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January 08, 2024

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APPLICATION NUMBER: *63/430,287*
FILING DATE: *December 05, 2022*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US63/430,287*

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Under Secretary of Commerce
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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):

COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME

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

☐ CD(s), Number of CDs _____

☒ Drawing(s) *Number of Sheets* 5

☐ Other (specify) _____

☒ Specification (e.g. description of the invention) *Number of Pages* 30

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.

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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.**

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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: _____

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"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."

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SIGNATURE /Caleb A. Bates/ Date December 5, 2022

TYPED or PRINTED NAME Caleb A. Bates REGISTRATION NO. 77,139 *(if appropriate)*

TELEPHONE +1 (212) 641-2270 Docket Number: 54925-0003P01

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	54925-0003P01
	Application Number	
Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

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	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME		
Attorney Docket Number	54925-0003P01	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	Suggested Figure for Publication (if any)	

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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.

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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).
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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)

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0003P01
	Application Number	
Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

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).

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

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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.

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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.

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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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0003P01
	Application Number	
Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0003P01
	Application Number	
Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

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.

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

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

Mailing Address Information For Assignee including Non-Applicant Assignee:

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Address 2			
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Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

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Signature:

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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	/Caleb Bates/			Date (YYYY-MM-DD)	2022-12-05
First Name	Caleb	Last Name	Bates	Registration Number	77139

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The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

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.

COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME

FIELD

The present invention generally relates to 3,4-methylenedioxymethamphetamine (MDMA) particles, dosage forms, and uses thereof.

BACKGROUND

Central nervous system (CNS) disorders can have a devastating impact on the afflicted individuals, their families, and society at large. These disorders can be challenging to treat, as the therapies often have significant undesired side effects. As such, novel treatments for such disorders are needed.

MDMA has been studied in late stage clinical trials for the treatment of subjects with post-traumatic stress disorder (PTSD). Earlier-stage clinical trials exploring its efficacy in treating a variety of disorders are ongoing.

MDMA has multiple solid-state forms, including a hydrate that readily forms under ambient conditions, particularly during grinding and in high-humidity environments. This results in significant difficulty in preparing consistent, stable, safe, and effective dosage forms of MDMA. As such, novel MDMA formulations are needed.

SUMMARY

The present disclosure is based, in part, on surprising and unexpected discoveries related to particle size in formulations of MDMA and use of such formulations in therapy.

Some embodiments provide a composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size is from about 50 μm to about 400 μm.

Some embodiments provide a dosage form comprising a composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size is from about 50 μm to about 400 μm, and optionally one or more additional pharmaceutically acceptable excipients.

Some embodiments provide a method of treating a subject in need thereof, comprising administering to the subject a dosage form as described herein (i.e., comprising MDMA or a pharmaceutically acceptable salt and/or solvate thereof and one or more pharmaceutically acceptable excipients).

BRIEF DESCRIPTION OF THE DRAWINGS

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

FIG. 2 shows exemplary particles comprising MDMA, a diluent, and a lubricant, after milling

FIG. 3 shows the milled particles of Figure 2 analyzed via PSD.

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

FIG. 5 shows the XRPD spectra of MDMA monohydrate (5A), MDMA Form III (5B), and MDMA Form II (5C).

DETAILED DESCRIPTION

Reference will now be made in detail to certain embodiments of the present disclosure, examples of which are illustrated in the accompanying structures and formulas. While the present disclosure will be described in conjunction with the enumerated embodiments, it will be understood that the present disclosure is not limited to these embodiments. On the contrary, the present 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 present 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 present disclosure, unless explicitly disclaimed or improper. Combinations of embodiments are not limited to the specific combinations claimed via the multiple dependent claims.

Definitions

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. A composition can refer to a product suitable for administration to a subject, but for clarity, compositions for pharmaceutical use are generally referred to as "dosage forms" herein.

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.

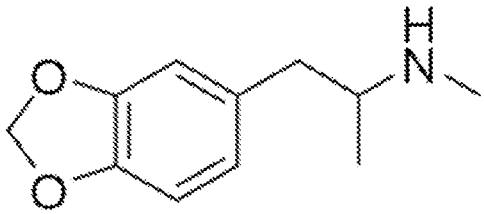
As use herein, particle size is expressed in terms of volume diameter and the particle size distribution is expressed in terms of Dv50, Dv10, and Dv90. A Dv90 value, for example, represents that 90% of particles formed are below a certain threshold. For instance, a Dv90 below 420 μm means that 90% of 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.

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 "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 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.

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.

Particles of MDMA

Consistent dosing to provide safe and effective MDMA levels for treatment has been challenging. Current manufacturing and formulation protocols for therapeutic MDMA provides formulations containing particles with an average particle size in excess of 600 micrometers (μm or micron) (e.g., 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.

The present disclosure provides a solution to this problem.

Some embodiments provide particles of 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof having an average particle size from about 50 μm to about 400 μm.

In some embodiments, the particles have desirable bulk properties and processability for preparing dosage forms suitable for administration to a subject.

MDMA isolated from the current chemical synthesis is a highly-pure, coarse solid with varying particle size. The coarse MDMA, with a typical Dv90 from 800 and 1600 μm and a typical particle size range from 500 μm to 1100 μm, does not yield a uniform blend. The distribution of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, in the resultant dosage form is uneven, leading to an unacceptably high rate of batch failure.

