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International application number:		**PCT/US2023/082367**
International filing date:		**04 December 2023 (04.12.2023)**
Document type:		**Certified copy of priority document**
Document details:	Country/Office:	**US**
	Number:	**63/463,170**
	Filing date:	**01 May 2023 (01.05.2023)**
Date of receipt at the International Bureau:		**08 January 2024 (08.01.2024)**

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

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Application number: 63463170

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 08, 2024

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***63/463,170***
FILING DATE: ***May 01, 2023***

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS ***US63/463,170***

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Under Secretary of Commerce
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Application Number: 63463170 Document Date: 05/01/2023

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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):

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

☐ CD(s), Number of CDs _____

☒ Drawing(s) *Number of Sheets* 7

☐ Other (specify) _____

☒ Specification (e.g. description of the invention) *Number of Pages* 97

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.**

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."

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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 /William T. Spencer, Reg. No. 73,609/ Date 5/1/2023

TYPED or PRINTED NAME William T. Spencer REGISTRATION NO. 73,609 *(if appropriate)*

TELEPHONE +1-212-641-2270 Docket Number: 54925-0009P02

51193468.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	54925-0009P02
	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	54925-0009P02	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	7	Suggested Figure for Publication (if any)	

PTO/AIA/14 (01-22)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P02
	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	54925-0009P02
	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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P02
	Application Number	
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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.

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P02
	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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0009P02
	Application Number	
Title of Invention	METHODS OF TREATING EATING DISORDERS	

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:

Address 1			
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:

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NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

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	/William T. Spencer, Reg. No. 73,609/			Date (YYYY-MM-DD)	2023-05-01
First Name	William	Last Name	Spencer	Registration Number	73609

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

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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.

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 in 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, the empathogenic medicament is MDMA.

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 hydrates of MDMA HCl that readily forms under ambient conditions, particularly during grinding and in high-humidity environments. In addition, the free base of MDMA is an oil at room temperature. 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 have 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 HCl 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 on a free base basis of MDMA. 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 on a free base basis of MDMA. 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 on a free base basis of MDMA. 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 on a free base basis of MDMA. 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 on a free base basis of MDMA. 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 on a free base basis of MDMA.

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 HCl 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 (e.g., prior to blending with the other components of the composition).

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

In some cases, about 100 mg of the particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA, are administered. In some cases, wherein the about 100 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA, 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 on a free base basis of MDMA, 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 on a free base basis of MDMA, are administered. In some cases, the about 120 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA, 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 on a free base basis of MDMA, 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 on a free base basis of MDMA, are administered. In some cases, about 140 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA, 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 on a free base basis of MDMA, 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 on a free base basis of MDMA, are administered. In some cases, the about 160 mg of particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA, 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 on a free base basis of MDMA, 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 psychotherapy session. In some cases, the therapeutically effective amount of the MDMA particles is administered at different times during a single psychotherapy session.

In any of the methods described herein, the individual dosage units may be administered during one or more psychotherapy sessions. In some cases, the dosage units may be administered during one psychotherapy session. In some cases, the dosage units may be administered during two psychotherapy sessions. In some cases, the dosage units may be administered during three psychotherapy sessions. In some cases, the dosage units may be administered during more than three psychotherapy 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 psychotherapy 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 psychotherapy 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 psychotherapy 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 psychotherapy 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 MDMA hydrochloride particles isolated from the synthetic process.

FIG. 2 shows exemplary particles comprising MDMA after milling.

FIG. 3 shows the particle size distribution (PSD) of the milled particles of FIG. 2.

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

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

FIG. 6 shows the schedule of dosing and psychotherapy sessions for MDMA HCl, in which the doses are expressed on a free base basis of MDMA.

FIG. 7 shows a comparison of EAT-26 scores obtained by subjects, before and after completing MDMA- or placebo-assisted psychotherapy.

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

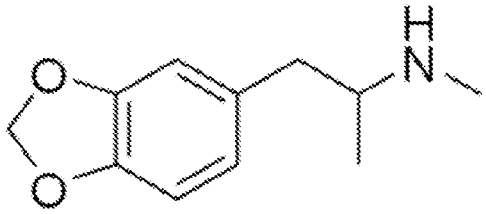
As particles are often non-spherical, it is difficult and complex to provide dimensional descriptions of these non-spherical particles. As used herein, "volume diameter" refers to the diameter of a sphere with a volume equivalent to that of the non-spherical particle. In some embodiments, the particle 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 (i.e., scalemic) 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 "psychotherapy session" refers to a period of time during which communication (e.g., oral communication) between a subject and a psychotherapist to improve psychological functioning, well-being, and coping mechanisms in the subject occurs. In some embodiments, the psychotherapist is a person who has received training to administer psychotherapy (e.g., a psychiatrist, psychologist, or licensed social worker).

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 administration by another person.

