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METHODS OF TREATING EATING DISORDERS

FIELD

The present disclosure generally relates to particles comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, pharmaceutical compositions and dosage forms containing these particles, and methods of using pharmaceutical compositions and dosage forms containing these particles to treat subjects suffering from eating disorders.

BACKGROUND

Eating disorders (EDs) and post-traumatic stress disorder (PTSD) are interrelated psychiatric disorders that can have a devastating impact on the afflicted individuals, their families, and society at large. Significantly higher rates of PTSD or PTSD symptoms have been associated with EDs and ED symptoms, and vice versa. EDs and PTSD also share several common risk factors that may contribute their co-occurrence. Both disorders are associated with high degrees of morbidity and mortality, including suicide and self-harm.

EDs are characterized by severe disturbances in eating behavior and body weight (1) and frequently occur adolescents, often leading to multiple psychiatric and somatic complications as well as having a significant negative impact on quality of life, and even mortality (2, 3). See, e.g., Schmidt, et al., Lancet Psychiatry, 2016;3:313–15 and Pasold et al., Clin Child Psychol Psychiatry. 2014;19:299–312. Indeed, individuals with EDs have significantly elevated mortality rates than the same age cohort in the general population. See, e.g., Crow et al., Am J Psychiatry. 2009;166:1342–6.

These disorders can be challenging to treat, as many existing therapies exhibit low efficacy and often have significant undesired side effects. As such, novel treatments for these disorders are needed.

SUMMARY

The present disclosure provides a method of using a pharmaceutically-acceptable empathogenic medicament, administered in a therapeutic setting, to treat a subject suffering from an eating disorder.

In some embodiments, MDMA is isolated as a pharmaceutically acceptable salt of the freebase form of MDMA. This salt is a substantially crystalline solid with a significant number of particles with volume diameters in excess of 600 microns, as determined by laser diffraction. Formulation testing revealed that these larger particles are inadequate for batch consistency and desirable dissolution parameters, creating the need for MDMA solids with reduced particle size and improved particle size uniformity.

MDMA has multiple solid-state forms, including a hydrate that readily forms under ambient conditions, particularly during grinding and in high-humidity environments. To maintain batch consistency in MDMA pharmaceutical formulations, a method of particle size reduction that does not result in hydrate formation is needed.

Provided herein are particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, that maintain a smaller average diameter. Applicant has identified that reducing the crystalline size to about 420 micrometers as measured by Dv90 avoids hydrate formation.

In one aspect, the present disclosure provides particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, substantially smaller than about 610 microns, with a Dv90 below about 420 microns and a particle size range of less than about 400 microns. The improved bulk solid properties of crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, with reduced particle size and increased particle size uniformity provide acceptable batch consistency during the formulation process, enabling the production of pharmaceutically acceptable compositions or pharmaceutically acceptable dosage forms, or salts thereof, as well as a dissolution rate suitable for a high solubility/permeability drug product.

In another aspect, the present disclosure provides a method of producing crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, comprising particles substantially smaller than about 610 microns, with a Dv90 below 420 microns and a particle size range of less than 400 microns, that avoids hydrate formation and maintains suitable flowability in the milled product.

In another aspect, the present disclosure provides pharmaceutical compositions and dosage forms manufactured from crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate

thereof, comprising particles substantially smaller than about 610 microns, with a Dv90 below 420 microns and a particle size range of less than 400 microns.

In another aspect, the present disclosure provides a method of treating subjects suffering from an eating disorder by providing a pharmaceutical composition containing crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, comprising particles substantially smaller than about 610 microns, with a Dv90 below 420 microns and a particle size range of less than 400 microns in a therapeutic setting.

In any of the compositions described herein, substantially all of the crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, particles are smaller than about 610 microns, and the Dv90 is below about 400 microns. In some cases, the Dv90 is from about 0.01 microns to about 400 microns. In some cases, less than 10% of the particles have a particle size (Dv10) below about 10 microns. In some cases, from about 0% to about 10% of the particles have a particle size (Dv10) from about 0.01 microns to about 10 microns. In some cases, the median particle size (Dv50) is from about 100 microns to about 200 microns.

In any of the compositions described herein, the chemical purity is greater than 98% and no single impurity is present in an amount greater than 0.5% as determined by HPLC. In some cases, wherein the chemical purity is greater than 99% and no single impurity is present in an amount greater than 0.5% as determined by HPLC.

In any of the compositions described herein, the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, particles are substantially free of MDMA monohydrate.

In any of the compositions described herein, the dissolution rate in water is greater than or equal to 80% of the mass of the particles in 30 minutes.

In some cases, the compositions described herein comprises about 1 mg to about 150 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some cases, the compositions described herein include about 35 mg to about 45 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some cases, the compositions described herein include about 55 mg to about 65 of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some cases, the compositions described herein include about 75 mg to about 85 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some cases, the compositions described herein include about 95 mg to about 105 mg of

particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some cases, the compositions described herein include comprising about 115 mg to about 125 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

In any of the compositions described herein, the particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are prepared by a process comprising the step of reducing MDMA particle size and increasing MDMA particle size uniformity by screen-milling under an inert atmosphere. In some cases, the coarse MDMA particles do not undergo an additional size-reducing process.

In some cases, the median particle size (Dv50) of coarse MDMA particles is greater than 400 microns. In some cases, the coarse MDMA particles are substantially free of MDMA monohydrate.

In some cases, the coarse MDMA particles are heated to a temperature of 50-70 °C in an environment with an ambient pressure below 1 atmosphere, prior to entering the screen mill. In some cases, the coarse MDMA particles are fed into the screen mill in the absence of applied pressure. In some cases, inert atmosphere in the method is substantially free of moisture. In some cases, the inert atmosphere comprises substantially dry nitrogen gas.

In some cases, the compositions described herein can additionally include a diluent. In some cases, the diluent is a sugar alcohol. In some cases, the diluent has a moisture content of less than 0.25% by mass, prior to blending.

In some cases, the compositions described herein can additionally include a lubricant. In some cases, the lubricant includes a pharmaceutically acceptable salt of a saturated fatty acid.

In some cases, the dosage form (*e.g.*, oral dosage form) can be a capsule. In some cases, the dosage form (*e.g.*, oral dosage form) can be a tablet.

In some cases, the dosage form (*e.g.*, oral dosage form), includes one or more individual dosage units. In some cases, the dosage form includes one individual dosage unit. In some cases, the dosage form includes at least two individual dosage units. In some cases, the dosage form includes at least three individual dosage units. In some cases, each of the one or more individual dosage units comprises a capsule.

In some cases, the one or more individual dosage units are administered during a single therapy session. In some cases, the one or more individual dosage units are administered at different times during the single therapy session.

In some cases, about 100 mg of the particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered. In some cases, wherein the about 100 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered in one dose. In some cases, the about 100 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered in two doses.

In some cases, about 120 mg of the particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered. In some cases, the about 120 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered in one dose. In some cases, the about 120 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered in two doses.

In some cases, about 140 mg of the particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered. In some cases, about 140 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered in one dose. In some cases, the about 140 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered in two doses.

In some cases, about 160 mg of the particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered. In some cases, the about 160 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered in one dose. In some cases, the about 160 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are administered in two doses.

In some cases, the therapeutically effective amount of the MDMA particles is orally administered. In some cases, the therapeutically effective amount of the MDMA particles is administered in a capsule. In some cases, the therapeutically effective amount of the MDMA particles is administered in a tablet.

In some cases, the therapeutically effective amount of the MDMA particles is administered as one or more individual dosage units during a single therapy session. In some cases, the therapeutically effective amount of the MDMA particles is administered at different times during a single therapy session.

In any of the methods described herein, the individual dosage units may be administered during one or more therapy sessions. In some cases, the dosage units may be administered during one therapy session. In some cases, the dosage units may be administered during two therapy sessions. In some cases, the dosage units may be administered during three therapy sessions. In some cases, the dosage units may be administered during more than three therapy sessions.

In any of the methods described herein, the administration of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, during one or more therapy sessions may be used to treat a subject suffering from one or more symptoms of disordered eating. In some cases, the subject may have one or more symptoms of disordered eating associated with an eating disorder. In some cases, the subject may have an eating disorder. In some cases, the subject may have a clinically diagnosed eating disorder. In some cases, the subject may be receiving one or more treatments or therapies for a clinically diagnosed eating disorder. In some cases, the subject may have a history of receiving one or more treatments or therapies for a clinically diagnosed eating disorder. In some cases, the subject may not have received any treatments or therapies for an eating disorder.

In any of the methods described herein, the administration of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, during one or more therapy sessions may be used to treat a subject suffering from an eating disorder. In some cases, the eating disorder is co-associated with a post-traumatic stress disorder. In some cases, the eating disorder is anorexia nervosa. In some cases, the eating disorder is bulimia nervosa. In some cases, the eating disorder is binge eating disorder. In some cases, the eating disorder is orthorexia. In some cases, the eating disorder is eating disorder not otherwise specified (EDNOS). In some cases, the eating disorder is purging disorder. In some cases, the eating disorder is rumination disorder. In some cases, the eating disorder is atypical anorexia nervosa. In some cases, the eating disorder is avoidant/restrictive food disorder. In some cases, the eating disorder is other specified feeding or eating disorder (OSFED).

In any of the methods described herein, the subject being treated for an eating disorder by administration of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, during one or more therapy sessions may have a body mass index (BMI) below, above, or within the "Healthy Weight" range (18.5 to 24.9). In some cases, the subject may have a BMI in the "underweight" range (*i.e.*, below 18.5). In some cases, the subject may have a BMI in the "overweight" range (*i.e.*, 25.0 to 29.9). In some cases, the subject may have a BMI in the "obese" range (*i.e.*, above 30.0). BMI is calculated by dividing a subject's weight in kilograms by square of the same subject's height in meters.

In any of the methods described herein, the subject being treated by administration of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, during one or more therapy sessions may suffer from one or more symptoms of disordered eating.

All publications, patents, patent applications, and information available on the internet and mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, patent application, or item of information was specifically and individually indicated to be incorporated by reference. To the extent publications, patents, patent applications, and items of information incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

Where values are described in terms of ranges, it should be understood that the description includes the disclosure of all possible sub-ranges within such ranges, as well as specific numerical values that fall within such ranges irrespective of whether a specific numerical value or specific sub-range is expressly stated.