In some embodiments, the particles are substantially smaller than about 610 μm. In some embodiments, substantially all of the particles may have volume diameters below about 610 μm.

In some embodiments, substantially all of the particles may have at least one dimension smaller than about 610 μm.

In some embodiments, the particles 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 about 250 μm to about 420 μm, to a particle size range from about 250 μm to about 350 μm. In certain embodiments, the Dv90 value for the particles 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 some embodiments, the particles are more uniformly distributed than are the crude particles isolated from the synthetic process. In some embodiments, the particles have a particle size range that is less than 400 μm. In some embodiments, the particle size range for the particles is in the range of 200 μm to 400 μm, 230 μm to 380 μm, or 250 μm to 350 μm.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof are synthesized using the cGMP process disclosed in, for example, Scheme 1 of Nair, et al., ACS Omega 20022, 7, pp. 900-907, which is herein incorporated by reference in its entirety for all purposes, including all figures, drawings, and supplemental information.

In some embodiments, the present disclosure provides, in part, particles smaller than about 610 μm in the composition as well as the dosage form. More specifically, particles with reduced particle size and increased particle size uniformity with a Dv90 below about 420 microns provide acceptable batch consistency enabling the production of pharmaceutically acceptable dosage forms.

Some embodiments provide a method of producing particles of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, where the particles are 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.

Some embodiments provide a dosage form and dosage forms manufactured from the composition described herein, i.e., comprising particles substantially smaller than about 610 microns, with a Dv90 below 420 microns and a particle size range of less than 400 microns.

Some embodiments provide a dosage form and dosage forms manufactured from particles larger than 610 microns, but are reduced to the desired particle size of less than 610 microns with a Dv90 below 420 microns during the manufacturing of the finished product by milling or other means with one or more pharmaceutically acceptable excipients.

In some embodiments, substantially all of the particles are (i) smaller than about 610 microns, and (ii) have a Dv90 is below about 400 microns. In some embodiments, the Dv90 is from about 0.01 μm to about 400 μm. In some embodiments, less than 10% of the particles have a particle size (Dv10) below about 10 microns. In some cases, from about 0% and about 10% of the particles have a particle size (Dv10) from about 0.01 μm to about 10 μm. In some embodiments, the median particle size (Dv50) is from about 100 μm and about 200 μm.

In some embodiments, the particles described herein are substantially free of MDMA monohydrate.

In some embodiments, the dissolution in water is greater than or equal to 80% of the mass of the MDMA in 30 minutes.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in amorphous form. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in substantially amorphous form. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in crystalline form. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in substantially crystalline form. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is free of MDMA monohydrate. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially free of MDMA monohydrate. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in one or more forms as described in Nair, et al., supra.

In some embodiments, the particles are prepared by a process comprising the step of reducing particle size and increasing particle size uniformity by screen-milling under an inert atmosphere.

In some cases, the particles are prepared by a process comprising the step of reducing particle size and increasing particle size uniformity by screen-milling. In some cases, the coarse particles do not undergo an additional size-reducing process.

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

In some cases, the coarse 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 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 embodiments, the particles consist essentially of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

Particles of MDMA and Excipient(s)

Some embodiments provide a composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size is from about 50 μm to about 400 μm.

In some embodiments, the composition have desirable bulk properties and processability for preparing dosage forms suitable for administration to a subject.

MDMA isolated from the current chemical synthesis is a highly-pure, coarse solid with varying particle size. The coarse MDMA, with a typical Dv90 from 800 and 1600 μm and a typical particle size range from 500 μm to 1100 μm, does not yield a uniform blend. The distribution of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, in the resultant dosage form is uneven, leading to an unacceptably high rate of batch failure.

It was initially proposed that acceptable particle size could be achieved by ball-milling the coarse particles 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 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. Alternatively, the particle of the desired particle size can be produced by milling of the blends of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and other pharmaceutically acceptable excipient(s) or by other processes such as wet granulation.

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

In some embodiments, the particles 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 about 250 μm to about 420 μm, to a particle size range from about 250 μm to about 350 μm. In certain embodiments, the Dv90 value for the particles 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 some embodiments, the particles are more uniformly distributed than are the crude particles isolated from the synthetic process. In some embodiments, the particles have a particle size range that is less than 400 μm. In some embodiments, the particle size range for the particles is in the range of 200 μm to 400 μm, 230 μm to 380 μm, or 250 μm to 350 μm.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, used to form the particles are synthesized using the cGMP process disclosed in, for example, Scheme 1 of Nair, et al., supra. .

In some embodiments, the present disclosure provides, in part, particles smaller than about 610 μm in the composition as well as the dosage form. More specifically, particles with reduced particle size and increased particle size uniformity with a Dv90 below about 420 microns provide acceptable batch consistency enabling the production of pharmaceutically acceptable dosage forms.

Some embodiments provide a method of producing a composition 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, wherein the particles comprise MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

Some embodiments provide a dosage form and dosage forms manufactured from the composition described herein, i.e., comprising particles substantially smaller than about 610 microns, with a Dv90 below 420 microns and a particle size range of less than 400 microns.

Some embodiments provide a dosage form and dosage forms manufactured from particles larger than 610 microns, but are reduced to the desired particle size of less than 610 microns with a Dv90 below 420 microns during the manufacturing of the finished product by milling or other means with one or more pharmaceutically acceptable excipients.