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% (e.g., greater than 92%, greater than 94%, greater than 96%, greater than 98%, or greater than 99%). For example, the composition is substantially free of MDMA·HCl hydrate, i.e., of the MDMA present in the composition, less than 10% is MDMA·HCl hydrate (e.g., less than 8%, less than 6%, less than 4%, less than 2%, or less than 1% is MDMA·HCl hydrate). For example, the MDMA is "substantially pure", meaning that the MDMA contains less than 10% of compounds or substances that are not MDMA (e.g., less than 8%, less than 6%, less than 4%, less than 2%, or less than 1% of compounds or substances that are not MDMA). In some embodiments, substantially pure MDMA contains greater than 90% (e.g., greater than 92%, greater than 94%, greater than 96%, greater than 98%,

or greater than 99%) of a single solid form (e.g., polymorph), a single salt, or a single solvate of MDMA.

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, wherein "X" is one numerical limit of the range and "Y" is the other numerical limit of the range. 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 benzothiophenes (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 the knowledge of the Applicant, not yet been explored.

In contrast, 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 $\geq$ 11) and "clinical" (score $\geq$ 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 MDMA·HCl 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 some embodiments, 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 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 some embodiments, the average particle size of the MDMA is from about 50 μm to about 400 μm. In some embodiments, the average particle size of the composition is from about 50 μm to about 100 μm, 100 μm to about 150 μm, 150 μm to about 200 μm, 200 μm to about 250 μm, 250 μm to about 300 μm, 350 μm to about 400 μm, 50 μm to about 150 μm, 150 μm to about 250

μm, 250 μm to about 400 μm, 200 μm to about 400 μm, 100 μm to about 300 μm, or 200 μm to about 400 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 some embodiments, the Dv10 value of the particles is from about 5 μm to about 40 μm, about 5 μm to about 30 μm, about 5 μm to about 20 μm, about 5 μm to about 15 μm, about 10 μm to about 40 μm, about 15 μm to about 40 μm, about 20 μm to about 40 μm, about 25 μm to about 40 μm, about 10 μm to about 35 μm, about 15 μm to about 35 μm, about 18 μm to about 32 μm, about 20 μm to about 30 μm, about 20 μm to about 25 μm, about 25 μm to about 30 μm, about 5 μm, about 10 μm, about 15 μm, about 20 μm, about 21 μm, about 22 μm, about 23 μm, about 24 μm, about 25 μm, about 26 μm, about 27 μm, about 28 μm, or about 29 μm.

In some embodiments, the Dv50 value of the particles is from about 100 μm to about 200 μm, about 110 μm to about 190 μm, about 120 μm to about 180 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, or about 100 μm to about 200 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 (e.g., have a smaller particle size range) than are the crude MDMA particles isolated from the synthetic process. In some embodiments, the particles have a particle size range that is less than about 600 μm (e.g., less than about 500 μm, less than about 420 μm, or less than about 400 μm). In some embodiments, the particle size range is about 5 μm to about 500 μm (e.g.,

about 5 μm to about 420 μm, about 20 μm to about 353 μm, about 20 μm to about 326 μm, about 21 μm to about 353 μm, about 21 μm to about 342 μm, about 21 μm to about 326 μm, about 24 μm to about 353 μm, about 29 μm to about 342 μm, about 34 μm to about 341 μm, about 200 μm to about 400 μm, about 230 μm to 380 μm, or about 250 μm to 350 μm.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is amorphous. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially amorphous. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is crystalline. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially crystalline. In some embodiments, the particles described herein are substantially free of MDMA HCl monohydrate.

In some embodiments, the dissolution rate in water is greater than or equal to 50% (e.g., 60%, 70%, 80%, 85%, 90%, 95%, 98%, or 99%) of the mass of the MDMA in 30 minutes. In some embodiments, the dissolution rate in water is greater than or equal to 80% of the mass of the MDMA in 30 minutes.

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

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.

MDMA isolated from the current chemical synthesis is a highly pure, coarse solid with varying particle size. The coarse MDMA, having a typical Dv90 from 800 μm to 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 resulting dosage form is uneven, leading to an unacceptably high rate of batch failure. In some embodiments, the median particle size (Dv50) of the coarse particles is greater than 400 μm. In some embodiments, the coarse particles are substantially free of a hydrate (e.g., monohydrate) of a pharmaceutically acceptable salt of MDMA. In some embodiments, the coarse particles are substantially free of MDMA HCl monohydrate.

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.

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 of the composition is from about 50 μm to about 400 μm. The excipients can be any excipients described herein, for example, magnesium stearate and/or mannitol.

In some embodiments, the average particle size of the composition is from about 50 μm to about 100 μm, 100 μm to about 150 μm, 150 μm to about 200 μm, 200 μm to about 250 μm, 250 μm to about 300 μm, 350 μm to about 400 μm, 50 μm to about 150 μm, 150 μm to about 250 μm, 250 μm to about 400 μm, 200 μm to about 400 μm, 100 μm to about 300 μm, or 200 μm to about 400 μm.