Various embodiments of the features of this disclosure are described herein. However, it should be understood that such embodiments are provided merely by way of example, and numerous variations, changes, and substitutions can occur to those skilled in the art without departing from the scope of this disclosure. It should also be understood that various alternatives to the specific embodiments described herein are also within the scope of this disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows exemplary coarse crystalline MDMA hydrochloride particles isolated from the synthetic process

FIG. 2 shows exemplary particles comprising crystalline MDMA after milling

FIG. 3 shows milled MDMA material analyzed via PSD.

FIG. 4 shows an HPLC chromatograph for coarse MDMA crystals isolated from the synthetic process.

FIG. 5 shows a comparison of EAT-26 scores obtained by subjects, before and after completing MDMA- or placebo-assisted therapy.

DETAILED DESCRIPTION

Reference will now be made in detail to certain embodiments of the disclosure, examples of which are illustrated in the accompanying structures and formulas. While the disclosure will be described in conjunction with the enumerated embodiments, it will be understood that the disclosure is not limited to these embodiments. On the contrary, the disclosure is intended to cover all alternatives, modifications, and equivalents that can be included within the scope of the present disclosure as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present disclosure.

Any of the embodiments described herein, including those described under different aspects of the disclosure and different parts of the specification (including embodiments described only in the Examples) can be combined with one or more other embodiments of the disclosure, unless explicitly disclaimed or improper. Combinations of embodiments are not limited to the specific combinations claimed via the multiple dependent claims.

Definitions

As particles are often non-spherical, it is difficult and complex to provide dimensional descriptions of these non-spherical particles. As used herein, "volume diameter" refers to the diameter of a sphere with a volume equivalent to that of the non-spherical particle. In certain embodiments, the particle sizes described herein are measured using a laser diffraction technique that correlates light scattering to particle volume, from which effective length or effective diameter is calculated. The distribution is based on a measurement of thousands of particles. Particle

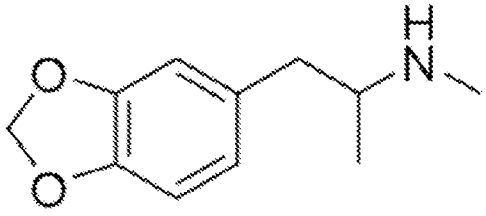
samples can be in dry form, in slurry form, or in the form of suspension. In one embodiment, the particle sample is suspended in a solution of cyclohexane. In another embodiment, the instrument used to determine particle size and distribution is Malvern Mastersizer 3000.

As use herein, particle size is expressed in terms of volume diameter and the particle size distribution is expressed in terms of Dv50, Dv10, and Dv90. A Dv90 value, for example, represents that 90% of particles formed are below a certain threshold. For instance, a Dv90 below 420 μm means that 90% of particles formed have a lower diameter than 420 μm. As used herein, "Dv50", also known as the median particle diameter, corresponds to the value for which 50% of the particles have a lower volume diameter, and 50% of the particles have a higher volume diameter. "Dv90" corresponds to the value for which 90% of the particles have a lower volume diameter, and 10% of the particles have a higher volume diameter. "Dv10" corresponds to the value for which 10% of the particles have a lower volume diameter, and 90% of the particles have a higher volume diameter.

As used herein, "particle size range" corresponds to a value obtained by subtracting the Dv10 from the Dv90. The "Dv10 – Dv90 range" may be calculated from the Dv10 and Dv90 obtained from a single sample, or it may be calculated by averaging the Dv10 and Dv90 values obtained, individually, from a plurality of samples taken from the same batch.

Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example, within 20% of the stated value. As used herein, "about" a specific value also includes the specific value, for example, about 10% includes 10%.

As used herein, the term "MDMA" refers to the compound 3,4-methylenedioxymethamphetamine, having the structure:



In some embodiments, the MDMA is racemic. In some embodiments, the MDMA is (S)-MDMA, in some embodiments, the MDMA is (R)-MDMA. In some embodiments, the MDMA is a non-racemic mixture of (S)-MDMA and (R)-MDMA.

As used herein, the abbreviation API refers to MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. As used herein, API or MDMA can also be referred to as the "active ingredient" or the "active agent.

"Pharmaceutically acceptable composition" refers to a composition that is suitable for administration to a mammal, particularly, a human.

The term "treating" refers to administering a therapy in an amount, manner, or mode effective to improve a condition, symptom, or parameter associated with a disease or disorder. The term "treating" or "treatment" covers the treatment of a disease or disorder described herein, in a subject, such as a human, and includes: (i) inhibiting a disease or disorder, *i.e.*, arresting its development; (ii) relieving a disease or disorder, *i.e.*, causing regression of the disease or disorder; (iii) slowing progression of the disease or disorder; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder.

The term "therapeutic" as used herein means a treatment. A therapeutic effect is obtained by suppression, remission, or eradication of a disease state.

The term "prevent" or "preventative" as used herein means a prophylactic treatment. A preventative effect is obtained by delaying the onset of a disease state or decreasing the severity of a disease state when it occurs.

The term "eating disorder" as used herein means any mental condition in which there is a persistent disturbance of eating behavior either associated with or observed in conjunction with an impairment of physical and/or mental health.

The term "therapeutically effective amount", "prophylactically effective amount", or "effective amount" refers to an amount of the agent that, when administered, is sufficient to cause the desired effect. For example, an effective amount of MDMA particles may be an amount sufficient to have a beneficial effect on the subject (*e.g.*, to lessen symptoms of disease or disorder). The therapeutically effective amount of the agent may vary depending on the tumor being treated and its severity as well as the age, weight, etc., of the subject to be treated. In the methods described herein, the therapeutic compounds may be administered to a subject having one or more signs or symptoms of a disease or disorder.

The term "pharmaceutically acceptable" indicates that the compound, or salt or composition thereof is compatible chemically and/or toxicologically with the other ingredients comprising a formulation and/or the subject being treated therewith.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically acceptable salts may be prepared in situ during the final isolation and purification of the compound, or by separately reacting the purified compound in its free base form with a suitable acid. Suitable acids include pharmaceutically acceptable inorganic acids and pharmaceutically acceptable organic acids. Representative pharmaceutically acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methylnitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, hydroxyacetate, phenyl acetate, propionate, butyrate, isobutyrate, valerate, maleate, hydroxymaleate, acrylate, fumarate, malate, tartrate, citrate, salicylate, p-aminosalicyclate, glycollate, lactate, heptanoate, phthalate, oxalate, succinate, benzoate, o-acetoxybenzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, mandelate, tannate, formate, stearate, ascorbate, palmitate, oleate, pyruvate, pamoate, malonate, laurate, glutarate, glutamate, estolate, methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate, benzenesulfonate (besylate), p-aminobenzenesulfonate, p-toluenesulfonate (tosylate),napthalene-2-sulfonate, ethanedisulfonate, and 2,5-dihydroxybenzoate.

The term "administering" or "administration" of a therapy (*e.g.*, MDMA) to a subject includes any route of introducing or delivering a compound to a subject to perform its intended function. Administration can be carried out by any suitable route, including orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or subcutaneously), or topically. Administration includes self-administration and the administration by another.

The term "subject" refers to any animal amenable to the methods described herein. In some embodiments, the subject is a mammal. In some embodiments, the mammal is a mouse, a rat, a guinea pig, a non-human primate, a dog, a cat, or a domesticated animal (*e.g.*, horse, cow, pig, goat, sheep). In some embodiments, the subject is a human.

"Optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occur and instances where it does not.

All numerical designations, *e.g.*, pH, temperature, time, concentration, amounts, and molecular weight, including ranges, are approximations which are varied (+) or (-) by 10%, 1%> or 0.1%, as appropriate. It is to be understood, although not always explicitly stated, that all

numerical designations may be preceded by the term "about." It is also to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

The term "each," when used in reference to a collection of items, is intended to identify an individual item in the collection but does not necessarily refer to every item in the collection, unless expressly stated otherwise, or unless the context of the usage clearly indicates otherwise.

The term "substantially" is used herein to refer to greater than 90%, preferably greater than 95%, and more preferably greater than 98%. For example, some embodiments described herein refer to a composition comprising MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the composition is substantially free of MDMA hydrate, i.e., of the MDMA present in the composition, less than 10% is MDMA hydrate, preferably less than 5%, and most preferably less than 2%.

To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that wherein a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

MDMA-Assisted Therapy

Some embodiments provide a method for treating a subject suffering from an eating disorder (ED) comprising administering a pharmaceutical composition comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, in a therapeutic environment.

MDMA-assisted therapy has emerged a highly efficacious integrated intervention for subjects with treatment-resistant PTSD (Jerome et al., 2020; Mitchell, J.M. et al., 2021; Mithoefer et al., 2019; Mithoefer et al., 2018; Sessa et al., 2019; Wang et al., 2021). Significantly higher rates of PTSD or PTSD symptoms have been associated with EDs and ED symptoms and vice versa (Dansky et al., 1997; Ferrell et al., 2020; Hudson et al., 2007; Mitchell et al., 2012). EDs and PTSD share several common risk factors that may contribute to their co-occurrence, including female gender, history of personal and/or family psychiatric disorder, history of child maltreatment or other prior traumas, higher trauma dose and severity, personality factors, and lack of social supports (Brewerton, 2018). Both EDs and PTSD have high degrees of morbidity and mortality,

including suicide and self-harm (Arcelus et al., 2011; Fichter and Quadflieg, 2016; Gradus et al., 2010, 2015; Himmerich et al., 2019; Lee et al., 2014; Mandelli et al., 2018; Papadopoulos et al., 2009; Preti et al., 2011; Roberts et al., 2020; Smink et al., 2012; Stein et al., 2010). Individuals with both disorders (ED-PTSD) have significantly greater psychiatric and medical comorbidity, higher symptom severity, higher treatment dropout rates, worse prognosis, and poorer quality of life (Brewerton, 2018; Brewerton et al., 2020; Trottier, 2020).

