclodextrin USP, propylene glycol USP, xanthan gum NF (e.g., XANTURAL® 75), xylitol BP, rosmarinic acid, and purified water.

[368] In embodiments, a sublingual spray formulation comprises psilocin, a modified  $\beta$ -cyclodextrin USP,

propylene glycol USP, xanthan gum NF (e.g., XANTURAL® 75), xylitol BP, rosmarinic acid, polysorbate 80 USP/NF, menthol USP, and purified water.

[369] In embodiments, a sublingual spray formulation comprises psilocin,  $\beta$ -cyclodextrin USP, propylene glycol USP, carbomer homopolymer type B USP NF (e.g., CARBOPOL® 974P NF), triethanolamine, xylitol BP, rosmarinic acid, and purified water.

[370] In embodiments, a sublingual spray formulation comprises psilocin, a modified  $\beta$ -cyclodextrin USP, propylene glycol USP, carbomer homopolymer type B USP NF (e.g., CARBOPOL® 974P NF), triethanolamine, xylitol BP, rosmarinic acid, polysorbate 80 USP/NF, menthol USP, and purified water.

[371] In embodiments, a sublingual spray formulation comprises psilocin,  $\beta$ -cyclodextrin USP, propylene glycol USP, XANTURAL® 75, xylitol BP, rosmarinic acid, and purified water.

[372] In embodiments, a sublingual spray formulation comprises psilocin, a modified  $\beta$ -cyclodextrin USP, propylene glycol USP, XANTURAL® 75, xylitol BP, rosmarinic acid, polysorbate 80 USP/NF, menthol USP, and purified water.

[373] In embodiments, a sublingual spray formulation comprises psilocin,  $\beta$ -cyclodextrin USP, propylene glycol USP, CARBOPOL® 974P NF, triethanolamine, xylitol BP, rosmarinic acid, and purified water.

[374] In embodiments, a sublingual spray formulation comprises psilocin, a modified  $\beta$ -cyclodextrin USP, propylene glycol USP, CARBOPOL® 974P NF, triethanolamine, xylitol BP, rosmarinic acid, polysorbate 80 USP/NF, menthol USP, and purified water.

[375] In some preferred embodiments, the modified  $\beta$ -cyclodextrin is sulfobutylether  $\beta$ -cyclodextrin.

[376] In embodiments, the mucoadhesive polymer is xanthan gum or CARBOPOL® 974P NF. In embodiments, the mucoadhesive polymer is not chitosan. In some embodiments where the mucoadhesive polymer is xanthan gum or CARBOPOL® 974P NF, the disclosed formulation further comprises an alkaline agent, such as for pH neutralization. In embodiments, the taste-masking agent is xylitol or menthol. In some embodiments, where the taste-masking agent is insoluble in water, such as menthol, the taste-masking is first dissolved, e.g., in polysorbate-80. In embodiments, the antioxidant is rosmarinic acid or  $\alpha$ -tocopherol. In embodiments, the antioxidant is not insoluble in water. In embodiments, the antioxidant is not  $\alpha$ -tocopherol.

[377] In other exemplary embodiments, a disclosed compound in any of the above examples (e.g., a psychedelic compound, such as a tryptamine, phenethylamine, or lysergamide) will be appreciated to include, and may be substituted with, another disclosed compound (e.g., another psychedelic compound, such as another tryptamine, phenethylamine, or lysergamide), with other variations as known in view of this disclosure. Likewise, the other ingredients disclosed in the above formulation examples may be substituted with any other disclosed ingredients of the same class and their equivalents, with amounts adjusted as would be known by reference to this disclosure and ordinary skill in the art. Hence, reference to particular compounds and ingredients is understood as merely illustrative, and both active and inactive agents in any Example may be substituted by other disclosed compounds or their equivalents. Any disclosed formulation

examples therefore are not limited to the specific compounds and ingredients listed, or limited to a single ingredient of any class alone, but may also include other ingredients and compounds, both active and inactive, of any of the disclosed classes, as well as additional ingredients or agents of one or more other classes, including additional active and/or inactive agents or compounds.

[378] For any of the psychedelic compounds or other compounds or ingredients disclosed herein, substitution of the compound by its ion, free base, salt form, polymorph, hydrate or solvate form, co-crystal, or an isomer or enantiomerically enriched mixture, shall be an alternative embodiment within the scope of the disclosure (with modifications to the formulation and dose amounts made according to the teachings herein and ordinary skill, if necessary or desired).

[379] An alternative formulation of every formulation disclosed herein is the same formulation, consisting only of the disclosed and listed compounds and ingredients. An alternative formulation of every formulation disclosed herein is the same formulation, consisting essentially of the disclosed and listed compounds and ingredients. All other formulations within the scope of the disclosure, unless expressly described or claimed otherwise, should be understood to comprise the disclosed and listed compounds and ingredients, and thus be open-ended and in embodiments may include additional active or inactive compounds and ingredients.

#### **Example 2: Solution Stability of Compounds in Disclosed Formulations**

[380] The solution stability of compounds in disclosed sublingual spray formulations is determined according to methods known to those of skill. For example, in disclosed formulations wherein the compound is psilocin, relevant decomposition products, such as oxidation products, or oligomers formed by oxidative coupling (such as oxidative dimerization) are characterized according to known methods (Lenz et al. *Chem Eur J.* 2021; 27: 12166-12171). Results can show that disclosed formulations impart improved solution stability and/or increased resistance to oxidative decomposition to compounds contained therein.

#### **Example 3: Solubility Screening of Compounds in Disclosed Formulations**

[381] The solubility of disclosed sublingual spray formulations is determined according to methods known to those of ordinary skill. For example, in disclosed formulations wherein the compound is psilocin, relevant cosolvents (for example, lecithin, propylene glycol, xanthan gum, and cyclodextrin), solubilization excipients, pH adjustment factors, and water-soluble technologies are characterized according to known methods, such as through kinetic (microfiltration, centrifugation, precipitative) and thermodynamic (saturation, dissolution, potentiometric) methods. (Könczöl & Dargó. *Drug Discov Today Technol.* 2018; 27: 3-10). Results can show that disclosed formulations impart improved solution solubility of compounds contained therein at a variety of dose concentrations. Solubility studies are performed with gradual increments of, e.g., psilocin in a given solvent to determine saturation solubility. Saturation solubility helps determine the highest, e.g., psilocin concentration which can be achieved using a specific solvent.

#### **Example 4: Compatibility Screening of Compounds and Excipients in Formulations**

[382] The compatibility of disclosed sublingual spray formulations is determined according to methods

known to those of ordinary skill. For example, in disclosed formulations wherein the compound is psilocin, excipient-excipient and excipient-psilocin compatibilities are characterized according to known methods, such as Differential Scanning Calorimetry (DSC), isothermal stress testing-Fourier transform infrared spectroscopy (FTIR), and powder X-ray diffraction (PXPD). (Skoog, Holler, & Nieman. *Principles of Instrumental Analysis*. 5th ed. Brooks Cole; 1985) For example, comparing psilocin and excipients via DSC curves, peaks, and other enthalpy variations can indicate the presence of an interaction. (Rosasco et al. *J Therm Anal Calorim*. 2018; 134: 1929-1941) Isothermal stress testing can be performed to determine psilocin content through a variety of psilocin-excipient blends (Marothu et al. *Annales Pharm Franç*. 2015: 442-451). PXPD can be utilized to identify modifications to the crystalline structure of psilocin when in the presence of excipients. (Thakral et al. *J Pharm Sciences*. 2018; 107(12): 2969-2982) Results can show that disclosed formulations impart improved compatibility of compounds and excipients contained therein.

#### **Example 5: *In vitro* Mucosal Properties of Disclosed Formulations**

[383] The mucosal properties of disclosed sublingual spray formulations are determined according to methods known to those of ordinary skill. Such methods can be *in vitro* methods. For example, mucosal properties can be characterized according to known methods, such as animal buccal mucosal models (human, rat, hamster, chicken, sheep, cow, dog, rabbit, monkey, porcine), animal non-buccal mucosal models (esophageal, chorioallantoic, mouth floor, vaginal), diffusion cell models (cheek, TR146, EpiOralR™), and bionic barrier models (PAMPA, PVPA, Permeapad®, AMI-system) (Wang et al. *J Drug Deliv Sci Technol*. 2021; 61: 102122). Results can show that disclosed formulations impart improved mucosal delivery properties such as reduced irritation and increased permeation of compounds contained therein.

#### **Example 6: Accelerated Stability of Compounds in Disclosed Formulations**

[384] The stability of disclosed sublingual spray formulations is determined according to methods known to those of ordinary skill. The stability can be tested via accelerated stability methods, which are designed to increase the rate of chemical and physical degradation to reduce the time required to achieve results from traditional stability testing. For example, accelerated stability can be studied for a predetermined amount of time under International Council for Harmonisation (ICH) conditions (see, e.g., ICH Q1A(R2), ICH Q1B, and ICH QA Guidelines). Results can show that disclosed formulations impart improved stability of compounds contained therein in an accelerated stability assay.

#### **Example 7: Spray Plume Characteristics of Compounds in Disclosed Formulations**

[385] The spray plume disclosed sublingual spray formulations is determined according to methods known to those of ordinary skill. For example, spray plume can be studied using a system such as SprayView™, a combination of laser lights, high-speed cameras, and spray pattern analysis algorithms (Smyth et al. *Pharm Res*. 2006; 23: 1591-1596). Results can show that spray plume characteristics of disclosed formulations promote absorption of compounds contained therein.

**Example 8: Initial Development of Disclosed Sublingual Spray Formulations**

[386] Initial development of psilocin sublingual spray formulations was conducted, with an aim to develop formulations that could be tested to determine whether the solubility of psilocin could be increased above its normal water solubility of ca. 4 mg/mL. Proposed formulations were developed for testing, with  $\beta$ -cyclodextrin ( $\beta$ -CD) and a modified  $\beta$ -cyclodextrin (sulfobutylether  $\beta$ -cyclodextrin, SBE- $\beta$ -CD) to enhance solubility.