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

It was initially proposed that acceptable MDMA particle size could be achieved by ball-milling the coarse MDMA 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 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. Alternatively, particles 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, forming particles of a composition comprising MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

In some embodiments, the composition 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 Dv10 value of the particles is from about 5 μm to about 40 μm, about 5 μm to about 30 μm, about 5 μm to about 20 μm, about 5 μm to about 15 μm, about 10 μm to about 40 μm, about 15 μm to about 40 μm, about 20 μm to about 40 μm, about 25 μm to about 40 μm, about 10 μm to about 35 μm, about 15 μm to about 35 μm, about 18 μm to about 32 μm, about 20 μm to about 30 μm, about 20 μm to about 25 μm, about 25 μm to about 30 μm, about 5 μm, about 10 μm, about 15 μm, about 20 μm, about 21 μm, about 22 μm, about 23 μm, about 24 μm, about 25 μm, about 26 μm, about 27 μm, about 28 μm, or about 29 μm.

In some embodiments, the Dv50 value of the particles is from about 100 μm to about 200 μm, about 110 μm to about 190 μm, about 120 μm to about 180 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, or about 100 μm to about 200 μm.

In some embodiments, the Dv90 value of the particles is from about 0.01 μm to about 400 μm, 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 composition particles are more uniformly distributed (e.g., have a smaller particle size range) than are the crude MDMA particles isolated from the synthetic process (i.e., the coarse particles). In some embodiments, the composition particles have a particle

size range that is less than about 600 μm (e.g., less than about 500 μm, less than about 420 μm, or less than about 400 μm). In some embodiments, the particle size range is about 5 μm to about 500 μm (e.g., about 5 μm to about 420 μm, about 20 μm to about 353 μm, about 20 μm to about 326 μm, about 21 μm to about 353 μm, about 21 μm to about 342 μm, about 21 μm to about 326 μm, about 24 μm to about 353 μm, about 29 μm to about 342 μm, about 34 μm to about 341 μm, about 200 μm to about 400 μm, about 230 μm to 380 μm, or about 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, composition particles with reduced particle size and increased particle size uniformity with a Dv90 below about 420 μm 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 μm, with a Dv90 less than 420 μm and a particle size range of less than 400 μm, wherein the particles comprise MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients. In some embodiments, the method produces substantially no hydrate (e.g., monohydrate) of a pharmaceutically acceptable salt of MDMA (e.g., MDMA·HCl). In some embodiments, the particles produced have a higher flowability than coarse MDMA particles.

Some embodiments provide a dosage form prepared from a composition described herein. In some embodiments, the composition comprises particles substantially smaller than about 610 μm, with a Dv90 below 420 μm and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a composition comprising particles substantially smaller than about 610 μm, with a Dv90 less than 420 μm and a particle size range of less than 400 μm, 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 prepared by a method comprising:

blending particles having an average particle size greater than 610 μm with one or more pharmaceutically acceptable excipients;

changing the average particle size of the particles to less than 610 μm and a Dv90 below 420 μm;

wherein the particles comprise MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

In some embodiments, the changing comprises milling the particles with the one or more pharmaceutically acceptable excipients.

In some embodiments, substantially all of the particles are (i) smaller than about 610 μm, and (ii) have a Dv90 lesser than about 400 μm. 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 μm. In some embodiments, from about 0% to 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 are substantially free of MDMA HCl monohydrate.

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

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

In some embodiments, the composition includes a diluent. In some embodiments, the diluent is a sugar alcohol. In some embodiments, the diluent has a moisture content of less than 0.25% by mass, prior to blending with the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof.

In some embodiments, 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 embodiments, the lubricant includes a pharmaceutically acceptable salt of a saturated fatty acid.

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. In some embodiments, the coarse particles do not undergo an additional size-reducing process.

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

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

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 HCl 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 HCl 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. In some embodiments, the dosage form is substantially free of a hydrate of a pharmaceutically acceptable salt of MDMA. In some embodiments, the dosage form is substantially free of MDMA·HCl monohydrate. In some embodiments, the dosage form comprises no detectable MDMA·HCl monohydrate. 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 on a free base basis of MDMA, and one or more carriers or excipients. In certain embodiments, the oral dosage forms of the present disclosure may contain about 20 mg of the API, about 25 mg of the API, about 30 mg of the API, about 35 mg of the API, about 40 mg of the API, about 45 mg of the API, about 50 mg of the API, about 55 mg of the API, about 60 mg of the API, about 65 mg of the API, about 70 mg of the API, about 75 mg of the API, about 80 mg of the API, about 85 mg of the API, about 90 mg of the API, about 95 mg of the API, about 100 mg of the API, about 105 mg of the API, about 110 mg of the API, about 115 mg of the API, about 120 mg of the API, about 125 mg of the API, about 130 mg of the API, about 135 mg of the API, about or 140 mg of the API.