Many have identified eating disorder treatment as a speculative target for empathogen-assisted therapy, typically using MDMA as a secondary therapeutic agent in conjunction with other substances. WO2022061242A1 discloses novel tryptamine derivatives, and claims both that these tryptamine derivatives offer MDMA-like therapeutic properties with fewer MDMA-associated undesirable side effects *and* that MDMA may be used as a secondary active ingredient in compositions containing the novel tryptamine derivatives. Similarly, WO2021252538A2 and WO2022010937A1 respectively describe a variety of novel benzofurans and benzothiopenes as potential substitutes for MDMA in empathogen-assisted therapy, while also mentioning that co-formulations containing MDMA and one or more of the novel benzofurans or benzothiopenes (respectively) may be useful. US20170312308A1 describes a method of treating anxiety with a xenon-containing composition, which may be used in conjunction with (among many other medicaments) MDMA. WO2023283386A2 describes a therapeutic composition containing a hallucinogenic agent and an empathogen, the latter of which may be MDMA, and proposes that this composition may be used to treat a variety of central nervous system conditions, including eating disorders. WO2022246572A1 describes a formulation containing one or more hallucinogens and one or more fatty acids, which may be used to treat a variety of serotonin receptor-related disorders, including eating disorders. Eating disorder treatment is also referenced as a potential use case for pharmaceutical compositions made from deuterated MDMA derivatives (WO2022038171A1) and non-racemic mixtures of (*R*)- and (*S*)-MDMA (WO2022256720A2). Whether any of one these medicaments is *actually*, rather than speculatively, useful in treating subjects suffering from eating disorders has, to the best of our knowledge, not yet been explored.

Contrastingly, the pharmaceutical compositions comprising particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, substantially smaller than about 610 microns described herein have been demonstrated to reduce symptoms of disordered eating in subjects suffering from comorbid PTSD, when administered in a structured,

therapeutic program. Subjects with eating disorder symptoms meeting the "at-risk" (score ≥ 11) and "clinical" (score ≥ 20) thresholds established by the EAT-26 questionnaire saw meaningful and clinically-significant score reductions following treatment with the MDMA-containing pharmaceutical compositions described herein.

MDMA Particles

In a first aspect, the present disclosure provides 3,4-methylenedioxymethamphetamine particles that have desirable bulk properties and processability for drug product manufacturing. MDMA isolated from the current chemical synthesis is a highly-pure, crystalline solid that is dimensionally unsuitable for drug product manufacturing. The coarse MDMA, with a typical Dv90 from about 800 microns to about 1600 microns and a typical particle size range from about 500 microns to about 1100 microns, does not blend satisfactorily with excipients during the formulation process. The distribution of API and excipient compound(s) in the resultant pharmaceutical composition is uneven, leading to an unacceptably high rate of batch failure. Furthermore, pharmaceutical compositions formulated from coarse MDMA particles do not reliably dissolve at a rate sufficient to ensure a reproducible subject experience.

MDMA has multiple solid-state forms, including a monohydrate that readily forms under ambient conditions, particularly during grinding and in high-humidity environments. The hydrate is significantly more hygroscopic than the API, and can adsorb up to two additional molar equivalents of surface moisture when fine particles are exposed to a high-humidity environment for an extended period of time. It is therefore necessary to reduce MDMA particle size in an environment that is unfavorable for hydrate formation.

It was initially proposed that acceptable MDMA particle size could be achieved by ball-milling the coarse MDMA crystals in the presence of a non-aqueous liquid dispersant. This was undesirable due to the high purity of the MDMA isolate, which was suitable for formulation without an additional purification step. It was unexpectedly discovered that MDMA particles with the reduced particle size and more uniform particle size range necessary for drug product manufacturing can be produced under dry conditions using a screen mill, under an inert atmosphere.

In one embodiment, the MDMA particles of the present disclosure are substantially smaller than about 610 μm. In some embodiments, substantially all of the MDMA particles of the present

disclosure may have volume diameters below about 610 μm. In some embodiments, substantially all of the MDMA particles of the present disclosure may have at least one dimension smaller than about 610 μm.

In one embodiment, the MDMA particles of the present disclosure have a Dv10 from about 5 μm to about 40 μm, a Dv50 from about 100 μm to about 200 μm, a Dv90 from about 250 μm to about 420 μm, to about a particle size range from about 250 μm to about 350 μm. In certain embodiments, the Dv90 value for the MDMA particles of the present disclosure is from about 250 μm to about 420 μm, from about 250 μm to about 400 μm, from about 250 μm to about 380 μm, from about 270 μm to about 380 μm, from about 270 μm to about 360 μm, from about 270 μm to about 350 μm, from about 270 μm to about 420 μm, from about 290 μm to about 420 μm, from about 290 μm to about 400 μm, from about 290 μm to about 380 μm, from about 310 μm to about 420 μm, from about 310 μm to about 400 μm, from about 310 μm to about 380 μm, from about 330 μm to about 420 μm, from about 330 μm to about 400 μm, from about 330 μm to about 380 μm, from about 350 μm to about 420 μm, from about 350 μm to about 400 μm, or from about 370 μm to about 420 μm.

In one embodiment, the MDMA particles of the present disclosure are more uniformly distributed than are the crude MDMA particles isolated from the synthetic process. In certain embodiments, the MDMA particles of the present disclosure have a particle size range that is less than 400 μm. In one embodiment, the particle size range for the MDMA particles of the present disclosure is in the range of 200 μm to 400 μm, 230 μm to 380 μm, or 250 μm to 350 μm.

In certain embodiments, the coarse MDMA crystals used to form the MDMA particles of the present disclosure are synthesized using the cGMP process disclosed in, for example, Scheme 1 of Nair *et. al.,* ACS Omega 2022, 7, 1, 900–907, which is incorporated herein in its entirety by reference. The chemical purity of these coarse MDMA crystals as determined by a validated HPLC methodology may exceed 98% of total peak area. In some embodiments, the chemical purity of the coarse MDMA crystals exceeds 99% of total peak area. In some embodiments, the chemical purity of the coarse MDMA crystals exceeds 99.5% of total peak area. In some embodiments, the chemical purity of the coarse MDMA crystals exceeds 99.9% of total peak area.

Methods of Manufacturing MDMA

The MDMA particles of the present disclosure can be prepared by any suitable processes known in the art. In certain embodiments, the MDMA particles of the present disclosure are prepared by a process described herein.

In one aspect, the present disclosure provides new processes for preparing the MDMA particles of the present disclosure.

In one embodiment, the process comprises the step of reducing MDMA particle size by screen milling under an inert atmosphere. Screen milling processes known in the art can be used in the processes of the present disclosure. In one embodiment, screen milling in the processes of the present disclosure is performed using a conical screen miller, *e.g.*, a Ytron-Quadro Comill. One process of the present disclosure comprises the step of screen milling a batch of coarse particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, until the desired particle size reduction and increased particle uniformity are achieved.

In a first process, the coarse particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are substantially dried under a vacuum at 50-70 °C, then fed into a screen mill under an inert atmosphere that may comprise substantially dry nitrogen or any other substantially dry gas. The solids are fed into the mill in the absence of applied pressure, and captured in a collection bag upon exit.

In certain embodiments, the coarse particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are fed into the screen mill in batches of approximately 250 grams, 500 grams, 1000 grams, or 2000 grams. In certain embodiments, the milling process is conducted at a rate of approximately 10 grams per minute, 15 grams per minute, 20 grams per minute, 25 grams per minute, or 50 grams per minute.

In certain embodiments, the screen milling in the processes described above is carried out by hand-feeding the coarse crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, into the screen mill to avoid compacting and buildup within the mill.

In certain embodiments, a mill speed of 3000, 4000, 5000, 6000, 7000, or 8000 rpm is used.

In certain embodiments, the screen used in the processes described above is a stainless-steel conical screen.

In some embodiments, any one of the processes described above further comprises recovering and storing the MDMA particles after the screen milling step.

Pharmaceutical Compositions

In other aspects, the present disclosure provides pharmaceutical compositions prepared from particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, substantially smaller than about 610 μm, with a Dv90 below 420 microns and a particle size range of less than 400 microns, and one or more pharmaceutically acceptable carriers or excipients. Pharmaceutical compositions prepared from crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, of the present disclosure exhibit negligible or significantly diminished agglomeration during processing, uniform composition, and a high batch success rate. In addition, the pharmaceutical compositions provided by the present disclosure have bulk properties suitable for processing into dosage forms in accordance with other aspects of the present disclosure.

MDMA monohydrate, which those skilled in the art will recognize as a solid-state form of MDMA with one molar equivalent of water in its crystal structure, forms readily from anhydrous MDMA in high-humidity environments or when smaller particles are subjected to moderate pressures. The pharmaceutical compositions of the present disclosure have robust shelf-stability under normal ambient conditions, particularly after being processed into the dosage forms of the present disclosure; however, the ease with which MDMA monohydrate forms under conditions that may be present in certain formulation procedures necessitates additional care during the formulation process. Carriers and excipients used in the present disclosure may have properties that make hydrate formation less favorable during blending or other processing steps.

Any carriers and excipients known in the art may be used in the pharmaceutical compositions of the present disclosure. In certain embodiments, the carriers and excipients used in the pharmaceutical formulations provided by the present disclosure may have reduced hygroscopicity or low residual moisture content.

Pharmaceutical carriers or excipients in accordance with the present disclosure may be selected for their compatibility with a given dosage form. Exemplary excipients for oral formulations include, but are not limited to: diluents, such as microcrystalline cellulose, starch, mannitol, calcium hydrogen phosphate anhydrous or co mixtures of silicon dioxide, calcium carbonate, microcrystalline cellulose and talc; disintegrants, such as sodium starch glycolate or croscarmellose sodium; binders, such as povidone, co povidone or hydroxyl propyl cellulose;

lubricants, such as magnesium stearate or sodium stearyl fumarate; glidants, such as colloidal silicon dioxide; and film coats, such as Opadry II white or PVA based brown Opadry II. Exemplary excipients for topical formulations include, but are not limited to: polymers, such as xanthan gum or hydroxypropyl methylcellulose; preservatives, such as methyl- and propylparaben; surface-acting agents such as sodium lauryl sulfate, phosphatidylcholine, betaines, or polyoxyethylene sorbitan fatty acid esters; and penetration enhancers such as ethanol, dimethyl sulfoxide, dimethyl isosorbide, isopropyl myristate or propylene glycol. Exemplary excipients for respiratory dosage forms include, but are not limited to: propellants such as heptafluoropropane and other hydrofluorocarbons; surface-active agents such as sorbitan trioleate, oleic acid, or sorbitan sesquioleate; solubility enhancers such as ethanol, propylene glycol, or glycerol; flow improvers such as lactose; buffering agents such as sodium citrate or sodium phosphate; osmolality-modifying agents such as sodium chloride or mannitol; antioxidants; and preservatives. Exemplary excipients for parenteral dosage forms include, but are not limited to: bulking agents such as sucrose, mannitol, or sorbitol; buffering agents such as sodium citrate, tris base-65, tris acetate, or sodium phosphate; antioxidants such as acetone sodium bisulfite or ascrobyl palmitate; solubilizing agents such as polyvinyl pyrollidone or lecithin; preservatives such as benzalkonium chloride, paraben propyl, phenol, or thimerosal; lyoprotectants such as sucrose, trehalose, or mannitol; chelating agents such as calcium disodium EDTA or calteridol; and solvents and cosolvents such as castor oil, PEG 300, N-methyl-2-pyrrolidone, or propylene glycol.