[387] Development is designed around dosage delivery requirements and the goals of, inter alia, increasing psilocin solubility and maintaining or increasing psilocin stability. A sublingual spray with a low dose volume and a high psilocin concentration is desired, which is understood to have remained out of reach despite other efforts. Certain other non-limiting parameters of the research are considered for inclusion in proposed formulations: solubility enhancers (e.g., solvents, excipients), to achieve higher psilocin solubility; mucoadhesive polymers, to enable increased residence time of the formulation so it can permeate through sublingual mucosa; penetration enhancers, to sufficiently enable penetration of psilocin through sublingual mucosa; polymers, demonstrating sufficient viscosity so that the formulation can maintain integrity in sublingual cavity; antioxidants, to sufficiently protect against oxidation of psilocin.

[388] The following variables are utilized: (1) selecting a solvent system (e.g., water, propylene glycol) to dissolve  $\beta$ -CD and SBE- $\beta$ -CD at the highest possible concentration; (2) selecting a mucoadhesive polymer (e.g., chitosan, xanthan gum, CARBOPOL® 974P NF); (3) selecting a taste-masking agent (e.g., xylitol, menthol); and (4) selecting one or more antioxidant(s) (e.g., rosmarinic acid,  $\alpha$ -tocopherol).

[389] Psilocin solubility will be assessed using the following solvent systems: water; water containing  $\beta$ -cyclodextrin; water containing a modified  $\beta$ -cyclodextrin; propylene glycol (PG); and polysorbate 80.

[390] Formulations using xanthan gum as a mucoadhesive polymer include those in Table 1, and formulations using CARBOPOL® as a mucoadhesive polymer include those in Table 2, as shown below. Each proposed formulation was represented using an abbreviation (e.g., Formulation 1 = F1).

[391] The weight concentration of the solutions for each formulation was determined as a percentage of weight per weight (%w/w). Formulas where the Water:PG ratio is preceded with the pound sign (#) denote that placebo formulations with the ratio displayed viscous behavior. "Q.s.," such as with the purified water (q.s.), means that the component is added *quantum satis* up to the volume or amount.

**TABLE 1.** Proposed Formulations Using Xanthan Gum as Mucoadhesive Polymer

	Weight Concentration of Solution (%w/w)					
	F1	F2	F3	F4	F5	F6
Solvent system	Water:PG 2:1	Water:PG 5:1	#Water:PG 1:1	Water:PG 2:1	Water:PG 5:1	#Water:PG 1:1
Psilocin	20	20	20	20	20	20
$\beta$ -cyclodextrin USP	30	25	35	-	-	-
SBE- $\beta$ -CD USP	-	-	-	30	30	30

Propylene glycol USP	14.3	7.15	21.25	12.5	6.25	18.75
Xanthan gum NF (XANTURAL® 75)	0.15	0.15	0.15	0.15	0.15	0.15
Xylitol BP	0.2	0.2	0.2	0.2	0.2	0.2
Rosmarinic acid	0.02	0.02	0.02	0.02	0.02	0.02
Polysorbate 80 USP/NF	-	-	-	1	1	1
Menthol USP	-	-	-	0.05	0.05	0.05
Purified water (q.s)	28.6	35.75	21.25	25	31.25	18.75

**TABLE 2.** Proposed Formulations Using CARBOPOL® as Mucoadhesive Polymer

	Weight Concentration of Solution (%w/w)					
	F7	F8	F9	F10	F11	F12
Solvent system	Water:PG 2:1	Water:PG 5:1	Water:PG 1:1	Water:PG 2:1	Water:PG 5:1	Water:PG 1:1
Psilocin	20	20	20	20	20	20
β-cyclodextrin USP	30	25	35	-	-	-
SBE-β-CD USP	-	-	-	30	30	30
Propylene glycol USP	14.3	7.15	21.25	12.5	6.25	18.75
CARBOPOL® 974P NF	0.10	0.10	0.10	0.10	0.10	0.10
Triethanolamine	<i>quantum satis (q.s.)</i> to pH 6.3					
Xylitol BP	0.2	0.2	0.2	0.2	0.2	0.2
Rosmarinic acid	0.02	0.02	0.02	0.02	0.02	0.02
Polysorbate 80 USP/NF	-	-	-	1	1	1
Menthol USP	-	-	-	0.05	0.05	0.05
Purified water (q.s.)	28.6	35.75	21.25	25	31.25	18.75

[392] Further formulation development work continued as detailed in the Example below and in Tables 3-6.

#### **Example 9: Preparation of Exemplary Sublingual Spray Formulations**

[393] Four different formulations were subsequently designed for further development, based inter alia on comparing the use of CARBOPOL® as a mucoadhesive polymer with the use of xanthan gum as a mucoadhesive polymer, and comparing the use of β-cyclodextrin versus the modified β-cyclodextrin (SBE-β-CD). Four different formulations were worked up, and these formulations were prepared and tested, according to the procedures and summary tables below, and with the results presented that follow.

##### **a. Preparation of a Formulation with Xanthan Gum and a Modified β-Cyclodextrin**

[394] The procedure for the preparation of an exemplary such formulation is as follows:

[395] Phase A: Prepare a modified  $\beta$ -cyclodextrin stock solution, by adding 10 g SBE- $\beta$ -CD USP to a container containing 20 g purified water, followed by stirring until a clear solution is obtained.

[396] Phase B: Step (1) Weigh 10 g propylene glycol, in a tared container; Step (2) Add 280 mg psilocin and stir until a clear solution is obtained, approximately 20 minutes.

[397] Phase C: Step (3) Weigh 3g modified  $\beta$ -cyclodextrin stock solution from Phase A in a tared container; Step (4) Add 25 mg psilocin and stir until clear solution is obtained, approximately, 20 minutes; Step (5) Add 22.5 mg xanthan gum and stir until clear solution is obtained; Step (6) Add 45 mg xylitol and stir until clear solution is obtained; Step (7) Add 7.5 mg rosmarinic acid and stir until clear solution is obtained; Step (8) Add 15 mg vitamin E-TPGS and stir until clear solution is obtained; Step (9) Weigh 6 mg menthol and mix with 150 mg polysorbate-80, to obtain clear solution; then add this solution to the solution of step 8 and stir until a clear solution is obtained; Step (10) Add the solution from step 9 to Phase B under stirring; continue to stir for 5-10 minutes; Step (11) Measure the pH of the solution obtained in step 10 and if required adjust to a pH of 6.5-7.0 using 0.5 N HCl; Step (12) Purge solution with argon gas and store away from light.

**TABLE 3:** Formulation 1 Summary: Xanthan Gum and a Modified  $\beta$ -Cyclodextrin

Material	Item code	%w/w	Lot No.	Qty added, g
Psilocin	222456	1.86	6846D	0.305
SBE- $\beta$ -CD USP	222452	6.11	6835D	1.0
Propylene glycol BP	213845	61.12	6840D	10.0
Xanthan gum NF (XANTURAL® 75)	222301	0.14	6832D	0.0225
Xylitol BP	222134	0.28	6841D	0.045
Rosmarinic acid	222451	0.05	6833D	0.0075
Menthol USP	222445	0.04	6824D	0.006
Polysorbate-80 USP/NF	222300	0.92	6839D	0.15
Vitamin E - TPGS	N/A	0.09	6362D	0.015
Purified water	N/A	12.22	N/A	2.0
0.5 N HCl solution	N/A	17.17	N/A	2.81

[398] In an exemplary preparation of the formulation, the formulation was prepared as above, following steps 1 through 10. At step 11, an initial pH was measured for the solution of step 10 of 9.92; the pH was then adjusted to 6.50, with an amount of 2.81 g of 0.5 N HCl consumed. Following step 12, the sample was submitted to an analytical lab for chromatographic analysis (Mayne Pharma Services; Salisbury, SA, Australia). Briefly, the test sample (~100  $\mu$ g/mL in diluent solution) was separated with an Atlantis C18 column (3  $\mu$ m, 4.6 x 150 mm) in comparison with a blank solution (diluent solution) and a standard solution (100  $\mu$ g/mL of psilocin in diluent solution). The mobile phases used included A: 0.1% formic acid in Milli Q

ultrapure water and B: 100% acetonitrile. The diluent solution consisted of 0.1% formic acid and 90% methanol. Further chromatographic parameters used include a flow rate of 1.3 mL/min, ultraviolet (UV) detection at 264 nm, an injection volume of 10  $\mu$ L, and a sample runtime of 15 minutes. In both the standard and test solutions, the retention time for psilocin was found to be approximately 5 minutes. Based on the actual yield, a psilocin concentration of 19.95 mg/g was calculated. Analysis determined an actual concentration of 19.79 mg/g, or 99.19% of the label claim.

**b. Preparation of a Formulation with Xanthan Gum and  $\beta$ -Cyclodextrin**

[399] The procedure for the preparation of an exemplary such formulation is as follows:

[400] Phase A: Prepare a  $\beta$ -cyclodextrin stock solution, by adding 10 g  $\beta$ -Cyclodextrin USP to a container containing 20 g purified water, followed by stirring until a clear solution is obtained.

[401] Phase B: Step (1) Weigh 10 g propylene glycol, in a tared container; Step (2) Add 280 mg psilocin and stir until a clear solution is obtained, approximately 20 minutes.

[402] Phase C: Step (3) Weigh 3g  $\beta$ -cyclodextrin stock solution from Phase A in a tared container; Step (4) Add 25 mg psilocin and stir until clear solution is obtained, approximately, 20 minutes; Step (5) Add 22.5 mg xanthan gum and stir until clear solution is obtained; Step (6) Add 45 mg xylitol and stir until clear solution is obtained; Step (7) Add 7.5 mg rosmarinic acid and stir until clear solution is obtained; Step (8) The resulting solution of step 7 was very viscous, hence 1 g  $\beta$ -cyclodextrin Stock Solution from Phase A was added to achieve stirring; Step (9) Weigh 6 mg menthol and mix with 150 mg polysorbate-80, to obtain clear solution; then add this solution to the solution of step 8 and stir until a clear solution is obtained; Step (10) Add the solution from step 9 to Phase B under stirring; continue to stir for 5-10 minutes; Step (11) Measure the pH of the solution obtained in step 10 and if required adjust to a pH of 6.5-7.0 using 0.5 N HCl and/or 0.2 N NaOH; Step (12) Purge solution with argon gas and store away from light.