In some embodiments, the dosage form comprises about 1 mg to about 150 mg of API. In some embodiments, the dosage form comprises about 17 mg to about 126 mg of API. In some embodiments, the dosage form comprises about 1 mg to about 50 mg of API. In some embodiments, the dosage form comprises about 68 mg to about 100 mg of API. In some embodiments, the dosage form comprises about 50 mg to about 130 mg of API. In some embodiments, the dosage form comprises about 25 mg to about 75 mg of API. In some embodiments, the dosage form comprises about 50 mg to about 100 mg of API. In some embodiments, the dosage form comprises about 75 mg to about 125 mg of API. In some embodiments, the dosage form comprises about 100 mg to about 150 mg of API.

In some embodiments, the amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is expressed on a free base basis of MDMA.

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 on a free base basis of MDMA.

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 the API.

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 the API.

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 the API.

In some embodiments, the amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is MDMA hydrochloride (MDMA HCl). In some embodiments, the dosage form comprises about 1 mg to about 180 mg (e.g., about 20 mg to about 150 mg, about 30 mg to about 140 mg, about 40 mg to about 130 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg,

about 80 mg to about 120 mg, about 120 mg to about 180 mg, about 30 mg to about 50 mg, about 35 mg to about 45 mg, about 55 mg to about 65 mg, about 20 mg, about 40 mg, about 60 mg, about 80 mg, about 120 mg, about 150 mg, or about 180 mg) MDMA HCl. In some embodiments, the dosage form comprises about 120 mg to about 180 mg MDMA HCl. In some embodiments, the dosage form comprises about 20 mg to about 150 mg MDMA HCl. In some embodiments, the dosage form comprises about 80 mg to about 120 mg MDMA HCl. In some embodiments, the dosage form comprises about 40 mg to about 60 mg MDMA HCl. In some embodiments, the dosage form comprises about 20 mg MDMA HCl. In some embodiments, the dosage form comprises about 40 mg MDMA HCl. In some embodiments, the dosage form comprises about 60 mg MDMA HCl. In some embodiments, the dosage form comprises about 80 mg MDMA HCl. In some embodiments, the dosage form comprises about 100 mg MDMA HCl. In some embodiments, the dosage form comprises about 120 mg MDMA HCl. In some embodiments, the dosage form comprises about 150 mg MDMA HCl. In some embodiments, the dosage form comprises about 180 mg MDMA HCl.

In some embodiments, the dosage form, includes one or more individual dosage units. In some embodiments, the dosage form includes one individual dosage unit. In some embodiments, the dosage form includes at least two individual dosage units. In some embodiments, the dosage form includes three individual dosage units. In some embodiments, the dosage form includes at least three individual dosage units. In some embodiments, each of the one or more individual dosage units comprises a capsule. In some embodiments, each of the one or more individual dosage units comprises a tablet.

As used herein, an individual dosage unit (i.e., a tablet or capsule provided in a blister pack) has the same characteristics of the dosage forms described herein that are not comprised of individual dosage units (i.e., the dosage forms such as tablets, capsules, and the like). As such, each individual dosage unit is a dosage form comprising MDMA, or a pharmaceutically acceptable salt and/or solvate thereof (for example, about 40 mg MDMA·HCl; or about 60 mg MDMA·HCl).

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

MDMA, wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm; and

α-lactose monohydrate.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

MDMA; and

α-lactose monohydrate;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

MDMA HCl, wherein substantially all of the MDMA HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm; and

α-lactose monohydrate.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

MDMA HCl; and

α-lactose monohydrate;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

about 20 mg to about 150 mg MDMA HCl, wherein substantially all of the MDMA HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm; and

α-lactose monohydrate.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

about 20 mg to about 150 mg MDMA HCl; and

α-lactose monohydrate;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 40 mg to about 60 mg MDMA HCl, wherein substantially all of the MDMA HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 40 mg to about 60 mg MDMA HCl;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 40 mg MDMA HCl, wherein substantially all of the MDMA HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 40 mg MDMA HCl;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 60 mg MDMA HCl, wherein substantially all of the MDMA HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 60 mg MDMA HCl;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 34 mg MDMA on a free base basis of MDMA, wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 34 mg MDMA on a free base basis of MDMA;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 50 mg MDMA on a free base basis of MDMA, wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 50 mg MDMA on a free base basis of MDMA;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

In some embodiments, the dosage form comprises about 0.1% to about 10% (e.g., about 0.1% to about 8%, about 0.1% to about 5%, about 0.1% to about 4%, about 0.1% to about 2%, about 0.5% to about 1.5%, or about 1%) by weight of magnesium stearate. In some embodiments, the dosage form comprises about 1% by weight of magnesium stearate.

In some embodiments, the dosage form comprises about 25% to about 75% (e.g., about 25% to about 65%, about 25% to about 55%, about 25% to about 50%, about 25% to about 35%, about 35% to about 75%, about 50% to about 75%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55%, or about 49%) by weight of mannitol. In some embodiments, the dosage form comprises about 49% by weight of mannitol.