In a specific embodiment, a pharmaceutical composition of the present disclosure comprises particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, substantially smaller than about 610 μm, with a Dv90 below 420 microns and a particle size range of less than 400 microns, a binder comprising a polyalcohol, and a lubricant comprising a pharmaceutically acceptable salt of a saturated fatty acid.

Dosage Forms

In other aspects, the present disclosure provides dosage forms comprising particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, substantially smaller than about 610 μm, with a Dv90 below 420 microns and a particle size range of less than 400 microns. The dosage forms provided by the present invention may comprise crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, or

pharmaceutical compositions containing crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, in accordance with any embodiment of the present disclosure. The dosage forms may be intended for topical, oral, nasal, mucosal, respiratory, transdermal, or parenteral administration.

Oral dosage forms provided by the present disclosure may be solid formulations such as tablets, capsules, pills, wafers, films, and lozenges, or liquid formulations such as aqueous solutions, elixirs, and syrups. Solid and liquid formulations in accordance with the present disclosure may also be incorporated into liquid or solid comestibles.

In certain embodiments, the oral dosage forms provided by the present disclosure may comprise encapsulated pharmaceutical formulations provided by any other embodiment of the present disclosure. Capsules used for the oral dosage form of the present disclosure may be hard-shelled or soft-shelled. The capsules may comprise collagenous gelatin, fish gelatin, hydroxypropyl methylcellulose, starch, pullulan, polyvinyl acetate, or any other material known to a person skilled in the art to be useful for encapsulating oral dosage forms.

Topical dosage forms provided by the present disclosure may be liquid formulations such as aqueous solutions and emulsions, which may be applied directly to the skin and/or mucous membranes, or aerosolized for respiratory administration. Alternatively, topical dosage forms provided by the present disclosure may be formulated as creams, foams, gels, lotions, and ointments.

Respiratory dosage forms provided by the present disclosure may comprise solid compositions formulated for use in dry-powder inhalers, or liquid compositions formulated for use in metered-dose inhalers or nebulizers.

Parenteral dosage forms provided by the present disclosure may comprise liquid solutions, suspensions, emulsions, or reconstituted lyophilized powders, suitable for administration by injection.

In some embodiments, the dosage forms of the present disclosure are oral dosage forms comprising a capsule formed from a cellulose-based polymer, crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more carriers or excipients.
In certain embodiments, the oral dosage forms of the present disclosure may contain 20 mg of the API, 25 mg of the API, 30 mg of the API, 35 mg of the API, 40 mg of the API, 45 mg of the API, 50 mg of the API, 55 mg of the API, 60 mg of the API, 65 mg of the API, 70 mg of the API, 75

mg of the API, 80 mg of the API, 85 mg of the API, 90 mg of the API, 95 mg of the API, 100 mg of the API, 105 mg of the API, 110 mg of the API, 115 mg of the API, 120 mg of the API, 125 mg of the API, 130 mg of the API, 135 mg of the API, or 140 mg of the API.

Methods of Use

Diagnosis of an eating disorder can use a variety of assessments, tests, or questionnaires. Non-limiting examples of eating disorder assessments include the eating attitudes test, Ben-Tovim Walker body attitudes questionnaire, the body attitudes test, the eating disorder inventory, and the SCOFF questionnaire.

The Eating Attitudes Test (EAT or EAT-26) is a standardized self-reported questionnaire of symptoms and concerns characteristic of eating disorders. The EAT-26 uses a six-point scale based on how often the individual engages in specific behaviors. The questions may be answered: Always, Usually, Often, Sometimes, Rarely, and Never. Completing the EAT-26 yields a "referral index" based on three criteria: 1) the total score based on the answers to the EAT-26 questions; 2) answers to the behavioral questions related to eating symptoms and weight loss, and 3) the individual's body mass index (BMI) calculated from their height and weight. In some cases, an individual can be recommended for additional care if the individual meets a "cut off" score or threshold on one or more criteria. For example, if an individual score higher than a 20, the individual should be referred to a qualified professional for potential diagnosis of an eating disorder. (See, for example, Garner, D.M., & Garfinkel, P.E. (1979).Psychological Medicine, 9, 273-279.)

The Ben-Tovim Walker Body Attitudes Questionnaire (body attitude questionnaire, BAQ) is a 44 item self-report questionnaire divided into six subscales that measures an individual's attitude towards their own body. The six subscales measured by the BAQ are: overall fatness, self-disparagement, strength, salience of weight, feelings of attractiveness, and consciousness of lower body fat. (See, for example, Ben-Tovim and Walker (1991). Psychological Medicine. 21 (3): 775–84.)

The body attitudes test (BAT) measures an individual's subjective body experience and attitudes towards one's own body. It is a questionnaire composed of twenty items which yields four different factors that evaluate the internal view of the individual's own body. Subjects are asked to score each statement 0–5, 0 meaning they do not relate to the statement at all, and 5

meaning the statement frequently describes their sentiment. The following are examples of questions asked in the assessment:

1. I feel displeased when comparing my body to others.
2. I do not recognize my body as my own.
3. My body is too wide.
4. I am pleased with my body shape.
5. I feel the need to lose weight.
6. I see my breasts as too big.
7. I feel the need to conceal my body in looser clothing.
8. I avoid my reflection because it upsets me.
9. I do not struggle with relaxing.
10. I feel like every aspect of my body is broad.
11. My body negatively weighs on me.
12. There is a dissonance between my body and I.
13. At times, I feel like my body is swollen.
14. I feel threatened by my physical appearance.
15. I take great pride in my body size.
16. I feel like I look pregnant.
17. I always feel very tense.
18. I tend to be jealous of other people's looks.
19. Aspects of my physical appearance scare me.
20. I often scrutinize my own reflection.

The answers to these questions are analyzed to provide information regarding four factors that evaluate the individual's subjective view on their body: negative appreciation of body size, lack of familiarity with one's own body, general body dissatisfaction, and rest factor. (See, for example, Probst et al (1995) Eating Disorders, 3 (2): 133–144.).

The eating disorder inventory is a self-report questionnaire used to assess the presence of eating disorders, (a) anorexia nervosa both restricting and binge-eating/purging type; (b) bulimia nervosa; and (c) eating disorder not otherwise specified including binge eating disorder. There are three versions of the inventory. (See, for example, Garner et al. 1983. International Journal of Eating Disorders. 2 (2): 15–34.).

The original eating disorder inventory (called the eating disorder inventory, EDI) is a 64 questions test, divided into eight subscales. Each question is on a 6-point scale (ranging from "always" to "never"), rated 0–3. The score for each sub-scale is then summed. The 8 subscale scores on the EDI are drive for thinness (an excessive concern with dieting, preoccupation with weight, and fear of weight gain), bulimia, body dissatisfaction, ineffectiveness (assessment of feelings of inadequacy, insecurity, worthlessness and having no control over their lives), perfectionism, interpersonal distrust (reluctance to form close relationships), interoceptive awareness (measures the ability of an individual to discriminate between sensations and feelings, and between the sensations of hunger and satiety), and maturity fears (the fear of facing the demands of adult life).

The eating disorder inventory-2 (EDI-2) retains the original format of the EDI with the inclusion of 27 new items divided into three additional subscales: asceticism (the avoidance of sexual relationships), impulse regulation, and social insecurity (social fears and insecurity). EDI-2 is used for both males and females over age 12

The eating disorder inventory-3 (EDI-3) contains 91 items divided into twelve subscales rated on a 0-4 point scoring system. Three items on the EDI-3 are specific to eating disorders, and 9 are general psychological scales that are relevant to eating disorders. The inventory yields six composite scores: eating disorder risk, ineffectiveness, interpersonal problems, affective problems, over control, and general psychological maladjustment.

The SCOFF questionnaire is a series of five questions used to indicate the presence of an eating disorder. (See, for example, Morgan et al. (2000) West J Med. 172 (3): 164–5.).

Some embodiments provide a method for treating an eating disorder in a subject in need thereof comprising administering a pharmaceutical composition comprising particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutically acceptable salt and/or solvate thereof, substantially smaller than about 610 μm, with a Dv90 below 420 microns and a particle size range of less than 400 microns.

Some embodiments provide a method for treating an eating disorder in a subject in need thereof comprising (a) determining that the subject has an eating disorder; and (b) administering a pharmaceutical composition comprising particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutically acceptable salt and/or solvate thereof, substantially smaller than about 610 μm, with a Dv90 below 420 microns and a particle size range of less than 400 microns.

Some embodiments provide a method for treating an eating disorder, comprising administering to a subject previously identified of diagnosed as having an eating disorder, a pharmaceutical composition comprising particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, substantially smaller than about 610 μm, with a Dv90 below 420 microns and a particle size range of less than 400 microns.

In some embodiments, the method further comprising providing psychotherapy to the subject, for example, in an in-patient and/or out-patient setting.

In certain embodiments, the pharmaceutical composition may be administered in a therapeutic setting. The therapeutic setting may be a medical facility (*e.g.*, a hospital), a practitioner's office, a private home, an outdoor space, or any other building or physical environment designated for MDMA-assisted therapy in accordance with the present disclosure
In certain embodiments, the subject may be suffering from one or more central nervous system disorders, including mood, anxiety, or trauma-linked disorders, such as post-traumatic stress disorder, anxiety disorder, major depressive disorder, obsessive compulsive disorder, bipolar disorder, dysthymic disorder; neurological disorders such as Parkinson's disease, epilepsy, recurrent migraines, stroke, or post-concussion syndrome; alcohol use disorder; attention deficit hyperactivity disorder (ADHD); eating disorders such as anorexia nervosa, bulimia, or binge eating disorder; autism and autism spectrum disorders; neuropsychiatric diseases or disorders; or neurodegenerative diseases. In some embodiments, the subject is suffering from an eating disorder.