**TABLE 4.** Formulation 2 Summary: Xanthan Gum and  $\beta$ -Cyclodextrin

Material	Item code	%w/w	Lot No.	Qty added, g
Psilocin	222456	1.98	6846D	0.305
$\beta$ -Cyclodextrin USP	222453	6.49	6834D	1.0
Propylene glycol BP	213845	64.94	6840D	10.0
Xanthan gum NF (XANTURAL® 75)	222301	0.19	6832D	0.03
Xylitol BP	222134	0.29	68410	0.045
Rosmarinic acid	222451	0.05	6833D	0.0075
Menthol USP	222445	0.04	6824D	0.006
Polysorbate-80 USP/NF	222300	0.97	6839D	0.15
Vitamin E - TPGS	N/A	0.10	6362D	0.015

Purified water	N/A	12.99	N/A	2.0
0.5 N HCl solution	N/A	11.95	N/A	1.84

[403] In an exemplary preparation of the formulation, the formulation was prepared as above, following steps 1 through 10. At step 11, an initial pH was measured for the solution of step 10 of 9.81; the pH was then adjusted to 2.8, with an amount of 2.64 g of 0.5 N HCl consumed, and then adjusted to a pH of 6.92 with an amount of 0.56 g of 0.2 N NaOH consumed. Following step 12, the sample was submitted to the analytical lab for chromatographic analysis (Mayne Pharma) as described above. Based on the actual yield (16.74 g), a psilocin concentration of 18.21 mg/g was calculated. Analysis determined an actual concentration of 17.90 mg/g, or 98.29% of the label claim.

**c. Preparation of a Formulation with CARBOPOL® and a Modified  $\beta$ -Cyclodextrin**

[404] The procedure for the preparation of an exemplary such formulation is as follows:

[405] Phase A: Prepare a modified  $\beta$ -cyclodextrin stock solution, by adding 10 g SBE- $\beta$ -CD USP to a container containing 20 g purified water, followed by stirring until a clear solution is obtained.

[406] Phase B: Prepare a 0.6%w/w CARBOPOL® 974P slurry, by dispersing 0.3g CARBOPOL® 974P, in 40 g purified water under stirring. Continue stirring until no lumps are observed. Neutralize the pH of the CARBOPOL® dispersion using a 50%w/w triethanolamine solution. For example, where the initial pH is 3.24, a final pH of 5.7 is achieved by consuming 0.44 g 50 %w/w triethanolamine solution, and making up the weight using purified water, to 50 g.

[407] Phase C: Step (1) Weigh 10 g propylene glycol, in a tared container; Step (2) Add 280 mg psilocin and stir until a clear solution is obtained, approximately 20 minutes.

[408] Phase D: Step (3) Weigh 3 g modified  $\beta$ -cyclodextrin stock solution from Phase A in a tared container; Step (4) Add 25 mg psilocin and stir until clear solution is obtained, approximately, 20 minutes; Step (5) Add 45 mg xylitol and stir until clear solution is obtained; Step (6) Add 7.5 mg rosmarinic acid and stir until clear solution is obtained; Step (7) Add 15 mg vitamin E-TPGS and stir until clear solution is obtained; Step (8) Weigh 6 mg menthol and mix with 150 mg polysorbate-80, to obtain clear solution; then add this solution to the solution of step 7 and stir until a clear solution is obtained; Step (9) Add the solution from step 8 to Phase C under stirring; continue to stir for 5-10 minutes; Step (10) Measure the pH of the solution obtained in step 9 and if required adjust to a pH of 6.5-7.0 using 0.5 N HCl; Step (11) To 7.0 g of the solution from step 10, the CARBOPOL® slurry prepared in Phase B is added in small portions until a viscous sample is obtained; Step (12) Purge solution with argon gas and store away from light.

**TABLE 5.** Formulation 3 Summary: CARBOPOL® and a Modified  $\beta$ -Cyclodextrin

Material	Item code	%w/w	Lot No.	Qty added, g
Psilocin	222456	1.82	6846D	0.305

SBE- $\beta$ -CD USP	222452	5.98	6835D	1.0
CARBOPOL® 974P slurry, 0.6%w/w	222238	2.43*	6354D	0.407*
Propylene glycol BP	213845	59.82	6840D	10.0
Xylitol BP	222134	0.27	6841D	0.045
Rosmarinic acid	222451	0.04	68330	0.0075
Menthol USP	222445	0.04	6824D	0.006
Polysorbate-80 USP/NF	222300	0.90	6839D	0.15
Vitamin E - TPGS	N/A	0.09	6362D	0.015
Purified water	N/A	11.96	N/A	2.0
0.5 N HCl solution	N/A	16.63	N/A	2.78

\*CARBOPOL® slurry was added to a portion of the total batch size.

[409] In an exemplary preparation of the formulation, the formulation was prepared as above, following steps 1 through 12. At step 10, an initial pH was measured for the solution of step 9 of 10.16; the pH was adjusted to 6.78, with an amount of 2.78 g of 0.5 N HCl consumed. Subsequently, the net quantity of the batch was calculated to be 15.6191 g. At step 11, the quantity of Phase B added was 407 mg, and the pH of this solution was determined to be 6.23. Following step 12, the sample was submitted to the analytical lab for chromatographic analysis as above. Based on the actual yield of 7.407 g, the psilocin concentration was calculated to be 18.45 mg/g. Analysis of the sample determined a psilocin concentration of 19.14 mg/g or 103.74% of the label claim.

**d. Preparation of a Formulation with CARBOPOL® and  $\beta$ -Cyclodextrin**

[410] The procedure for the preparation of an exemplary such formulation is as follows:

[411] Phase A: Prepare a  $\beta$ -cyclodextrin stock solution, by adding 10 g  $\beta$ -Cyclodextrin USP to a container containing 20 g purified water, followed by stirring until a clear solution is obtained.

[412] Phase B: Prepare a 0.6%w/w CARBOPOL® 974P slurry, by dispersing 0.3 g CARBOPOL® 974P, in 40 g purified water under stirring. Continue stirring until no lumps are observed. Neutralize the pH of the CARBOPOL® dispersion using a 50%w/w triethanolamine solution. For example, where the initial pH is 3.24, a final pH of 5.7 is achieved by consuming 0.44 g 50 %w/w triethanolamine solution, and making up the weight using purified water, to 50 g.

[413] Phase C: Step (1) Weigh 10 g propylene glycol, in a tared container; Step (2) Add 280 mg psilocin and stir until a clear solution is obtained, approximately 20 minutes.

[414] Phase D: Step (3) Weigh 3 g  $\beta$ -cyclodextrin stock solution from Phase A in a tared container; Step (4) Add 25 mg psilocin and stir until clear solution is obtained, approximately, 20 minutes; Step (5) Add 45 mg xylitol and stir until clear solution is obtained; Step (6) Add 7.5 mg rosmarinic acid and stir until clear

solution is obtained; Step (7) Add 15 mg vitamin E-TPGS and stir until clear solution is obtained; Step (8) Weigh 6 mg menthol and mix with 150 mg polysorbate-80, to obtain clear solution; then add this solution to the solution of step 7 and stir until a clear solution is obtained; Step (9) Add the solution from step 8 to Phase C under stirring; continue to stir for 5-10 minutes; Step (10) Measure the pH of the solution obtained in step 9 and if required adjust to a pH of 6.5-7.0 using 0.5 N HCl; Step (11) To 7.0 g of the solution from step 10, the CARBOPOL® slurry prepared in Phase B is added in small portions until a viscous sample is obtained; Step (12) Purge solution with argon gas and store away from light.

**TABLE 6.** Formulation 4 Summary: CARBOPOL® and  $\beta$ -Cyclodextrin

Material	Item code	%w/w	Lot No.	Qty added, g
Psilocin	222456	1.82	6846D	0.305
$\beta$ -Cyclodextrin USP	222453	5.86	6834D	1.0
CARBOPOL® 974P slurry, 0.6%w/w	222238	5.19*	6354D	0.8853*
Propylene glycol BP	213845	58.60	6840D	10.0
Xylitol BP	222134	0.26	6841D	0.045
Rosmarinic acid	222451	0.04	6833D	0.0075
Menthol USP	222445	0.04	6824D	0.006
Polysorbate-80 USP/NF	222300	0.88	6839D	0.15
Vitamin E -TPGS	N/A	0.09	6362D	0.015
Purified water	N/A	11.72	N/A	2.0
0.5 N HCl solution	N/A	15.53	N/A	2.78

[415] \*CARBOPOL® slurry was added to a portion of the total batch size.

[416] In an exemplary preparation of the formulation, the formulation was prepared as above, following steps 1 through 12. At step 10, an initial pH was measured for the solution of step 9 of 9.94; the pH was adjusted to 6.84, with an amount of 2.65 g of 0.5 N HCl consumed. Subsequently, the net quantity of the batch was calculated to be 15.7175 g. At step 11, the quantity of Phase B added was 885.3 mg, and the pH of this solution was determined to be 5.63; after consuming 0.04 g of Triethanolamine solution 50%w/w, the final pH was measured as 7.49. Following step 12, the sample was submitted to the analytical lab for chromatographic analysis as above. Based on the actual yield of 8.8853 g, the psilocin concentration was calculated to be 17.47 mg/g. Analysis of the sample determined a psilocin concentration of 18.27 mg/g or 104.58% of the label claim. The studies surprisingly demonstrated that the concentration of psilocin can be increased substantially above its solubility in water, by using one of the solvent systems of the disclosure, and as described in the formulation examples above, for example by over four times, or by about five times, including, e.g., to over 18 mg/g and to about 20 mg/g, i.e., to over 1.8%w/w, and to about 2.0%w/w (as will

be readily appreciated by those of skill, mg/g amounts are convertible into %w/w amounts by dividing by 10).