In some embodiments, the dosage form comprises about 25% to about 75% (e.g., about 25% to about 65%, about 25% to about 55%, about 25% to about 50%, about 25% to about 35%, about 35% to about 75%, about 50% to about 75%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55%, or about 50%) by weight of MDMA HCl. In some embodiments, the dosage form comprises about 50% by weight of MDMA HCl.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 60 mg MDMA HCl, wherein substantially all of the MDMA HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 1% by weight of magnesium stearate; and

about 49% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 60 mg MDMA HCl;

about 1% by weight of magnesium stearate; and

about 49% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

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, 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 or 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 comprises 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 psychotherapy sessions, three individual psychotherapy sessions, four individual psychotherapy sessions, five individual psychotherapy sessions, six individual psychotherapy sessions, seven individual psychotherapy sessions, eight individual psychotherapy sessions, nine individual psychotherapy sessions, or ten individual psychotherapy sessions. The individual psychotherapy 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 psychotherapy 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 psychotherapy 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.

In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 80 mg to about 170 mg on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 102 mg to about 150 mg on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 102 mg on a free base basis of MDMA. In some

embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 150 mg on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day should not exceed about 150 mg on a free base basis of MDMA.

In some embodiments, the dose of MDMA HCl, or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA, administered in one day is about 90 mg to about 210 mg. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA, administered in one day is about 120 mg to about 180 mg. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA, administered in one day is about 120 mg. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA, administered in one day is about 180 mg. In some embodiments, the dose of MDMA on a free base basis of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day should not exceed about 180 mg.

Some embodiments provide a method of treating an eating disorder in a subject in need thereof, comprising:

administering one or more individual dosage units during a psychotherapy session;

wherein each individual dosage unit comprises a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA;

wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a method of treating an eating disorder in a subject in need thereof, comprising:

administering one or more individual dosage units during a psychotherapy session;

wherein each individual dosage unit comprises a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a method of treating an eating disorder in a subject in need thereof, comprising:

administering one or more individual dosage units during a first psychotherapy session;

administering one or more individual dosage units during a second psychotherapy session at least 21 days after the first psychotherapy session;

administering one or more individual dosage units during a third psychotherapy session at least 21 days after the second psychotherapy session;

wherein each individual dosage unit comprises a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA;

wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a method of treating an eating disorder in a subject in need thereof, comprising:

administering one or more individual dosage units during a first psychotherapy session;

administering one or more individual dosage units during a second psychotherapy session at least 21 days after the first psychotherapy session;

administering one or more individual dosage units during a third psychotherapy session at least 21 days after the second psychotherapy session;

wherein each individual dosage unit comprises a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

In some embodiments, the one or more individual dosage units administered during a psychotherapy session is one individual dosage unit. In some embodiments, the one or more individual dosage units administered during a psychotherapy session is two individual dosage units. In some embodiments, the one or more individual dosage units administered during a psychotherapy session is three individual dosage units.

In some embodiments, when the one or more individual dosage units is two or more individual dosage units, the method comprises administering the individual dosage units at different times during the psychotherapy session. In some embodiments, when the one or more individual dosage units is two or more individual dosage units, the method comprises administering the individual dosage units at the same time during the psychotherapy session.

In some embodiments, the one or more individual dosage units is three individual dosage units; two of the individual dosage units are administered at the same time; and the third individual dosage unit is administered at a different time during the psychotherapy session. In some embodiments, the one or more individual dosage units is three individual dosage units; the first and second of the individual dosage units are administered at the same time; and the third individual dosage unit is administered after the first and second individual dosage units during the psychotherapy session. In some embodiments, the third individual dosage unit is administered about 5 minutes to about 5 hours (e.g., about 15 minutes to about 5 hours, about 30 minutes to about 5 hours, about 1 hour to about 5 hours, about 1.5 hours to about 5 hours, about 2 hours to about 5 hours, about 3 hours to about 5 hours, about 5 minutes to about 4 hours, about 5 minutes to about 3 hours, about 5 minutes to about 2 hours, about 5 minutes to about 1 hour, about 30 minutes to about 4 hours, about 45 minutes to about 3 hours, about 1 hour to about 2.5 hours, about 1 hour to about 2 hours, about 1 hour and 15 minutes to about 1 hour and 45 minutes, about 1 hour and 15 minutes to about 2 hours and 15 minutes, about 1.5 hours to about 2 hours, about 1.5 hours, about 1 hour and 45 minutes, or about 2 hours) after the first and second individual dosage units. In some embodiments, the third individual dosage unit is administered about 1.5 hours to about 2 hours after the first and second individual dosage units.

In some embodiments, each individual dosage unit comprises a capsule. In some embodiments, the capsule comprises hydroxypropylmethylcellulose (HPMC). In some embodiments, the capsule contains a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA. In some embodiments, the composition comprises about 0.1% to about 10% by weight of magnesium stearate and about 25% to about 75% by weight of mannitol.