The pharmaceutical composition may be administered in any pharmaceutically acceptable dosage form, including dosage forms provided in accordance with any embodiment of the present disclosure. The pharmaceutical composition may be administered on one occasion, or on multiple individual occasions.

In certain embodiments, the pharmaceutical composition is administered during two individual therapy sessions, three individual therapy sessions, four individual therapy sessions, five individual therapy sessions, six individual therapy sessions, seven individual therapy sessions, eight individual therapy sessions, nine individual therapy sessions, or ten individual therapy sessions. The individual therapy sessions may occur at regular intervals, *e.g.*, every two weeks, or at non-regular intervals that may vary in accordance with a subject's individual needs or protocols established for treating the subject's indicated disease or disorder.

In some embodiments, an oral dosage form comprising the pharmaceutical composition in accordance with any embodiment of the present disclosure is administered to a subject suffering from a central nervous system disease or disorder. The oral dosage form is administered in a therapeutic setting during multiple individual therapy sessions, wherein at least one therapist is present.

In some embodiments, the pharmaceutical composition is administered in two separate dosage components, an initial dose and a supplementary dose, during the same therapy session. The initial dose may comprise about 25 to about 150 mg of the API, and the supplementary dose may comprise about 10 to about 70 mg of the API.

In some embodiments, the initial and supplementary dosage components are physically separated from each other (*e.g.*, as two capsules, two tablets, or one capsule and one tablet) and are provided in a kit (*e.g.*, a blister pack). In some embodiments, initial and supplementary dosage components are both part of one dosage form (*e.g.*, a pill, a tablet, or a capsule).

In some embodiments, the only active ingredient in the initial and supplemental dosage components, respectively, is MDMA.

EXAMPLES

These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1. Preparation of High-Purity Crystalline MDMA

This example provides methods of preparing high-purity crystalline MDMA. To a 50 L reaction vessel were added 4107.3 g crude MDMA·HCl and 41000 mL 2-propanol. The batch temperature was raised to 67.2 °C, while stirring, and the mixture was then stirred for 30 minutes at 67.2 °C until all of the solids dissolved. Stress-tests had demonstrated stability for 72 hours at 70-80 °C, proving the thermal stability of MDMA·HCl.

The batch was then transferred through a 1.2 μm in-line filter capsule, using positive pressure, to a clean, 50 L reaction vessel, fitted with a jacket that had been pre-heated to 66.1 °C. In this new reaction vessel, the batch was cooled to 55.3 °C, over the course of 90 minutes. 41.1 g of MDMA·HCl Form 1 seed crystal (0.18 mol, 0.008 equivalents) were then added, and the batch

was stirred at the same temperature for 30 minutes. The batch was cooled to 15.2 °C at a rate of 3 °C/hour, then stirred at this temperature for an additional 10 hours.

The white suspension was removed from the mother liquor via vacuum filtration over a filter plate fitted with a filter cloth then washed with 8220 mL 2-propanol. The filter cake was transferred to a drying oven, and dried under vacuum (140 mbar) for 19 hours at 56.6 °C. The collected MDMA·HCl was a white solid weighing 3548.3 g (85.5% yield; 99.95% peak area, 99.64% w/w by HPLC). No single impurity exceeded 0.02% of peak area by HPLC, and residual solvents (methanol, <6 ppm; 2-propanol, 490 ppm) were found to be within the target range.

Example 2. General Description of Screen Milling Process

1911 g MDMA, split into four sub-lots, was fed into an Ytron-Quadro Comill with a stainless steel 610 screen and a rounded mixing drive. The solids were fed into the mill under an inert atmosphere, without pressure applied, and passed directly into a polyethylene collection bag with an earthing cable protecting the equipment from static discharge. A mill speed of 6000 rpm was utilized. The feeding of all four batches was conducted by hand and took place over 30 minutes to avoid a significant build up within the mill. The mass of MDMA recovered from the mill was 1880 g, as measured after analytical sampling. Milling was in general rapid and facile. XRPD data indicated no evidence of MDMA monohydrate formation in any of the four sub-lots. The milled product was found to be 99.9% MDMA by HPLC (100.0% on a dry basis). **FIG. 1** shows MDMA particles before milling, and **FIG. 2** shows MDMA particles after milling. Particle size of MDMA recovered from this experiment for each sample/lot is shown in Table 1. The results show that each of the four sub-lots consistently showed a Dv90 of less than 400 μm.

TABLE 1: Particle Size of MDMA Measured by Laser Diffraction.

Sample	**Dv90**	**Dv50**	**Dv10**
CJS194-1	342 μm	170 μm	29.0 μm
CJS194-2	326 μm	135 μm	20.0 μm
CJS194-3	326 μm	134μm	20.9 μm
CJS194-4	353 μm	161μm	23.8 μm
CJS194-5 (blend of lots 1-4)	341 μm	151 μm	23.4 μm

Input 201101	844 μm	512 μm	376 μm

Example 3. Assessment of Eating Disorder Psychopathology Before and After MDMA-Assisted Therapy (MDMA-AT)

Exploratory data on ED psychopathology were analyzed that were collected as part of a Phase 3 trial (trial ID: NCT03537014, which is herein incorporated by reference in its entirety), which was a double-blind randomized controlled study that compared efficacy and safety of MDMA-AT between placebo and MDMA groups for treatment of PTSD. EAT-26 was included as a pre-specified exploratory measure to assess participants' attitudes about eating and food in addition to the presence of previously undetected EDs. EAT-26 assessments were collected at baseline (visit 4) and study termination (visit 20). This self-reported questionnaire consists of 25 components, each rated on a six-point scale of 0 (Never) to 3 (Always), plus an additional component rated from 0 (Always) to 3 (Never). The 27th item addresses occurrence and frequency of specific eating behaviors, such as binge eating. Scores were combined to produce a total EAT-26 score, ranging from 0 to 78, with lower values indicating fewer symptoms. Participants meeting a total cut-off score of 20 or greater are considered likely candidates for having an ED diagnosis and warrant referral to a qualified professional. Lowering the cut-off score to 11 has been shown to improve sensitivity rates in a wider range of EDs such as binge eating disorder (BED) and eating disorder not otherwise specified (EDNOS) (Orbitello et al., 2006).

Among a total of 90 participants who were randomized and received treatment, 89 participants completed the EAT-26 assessment at baseline, and seven participants withdrew from the study and were missing follow-up data (3 MDMA, 4 placebo). A total of 82 of 90 participants (91.1%) completed both baseline and follow-up EAT-26 assessments and were included in the final analysis. This preliminary analysis of an exploratory measure included only completers of both EAT-26 scores at baseline and follow-up assessments to avoid imputation of data that would attenuate the accuracy of results. Of the 89 initial participants, 15 (15.7%) met criteria for a current ED (binge eating disorder (BED): n = 5; other specified feeding and eating disorder (OSFED): n = 9), and 13 others (14.6%) had a previous history of an ED (anorexia nervosa – binge-purge type (AN-BP); bulimia nervosa (BN): n = 6; OSFED: n = 6). The baseline sample consisted of participants who were majority female (65.2%), identified as women (62.9%), non-Hispanic White

or Latino (89.9%), college graduates (70.8%), and the mean (SD) age was 41.0 (12.00) years. In total, 17 participants had been prescribed sertraline, of which 8 and 9 were assigned to the MDMA and placebo treatment groups, respectively. Furthermore, 6 participants had been prescribed paroxetine, which were equally distributed between MDMA and placebo treatment groups (3 and 3, respectively). At baseline, BMI (kg/m2) scores were in the 'normal' range (BMI 18.5–24.9) in 56.2%, 'overweight' (BMI 25.0–29.9) in 28.1%, and 'obese' (BMI ≥30) in 15.7% of participants. There were no treatment group differences in demographic variables or baseline ACE, BDI-II, CAPS-5, or lifetime C-SSRS assessments. Sample demographics and baseline characteristics are summarized in Table 1. Mean BMI (SD) was 26.0 (4.8) kg/m2 in the MDMA-AT group and 24.8 (4.2) kg/m2 in the PLAC-AT group (t = 1.3, p = .2).

At baseline, 13 (15%) of the 89 participants starting the study had EAT-26 scores ≥20, which is defined as within the "clinical" range (Garfinkel and Newman, 2001; Garner et al., 1982), and 28 (31.5%) had total EAT-26 scores ≥11, which has been defined as an "at risk" range (Orbitello et al., 2006). Among the study completers (n = 82), 11 (13.4%) had baseline EAT-26 scores in the "clinical" range (≥20) and 24 (29.3%) had EAT-26 scores in the "at risk" range (≥11). Otherwise, there were no significant differences in baseline EAT-26 scores between the placebo and MDMA groups in study completers.

In the total sample, there was a significant treatment group difference in EAT-26 change scores between placebo and MDMA groups after adjusting for baseline EAT-26 scores [F (2,79) = 4.68, p = .0335; Hedge's g = 0.33]. The MDMA group had a statistically significant within-subject mean (SD) reduction (improvement) in EAT-26 scores of −3.04 (6.24) from baseline to follow-up (p = .02), and this reduction in EAT-26 scores was significantly greater compared to a reduction of -.68 (8.04) in the placebo group.

Additional subset analyses indicated participants with greater baseline EAT-26 scores generally had significantly greater improvement at follow-up. Approximately 12 (30.0%) placebo and 12 (28.6%) MDMA participants indicated having a baseline EAT-26 score ≥11; and 6 (15.0%) placebo and 5 (11.9%) MDMA participants had baseline EAT-26 score ≥20. In the baseline EAT-26 ≥ 11 subset sample, the MDMA group (women = 7, men = 4, non-binary = 1) had a statistically significant within-subject mean (SD) reduction in EAT-26 scores of −9.58 (7.59) (p = .0007), and this was significantly greater compared to a reduction of −3.58 (14.29) in the placebo group (women = 9, men = 3) [F (2,21) = 9.45; p = .0058; Cohen's d = 0.52]. Analysis of reliable and

clinically meaningful change in the EAT-26 ≥ 11 subset sample showed that only the MDMA group yielded an RCI score indicative of reliable change (RCI = -2.16), compared to an RCI score of −0.43 for the placebo group. In women, the difference in change scores among those with baseline EAT-26 ≥ 11 was statistically significant between MDMA vs. placebo [F (2, 14) = 17.68; p = .0009; Hedge's g = 0.63). Analysis of reliable and clinically meaningful change in women with EAT-26 ≥ 11 showed that the MDMA group produced an RCI score indicative of reliable change (RCI = -2.90), which was not seen in the placebo group (−0.50).