### **Example 10: Further Development of Disclosed Sublingual Spray Formulations**

[417] Experiments were performed to determine if psilocin solubility could be enhanced. Solubility study experiments include those summarized in Tables 5 and 6 below, and as further described below. Test solutions for each experiment ("Exp." = experiment) were prepared as follows, with certain results noted. Solubility was observed and recorded after a solution was left overnight.

[418] **Exp. 1** (Water): 40 mg psilocin was weighed and added to 10 g purified water, followed by stirring to obtain solution. Psilocin was insoluble at this concentration of 4 mg/g.

[419] **Exp. 2** (Propylene glycol): 40 mg psilocin was weighed and added to 10 g propylene glycol, followed by stirring to obtain solution. Psilocin was soluble at this concentration of 4 mg/g.

[420] **Exp. 3** (Water:Propylene glycol, 2:1 ratio): A solvent mixture of water and propylene glycol was prepared with 2:1 ratio, by mixing 10 g purified water with 5 g propylene glycol. 40 mg psilocin was weighed and added to 10 g of the 2:1 water:propylene glycol solvent mixture, followed by stirring to obtain solution. Psilocin was partially soluble at this concentration of 4 mg/g.

[421] **Exp. 4** ( $\beta$ -Cyclodextrin solution, 30% w/w): 3g  $\beta$ -cyclodextrin was dissolved in 10g purified water to obtain  $\beta$ -cyclodextrin solution at 30% w/w concentration. 21 mg psilocin was weighed and added to 5 g of the  $\beta$ -cyclodextrin solution, 30% w/w, followed by stirring to obtain solution. Psilocin was partially soluble at this concentration of 4.2 mg/g.

[422] **Exp. 5** (Modified  $\beta$ -cyclodextrin solution, 30% w/w): 3g SBE- $\beta$ -CD was dissolved in purified water to obtain modified  $\beta$ -cyclodextrin solution at 30% w/w concentration. 21 mg psilocin was weighed and added to 5 g of the  $\beta$ -cyclodextrin solution, 30% w/w, followed by stirring to obtain solution. Psilocin was soluble at this concentration of 4.2 mg/g.

[423] **Exp. 6** (Polysorbate-80 solution, 1% w/w): 0.1g polysorbate-80 was dissolved in 10g purified water to obtain polysorbate-80 solution at 1% w/w concentration. 40 mg psilocin was weighed and added to 10 g of the polysorbate-80 solution at 1% w/w followed by stirring. Psilocin was insoluble at concentration of 4 mg/g.

[424] **Exp. 7** (Water:Propylene glycol, 1:1 ratio): A solvent mixture of water and propylene glycol was prepared with 1:1 ratio, by mixing 5 g purified water with 5 g propylene glycol. 40 mg psilocin was weighed and added to 10 g of the 1:1 water:propylene glycol solvent mixture, followed by stirring to obtain solution. Psilocin was partially soluble at this concentration of 4 mg/g.

[425] **Exp. 8** (Dry mix of modified  $\beta$ -cyclodextrin and psilocin in water): 40 mg psilocin was weighed and physically mixed with 3.5 g modified  $\beta$ -cyclodextrin. This physical mixture was added to 10 g purified water, followed by stirring to obtain solution. Psilocin was soluble at this concentration of 2.9 mg/g.

[426] **Exp. 9** (Dry mix of modified  $\beta$ -cyclodextrin and psilocin in water): 80 mg psilocin was weighed and physically mixed with 3.5 g modified  $\beta$ -cyclodextrin. This physical mixture was added to 10 g purified water, followed by stirring to obtain solution. Psilocin was partially soluble at this concentration of 5.9 mg/g.

[427] **Exp. 10** (Dry mix of modified  $\beta$ -cyclodextrin and psilocin in 1:1 water:propylene glycol): A solvent mixture of water and propylene glycol was prepared with 1:1 ratio, by mixing 5g purified water with 5g propylene glycol. 80 mg psilocin was weighed and physically mixed with 3.5 g SBE- $\beta$ -CD. This physical mixture was added to 10 g of the 1:1 Purified water:Propylene glycol solvent mixture, followed by stirring to obtain solution. Psilocin was partially soluble at this concentration of 5.9 mg/g.

**TABLE 7.** Summary Results of Initial Solubility Study Experiments

Exp.	Description	Psilocin	Strength	Observation
1	Water (10 g)	40 mg	4 mg/g	Not soluble
2	Propylene Glycol (PG) (10 g)	40 mg	4 mg/g	Soluble
3	Water : PG 2:1 (10 g)	40 mg	4 mg/g	Partially soluble
4	5 g of [Water (10 g) + $\beta$ -cyclodextrin (3 g)]	21 mg	4.2 mg/g	Soluble (few undissolved particles)
5	5 g of [Water(10 g) + SBE- $\beta$ -CD (3 g)]	21 mg	4.2 mg/g	Soluble
6	Water (9.9 g) + Polysorbate 80 (0.1 g)	40 mg	4 mg/g	Not Soluble
7	Water : PG 1:1 (10 g)	40 mg	4 mg/g	Partially soluble
8	Water (10 g) + Physical mixture of 3.5 g of SBE- $\beta$ -CD + 40 mg of Psilocin	40 mg	2.9 mg/g	Soluble
9	Water (10 g) + Physical mixture of 3.5 g of SBE- $\beta$ -CD + 80 mg of Psilocin	80 mg	5.9 mg/g	Partially Soluble
10	Water (5 g) + PG (5 g) + Physical mixture of 3.5 g of SBE- $\beta$ -CD + 80 mg of Psilocin	80 mg	5.9 mg/g	Partially soluble (Better than Exp. 9)

[428] Unexpectedly, it was determined that, inter alia: (1) psilocin is highly soluble in propylene glycol; (2) the modified  $\beta$ -cyclodextrin is better for solubilizing psilocin than  $\beta$ -cyclodextrin; (3) the mixture of water and propylene glycol helps in the solubilization of psilocin. Additional experiments were performed as follows.

[429] To the propylene glycol solution of Exp. 2 (40 mg psilocin in 10 g propylene glycol, wherein the psilocin was soluble at a concentration of 4 mg/g), subsequently (**Exp. 2+**) psilocin was incrementally added in 40 mg aliquots until saturation solubility was observed (see additional results in Table 6). Saturation solubility was observed when the total amount of psilocin added was 280 mg (28 mg/g).

[430] The ability to dilute the 28 mg/g solution in propylene glycol without causing the psilocin to crash from solution was tested (**Exp. 12**). To 5 g of the 28 mg/g solution, 0.5 g of water was added. The psilocin remained in solution. To 5 g of the 28 mg/g solution, 1.5 g of water with SBE- $\beta$ -CD was added. The psilocin remained in solution. It is determined that once psilocin is solubilized in PG, it can be diluted, for example to obtain a standard concentration of psilocin, to prevent crashing, and/or to provide stability.

[431] **Exp. 11** (Modified  $\beta$ -cyclodextrin, propylene glycol and water): 3.5g SBE- $\beta$ -CD was weighed and

added to 10g propylene glycol followed by stirring. A suspension was obtained. To this suspension, water was added in small portions until a clear solution was obtained. A total of 3g purified water was required to obtain the clear solution. 102 mg psilocin was weighed and added to this solution followed by stirring. A clear solution was obtained. An additional quantity of 53.5 mg psilocin was weighed and added to the solution followed by stirring. A clear solution was obtained, at a psilocin concentration of 9.42 mg/g.

**TABLE 8.** Summary Results of Additional Solubility Study Experiments

Exp.	Excipient	Psilocin	Strength	Observation
2+	PG (10 g)	40 mg + 40 mg + 40 mg + 40 mg + 40 mg (280 mg)	28 mg/g	Soluble up to 24 mg, Undissolved matter observed at 28 mg concentration
12	PG (5 g from Exp 2) + 0.5 g of water + 1.5 g of water containing SBE- $\beta$ -CD		28 mg/g (pre-dilution)	No Psilocin Crash. Once Psilocin is solubilized in PG, can be diluted
11	PG (10 g) + water (3 g) + 3.5 g of SBE- $\beta$ -CD	102 mg + 53.5 mg	9.42 mg/g	Soluble

[432] Yet further experiments were performed in developing the formulations, as described below.

[433] In a further experiment (**Exp. 13:** Paste of modified  $\beta$ -cyclodextrin and psilocin in water, slurry method) 206 mg psilocin was weighed and physically mixed with 3.5g SBE- $\beta$ -CD. To this physical mixture, 5.62 g purified water was added to obtain a paste. This paste was added to 10 g propylene glycol followed by stirring to obtain solution. Psilocin was partially soluble at this concentration of 10.77 mg/g.

[434] In a further experiment (**Exp. 14:** Formulation 1), at a batch size of 14 g, a formulation was prepared in two phases. In phase 1, 10 g PG was combined with 240 mg psilocin. In phase 2, 3 g water (from 35% SBE- $\beta$ -CD stock solution) was combined with 13.3 mg psilocin (considering approx. 4.2 g of psilocin solubility in water : SBE- $\beta$ -CD mixture), 22.5 mg xanthan gum, 30 mg xylitol, 3 mg rosmarinic acid, and 6 mg menthol in 150 mg polysorbate-80. The volume was made up to 14 g with 35% SBE- $\beta$ -CD stock solution. The formulation therefore comprised 240 mg + 13.3 mg for a total of 253.3 mg psilocin, with a strength of 18.1 mg/g. It was observed that the formulation was soluble.

[435] Following the experiments, it was surprisingly determined that psilocin solubility could be significantly enhanced, with results of the experiments showing an increase of at least 4.5-fold, specifically from 4 mg/g to at least 18 mg/g. Such increased solubility permits an administration volume of or below 1.1 mL, at standard psilocin dosing amounts for administration.

[436] In view of the above solubility experiments, sublingual oromucosal spray formulations were developed with  $\beta$ -cyclodextrin, a modified  $\beta$ -cyclodextrin, and PG as solubility enhancers of psilocin.

#### **Example 11: Phase 1 Single Ascending Dose Study of Sublingually delivered Psilocin**

[437] A Phase 1, Single Centre, Randomised, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, of Sublingually delivered Psilocin in Healthy

Adult Volunteers is planned. The study drug will be SP-001, a sublingual spray developed by Spiritus Bioscience, Inc., comprising psilocin. The study will take place at CMAX BioMed City, Adelaide, Australia.