In some embodiments, the composition comprises about 0.1% to about 10% (e.g., about 0.1% to about 8%, about 0.1% to about 5%, about 0.1% to about 4%, about 0.1% to about 2%,

about 0.5% to about 1.5%, or about 1%) by weight of magnesium stearate. In some embodiments, the composition comprises about 1% by weight of magnesium stearate.

In some embodiments, the composition comprises about 25% to about 75% (e.g., about 25% to about 65%, about 25% to about 55%, about 25% to about 50%, about 25% to about 35%, about 35% to about 75%, about 50% to about 75%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55%, or about 49%) by weight of mannitol. In some embodiments, the composition comprises about 49% by weight of mannitol.

In some embodiments, the composition comprises about 34 mg to about 50 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA. In some embodiments, the composition comprises about 34 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA. In some embodiments, the composition of the one or more individual dosage units administered during the first psychotherapy session comprises about 34 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA. In some embodiments, the composition comprises about 50 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA. In some embodiments, the composition of the one or more individual dosage units administered during the second and third psychotherapy sessions comprises about 50 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA.

In some embodiments, the MDMA or a pharmaceutically acceptable salt and/or solvate thereof is MDMA HCl. In some embodiments, the composition comprises about 1 mg to about 180 mg (e.g., about 20 mg to about 150 mg, about 30 mg to about 140 mg, about 40 mg to about 130 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 80 mg to about 120 mg, about 120 mg to about 180 mg, about 30 mg to about 50 mg, about 35 mg to about 45 mg, about 55 mg to about 65 mg, about 20 mg, about 40 mg, about 60 mg, about 80 mg, about 120 mg, about 150 mg, or about 180 mg) MDMA HCl. In some embodiments, the composition comprises about 120 mg to about 180 mg MDMA HCl. In some embodiments, the composition comprises about 20 mg to about 150 mg MDMA HCl. In some embodiments, the composition comprises about 80 mg to about 120 mg MDMA HCl. In some embodiments, the composition comprises about 40 mg to about 60 mg MDMA HCl. In some embodiments, the composition comprises about 20 mg MDMA HCl. In some embodiments, the composition comprises about 40 mg MDMA HCl. In some embodiments, the composition comprises about 60 mg MDMA HCl. In some embodiments, the

composition comprises about 80 mg MDMA HCl. In some embodiments, the composition comprises about 100 mg MDMA HCl. In some embodiments, the composition comprises about 120 mg MDMA HCl. In some embodiments, the composition comprises about 150 mg MDMA HCl. In some embodiments, the composition comprises about 180 mg MDMA HCl. In some embodiments, the composition of the one or more individual dosage units administered during the first psychotherapy session comprises about 40 mg MDMA HCl. In some embodiments, the composition of the one or more individual dosage units administered during the second and third psychotherapy sessions comprises about 60 mg MDMA HCl.

In some embodiments, the second psychotherapy session is at least 21 days (e.g., at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, about 3 weeks to about 4 weeks, about 3 weeks to about 5 weeks, or about 3 weeks to about 6 weeks) after the first psychotherapy session. In some embodiments, the second psychotherapy session is about 3 weeks to about 5 weeks after the first psychotherapy session.

In some embodiments, the third psychotherapy session is at least 21 days (e.g., at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, about 3 weeks to about 4 weeks, about 3 weeks to about 5 weeks, or about 3 weeks to about 6 weeks) after the second psychotherapy session. In some embodiments, the third psychotherapy session is about 3 weeks to about 5 weeks after the second psychotherapy session.

In some embodiments, the subject consumed no food for at least 5 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 6 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 8 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 10 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 10 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 12 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 14 hours before administering the MDMA, or a pharmaceutically

acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 16 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 18 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 20 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 22 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 24 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

In some embodiments, the subject consumed food up to about 6 hours before administering the MDMA. For example, the subject consumed food up to about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 30 minutes, about 20 minutes, about 15 minutes, about 10 minutes, about 5 minutes, about 1 minute, about 30 seconds, or about 5 seconds before administering the MDMA. For example, the subject consumed food concurrently with administering the MDMA.

In some embodiments, the dose of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is 50 mg on a free base basis of MDMA. In some embodiments, the dose of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is 100 mg on a free base basis of MDMA. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is MDMA hydrochloride.

In some embodiments, the dose of the MDMA hydrochloride is 120 mg. In some embodiments, the method comprises measuring a C_{max} of about 100 ng/mL to about 500 ng/mL in the subject after administering the MDMA HCl. In some embodiments, the dose of the MDMA hydrochloride may be about 112 mg, about 114 mg, about 116 mg, about 118 mg, about 120 mg, about 122 mg, or about 124 mg. In some embodiments, the method comprises measuring a C_{max} of about 150 ng/mL to about 450 ng/mL, about 175 ng/mL to about 400 ng/mL, about 200 ng/mL to about 320 ng/mL, about 220 ng/mL to about 300 ng/mL, about 240 ng/mL to about 280 ng/mL, about 250 ng/mL to about 275 ng/mL, about 255 ng/mL to about 270 ng/mL, or about 158 ng/mL to about 164 ng/mL. In some embodiments, the method comprises measuring a C_{max} of about 261 ng/mL. The subranges and specific values may be selected based

on factors such as the participant's weight, age, and overall health, as well as the desired therapeutic effect and potential side effects of the MDMA.