In some embodiments, substantially all of the particles are (i) smaller than about 610 microns, and (ii) have a Dv90 is below about 400 microns. In some embodiments, the Dv90 is from about 0.01 μm to about 400 μm. In some embodiments, less than 10% of the particles have a particle size (Dv10) below about 10 microns. In some cases, from about 0% and about 10% of the particles have a particle size (Dv10) from about 0.01 μm to about 10 μm. In some embodiments, the median particle size (Dv50) is from about 100 μm and about 200 μm.

In some embodiments, the particles described herein are substantially free of MDMA monohydrate.

In some embodiments, the dissolution in water is greater than or equal to 80% of the mass of the MDMA in 30 minutes.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in amorphous form. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in substantially amorphous form. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in crystalline form. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in substantially crystalline form. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is free of MDMA monohydrate. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially free of MDMA monohydrate. In some embodiments, the MDMA,

or a pharmaceutically acceptable salt and/or hydrate thereof, is present in one or more forms as described in Nair, et al., supra.

In any of the compositions described herein, the particles are prepared by a process comprising the step of reducing particle size and increasing particle size uniformity by screen-milling under an inert atmosphere.

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, in the compositions described herein the desired particle size and particles size uniformity is achieved in the process of making the finished dosage form by milling or other means.

In some embodiments, 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 particles are prepared by a process comprising the step of reducing particle size and increasing particle size uniformity by screen-milling. In some cases, the coarse particles do not undergo an additional size-reducing process.

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

In some cases, the coarse 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 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 embodiments, the particles consist essentially of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

Dosage Forms

Some embodiments provide a dosage form comprising a composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate

thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size is from about 50 μm to about 400 μm; and optionally one or more additional pharmaceutically acceptable excipients.

Exemplary, non-limiting pharmaceutically acceptable excipients are described below. Additional excipients and general methods for preparing the types of dosage forms described herein can be found in, for example, Remington: The Science and Practice of Pharmacy, 23rd Edition (Elsevier Science, Amsterdam, NL. 2020). Such pharmaceutically acceptable excipients include, but are not limited to, binders, glidants, disintegrants, lubricants, carriers, diluents, buffers, tonicity modifying agents, polymers, thickening agents, penetration enhancers, surfactants, and solubility enhancers. *See, e.g.,* Remington's, *supra*. Some pharmaceutically acceptable excipients can be in more than one of the foregoing sub-categories. Pharmaceutically acceptable excipients also include dosage form coatings, for example, an extended release coating, abuse-deterrent coating, or a film-coating.

In some embodiments, pharmaceutically acceptable excipients used herein have reduced hygroscopicity and/or low residual moisture content.

In some embodiments, the pharmaceutically acceptable excipients used herein are independently selected from the group consisting of: microcellulose, lactose, starch, mannitol, calcium hydrogen phosphate anhydrous, silicon dioxide, calcium carbonate, microcellulose, talc, sodium starch glycolate, croscarmellose sodium, povidone, co povidone or hydroxyl propyl cellulose, magnesium stearate, sodium stearyl fumarate, and colloidal silicon dioxide.

In some embodiments, the dosage form comprises particles substantially smaller than about 610 μm, with a Dv90 below 420 μm and a particle size range of less than 400 μm. The dosage forms comprise MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, in accordance with any embodiment as described herein. The dosage forms may be intended for topical, oral, nasal, mucosal, respiratory, transdermal, or parenteral administration.

The dosage forms provided herein include, but are not limited to, 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 invention may also be incorporated into liquid or solid comestibles.

In some embodiments, the dosage form comprises encapsulated pharmaceutical formulations provided by any other embodiment as described herein. Capsules used for the dosage

form 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 dosage forms.

In some embodiments, the dosage form comprises liquid formulations formulated for topical administration, 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 invention may be formulated as creams, foams, gels, lotions, and ointments.

In some embodiments, the dosage form comprises solid compositions formulated for respiratory or inhalation administration, for example, for use in dry-powder inhalers, or liquid compositions formulated for use in metered-dose inhalers or nebulizers.

In some embodiments, the dosage form comprises a liquid solutions formulated for parenteral administration, such as suspensions, emulsions, or reconstituted lyophilized powders, suitable for administration by injection.

In some embodiments, the dosage form is a capsule, for example a cellulose-based capsule containing the composition described herein.

In some embodiments, the dosage form comprises about 1 mg to about 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the dosage form comprises about 1 mg to about 50 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the dosage form comprises about 25 mg to about 75 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the dosage form comprises about 50 mg to about 100 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the dosage form comprises about 75 mg to about 125 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the dosage form comprises about 100 mg to about 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

In some embodiments, the dosage form comprises about 12.5 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 37.5 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 62.5 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about

115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

In some embodiments, the dosage form comprises 12.5 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 37.5 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 62.5 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

In some embodiments, the dosage form comprises about 12.5 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 37.5 mg, about 40 mg, about 50 mg, about 60 mg, about 62.5 mg, about 75 mg, about 80 mg, about 100 mg, or about 125 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

In some embodiments, the dosage form comprises 12.5 mg, 15 mg, 20 mg, 25 mg, 30 mg, 37.5 mg, 40 mg, 50 mg, 60 mg, 62.5 mg, 75 mg, 80 mg, 100 mg, or 125 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

In some embodiments, the dosage form comprises particles 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 excipients.

In some embodiments, the dosage form comprises particles substantially smaller than about 610 microns that are products in the process of manufacturing the finished dosage forms by milling of the MDMA blends with suitable pharmaceutically excipients as described herein.