[438] Objectives: The primary objective is to evaluate the safety and tolerability of psilocin following a single sublingual dose administration in healthy adult volunteers. The secondary objectives are to characterize the pharmacokinetic (PK) properties of psilocin in plasma following a single sublingual dose administration; and to determine the maximum tolerated dose or the maximum feasible dose in the absence of establishing a maximum tolerated dose, and the recommended phase 2 dose of sublingual psilocin.

[439] Endpoints: Primary endpoints for safety and tolerability will be assessed based on: Frequency and severity of Treatment-Emergent Adverse Events and serious AEs (local and systemic); Heart rate, blood pressure, 12-lead ECG; Clinical laboratory safety tests; Brief Psychiatric Rating Scale (BPRS) assessment to monitor hallucinations as a safety parameter; Mystical Experience Questionnaire (MEQ); Cambridge Neuropsychological Test Automated Battery (CANTAB) Panel, and emotional processing scales; CANTAB global composite score; and Treatment-emergent adverse event (TEAE) monitoring.

[440] Secondary endpoints are PK parameters which will be calculated following single dosing and will include the following: Maximum concentration ( $C_{max}$ ), time to reach  $C_{max}$  ( $T_{max}$ ), area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration ( $AUC_{0-last}$ ), AUC from time zero to time  $\tau$  ( $AUC_{0-\tau}$ ). If the data are available, AUC from time zero to infinity ( $AUC_{0-inf}$ ), terminal elimination half-life ( $t_{1/2}$ ), apparent clearance (CL/F), and apparent volume of distribution ( $V_z/F$ ).

[441] Methodology: This is a phase 1, randomized, double-blind, placebo-controlled study to investigate the safety, tolerability, and PK of sublingually administered psilocin in a single-ascending dose study in adult healthy volunteers between 18-60 years of age, to establish the recommended phase 2 dose (RP2D). Oversight for the study will be provided by an SRC composed of the Principal Investigator, and the Sponsor's Medical Monitor (MM), and an Independent MM. The study plans to test single doses of Sublingual Psilocin in three cohorts. The decision to progress from Cohort 1 to Cohort 2 will be based on safety and tolerability data and not PK data from Cohort 1. However, the decision to progress from Cohort 2 to Cohort 3 will be based on review of safety and tolerability data from Cohort 2 and PK data from Cohort 1 by the SRC. A similar sequence will follow for subsequent progression decisions by the SRC for all the cohorts.

[442] Each part of the study will include a 28-day screening period, a treatment period, and follow-up period. In this Example, timings for post-dose assessments ECG, blood samples for PK analysis are stated in relation to completion of the most recent dose of study drug. Serial blood samples for PK analysis will be collected at multiple time points through 48 hours post-dose for the single dose. A follow up visit will take place one-week post treatment. The participants will be enrolled into 1 of up to 3 sequential cohorts (Cohorts 1 to 3). Each cohort will consist of 8 participants (6 participants receiving Sublingual Psilocin and 2 participants receiving placebo). Potential study participants who provide voluntary written informed consent will undergo screening evaluations to determine eligibility within 28 days before the start of treatment (Day

1). Eligible participants will be admitted to the clinical research unit (CRU) on Day -1.

[443] Participants in each cohort will be administered a single sublingual dose of their allocated study drug (i.e., placebo or Sublingual Psilocin) on Day 1. In each cohort, 2 sentinel participants (1 randomized to Sublingual Psilocin and 1 randomized to placebo) will be dosed before proceeding with dosing of the remainder of the cohort. The Investigator will review safety and tolerability data (from at least the first 24 hours after dosing), before progression from sentinel participants to the remainder of the cohort. If desired, the Investigator may consult with the members of the SRC before deciding whether to proceed with the rest of the cohort. The Investigator must notify (in writing) the other members of the SRC of their decision to proceed or not with the rest of the cohort as soon as the decision is made.

[444] Participants will be required to remain in the CRU for 24 hours following dosing and then be discharged from the CRU. Participants will then follow up with daily outpatient visits until all post-dose assessments have been completed (i.e., Day 5). A final Follow-up visit will be scheduled for 7 (+ 3) days (i.e., Day 12 + 3 days). Study visits and assessments will occur as delineated in the Schedule of Assessments and PK samples will be collected prior to study drug administration and at different time intervals after dosing, as delineated in the PK Blood Sampling Schedule.

[445] Sublingual Psilocin at three ascending doses are planned. A decision to proceed from the current dose to the next higher dose will be made only after the SRC has reviewed all available safety, tolerability and PK data (if available) for the participants in the preceding cohort(s).

[446] Participants: The study will be conducted in healthy adult subjects. Sufficient participants will be enrolled to obtain 24 evaluable subjects (8 per treatment arm; 6 treated and 2 placebo). Participants who withdraw or discontinue study medication may be replaced, unless the participant withdrew or stopped study medication due to treatment stopping criteria or a study drug -related adverse event (AE). The replacement participants will be assigned the same treatment sequence as the participants they are replacing.

[447] Criteria for Inclusion and Exclusion: As generally used and accepted in the field for such studies.

[448] Study Drug and Route of Administration: Single dose of psilocin via sublingual spray administration.

[449] Reference Therapy and Route of Administration: Single dose of placebo via sublingual spray.

[450] Duration of Treatment: Following completion of an outpatient Screening Period (to be completed within a 26-day window), the expected duration of study participation and treatment is 12 days (including one day as an inpatient, 5 days of outpatient clinic visits, and one follow-up outpatient visit).

[451] Criteria for Evaluation: Safety and Tolerability: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, ECGs, and presence of hallucinations (using BPRS questionnaire); Pharmacokinetics: PK parameters will be calculated from psilocin concentrations.

[452] Statistical Methods: As generally used and accepted in the field for such studies. For each treatment plasma concentrations or psilocin will be tabulated and summarized by treatment and nominal time using descriptive statistics which include, but are not limited to: number of subjects, arithmetic mean, standard

deviation, coefficient of variation, geometric mean, median, minimum and maximum. PK parameters for psilocin will be calculated:  $C_{max}$ ,  $T_{max}$ , area under concentration-time curve (AUC),  $AUC_{0-last}$ ,  $AUC_{0-T}$ ,  $AUC_{0-inf}$ ,  $t_{1/2}$ , CL/F. For Analysis Populations: Healthy volunteers' inclusion in each population will be determined before the final analysis. For Safety Population: All participants who receive study drug will be included in the Safety Population. The Safety Population will be used for the summaries of all safety assessments. The Safety Population will be based on the actual dose level if the actual dose is different from the intended dose level. For Pharmacokinetic Population: All participants who receive study drug and have a sufficiently evaluable concentration-time profile to allow determination of at least one PK parameter will be included in the PK population. An evaluable PK profile will be determined at the discretion of the pharmacokineticist following examination of participants with dosing or protocol deviations that could potentially affect the PK profile. The evaluable PK population will be used for the summaries of all PK data.

[453] Schedule of Assessments: As provided in Table 9 below.

**TABLE 9.** Schedule of Assessments

	Screening -28 to -1	Week 1		
		Day 1	Days 2	Day 7
Informed Consent	X			
Eligibility Criteria, Medical History, Height	X			
Demographics	X			
Subject Randomization	X			
Sublingual Psilocin (single dose)		X		
MEQ	X	X+		
CEQ		X+		
CGI-S		X+		
CGI-I				
BPRS		X+		
EEG		X+		
Plasma collection for PK analysis		X+	X	X <sup>3</sup>
Concomitant Medications	X	X	X	X
Safety Labs (hematology, serum chemistry)	X		X	X
Urinalysis	X		X	X
Pregnancy Test (where applicable)	X			
Physical Examination, Weight	X		X	X
Vital Signs	X		X	X
ECG	X		X	X
Adverse Events		X	X	X

† Baseline assessment prior to sublingual psilocin administration.

### **Example 12: Administration of Disclosed Formulations to an Individual Subject or Patient**

[454] An individual is administered or self-administers in a single session or in multiple sessions a disclosed sublingual spray formulation. The formulation is administered using a metered spray pump that delivers one or more fixed-volume sprays of the formulation to the sublingual mucosa. Post-administration, if the administered compound is a psychedelic, and the dose is intended to provide psychedelic effects, the individual experiences the psychoactive and psychedelic effects of the compound. Such effects can be assessed using methods known to those of skill in the art. For example, the individual is administered or self-administers any of the Mystical Experience Questionnaire (MEQ30), the Challenging Experience Questionnaire (CEQ), or the Hallucinogen Rating Scale (HRS), or like questionnaires known to those in the art, such as the Mysticism Scale (M-scale) or Hood Mysticism Scale (HMS), the Five Dimensional or 11 Dimensional Altered States of Consciousness Questionnaire (5D-ASC or 11D-ASC), the States of Consciousness Questionnaire (SOCQ), the Ego Dissolution Inventory (EDI), and the Phenomenology of Consciousness Inventory (PCI). Additional measures may be used to assess the qualities of each subjective experience, as would be understood and available to one of skill in the art. Regarding MEQ, CEQ, and the HRS, higher scores indicate a more mystical experience, a more challenging experience, and a more intense psychedelic experience, respectively. Preferably, an individual who is administered or self-administers a disclosed formulation experiences enhanced desirable and pleasurable effects, owing to many factors including, for example, the reliability and predictability of the metered dosing, the improved palatability of flavor of the formulation, and the reduction of unpleasant side effects (e.g., nausea).

[455] In embodiments, where a clinical effect is sought, for example in the treatment of alcohol use disorder (AUD) or another substance use disorder (SUD), the effects of administration are determined using an assessment, which may be self-administered, or administered by a clinician, and may be administered at a period following administration, as well as at or before administration (baseline), as will be known in the art.