In some embodiments, the method comprises measuring an AUC_{0-t} in the subject after administering MDMA HCl. In some embodiments, the measured AUC_{0-t} is about 2500 h*ng/mL to about 5000 h*ng/mL, about 3000 h*ng/mL to about 4500 h*ng/mL, about 3000 h*ng/mL to about 4200 h*ng/mL, about 3300 h*ng/mL to about 4000 h*ng/mL, about 3570 h*ng/mL to about 3770 h*ng/mL, about 3500 h*ng/mL to about 3600 h*ng/mL, about 3520 h*ng/mL to about 3580 h*ng/mL, about 3620 h*ng/mL to about 3730 h*ng/mL, or about 3670 h*ng/mL. In some embodiments, the measured AUC_{0-t} is about 3550 h*ng/mL. In some embodiments, the measured AUC_{0-t} is about 3670 h*ng/mL.

In some embodiments, the method comprises measuring an AUC_{0-72} in the subject after administering MDMA HCl. In some embodiments, the measured AUC_{0-72} is about 2500 h*ng/mL to about 5000 h*ng/mL, about 3000 h*ng/mL to about 4500 h*ng/mL, about 3500 h*ng/mL to about 4200 h*ng/mL, about 3700 h*ng/mL to about 3900 h*ng/mL, about 3750 h*ng/mL to about 3850 h*ng/mL, about 3800 h*ng/mL to about 4000 h*ng/mL, about 3870 h*ng/mL to about 3900 h*ng/mL, or about 3880 h*ng/mL. In some embodiments, the measured AUC_{0-72} is about 3800 h*ng/mL. In some embodiments, the measured AUC_{0-inf} is about 3880 h*ng/mL. In some embodiments, the method comprises measuring an AUC_{0-inf} in the subject after administering MDMA HCl. In some embodiments, the measured AUC_{0-inf} is about 2500 h*ng/mL to about 5000 h*ng/mL, about 3000 h*ng/mL to about 4500 h*ng/mL, about 3500 h*ng/mL to about 4200 h*ng/mL, about 3700 h*ng/mL to about 3900 h*ng/mL, about 3750 h*ng/mL to about 3850 h*ng/mL, about 3800 h*ng/mL to about 4000 h*ng/mL, about 3870 h*ng/mL to about 3900 h*ng/mL, or about 3890 h*ng/mL. In some embodiments, the measured AUC_{0-inf} is about 3800 h*ng/mL. In some embodiments, the measured AUC_{0-inf} is about 3890 h*ng/mL.

In some embodiments, the method comprises measuring a T_{max} in the subject after administering MDMA HCl. In some embodiments, the measured T_{max} is about 30 minutes to about 10 hours, about 30 minutes to about 4 hours, about 45 minutes to about 3 hours, about 2 hours to about 8 hours, about 4 hours to about 10 hours, about 6 hours to about 10 hours, about 2 hours to about 6 hours, about 3 hours to about 5 hours, about 1 hour to about 3 hours, about 1.5 hours to about 2.5 hours, about 1.7 hours to about 2.3 hours, or about 2 hours. In some

embodiments, the measured T_{max} is about 4 hours. In some embodiments, the measured T_{max} is about 2 hours.

In some embodiments, the method comprises measuring a $t_{1/2}$ in the subject after administering MDMA HCl. In some embodiments, the measured $t_{1/2}$ is about 2 hours to about 20 hours, about 3 hours to about 20 hours, about 4 hours to about 20 hours, about 4 hours to about 15 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 4 hours to about 6 hours, about 6 hours to about 20 hours, about 8 hours to about 20 hours, about 10 hours to about 20 hours, about 13 hours to about 20 hours, about 16 hours to about 20 hours, about 18 hours to about 20 hours, about 6 hours to about 12 hours, about 7 hours to about 11 hours, about 8 hours to about 10 hours, about 8 hours to about 8 hours, about 8.36 hours, or about 9 hours. In some embodiments, the measured $t_{1/2}$ is about 8.36 hours. In some embodiments, the measured $t_{1/2}$ is about 9 hours.

In some embodiments, the method comprises measuring a T_{lag} in the subject after administering MDMA HCl. In some embodiments, the measured T_{lag} is about 0 hours to about 2 hours, about 0.25 hours to about 1.5 hours, about 0.25 hours to about 0.75 hours, about 0.75 hours to about 1.25 hours, about 0.5 hours, about 0.75 hours, or about 1 hour. In some embodiments, the measured T_{lag} is about 0.5 hours. In some embodiments, the measured T_{lag} is about 0.5 hour.