In some embodiments, the dosage form comprises particles 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.

In some embodiments, the dosage form is substantially free of MDMA monohydrate. In some embodiments, the dosage form comprises no detectable MDMA monohydrate.

In some embodiments, the dosage form (*e.g.*, 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 embodiments, 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.

Methods of Use

Some embodiments provide a method of treating a subject in need thereof, comprising administering to the subject a dosage form as described herein (i.e., comprising MDMA or a pharmaceutically acceptable salt and/or solvate thereof and one or more pharmaceutically acceptable excipients).

In certain embodiments, the dosage form may be administered in a therapeutic setting.

Some embodiments provide a method of treating a subject having one or more central nervous system (CNS) disorders, comprising administering to the subject a dosage form as described herein (i.e., comprising MDMA or a pharmaceutically acceptable salt and/or solvate thereof and one or more pharmaceutically acceptable excipients).

In some embodiments, the one or more CNS disorders are independently mood, anxiety, or trauma-linked disorders.

In some embodiments, the one or more CNS disorders are independently autism spectrum disorders, neuropsychiatric diseases or disorders; or neurodegenerative diseases.

In some embodiments, the one or more CNS disorders are independently post-traumatic stress disorder (PTSD), anxiety disorder, major depressive disorder, obsessive compulsive disorder, bipolar disorder, dysthymic disorder; Parkinson's disease, epilepsy, recurrent migraines, stroke, or post-concussion syndrome; alcohol use disorder; attention deficit hyperactivity disorder (ADHD), anorexia nervosa, bulimia, binge eating disorder, or autism.

In some embodiments, the one or more CNS disorders is PTSD. In some embodiments, the one or more CNS disorders is treatment-resistant PTSD.

The dosage form may be administered in any pharmaceutically acceptable dosage form, including dosage forms provided in accordance with any embodiment as described herein. The dosage form may be administered on one occasion, or on multiple individual occasions.

In certain embodiments, the dosage form is administered during individual therapy. 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, the dosage form in accordance with any embodiment is orally administered to a subject suffering from a central nervous system disease or disorder. The dosage form is administered in a therapeutic setting during multiple individual therapy sessions, wherein at least one therapist is present.

In some embodiments, the dosage form is orally 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 MDMA or a pharmaceutically acceptable salt and/or solvate thereof, and the supplementary dose may comprise about 10 mg to about 70 mg of MDMA or a pharmaceutically acceptable salt and/or solvate thereof. 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 central nervous system disorder is a trauma-linked disorder or a stressor-linked disorder. In some cases, the central nervous system disorder is a mood disorder. In some cases, wherein the central nervous system disorder is an anxiety disorder. In some cases, the central nervous system disorder is post-traumatic stress disorder.

In some embodiments, the administering is performed during a therapy session. In some cases, the dosage form comprising about 100 mg of MDMA is administered. In some cases, about 100 mg of MDMA is administered in one dose. In some cases, about 100 mg of MDMA is administered in two doses.

In some embodiments, the dosage form comprising about 120 mg of MDMA is administered. In some cases, about 120 mg of MDMA is administered in one dose. In some cases, the about 120 mg of MDMA is administered in two doses.

In some embodiments, the dosage form comprising about 140 mg of MDMA is administered. In some cases, about 140 mg of MDMA is administered in one dose. In some cases, the about 140 mg of MDMA is administered in two doses.

In some embodiments, the dosage form comprising about 160 mg of MDMA is administered. In some cases, the about 160 mg of MDMA is administered in one dose. In some cases, the about 160 mg of MDMA is administered in two doses.

In some embodiments, the dosage form comprising the therapeutically effective amount of MDMA is orally administered. In some cases, the dosage form comprising the therapeutically effective amount of MDMA is administered in a capsule. In some cases, the dosage form comprising the therapeutically effective amount of MDMA is administered in a tablet.

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

EMBODIMENTS

1. A particle comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the particle is substantially smaller than about 610 μm.

2. The particle of embodiment 1, wherein the Dv90 is below about 420 μm, and the particle size range (Dv90-Dv10) is less than about 400 μm,

3. The particle of embodiment 2, wherein the Dv90 is below about 400 μm.

4. The particle of embodiments 1-3, wherein 0-10% of the particles have a particle size (Dv10) from about 0.01 μm to about 10 μm.

5. The particle of any one of the preceding embodiments, wherein the median particle size (Dv50) is from about 100 μm and about 200 μm.

6. The particle of any one of the preceding embodiments, wherein the chemical purity is from about 98-100% and no single impurity is present in an amount from about 0.5% to about 100% as determined by HPLC.

7. The particle of any one of the preceding embodiments, wherein the chemical purity is from 99-100% and no single impurity is present in an amount from about 0.5% to about 100% as determined by HPLC.

8. The particle of any one of the preceding embodiments, wherein the particle is substantially free of MDMA monohydrate.

9. A dosage form comprising the particles of any one of the preceding embodiments and a pharmaceutically acceptable salt.

10. The dosage form of embodiment 9, comprising about 1 mg to about 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

11. The dosage form of embodiment 9 or 10, comprising about 35 mg to about 45 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

12. The dosage form of any one of embodiments 9-11, comprising about 55 mg to about 65 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

13. The dosage form of any one of embodiments 9-12, comprising about 75 mg to about 85 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

14. The dosage form of any one of embodiments 9-13, comprising about 95 mg to about 105 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

15. The dosage form of any one of embodiments 9-14, comprising about 115 mg to about 125 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

16. The dosage form of any one of embodiments 9-15, wherein the dissolution rate in water exceeds 80% of the MDMA, by mass, in 30 minutes.