[456] In embodiments, the assessment is any one or more of the Severity of Alcohol Dependence Questionnaire (SADQ), Mini International Neuropsychiatric Interview 5 (MINI 5), Columbia Suicide Severity Rating Scale (C-SSRS), Alcohol Dependence Syndrome section of the SCID-5-CT (Clinical Trials Version), Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder 7 (GAD-7), Short Inventory of Problems for Alcohol (SIP), Alcohol Timeline Follow Back (TLFB), Clinical Institute Withdrawal Assessment for Alcohol—Revised Version (CIWA–Ar), Penn Alcohol Craving Scale (PACS), Obsessive Compulsive Drinking Scale (OCDS), Pittsburgh Sleep Quality Index (PSQI), Interpersonal reactivity Index (IRI), Short Form (36) Health Survey (SF-36), Self-Compassion Scale (SCS), and the Trauma History Questionnaire (THQ).

### **H. Exemplary Aspects and Embodiments**

[457] Among the various aspects and embodiments of the disclosure are the following, which will be understood to be exemplary and not limiting.

[458] In one exemplary aspect, provided is a sublingual spray formulation, comprising (i) a compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof, (ii) a pharmaceutically acceptable excipient, and (iii) a solvent system.

[459] In embodiments, the compound is a psychedelic compound.

[460] In embodiments, the psychedelic compound is a tryptamine. In embodiments, the tryptamine is psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof. In embodiments, the psilocin is in an amount so that a single dose is between about 1 mg and 30 mg, about 1 mg, about 5 mg, or about 10 mg. In embodiments, the tryptamine is DMT, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof. In embodiments, the DMT is in an amount so that a single dose is between about 1 mg and 30 mg, about 1 mg, about 5 mg, or about 10 mg.

[461] In embodiments, the psychedelic compound is a phenethylamine. In embodiments, the phenethylamine is 2C-B, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof. In embodiments, the 2C-B is in an amount so that a single dose is between about 1 mg and 100 mg, about 1 mg, about 5 mg, or about 10 mg. In embodiments, the phenethylamine is MDMA, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof. In embodiments, the MDMA is in an amount so that a single dose is between about 1 mg and 100 mg, about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 50 mg, or about 100 mg.

[462] In embodiments, the psychedelic compound is a lysergamide. In embodiments, the lysergamide is LSD, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof. In embodiments, the LSD is in an amount so that a single dose is between about 1  $\mu$ g and 200  $\mu$ g, about 10  $\mu$ g, about 25  $\mu$ g, about 50  $\mu$ g, about 100  $\mu$ g, or about 200  $\mu$ g.

[463] In embodiments, the excipient is a solubilizing agent, a penetration enhancer, an antioxidant, a taste-masking agent, a mucoadhesive polymer, or a flavoring agent.

[464] In embodiments, the excipient is a solubilizing agent. In embodiments, the solubilizing agent is a cyclodextrin, lecithin, propylene glycol, or xanthan gum, or a combination thereof. In embodiments, the solubilizing agent is a cyclodextrin.

[465] In embodiments, the excipient is a penetration enhancer. In embodiments, the permeation enhancer is 1,2-lauryl ether, aprotinin, azone, benzalkonium chloride, bromide, cetylpyridinium chloride, cetyltrimethyl ammonium, cyclodextrin, dextran sulfate, glycol, lauric acid, lauric acid, propylene, lysophosphatidylcholine, menthol, phosphatidylcholine, polyoxyethylene, polysorbate 80, sodium EDTA, chitosan, sodium glycocholate (SGC, NaGC), sodium deoxyglycocholate (SDGC, NaDGC), sodium taurocholate (STC, NaTC), sodium lauryl sulfate (SLS), sodium salicylate, sulfoxide, or a combination thereof.

[466] In embodiments, the excipient is an antioxidant. In embodiments, the antioxidant is a cyclodextrin, vitamin E, e.g., D- $\alpha$ -tocopherol, rosmarinic acid, or a combination thereof.

[467] In embodiments, the excipient is a taste-masking agent. In embodiments, the taste-masking agent is

a cyclodextrin, l-menthol, xylitol, or a combination thereof.

[468] In embodiments, the excipient is a mucoadhesive polymer. In embodiments, the mucoadhesive polymer is chitosan, gelatin guar gum, a lectin, sodium alginate, soluble starch, tragacanth, xanthan gum deacetylated gum, polyacrylic acid, polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, thiomers, polycarbophil, hyaluronic acid, dermatan sulfate, or a combination thereof.

[469] In embodiments, the excipient is a flavoring agent.

[470] In embodiments, the solvent system comprises water. In embodiments, the solvent system comprises propylene glycol.

[471] In embodiments, the formulation is for use in modulating neurotransmission in an individual.

[472] In another exemplary aspect is a method of modulating neurotransmission in a mammal, comprising administering to the mammal an effective amount of the formulation of any of the disclosed embodiments.

[473] In embodiments, the neurotransmission is serotonergic neurotransmission. In embodiments, modulating neurotransmission comprises one or more of: stimulating release of serotonin, and/or reducing serotonin uptake by inhibiting the function of a serotonin transporter (SERT). In embodiments, modulating neurotransmission treats a medical condition.

[474] In another exemplary aspect is a method of treating a medical condition in a subject in need of such treatment, the method comprising administering the formulation of any of the disclosed embodiments.

[475] In another exemplary aspect is the use of the formulation of any of the disclosed embodiments for the manufacture of a medicament for treating a medical condition.

[476] In embodiments, the medical condition is a mental health disorder. In embodiments, the mental health disorder is selected from the group consisting of post-traumatic stress disorder (PTSD), adjustment disorder, affective disorder, depression, atypical depression, postpartum depression, catatonic depression, a depressive disorder due to a medical condition, premenstrual dysphoric disorder, seasonal affective disorder, dysthymia, anxiety, phobia disorders, binge disorders, body dysmorphic disorder, alcohol or drug abuse or dependence disorders, a substance use disorder, substance-induced mood disorder, a mood disorder related to another health condition, disruptive behavior disorders, eating disorders, impulse control disorders, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), personality disorders, attachment disorders, and dissociative disorders. In embodiments, the mental health disorder is anxiety, depression, addiction, an eating disorder, an alcohol or drug abuse or dependence disorder, OCD, or PTSD. In embodiments, depression is major depressive disorder (MDD) or treatment-resistant depression (TRD). In embodiments, anxiety is generalized anxiety disorder (GAD) or menopause-related anxiety. In embodiments, the substance use disorder is any of alcohol use disorder, nicotine dependency, opioid use disorder, sedative, hypnotic, or anxiolytic use disorder, stimulant use disorder, or tobacco use disorder.

[477] In embodiments, the medical condition is a neurodegenerative disease. In embodiments, the

neurodegenerative disease is neurodegenerative dementia, Alzheimer's disease, or Parkinson's disease.

[478] In embodiments, the formulation is administered together with one or more sessions of psychotherapy or with patient monitoring.

[479] The foregoing description, for purposes of explanation, uses specific nomenclature to provide a thorough understanding of the invention. However, it will be apparent to one in the art that specific details are not required in order to practice the invention. Thus, the foregoing description of specific embodiments of the invention is presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise compositions, formulations, methods, or the like disclosed; many modifications and variations are possible in view of the above teachings. The embodiments were chosen and described in order to best explain the principles of the invention and its practical applications, through the elucidation of specific examples, and to thereby enable others skilled in the art to best utilize the invention and various embodiments with various modifications as are suited to the particular use contemplated, when such uses are beyond the specific examples disclosed.

[480] Accordingly, the scope of the invention shall be defined solely by the claims and their equivalents.

## CLAIMS

The invention claimed is:

1. A sublingual spray formulation comprising:
  - i. psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof;
  - ii. a solubilizing agent; and
  - iii. a solvent system.
2. The formulation of claim 1, wherein the concentration of psilocin in the formulation is greater than about 0.4% (w/w).
3. The formulation of claim 2, wherein the concentration of psilocin in the formulation is greater than about 1.0% (w/w).
4. The formulation of claim 3, wherein the concentration of psilocin in the formulation is greater than about 1.5% (w/w).
5. The formulation of claim 4, wherein the concentration of psilocin in the formulation is greater than about 1.8% (w/w).
6. The formulation of claim 5, wherein the concentration of psilocin in the formulation is about 2.0% (w/w).
7. The formulation of claim 1, wherein the concentration of psilocin in the formulation is at least 2-fold higher than the solubility limit of psilocin in an identical formulation lacking the solubilizing agent.
8. The formulation of claim 7, wherein the concentration of psilocin in the formulation is at least 4-fold higher than the solubility limit of psilocin in an identical formulation lacking the solubilizing agent.
9. The formulation of claim 1, wherein the solubilizing agent is a cyclodextrin, a surfactant, or a phospholipid.
10. The formulation of claim 9, wherein the cyclodextrin is sulfobutylether- $\beta$ -cyclodextrin.
11. The formulation of claim 10, comprising between about 1% and about 10% (w/w) of sulfobutylether- $\beta$ -cyclodextrin.
12. The formulation of claim 11, comprising between about 5% and about 7% (w/w) of sulfobutylether- $\beta$ -cyclodextrin.
13. The formulation of claim 12, comprising about 6% (w/w) of sulfobutylether- $\beta$ -cyclodextrin.

14. The formulation of claim 9, wherein the cyclodextrin is  $\beta$ -cyclodextrin.
15. The formulation of claim 14, comprising between about 1% and about 10% (w/w) of  $\beta$ -cyclodextrin.
16. The formulation of claim 15, comprising between about 5% and about 7% (w/w) of  $\beta$ -cyclodextrin.
17. The formulation of claim 16, comprising about 6% (w/w) of  $\beta$ -cyclodextrin.
18. The formulation of claim 1, wherein the solvent system comprises water.
19. The formulation of claim 18, wherein the solvent system further comprises an alcohol.
20. The formulation of claim 19, wherein the alcohol is propylene glycol (PG).
21. The formulation of claim 20, wherein the solvent system comprises water and PG in a water:PG ratio of between about 5:1 and about 1:5.
22. The formulation of claim 21, wherein the solvent system comprises water and PG in a water:PG ratio of between about 3:1 and about 1:3.
23. The formulation of claim 22, wherein the solvent system comprises water and PG in a water:PG ratio of between about 1:2 and about 1:3.
24. The formulation of claim 1, further comprising any of a penetration enhancer, an antioxidant, a taste-masking agent, a mucoadhesive polymer, and a flavoring agent.
25. The formulation of claim 1, further comprising a mucoadhesive polymer.
26. The formulation of claim 25, wherein the mucoadhesive polymer is xanthan gum.
27. The formulation of claim 26, comprising between about 0.1% and about 1.0% (w/w) of xanthan gum.
28. The formulation of claim 27, comprising between about 0.1% and about 0.2% (w/w) of xanthan gum.
29. The formulation of claim 25, wherein the mucoadhesive polymer is carbomer homopolymer type B.
30. The formulation of claim 29, comprising between about 0.01% and about 0.1% (w/w) of carbomer homopolymer type B.
31. The formulation of claim 30, comprising between about 0.01% and about 0.05% (w/w) of carbomer homopolymer type B.
32. The formulation of claim 1, further comprising a taste-masking agent.
33. The formulation of claim 32, wherein the taste-masking agent is xylitol.