In the baseline EAT-26 ≥ 20 subset sample, there was a statistically significant within-subject mean (SD) reduction in EAT-26 scores in both the placebo group (women = 6) (−13.50, SD = 12.35; p = .01) and MDMA group (women = 5, men = 1) (−14.08, SD = 8.96; p = .0047); however, the treatment group difference was not statistically significant. Analysis of reliable and clinically meaningful change in the EAT-26 ≥ 20 subset sample showed that only the MDMA group yielded an RCI score indicative of reliable change (RCI = -2.83), compared to an RCI score of −1.85 for the placebo group. The reduction in EAT-26 score was determined to be clinically meaningful for both MDMA and placebo groups. In women, the difference in change scores among those with baseline EAT-26 ≥ 20 was statistically significant between MDMA vs. placebo [F (1, 7) = 5.75; p = .0478; Hedge's g = 0.60)]. The change in EAT-26 score for women with baseline EAT-26 ≥ 20 from baseline to follow-up was indicative of reliable change (RCI = -18.80) and was determined to be clinically meaningful. Most significantly, in the placebo group, the proportion of those with EAT-26 ≥ 20 did not change from baseline to follow-up (n = 6, 15.0%); whereas in the MDMA group, the proportion of participants was reduced from 5 (11.90%) to 1 (2.38%).

Example 4. Method of Treating a Subject with MDMA-Assisted Therapy (MDMA-AT)

A flexible dose of MDMA hydrochloride salt (referred to as MDMA throughout) or placebo, followed by a supplemental half-dose unless contraindicated, was administered during the Treatment Period with manualized psychotherapy in three blinded monthly Experimental Sessions. This ~12-week Treatment Period was preceded by three Preparatory Sessions. During the Treatment Period, each Experimental Session was followed by three Integrative Sessions of non-drug psychotherapy. Experimental Sessions were followed by an overnight stay. The Primary Outcome measure, the change in Clinician Administered PTSD Scale (CAPS-5), was assessed by a blinded centralized Independent Rater (IR) pool multiple times throughout the study. Three

blinded manualized Experimental Sessions of psychotherapy assisted by flexible doses of MDMA HCl or placebo were administered (see Table 2 below). Initial doses per Experimental Session include 80 mg or 120 mg MDMA compounded with mannitol and magnesium stearate or indistinguishable weight placebos comprised entirely of mannitol and magnesium stearate, followed 1.5 to 2 hours later by a supplemental half-dose (40 mg or 60 mg MDMA HCl or placebo). Total amounts of MDMA HCl to be administered per Experimental Session range from 80 mg to 180 mg. All drug is encapsulated with HPMC capsules.

Table 2 Dose Regimen of MDMA or Placebo

Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 mg	40 mg	80 mg to 120 mg
2	80 or 120 mg	40 or 60 mg	80 mg to 180 mg
3	80 or 120 mg	40 or 60 mg	80 mg to 180 mg
		Total Cumulative Dose	240 mg to 480 mg

In the first Experimental Session, the initial dose will be 80 mg MDMA HCl or placebo. In the second and third Experimental Sessions, the initial dose may be increased to 120 mg MDMA HCl or placebo unless contraindicated. The choice of whether to keep the dose the same or change it from the first Experimental Session will be made by the therapy team the in consultation with the site physician based on observed response, tolerability to the previously administered dose, and discussion with the participant. In each Experimental Session, 1.5 to 2 hours after the initial dose is given, the participant will be administered a supplemental half-dose unless contraindicated. If an AE requiring medical attention occurs between the initial and supplemental dose this will be evaluated as a potential contraindication by the site physician. If a participant prefers not to take the supplemental dose, the reason will be documented. Participants will not know if they have been assigned MDMA or placebo but can indicate if they want the dose to change or remain the same.

The MDMA assisted therapy (MDMA-AT) approach is detailed in the "Manual for MDMA Assisted Therapy in the Treatment of PTSD," published by MAPS (MDMA Treatment Manual, available at maps.org/treatment-manual), which is incorporated herein in its entirety. Therapy during MDMA-AT sessions consisted of periods of introspection alternating with periods of communication between the participant and the cotherapist dyad. Participants were encouraged to remain with trauma-related memories, feelings, and/or thoughts as the cotherapist dyad provided support. MDMA-AT sessions lasted 6 to 8 hours and ended after drug effects returned to baseline.

Participants remained overnight at the site with a night attendant, except for four participants who did not stay overnight as part of a safety substudy. After each MDMA-AT session, participants received several follow-up visits, including three integrative sessions, where therapists facilitated participants' continued emotional processing, addressed any difficulties following the MDMA-AT session, and helped participants to apply any benefits gained in the MDMA-AT sessions to daily life. Participants worked with the same cotherapist dyad throughout the entire treatment period. The therapeutic approach is detailed in the MDMA Treatment Manual. A detailed treatment protocol can be found in Table 3 below.

Table 3 Treatment Protocol

Treatment Period		
Study Visit	**Visit Duration/ Visit Timing**	**Brief Description of Events**
Randomization	.5 hours/ Within 2 week of Baseline CAPS-5/ 24 to 48 hours before Exp. Session 1	Complete after enrollment and scheduling Exp. Session 1. Enter demographics in Medrio for use in randomization. The participant does not need to be present for this.
Experimental Session 1	8 hours + overnight/ Within 2 weeks of Baseline CAPS-5	8 hours with overnight stay. Dose is 80 mg with supplemental half-dose of 40 mg unless contraindicated.
Experimental Session 2	8 hours + overnight/ 21 to 35 days after Experimental Session 1	The second Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg plus supplemental half-dose unless contraindicated.
Experimental Session 3	8 hours + overnight/ 21 to 35 days after Experimental Session 2	The third Experimental Session lasts 8 hours with an overnight stay. Dose is 80 or 120 mg plus supplemental half-dose unless contraindicated.

Example 5. Method of Treating a Subject with MDMA-Assisted Therapy (MDMA-AT)

Across 12 U.S. study sites and 2 Canadian sites, a total of 37 unique cotherapist dyads provided MDMA-assisted therapy (MDMA-AT) for treatment under clinical supervision among participants with severe post-traumatic stress disorder (PTSD). Sites ranged from one to four cotherapist dyads, and each unique dyad treated one participant. Study participants were recruited from November 2017 to March 2019 via internet advertisements, provider referrals, and by word-of-mouth. Study sites conducted telephone screenings to assess initial eligibility prior to inviting participants on-site for further screening.

Eligibility criteria included confirmation of severe PTSD, which was defined as having a CAPS-5 Total severity score of 35 or greater. Participants were asked to agree to the study protocol including lifestyle modifications. Exclusionary criteria included past or present psychotic disorder, bipolar I disorder, pregnancy or lactation, current diagnosis of a substance use disorder (except for caffeine or nicotine), uncontrolled hypertension, weighing less than 48 kg, and other medical conditions contraindicated for MDMA such as cardiac conditions or cerebrovascular disease. Participants who were at serious risk of suicide or posed a risk to others were also ineligible. Participants with controlled hypertension underwent additional screening to confirm the absence of clinically significant underlying cardiovascular disease. Participants who were enrolled into the study were asked, under the supervision of a physician, to taper off psychiatric medications and any other medications that might have interfered with the effects or metabolism of MDMA.

Treatment

The MDMA-AT therapeutic approach is detailed in the "Manual for MDMA-Assisted Therapy in the Treatment of PTSD," published by MAPS (MDMA Treatment Manual, available at maps.org/treatment-manual). MDMA-AT was conducted over a duration of 9 to 15 weeks. Treatment periods consisted of three preparatory sessions before the first administration of MDMA and three MDMA experimental sessions, in which each session was followed by three integrative sessions. In preparatory sessions, participants met with their cotherapist dyad to develop therapeutic rapport, discuss their PTSD symptoms, and the upcoming MDMA-AT session. Therapists provided information on what to expect during the MDMA-AT sessions, including drug effects and strategies to manage any challenging experiences that may emerge.

Participants were offered a total of three open-label MDMA-AT sessions that were scheduled 3 to 5 weeks apart. In the first experimental session, participants were administered a divided dose of 80 mg MDMA initial + 40 mg MDMA supplemental (United States) or 100 mg MDMA initial + 50 mg MDMA supplemental (Canada). Supplemental doses were administered 1.5 to 2 hours after the initial dose. The purpose of the supplemental dose was to enable a longer period to process trauma during MDMA-AT sessions without significantly impacting the intensity of pharmacodynamic effects. The second and third experimental sessions utilized slightly higher divided doses of 120 mg MDMA + 60 mg MDMA (United States) and 125 mg MDMA + 62.5 mg MDMA (Canada). The nominal difference in MDMA doses between countries was due to drug

availability, where U.S. participants received racemic MDMA synthesized by David Nichols, PhD (Purdue University) and Canadian participants received racemic MDMA from Lipomed AG Switzerland.

Therapy during MDMA-AT sessions consisted of periods of introspection alternating with periods of communication between the participant and the cotherapist dyad. Participants were encouraged to remain with trauma-related memories, feelings, and/or thoughts as the cotherapist dyad provided support. MDMA-AT sessions lasted 6 to 8 hours and ended after drug effects returned to baseline. Participants remained overnight at the site with a night attendant, except for four participants who did not stay overnight as part of a safety substudy. After each MDMA-AT session, participants received several follow-up visits, including three integrative sessions, where therapists facilitated participants' continued emotional processing, addressed any difficulties following the MDMA-AT session, and helped participants to apply any benefits gained in the MDMA-AT sessions to daily life. Participants worked with the same cotherapist dyad throughout the entire treatment period. The therapeutic approach is detailed in the MDMA Treatment Manual.

WHAT IS CLAIMED IS:

1. A method of treating an eating disorder in a subject comprising administering to the subject a therapeutically effective amount of particles comprising crystalline 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, wherein the particles are substantially smaller than about 610 μm.

2. The method of claim 1, wherein the particles comprise crystalline MDMA, or a pharmaceutically acceptable salt thereof.

3. The method of claim 1 or 2, wherein the particles comprise crystalline MDMA hydrochloride.

4. The method of any one of claims 1-3, wherein the Dv90 of the particles is below about 420 μm, and the particle size range (Dv90-Dv10) of the particles is less than about 400 μm.