17. The dosage form of any one of embodiments 9-16, wherein the particles are prepared by a process comprising the step of reducing the particle size and increasing particle size uniformity by screen-milling under an inert atmosphere.

18. The dosage form of any one of embodiments 9-17, wherein the dosage form additionally comprises a diluent.

19. The dosage form of embodiment 18, wherein the diluent is a sugar alcohol.

20. The dosage form of embodiment 18 or 19, wherein the diluent has a moisture content from 0% to about 0.25% by mass, prior to blending.

21. The dosage form of embodiment 9, wherein the composition additionally comprises a lubricant.

22. The dosage form of embodiment 21, wherein the lubricant comprises a pharmaceutically acceptable salt of a saturated fatty acid.

23. The dosage form of any one of embodiments 9-22, wherein substantially all of the particles are smaller than about 610 μm.

24. The dosage form of any one of embodiments 9-23, wherein the Dv90 of the particles is from about 0.01 μm to about 400 μm.

25. The dosage form of any one of embodiments 9-24, wherein from about 0-10% of the particles have a particle size (Dv10) from about 0.01 μm to about 10 μm.

26. The dosage form of any one of embodiments 9-25, wherein the median particle size (Dv50) of the particles is from 100 μm to 200 μm.

27. The dosage form of any one of embodiments 9-26, wherein the chemical purity of the particles is from about 98-100% and no single impurity is present in an amount from about 0.5% to about 100% as determined by HPLC.

28. The dosage form of any one of embodiments 9-27, wherein the chemical purity of the particles is 99-100% and no single impurity is present in an amount from about 0.5% to about 100% as determined by HPLC.

29. The dosage form of any one of embodiments 9-27, wherein the particles are prepared by a process comprising the step of reducing particle size and increasing particle size uniformity by screen-milling under an inert atmosphere.

30. The dosage form of any one of embodiments 9-29, which is a capsule.

31. The dosage form of any one of embodiments 9-29, which is a tablet.

32. The dosage form of any one of embodiments 9-31, further comprising a diluent.

33. The dosage form of embodiment 32, wherein the diluent is a sugar alcohol.

34. The dosage form of embodiment 32 or 33, wherein the diluent has a moisture content of about 0-0.25% by mass, prior to blending.

35. The dosage form of any one of embodiments 9-34, comprising one or more individual dosage units.

36. The dosage form of embodiment 35, comprising one individual dosage unit.

37. The dosage form of embodiment 36, comprising at least two individual dosage units.

38. The dosage form of embodiment 37, comprising at least three individual dosage units.

39. The dosage form of any one of embodiments 48-51, wherein each of the one or more individual dosage units comprises a capsule.

40. The dosage form of any one of embodiments 48-52, wherein the one or more individual dosage units are administered during a single therapy session.

41. The dosage form of any one of embodiments 48-53, wherein the one or more individual dosage units are administered at different times during the single therapy session.

42. A method of treating a central nervous system disorder in a subject, the method comprising: administering to the subject a therapeutically effective amount of the particles of any one of embodiments 1-8 or the dosage form of any one of embodiments 9-42.

43. The method of embodiment 42, wherein the central nervous system disorder is a trauma-linked disorder or a stressor-linked disorder.

44. The method of embodiment 42, wherein the central nervous system disorder is a mood disorder.

45. The method of embodiment 42, wherein the central nervous system disorder is an anxiety disorder.

46. The method of embodiment 42, wherein the central nervous system disorder is post-traumatic stress disorder.

47. The method of any one of embodiments 42-46, wherein the administering is performed during a therapy session.

48. The method of any one of embodiments 42-47, wherein about 100 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered.

49. The method of embodiment 48, wherein the about 100 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in one dose.

50. The method of embodiment 48, wherein the about 100 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in two doses.

51. The method of any one of embodiments 42-50, wherein about 120 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered.

52. The method of embodiment 51, wherein the about 120 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in one dose.

53. The method of embodiment 51, wherein the about 120 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in two doses.

54. The method of any one of embodiments 42-53, wherein about 140 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered ministered.

55. The method of embodiment 54, wherein the about 140 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in one dose.

56. The method of embodiment 54, wherein the about 140 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in two doses.

57. The method of any one of embodiments 42-56, wherein about 160 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered.

58. The method of embodiment 57, wherein the about 160 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in one dose.

59. The method of embodiment 57, wherein the about 160 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in two doses.

60. The method of any one of embodiments 42-60, wherein the dosage form comprising the therapeutically effective amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is orally administered.

61. The method of embodiment 60, wherein the therapeutically effective amount of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in a capsule.

62. The method of embodiment 60, wherein the dosage form comprising the therapeutically effective amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in a tablet.

63. The method form of any one of embodiments 42-62, wherein the dosage form comprising the therapeutically effective amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered as one or more individual dosage units during a single dosing session.

64. The method form of any one of embodiments 42-62, wherein the dosage form comprising the therapeutically effective amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered at different times during a single therapy session.

65. The particles of embodiments 1 or 8, wherein the particles are prepared by a process comprising the step of reducing particle size and increasing particle size uniformity by screen-milling.