34. The formulation of claim 33, comprising between about 0.1% and about 1.0% (w/w) of xylitol.
35. The formulation of claim 34, comprising between about 0.2% and about 0.3% (w/w) of xylitol.
36. The formulation of claim 32, wherein the taste-masking agent is menthol.
37. The formulation of claim 36, comprising between about 0.01% and about 0.10% (w/w) of menthol.
38. The formulation of claim 37, comprising about 0.04% (w/w) of menthol.
39. The formulation of claim 1, further comprising an antioxidant.
40. The formulation of claim 39, wherein the antioxidant is rosmarinic acid.
41. The formulation of claim 40, comprising between about 0.01% and about 0.10% (w/w) of rosmarinic acid.
42. The formulation of claim 41, comprising about 0.05% (w/w) of rosmarinic acid.
43. The formulation of claim 39, wherein the antioxidant is vitamin E.
44. The formulation of claim 43, comprising between about 0.01% and about 1.0% (w/w) of vitamin E.
45. The formulation of claim 44, comprising about 0.10% (w/w) of vitamin E.
46. The formulation of claim 1, further comprising a polysorbate.
47. The formulation of claim 46, wherein the polysorbate is polysorbate 80.
48. The formulation of claim 47, comprising between about 0.5% and about 2.0% (w/w) of polysorbate 80.
49. The formulation of claim 48, comprising about 1.0% (w/w) of polysorbate 80.
50. A sublingual spray formulation comprising:
  - i. about 1.8% to about 2.0% (w/w) of psilocin;
  - ii. about 5% to about 7% (w/w) of sulfobutylether- $\beta$ -cyclodextrin;
  - iii. about 0.1% to about 0.2% (w/w) of xanthan gum;
  - iv. about 0.01% to about 1.0% (w/w) of a taste-masking agent;
  - v. about 0.01% to about 1.0% (w/w) of an antioxidant; and
  - vi. about 0.5% to about 2.0% (w/w) of polysorbate 80.
51. A sublingual spray formulation comprising:
  - i. about 1.8% to about 2.0% (w/w) of psilocin;

- ii. about 5% to about 7% (w/w) of sulfobutylether- $\beta$ -cyclodextrin;
  - iii. about 0.01% to about 0.1% (w/w) of carbomer homopolymer type B;
  - iv. about 0.01% to about 1.0% (w/w) of a taste-masking agent;
  - v. about 0.01% to about 1.0% (w/w) of an antioxidant; and
  - vi. about 0.5% to about 2.0% (w/w) of polysorbate 80.
52. A sublingual spray formulation comprising:
- i. about 1.8% to about 2.0% (w/w) of psilocin;
  - ii. about 5% to about 7% (w/w) of  $\beta$ -cyclodextrin;
  - iii. about 0.1% to about 0.2% (w/w) of xanthan gum;
  - iv. about 0.01% to about 1.0% (w/w) of a taste-masking agent;
  - v. about 0.01% to about 1.0% (w/w) of an antioxidant; and
  - vi. about 0.5% to about 2.0% (w/w) of polysorbate 80.
53. A sublingual spray formulation comprising:
- i. about 1.8% to about 2.0% (w/w) of psilocin;
  - ii. about 5% to about 7% (w/w) of  $\beta$ -cyclodextrin;
  - iii. about 0.01% to about 0.1% (w/w) of carbomer homopolymer type B;
  - iv. about 0.01% to about 1.0% (w/w) of a taste-masking agent;
  - v. about 0.01% to about 1.0% (w/w) of an antioxidant; and
  - vi. about 0.5% to about 2.0% (w/w) of polysorbate 80.
54. The formulation of any one of claims 1-53, further comprising a therapeutically effective amount of an additional active compound, or a pharmaceutically acceptable salt, hydrate, solvate, isomer, non-racemic mixture, isotopolog, prodrug, or derivative thereof.
55. The formulation of claim 54, wherein the additional active compound is selected from the group consisting of: amino acids, antioxidants, anti-inflammatory agents, analgesics, antineuropathic and antinociceptive agents, antimigraine agents, anxiolytics, antidepressants, antipsychotics, anti-PTSD agents, dissociatives, cannabinoids, immunostimulants, anti-cancer agents, antiemetics, orexigenics, antiulcer agents, antihistamines, antihypertensives, anticonvulsants, antiepileptics, bronchodilators, neuroprotectants, nootropics, empathsogens, psychedelics, monoamine oxidase inhibitors, tryptamines, terpenes, phenethylamines, sedatives, stimulants, serotonergic agents, and vitamins.
56. The pharmaceutical composition of claim 54, wherein the additional active compound acts to increase a therapeutic effect, provide an additional therapeutic effect, decrease an unwanted effect, increase stability or shelf-life, improve bioavailability, induce synergy, or alter pharmacokinetics or

pharmacodynamics.

57. The pharmaceutical composition of claim 56, wherein the additional therapeutic effect is an antioxidant, anti-inflammatory, analgesic, antineuropathic, antinociceptive, antimigraine, anxiolytic, antidepressant, antipsychotic, anti-PTSD, dissociative, immunostimulant, anti-cancer, antiemetic, orexigenic, antiulcer, antihistamine, antihypertensive, anticonvulsant, antiepileptic, bronchodilator, neuroprotective, empathogenic, psychedelic, sedative, or stimulant effect.
58. A sublingual spray formulation, such as the formulation of any one of claims 1-57, comprising:
  - i. a psychedelic compound, or a pharmaceutically acceptable salt, hydrate, solvate, metabolite, or prodrug thereof;
  - ii. a pharmaceutically acceptable excipient; and
  - iii. a solvent system.
59. A method of treating a medical condition in a subject in need of such treatment, the method comprising administering to the subject the formulation of any one of claims 1-53.
60. The method of claim 59, wherein the medical condition is a disorder linked to dysregulation or inadequate functioning of neurotransmission.
61. The method of claim 60, wherein the disorder linked to dysregulation or inadequate functioning of neurotransmission is that of monoaminergic neurotransmission.
62. The method of claim 61, wherein the disorder linked to dysregulation or inadequate functioning of neurotransmission is that of serotonergic, dopaminergic, or noradrenergic neurotransmission.
63. The method of claim 59, wherein the medical condition is a mental health disorder.
64. The method of claim 63, wherein the mental health disorder is selected from the group consisting of post-traumatic stress disorder (PTSD), adjustment disorder, affective disorder, depression, atypical depression, postpartum depression, catatonic depression, a depressive disorder due to a medical condition, premenstrual dysphoric disorder, seasonal affective disorder, dysthymia, anxiety, phobia disorders, binge disorders, body dysmorphic disorder, alcohol or drug abuse or dependence disorders, a substance use disorder, substance-induced mood disorder, a mood disorder related to another health condition, disruptive behavior disorders, eating disorders, impulse control disorders, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), personality disorders, attachment disorders, and dissociative disorders.
65. The method of claim 59, wherein the medical condition is a neurodegenerative disease.

66. The method of claim 65, wherein the neurodegenerative disease is Alzheimer's disease, amyotrophic lateral sclerosis or Charcot's disease, chronic traumatic encephalopathy, corticobasal degeneration, dementias including vascular dementia, Huntington's disease, Lytico-Bodig disease, mild cognitive impairment, multiple sclerosis, a motor neuron disease, neuromyelitis optica spectrum disorder, Parkinson's disease or Parkinsonisms, prion diseases, progressive supranuclear palsy, and traumatic brain injury.
67. The method of claim 59, wherein the medical condition is pain or a pain disorder.
68. The method of claim 67, wherein the pain disorder is any of arthritis, allodynia, atypical trigeminal neuralgia, trigeminal neuralgia, somatoform disorder, hypoesthesia, hyperalgesia, neuralgia, neuritis, neurogenic pain, phantom limb pain, analgesia, anesthesia dolorosa, causalgia, sciatic nerve pain disorder, degenerative joint disorder, fibromyalgia, visceral disease, chronic pain disorders, headache disorders, migraine headaches, chronic cluster headaches, concussion headache, short-lasting unilateral neuralgiform headache attacks, chronic fatigue syndrome, complex regional pain syndrome, neurodystrophy, plantar fasciitis, or pain associated with cancer.
69. The method of claim 59, wherein the medical condition is inflammation or an inflammatory disorder.
70. The method of claim 69, wherein the inflammation is any of skin inflammation, muscle inflammation, tendon inflammation, ligament inflammation, bone inflammation, cartilage inflammation, lung inflammation, heart inflammation, liver inflammation, pancreatic inflammation, kidney inflammation, bladder inflammation, gastric inflammation, intestinal inflammation, neuroinflammation, and brain inflammation.
71. The method of claim 59, wherein the formulation is administered together with one or more sessions of psychotherapy, psychological support, or patient monitoring
72. A method of modulating neurotransmission in an individual, comprising administering to the mammal an effective amount of the formulation of any one of claims 1-53.
73. The method of claim 72, wherein the neurotransmission is monoaminergic neurotransmission.
74. The method of claim 73, wherein the monoaminergic neurotransmission is serotonergic, dopaminergic, or noradrenergic neurotransmission.
75. The method of any one of claims 72-74, wherein modulating neurotransmission treats a medical condition.
76. A method of increasing neuroplasticity in a subject, comprising administering to the subject the

formulation of any one of claims 1-53.