5. The method of any one of claims 1-4, wherein the Dv90 of the particles is below about 400 μm.

6. The method of any one of claims 1-5, wherein 0-10% of the particles have a particle size from about 0.01 μm to about 10 μm.

7. The method of any one of claims 1-6, wherein the median particle size (Dv50) of the particles is from about 100 μm to about 200 μm.

8. The method of any one of claims 1-8, wherein the chemical purity of the particles is from about 98-100% and no single impurity is present in an amount from 0.5-100% as determined by HPLC.

9. The method of any one of claims 1-8 wherein the chemical purity of the particles is from about 99-100% and no single impurity is present in an amount from 0.5-100% as determined by HPLC.

10. The method of any one of claims 1-9, wherein the particles are substantially free of MDMA monohydrate.

11. The method of any one of claims 1-10, wherein the dissolution rate of the particles in water exceeds 80% by mass, in 30 minutes.

12. The method of any one of claims 1-11, wherein the eating disorder is anorexia nervosa, atypical anorexia nervosa, bulimia nervosa, binge-eating disorder, rumination disorder, avoidant/restrictive food disorder, orthorexia, purging disorder, or other specified feeding or eating disorder (OSFED).

13. The method of any one of claims 1-12, wherein the eating disorder is anorexia nervosa.

14. The method of any one of claims 1-13, wherein the eating disorder is atypical anorexia nervosa.

15. The method of any one of claims 1-12, wherein the eating disorder is bulimia nervosa.

16. The method of any one of claims 1-12, wherein the eating disorder is binge-eating disorder.

17. The method of any one of claims 1-12, wherein the eating disorder is rumination disorder.

18. The method of any one of claims 1-12, wherein the eating disorder is avoidant/restrictive food disorder.

19. The method of any one of claims 1-12, wherein the eating disorder is orthorexia.

20. The method of any one of claims 1-12, wherein the eating disorder is purging disorder.

21. The method of any one of claims 1-12, wherein the eating disorder is other specified feeding or eating disorder (OSFED).

22. The method of any one of claims 1-21, wherein the particles are administered to the subject in a pharmaceutically-acceptable dosage form.

23. The method of any one of claims 1-22, wherein the dosage form comprises about 1 mg to about 150 mg of particles.

24. The method of any one of claims 1-23, wherein the dosage form comprises about 35 mg to about 45 mg of the particles.

25. The method of any one of claims 1-23, wherein the dosage form comprises about 55 mg to about 65 mg of the particles.

26. The method of any one of claims 1-23, wherein the dosage form comprises about 75 mg to about 85 mg of the particles.

27. The method of any one of claims 1-23, wherein the dosage form comprises about 95 mg to about 105 mg of the particles.

28. The method of any one of claims 1-23, wherein the dosage form comprises about 115 mg to about 125 mg of the particles.

29. The method of any one of claims 22-27, wherein the dosage form is an oral dosage form.

30. The method of claim 29, wherein the dosage form additionally comprises a diluent.

31. The method of claim 30, wherein the diluent is a sugar alcohol.

32. The method of claim 30 or 31, wherein the diluent has a moisture content from about 0-0.25% by mass, prior to blending.

33. The method of any one of claims 1-32, wherein the composition additionally comprises a lubricant.

34. The method of claim 33, wherein the lubricant comprises a pharmaceutically acceptable salt of a saturated fatty acid.

35. The method of any one of claims 22-34, wherein the dosage form comprises one or more individual dosage units.

36. The method of claim 35, wherein the dosage form comprises one individual dosage unit.

37. The method of claim 35, wherein the dosage form comprises at least two individual dosage units.

38. The method of claim 35, wherein the dosage form comprises at least three individual dosage units.

39. The method of any one of claims 35-38, wherein each of the one or more individual dosage units comprises a capsule.

40. The method of any one of claims 22-39, wherein the one or more individual dosage units are administered during a single therapy session.

41. The method of any one of claims 22-40, wherein the one or more individual dosage units are administered at different times during the single therapy session.

ABSTRACT

This disclosure describes crystalline 3,4-methylenedioxymethamphetamine (MDMA) particles, pharmaceutical compositions thereof, and oral dosage forms thereof, and methods of using the same to treat an eating disorder in a subject.

51190229.docx

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. _____

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)

Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max):

METHODS OF TREATING EATING DISORDERS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☒ The address corresponding to Customer Number: 26191

OR

☐ Firm or Individual Name

Address

City	State	Zip
Country	Telephone	Email

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Application Data Sheet. See 37 CFR 1.76

☒ Drawing(s) *Number of Sheets* 5

☒ Specification (e.g. description of the invention) *Number of Pages* 38

☐ CD(s), Number of CDs _____

☐ Other (specify) _____

Fees Due: Filing Fee of $300 ($150 for small entity) ($75 for micro entity). If the specification and drawings exceed 100 sheets of paper, an application size fee is also due, which is $420 ($210 for small entity) ($105 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

METHOD OF PAYMENT OF THE FILING FEE AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Applicant must attach form PTO/SB/15A or B or equivalent.

☐ A check or money order made payable to the *Director of the United States Patent and Trademark Office* is enclosed to cover the filing fee and application size fee (if applicable).

☐ Payment by credit card. Form PTO-2038 is attached

☒ The Director is hereby authorized to charge the filing fee and application size fee (if applicable) or credit any overpayment to Deposit Account Number: 06-1050.

$120

TOTAL FEE AMOUNT ($)

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 10 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 2 of 2

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government. (NOTE: Providing this information on a provisional cover sheet, such as this Provisional Application for Patent Cover Sheet (Form PTO/SB/16), does not satisfy the requirement of 35 U.S.C. 202(c)(6), which requires that the specification contain a statement specifying that the invention was made with Government support and that the Government has certain rights in the invention.)

☒ No.

☐ Yes, the invention was made by an agency of the U.S. Government. The U.S. Government agency name is: _____

☐ Yes, the invention was made under a contract with an agency of the U.S. Government.

The contract number is: _____

The U.S. Government agency name is: _____

In accordance with 35 U.S.C. 2020(c)(6) and 37 CFR 401.14(f)(4), the specifications of any United States patent applications and any patent issuing thereon covering the invention, including the enclosed provisional application, must state the following:

"This invention was made with government support under [IDENTIFY THE CONTRACT] awarded by [IDENTIFY THE FEDERAL AGENCY]. The government has certain rights in the invention."

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

SIGNATURE /Michael Portnov/ Date 3/3/2023

TYPED or PRINTED NAME Michael Portnov REGISTRATION NO. 61225 *(if appropriate)*

TELEPHONE +1 (650) 839-5070 Docket Number: 54925-0009P01

51181773.doc

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P01
	Application Number	
Title of Invention	METHODS OF TREATING EATING DISORDERS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City		State/Province		Country of Residence	

Mailing Address of Inventor:

Address 1	
Address 2	

City		State/Province	
Postal Code		**Country**	

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. — Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	26191		
Email Address	apso@fr.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS OF TREATING EATING DISORDERS		
Attorney Docket Number	54925-0009P01	**Small Entity Status Claimed**	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	**Suggested Figure for Publication (if any)**	

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P01
	Application Number	
Title of Invention	METHODS OF TREATING EATING DISORDERS	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	26191		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P01
	Application Number	
Title of Invention	METHODS OF TREATING EATING DISORDERS	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P01
	Application Number	
Title of Invention	METHODS OF TREATING EATING DISORDERS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P01
	Application Number	
Title of Invention	METHODS OF TREATING EATING DISORDERS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
● Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	MAPS Public Benefit Corporation		
Mailing Address Information For Applicant:			
Address 1	3141 Stevens Creek Blvd # 40547		
Address 2			
City	San Jose	**State/Province**	CA
Country	US	Postal Code	95117
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (01-22)
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Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

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Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

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This Application Data Sheet must be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Michael Portnov/			Date (YYYY-MM-DD)	2023-03-03
First Name	Michael	Last Name	Portnov	Registration Number	61225

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (01-22)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P01
	Application Number	
Title of Invention	METHODS OF TREATING EATING DISORDERS	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