66. The method of embodiment 65, wherein the coarse particles do not undergo an additional size-reducing process.

67. The method of embodiment 65 or 66, wherein substantially all of the particles are smaller than about 610 μm.

68. The method of embodiment 65 or 66, wherein the median particle size (Dv50) of the coarse particles is from about 300 μm to about 900 μm.

69. The method of embodiment 68, wherein the coarse particles are substantially free of MDMA monohydrate.

70. The method of any of embodiments 67-69, wherein the coarse particles are heated to a temperature of 50-70 °C in an environment with an ambient pressure from about 0.1-1 atmosphere, prior to entering the screen mill.

71. The method of any one of embodiments 67-70, wherein the coarse particles are fed into the screen mill in the absence of applied pressure.

72. The method of any one of embodiments 65-71, wherein the milling method is conducted in an inert atmosphere that is substantially free of moisture.

73. The method of embodiment 72, wherein the inert atmosphere comprises substantially dry nitrogen gas.

74. The dosage form or method of any one of embodiments 1-73, wherein the MDMA, or a pharmaceutically acceptable salt and/or hydrate is present in the form of a pharmaceutically acceptable salt.

75. The dosage form or method of any one of embodiments 1-74, wherein the MDMA, or a pharmaceutically acceptable salt and/or hydrate is present in the form of the hydrochloride salt.

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 MDMA

This example provides methods of preparing high-purity 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). 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. 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). Study sites included private practice clinics in Charleston (SC), Boulder (CO), Fort Collins (CO), Los Angeles (CA), New Orleans (LA), San Francisco (CA), New York (NY), Boston (MA), Vancouver (British Columbia, Canada), and Montreal (Quebec, Canada); and the University of California, San Francisco (UCSF, CA), University of Connecticut (UC, CT), University of Wisconsin Madison (WI), and New York University (NY). 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 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. 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 or total duration of pharmacodynamic effects. The second and third experimental sessions offered a dose escalation to divided doses of 80 mg MDMA + 40 mg MDMA or 120 mg MDMA + 60 mg MDMA. The nominal difference in MDMA doses between countries was due to drug availability and challenges in import/export of a controlled substance, where U.S. participants received racemic MDMA synthesized by David Nichols, Ph.D. (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.

All publications, patents, patent applications, and information available on the internet and cited in the present disclosure 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.

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.

WHAT IS CLAIMED IS:

1. A composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size is from about 50 μm to about 400 μm.

2. The composition of claim 1, wherein the average particle size is from about 75 μm to about 200 μm.

3. The composition of claim 1 or 2, wherein the average particle size is from about 100 μm to about 200 μm.

4. The composition of any one of claims 1-3, wherein the average particle size is from 100 μm to 200 μm.

5. The composition of any one of claims 1-4, wherein the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is substantially pure.

6. The composition of any one of claims 1-5, wherein the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is substantially free of MDMA monohydrate.

7. A dosage form comprising the composition of any one of claims 1-6, and optionally one or more additional pharmaceutically acceptable excipients.

8. The dosage form of claim 7, wherein the dosage form comprises from about 1 mg to about 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

9. The dosage form of claim 7 or 8, wherein the one or more additional excipients are present.

10. The dosage form of any one of claims 7-9, wherein the one or more additional excipients are independently selected from a diluent and a lubricant.

11. The dosage form of any one of claims 7-10, wherein the dosage form comprises a diluent and a lubricant.

12. The dosage form of any one of claims 7-11, wherein the diluent is a sugar alcohol.

13. The dosage form of any one of claims 7-12, wherein the diluent has a moisture content from about 0-0.25% by mass, prior to blending.

14. The dosage form of any one of claims 7-13, wherein the lubricant comprises a pharmaceutically acceptable salt of a saturated fatty acid.

15. The dosage form of any one of claims 7-14, wherein the lubricant is a pharmaceutically acceptable salt of a saturated fatty acid.

16. The dosage form of any one of claims 7-15, wherein the dosage form is an dosage form.

17. The dosage form of claim 16, wherein the dosage form is a capsule.

18. The dosage form of claim 16, wherein the dosage form is a tablet.

19. A method of treating a subject in need thereof, comprising administering to the subject the dosage form of any one of claims 7-18.

ABSTRACT

This disclosure describes particles comprising 3,4-methylenedioxymethamphetamine (MDMA) or a pharmaceutically acceptable salt and/or solvate thereof, dose forms comprising same, and uses thereof, for example, for treating a disorder in a subject in need of such treatment.