77. The formulation of any one of claims 1-53 for use in the treatment of a medical condition.
78. The formulation of any one of claims 1-53 for use in modulating neurotransmission.
79. The formulation of any one of claims 1-53 for use in increasing neuroplasticity.
80. Use of the formulation of any one of claims 1-53 for the manufacture of a medicament for the treatment of a medical condition.
81. A metered spray delivery device comprising the formulation of any one of claims 1-53.
82. The device of claim 81, wherein the device is a multi-dose, unit dose, or bi-dose device.
83. The device of claim 81, wherein the device is spray pump, a pre-compression sublingual spray pump, a metered valve device, an actuated spray device, a side actuated spray device, a syringe sublingual spray device, a mucosal atomization device, or an electromechanical pump device.
84. The device of claim 81, configured to administer between about 0.1 mL and about 1.0 mL of the formulation per actuation.
85. A method of treating a medical condition in a subject in need of such treatment, the method comprising administering to the subject the formulation of claim 58.
86. A method of modulating neurotransmission in an individual, comprising administering to the mammal an effective amount of the formulation of claim 58.
87. A method of increasing neuroplasticity in a subject, comprising administering to the subject the formulation of claim 58.
88. The formulation of claim 58 for use in the treatment of a medical condition.
89. The formulation of claim 58 for use in modulating neurotransmission.
90. The formulation of claim 58 for use in increasing neuroplasticity.
91. Use of the formulation of claim 58 for the manufacture of a medicament for the treatment of a medical condition.
92. A metered spray delivery device comprising the formulation of claim 58.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/029173

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC: <b>A61K 36/07</b> (2024.01); <b>A61K 47/10</b> (2024.01); <b>A61K 47/40</b> (2024.01); <b>A61K 9/00</b> (2024.01); <b>A61P 25/30</b> (2024.01); <b>C07D 209/16</b> (2024.01); <b>A61P 25/14</b> (2024.01); <b>A61P 25/24</b> (2024.01) CPC: <b>A61K 36/078</b> ; <b>A61K 47/40</b> ; <b>A61K 9/006</b> ; <b>C07D 209/16</b> ; <b>A61K 47/10</b> ; <b>A61P 25/30</b> ; <b>A61K 2121/00</b> ; <b>A61P 25/24</b> ; <b>A61P 25/14</b>		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols) 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		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2022/0331344 A1 (RESURGENT BIOSCIENCES, INC) 20 October 2022 (20.10.2022) entire document	1-13, 18-23, 59-74, 76-84
Y	US 2015/0005337 A1 (ANTARES PHARMA IPL AG) 01 January 2015 (01.01.2015) entire document	1-13, 18-23, 59-74, 76-84
Y	US 2022/0387339 A1 (ESOLATE LTD) 08 December 2022 (08.12.2022) entire document	7, 8
Y	US 2018/0326090 A1 (CYDEX PHARMACEUTICALS, INC.) 15 November 2018 (15.11.2018) entire document	11-13
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> 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 <b>02 August 2024 (02.08.2024)</b>		Date of mailing of the international search report <b>19 September 2024 (19.09.2024)</b>
Name and mailing address of the ISA/US <b>Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450</b> Facsimile No. <b>571-273-8300</b>		Authorized officer <b>MATOS TAINA</b> Telephone No. <b>571-272-4300</b>

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/029173

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2022/246572 A1 (MINDSET PHARMA INC) 01 December 2022 (01.12.2022) entire document	60-62, 72-74, 76, 78, 79, 81-84
Y	US 2022/0169668 A1 (COMPASS PATHFINDER LIMITED) 02 June 2022 (02.06.2022) entire document	71
A	WO 2022/195011 A1 (CYBIN IRL LIMITED) 22 September 2022 (22.09.2022) entire document	1-13, 18-23, 59-74, 76-84
A	US 2019/0015319 A1 (NORTHRIVER PHARM LLC) 17 January 2019 (17.01.2019) entire document	1-13, 18-23, 59-74, 76-84
A	US 2010/0273895 A1 (STINCHCOMB et al.) 28 October 2010 (28.10.2010) entire document	1-13, 18-23, 59-74, 76-84

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.: **58, 75**  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-57, 59-74, and 76-84 are drawn to sublingual spray formulations, methods of treating thereof, methods of modulating thereof, methods of increasing neuroplasticity thereof, uses thereof, and metered spray delivery devices thereof.

The first invention of Group I+ is restricted to a sublingual spray formulation comprising: i. psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof; ii. a solubilizing agent, wherein the solubilizing agent is a cyclodextrin, wherein the cyclodextrin is sulfobutylether-beta-cyclodextrin; and iii. a solvent system, wherein the solvent system comprises water and propylene glycol; a sublingual spray formulations thereof, methods of treating thereof, methods of modulating thereof, methods of increasing neuroplasticity thereof, uses thereof, and metered spray delivery devices thereof. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed compound species presented in the claims (solubilizing agent – claim 10; solvent system – claim 21). It is believed that claims 1-13, 18-23, 59-74, and 76-84 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a sublingual spray formulation comprising: i. psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof; ii. a solubilizing agent, wherein the solubilizing agent is a cyclodextrin, wherein the cyclodextrin is beta-cyclodextrin; and iii. a solvent system, wherein the solvent system comprises water and propylene glycol, a sublingual spray formulations thereof, methods of treating thereof, methods of modulating thereof, methods of increasing neuroplasticity thereof, uses thereof, and metered spray delivery devices thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the “+” group(s) will result in only the first claimed invention to be searched/examined.

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-13, 18-23, 59-74, 76-84**

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
  - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
  - No protest accompanied the payment of additional search fees.

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the solubilizing agent and solvent system and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a sublingual spray formulation comprising: i. psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof; ii. a solubilizing agent; and iii. a solvent system; about 1.8% to about 2.0% (w/w) of psilocin; ii. about 5% to about 7% (w/w) of sulfobutylether-beta-cyclodextrin; iii. about 0.1% to about 0.2% (w/w) of xanthan gum; iv. about 0.01% to about 1.0% (w/w) of a taste-masking agent; v. about 0.01% to about 1.0% (w/w) of an antioxidant; and vi. about 0.5% to about 2.0% (w/w) of polysorbate 80; iii. about 0.01% to about 0.1% (w/w) of carbomer homopolymer type B; about 5% to about 7% (w/w) of beta-cyclodextrin; a method of treating a medical condition in a subject in need of such treatment thereof; a method of modulating neurotransmission in an individual thereof; a method of increasing neuroplasticity in a subject thereof; use of a formulation thereof; and a metered spray delivery device thereof, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2022/195011 A1 to Cybin Irl Limited, US 2019/0015319 A1 to Northriver Pharm, LLC, US 2010/0273895 A1 to Stinchcomb et al., and WO 2022/246572 A1 to Mindset Pharma Inc.

WO 2022/195011 A1 to Cybin Irl Limited teaches a sublingual spray formulation comprising: i. psilocin, or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof; ii. a solubilizing agent; and iii. a solvent system (Pg. 2, Para. 3, dosage forms of these stabilized forms of psilocin; Pg. 65, Para. 3, solubilizing agents; Pg. 61, Para. 3, sublingual administration; Pg. 55, Para. 2, sprays; Pg. 44, Para. 4, mixed aqueous-organic solvent solution); and about 1.8% to about 2.0% (w/w) of psilocin (Pg. 167, Para. 2, API (either psilocin-Jio or psilocybin) (2% w/w)); ii. about 5% to about 7% (w/w) of sulfobutylether-beta-cyclodextrin (Pg. 66, Para. 2, Cyclodextrins such as a-cyclodextrin, b-cyclodextrin ... sulfobutyl ether b-cyclodextrin; Pg. 86, last paragraph, a polymer is present in the solid dispersion in an amount of from about 0% to about 50% by weight); and about 5% to about 7% (w/w) of beta-cyclodextrin (Pg. 66, Para. 2, Cyclodextrins such as a-cyclodextrin, b-cyclodextrin ... sulfobutyl ether b-cyclodextrin; Pg. 86, last paragraph, a polymer is present in the solid dispersion in an amount of from about 0% to about 50% by weight).

US 2019/0015319 A1 to Northriver Pharm, LLC teaches iii. about 0.01% to about 0.1% (w/w) of carbomer homopolymer type B (Para. [0038], the mucoadhesive polymer is present in an amount of about 0.01 to about 30%, by weight of the composition; Para. [0037], Carbomer Homopolymer Type B); iii. about 0.1% to about 0.2% (w/w) of xanthan gum (Para. [0039], the polymer is xanthan gum in an amount of between about 0.25 and about 1%, by weight); iv. about 0.01% to about 1.0% (w/w) of a taste-masking agent (Para. [0050], the flavor or flavoring agent is present in an amount of about 0.1 to about 5%, by weight).

US 2010/0273895 A1 to Stinchcomb et al. teach v. about 0.01% to about 1.0% (w/w) of an antioxidant (Para. [0077], first antioxidant ... in the amount of about less than 1% by weight); and vi. about 0.5% to about 2.0% (w/w) of polysorbate 80 (Para. [0073], polysorbate 80 ... about 0.25% to about 15%, about 0.4% to about 10%, or about 0.5% to about 5%, of the total weight).

WO 2022/246572 A1 to Mindset Pharma Inc. teaches a method of treating a medical condition in a subject in need of such treatment thereof (Claim 17, method of treating or preventing a disease ... subject in need thereof); a method of modulating neurotransmission in an individual thereof (Claim 17, method of treating or preventing a disease ... subject in need thereof; Para. [0004], alterations ... to the brain's serotonergic system and other neurotransmitter systems); a method of increasing neuroplasticity in a subject thereof (Claim 17, method of treating or preventing a disease ... subject in need thereof; Para. [0020], increased neuroplasticity); use of a formulation thereof (Para. [00151], use of one or more hallucinogens); a metered spray delivery device thereof (Para. [00199], metered dose inhaler).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.