FIG. 1

FIG. 2

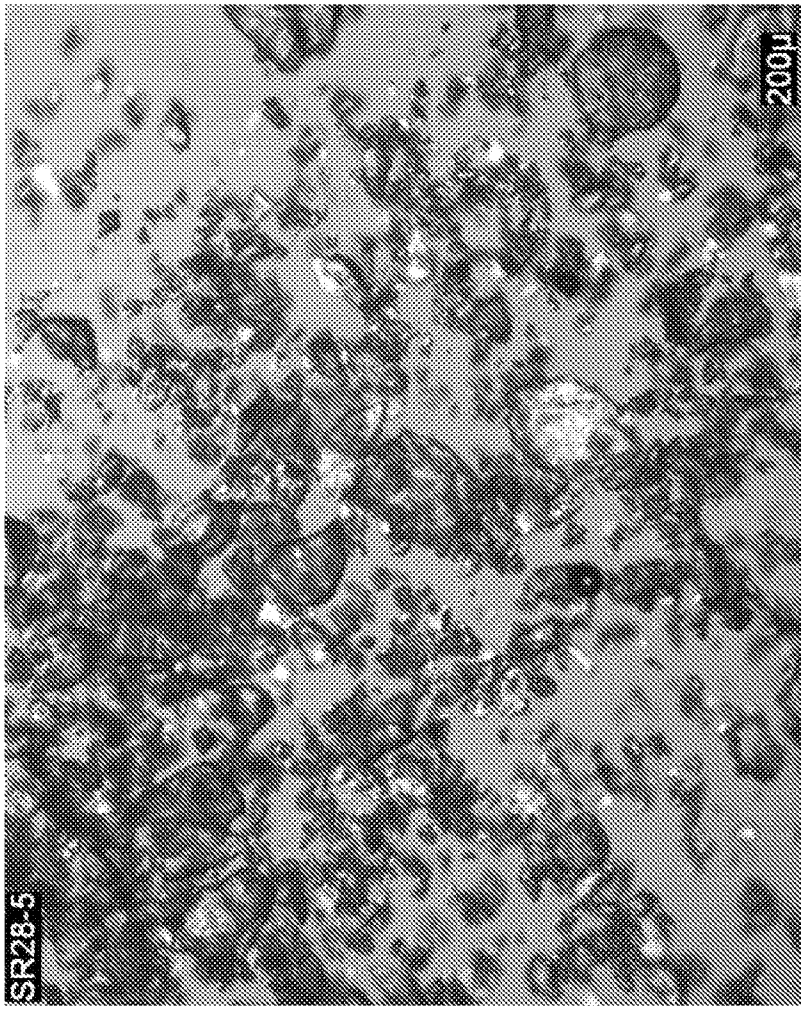


FIG. 3

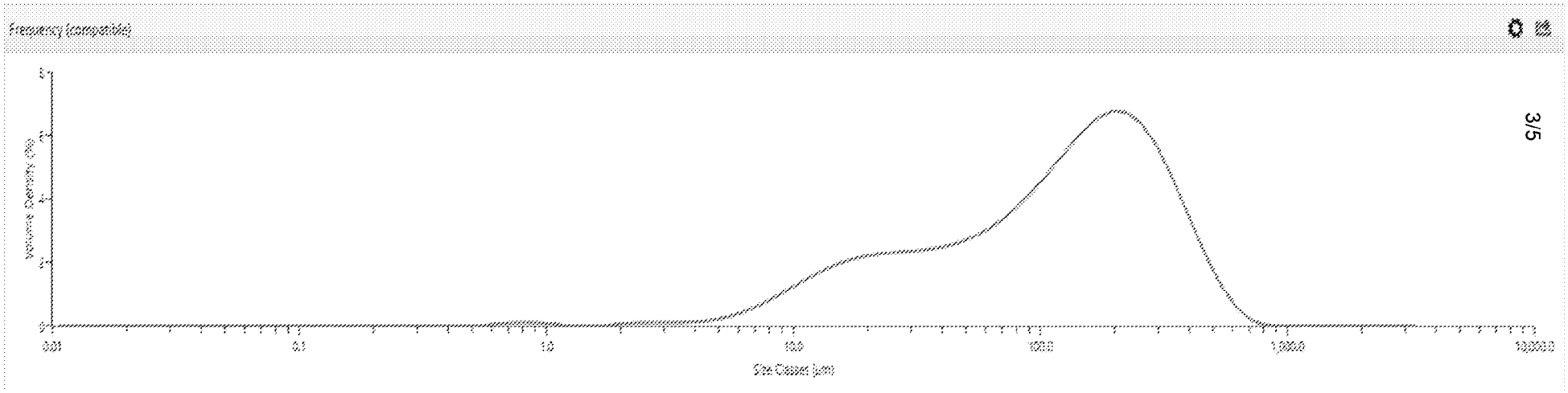
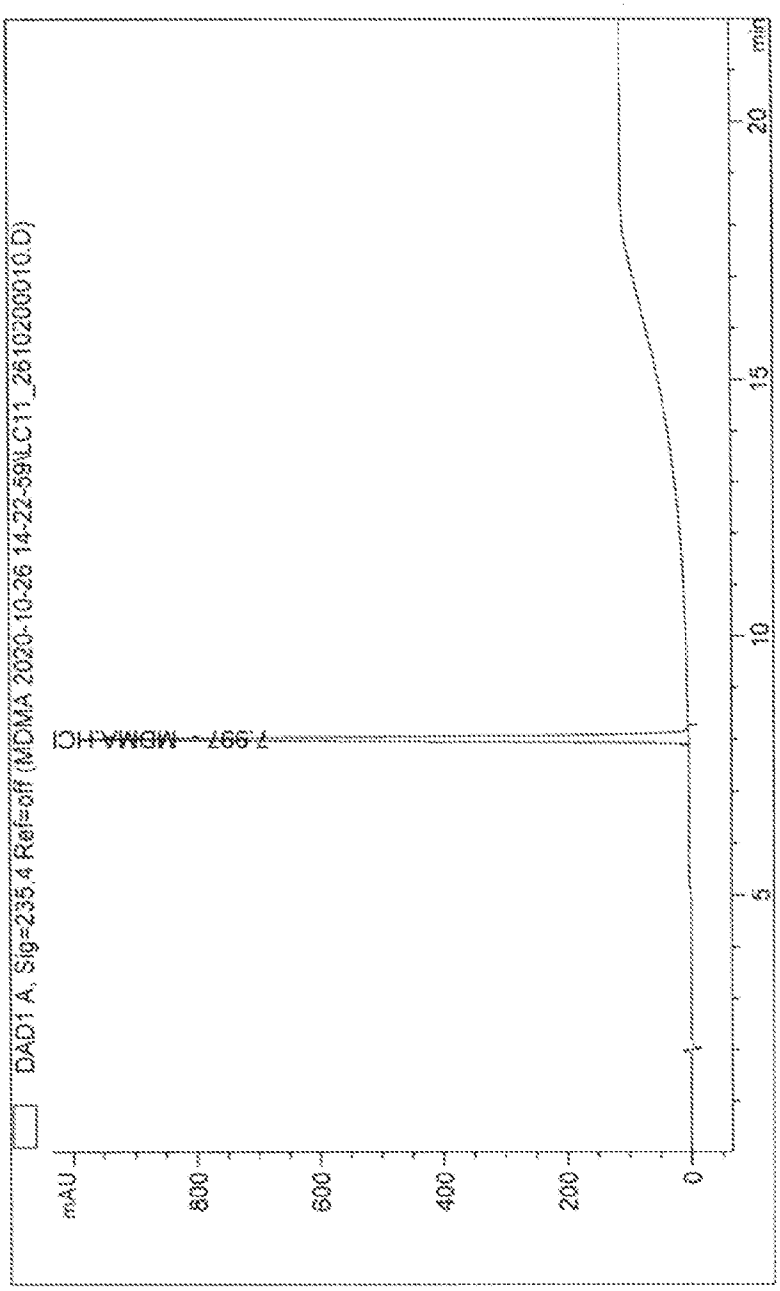


FIG. 4


DAD1 A, Sig=235,4 Ref=off (MDMA 2020-10-26 14-22-59\LC11_26102000\10.D)
mAU
800
600
400
200
0
5
10
15
20
min
MDMA - 7.997

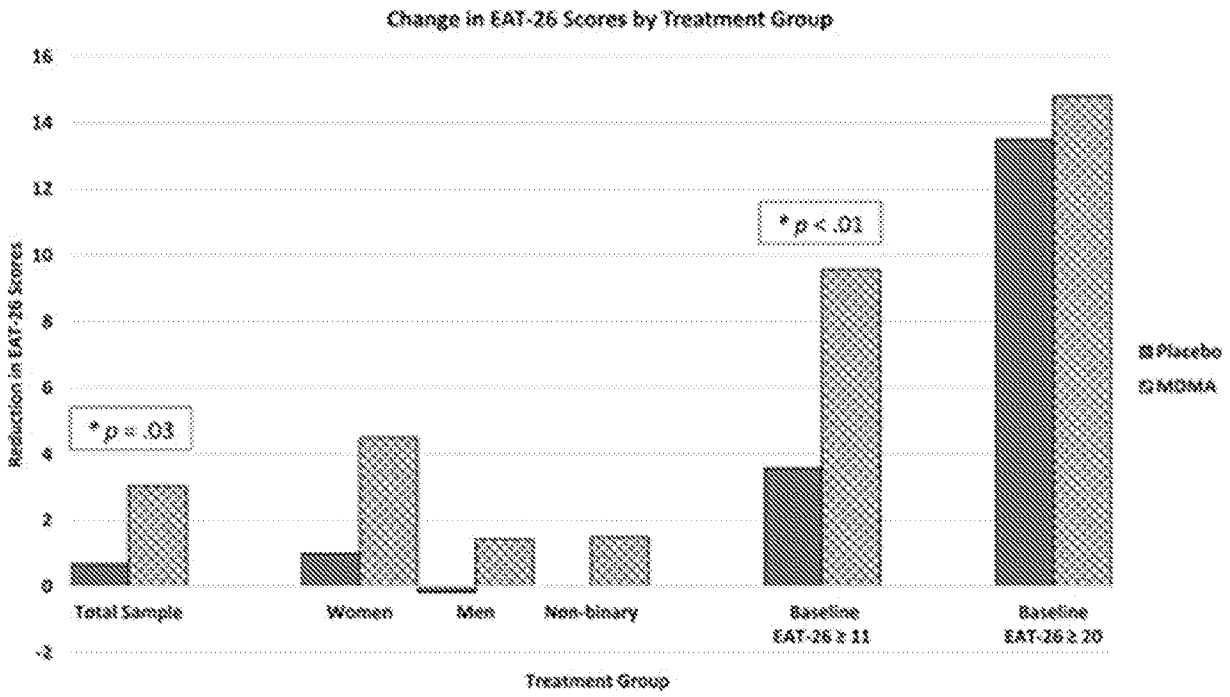

Change in EAT-26 Scores by Treatment Group
Reduction in EAT-26 Scores
16
14
12
10
8
6
4
2
0
-2
* p = .03
* p < .01
Placebo
MDMA
Total Sample
Women
Men
Non-binary
Baseline EAT-26 ≥ 11
Baseline EAT-26 ≥ 20
Treatment Group

FIG. 5

Electronic Acknowledgement Receipt

EFS ID:	47629330
Application Number:	63449928
International Application Number:	
Confirmation Number:	2783
Title of Invention:	Methods of Treating Eating Disorders
First Named Inventor/Applicant Name:	. .
Customer Number:	26191
Filer:	Michael Portnov/Kristine McGuirk
Filer Authorized By:	Michael Portnov
Attorney Docket Number:	54925-0009P01
Receipt Date:	03-MAR-2023
Filing Date:	
Time Stamp:	20:15:36
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$120
RAM confirmation Number	E202333K16455504
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		54925_0009P01_Specification.pdf	559649 2f7d767e09c6c894a69a06fc16b7aefb13dab192	yes	38

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	32
Claims	33	37
Abstract	38	38

Warnings:

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2	Provisional Cover Sheet (SB16)	54925_0009P01_Transmittal.pdf	133701 6315670c529d70cf0ce7eec300edac1ac335f6e6	no	2

Warnings:

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3	Application Data Sheet	54925_0009P01_ADS.pdf	2225663 6fecf029437bd538c3d370f718e145250cc83a10	no	8

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4	Drawings-other than black and white line drawings	54925_0009P01_Figs.pdf	1701742 ba25debdc2a8c531a632f3f1094dbe5d115d3269	no	5

Warnings:

Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	37367 a6b9c25907c5858795c5d6ef357e0b4b2af41f5a	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4658122	

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.