FIG. 1

FIG. 2

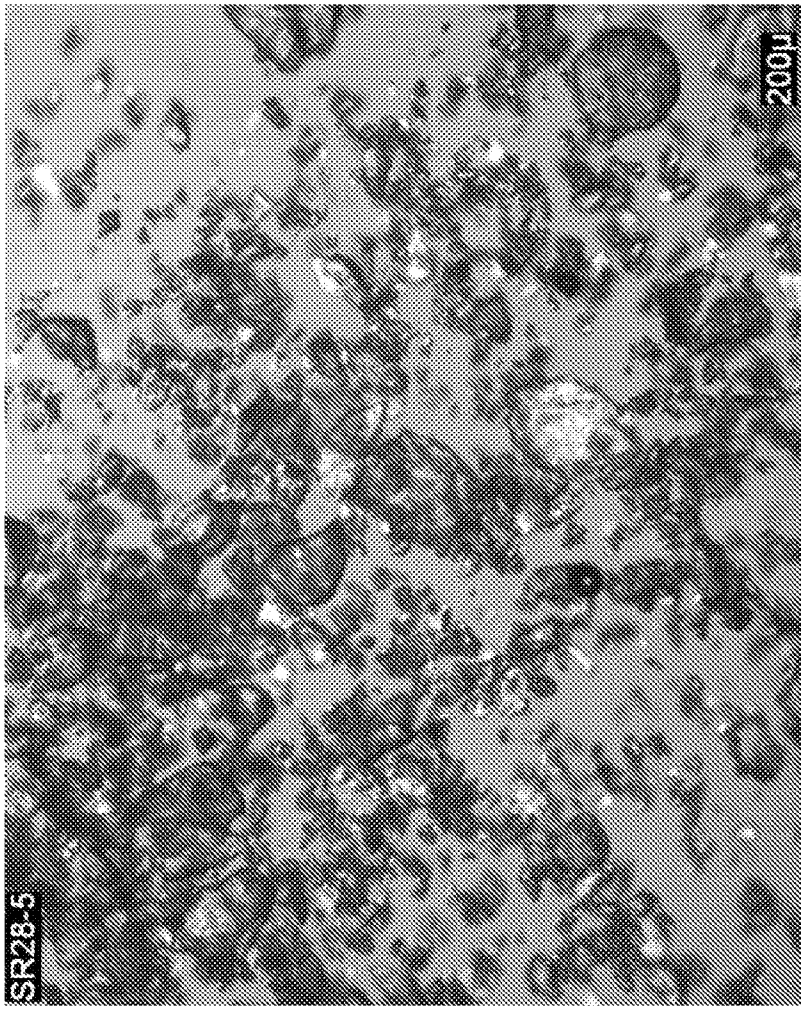


FIG. 3

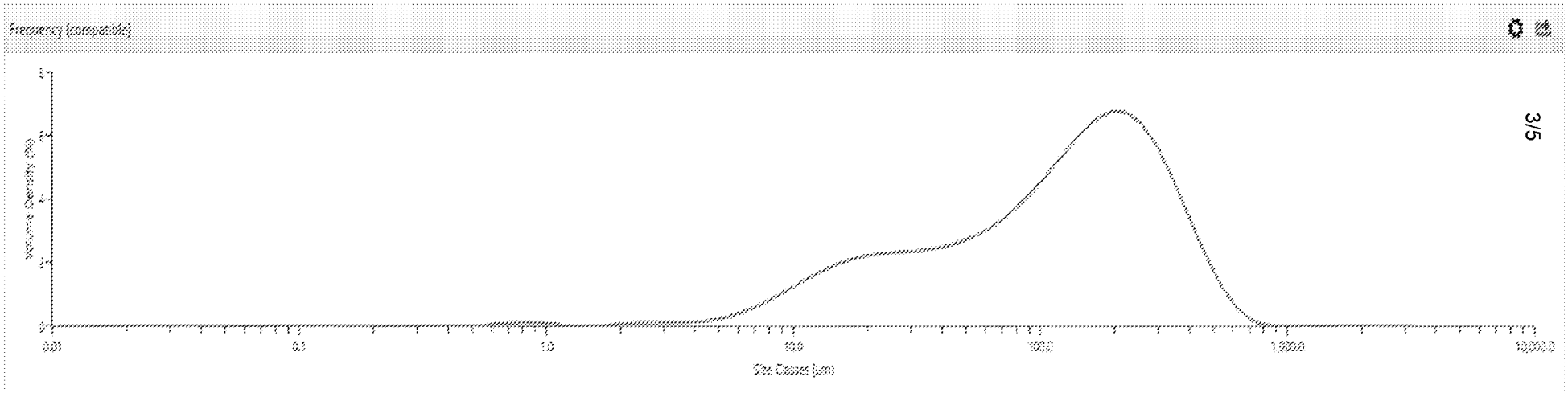


FIG. 4

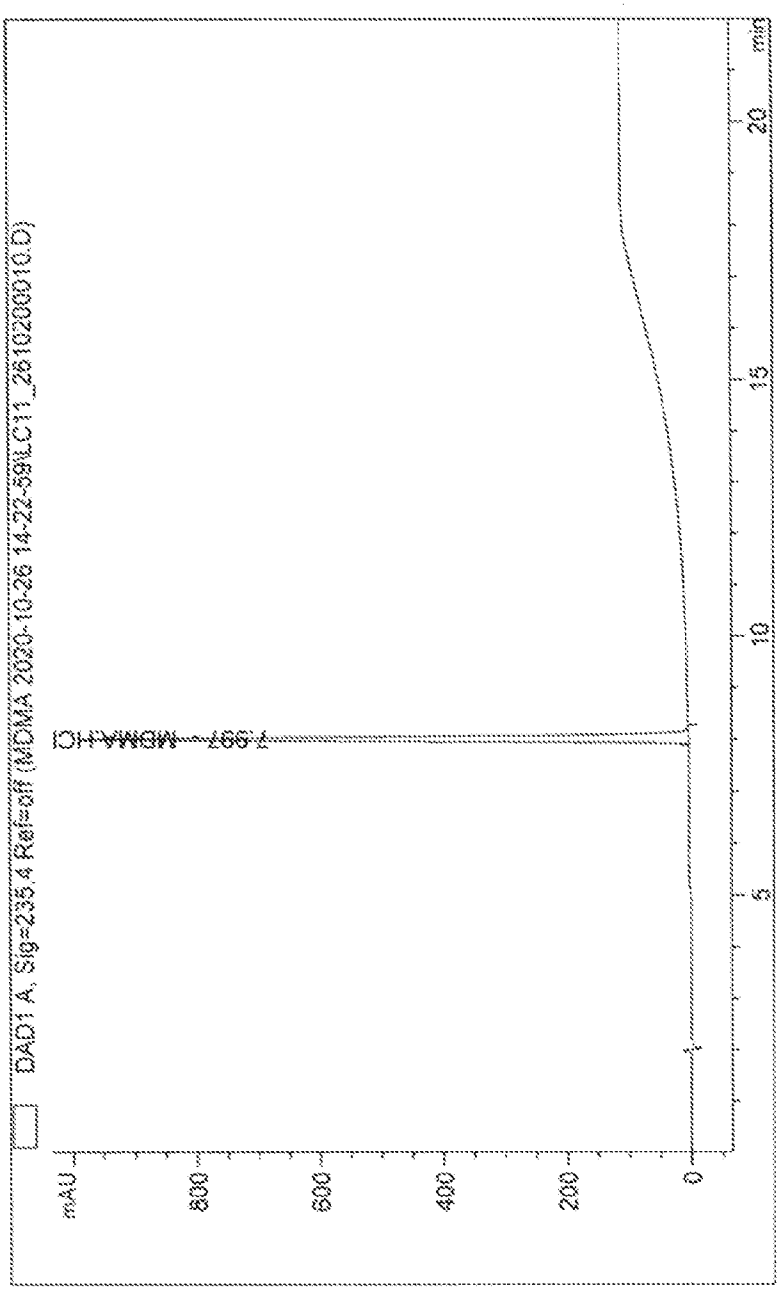

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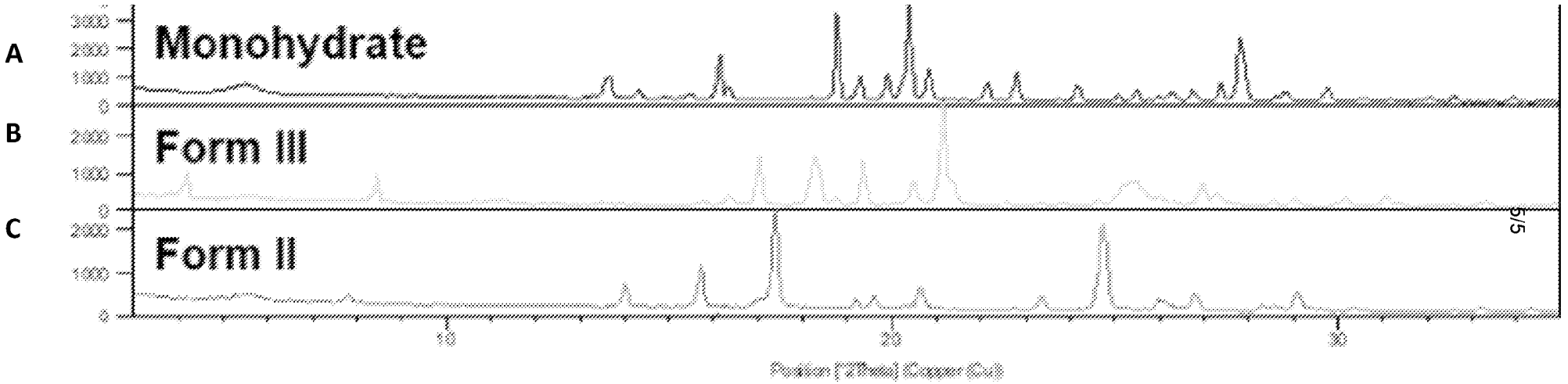
FIG. 5



See Nair, et al., ACS Omega 20022, 7, pp. 900-907

Electronic Acknowledgement Receipt

EFS ID:	47146894
Application Number:	63430287
International Application Number:	
Confirmation Number:	6137
Title of Invention:	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME
First Named Inventor/Applicant Name:	. .
Customer Number:	26191
Filer:	Caleb Allan Bates/Kristine McGuirk
Filer Authorized By:	Caleb Allan Bates
Attorney Docket Number:	54925-0003P01
Receipt Date:	05-DEC-2022
Filing Date:	
Time Stamp:	18:56:44
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$150
RAM confirmation Number	E2022B5I57111225
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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	Provisional Cover Sheet (SB16)	54925_0003P01_Transmittal.pdf	133679 338696b97efe324fb8ff2b37ff5af78669fc0161	no	2
Warnings:					
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Information:					
2	Application Data Sheet	54925_0003P01_ADS.pdf	2225609 ecaec567e3d4259e77e540583a405836e28c58b8	no	8
Warnings:					
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Given Name of First Inventor is a mandatory data field in the Application Data Sheet (ADS) form and is incorrectly entered in the attached form. You may remove the form to add the required data in order to correct the Informational Message or if you chose not to, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. By default, the USPTO will use the data inputted in the Application Data web screen that was entered via the EFS Web interface and the ADS information will be manually reviewed and keyed into USPTO systems.					
3		54925_0003P01_Specification.pdf	299780 bb23b2580914bbde26aef299e19101e66d0a006b	yes	30

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