In some embodiments, the method comprises measuring a CL/F in the subject after administering MDMA HCl. In some embodiments, the measured CL/F is about 1 L/h to about 100 L/h, about 1 L/h to about 70 L/h, about 10 L/h to about 60, about 20 L/h to about 50 L/h, about 30 L/h to about 40 L/h, about 32 L/h to about 36 L/h, about 35 L/h to about 40 L/h, about 34.5 L/h, or about 37.5 L/h. In some embodiments, the measured CL/F is about 368 L/h. In some embodiments, the measured CL/F is about 34.5 L/h. In some embodiments, the measured CL/F is about 368 L/h. In some embodiments, the measured CL/F is about 37.5 L/h.

In some embodiments, the method comprises measuring a Vd/F in the subject after administering MDMA HCl. In some embodiments, the measured Vd/F is about 100 L to about 800 L, about 200 L to about 700 L, about 300 L to about 600 L, about 400 L to about 500 L, about 400 L to about 420 L, about 410 L to about 450 L, about 420 L to about 440 L, about 425 L to about 435 L, about 412 L, or about 430 L. In some embodiments, the measured Vd/F is about 430 L. In some embodiments, the measured Vd/F is about 412 Vd/F.

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. **FIG. 1** shows the coarse MDMA hydrochloride particles isolated from the synthetic process, and **FIG. 4** shows an HPLC chromatogram for coarse MDMA particles isolated from the synthetic process. Other polymorphic forms were also prepared. **FIG. 5** shows the XRPD spectra of MDMA HCl monohydrate (5A), MDMA Form III (5B), and MDMA Form II (5C).

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 HCl 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. **FIG. 2** shows exemplary particles comprising MDMA after milling, and **FIG. 3** shows the particle size distribution (PSD) of the milled particles of FIG. 2.

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. Dosage Form Specifications.

Description of Drug Product

Two dosage strengths of the drug product are available including 34 mg MDMA (equivalent to 40.5 mg MDMA hydrochloride (MDMA HCl)) and 50 mg MDMA (equivalent to 59.5 mg MDMA HCl) in hydroxypropyl methylcellulose (HPMC) capsules. The capsules are imprinted and are filled with a composition comprising MDMA HCl. The appearance of the 34 mg dosage strength capsule is a Size 2, HPMC Swedish Orange / White Capsule imprinted with "MDMA

34" and the appearance of the 50 mg dosage strengths is a Size 2, HPMC Swedish Orange Capsule imprinted with "MDMA 50". Recipharm Aesica Queenborough Ltd. is the proposed manufacturer for commercial drug product.

Composition of Drug Product

HPMC capsules filled with a powder blend including MDMA HCl, mannitol, and magnesium stearate. The formulation of the powder blend is a proportional formulation. See Table 2 below for the composition of each of the dosage forms.

Table 2. Composition of the MDMA 34 mg and 50 mg Drug Product.

Component and Quality Standard (and Grade, if Applicable)	**Reference to Standard**	**Function**	**Strength (Label Claim)**			
			MDMA 34 mg Capsule		**MDMA 50 mg Capsule**	
			Quantity per Unit	**[% w/w]**	**Quantity per Unit**	**[% w/w]**
Active Substances(s)						
MDMA HCl, milled	In-house	Active API	40.50 mg[1]	50.0	59.50 mg[2]	50.0
Excipients						
Mannitol (Mannogem Powder)	USP / EP	Diluent	39.69 mg	49.0	58.31 mg	49.0
Magnesium Stearate	USP-NF / EP	Lubricant	0.81 mg	1.0	1.19 mg	1.0
Total	---	---	81.00 mg	100.0	119.00 mg	100.0
Size 2, HPMC Swedish Orange / White Capsules	In-house	Capsule	Average capsule weight 57 mg-65 mg	N/A	---	---
Size 2, HPMC Swedish Orange Capsules	In-house	Capsule	---	---	Average capsule weight 57 mg-65 mg	N/A

[1]40.50 mg of MDMA.HCl is equivalent to 34 mg MDMA free base.

[2]59.50 mg of MDMA.HCl is equivalent to 50 mg MDMA free base.

The composition and components of the HPMC capsule shells is provided in Table 3 and Table 4 below.

Table 3. Composition of the Size 2, HPMC Swedish Orange / White Capsules.

Component	Body: V44.900, WHITE OP. V900	Cap: V22.905, SWEDISH ORANGE OP. V905
Ferric Oxide, Red, E172, USP-NF	---	1.1817%
Titanium Dioxide, E171, USP/EP	2.0000%	0.4916%
Hypromellose, USP/EP	QSP 100%	QSP 100%

Table 4. Composition of the Size 2, HPMC Swedish Orange Capsules.

Component	Body and Cap: V22.905, SWEDISH ORANGE OP. V905
Ferric Oxide, Red, E172, USP-NF	1.1817%
Titanium Dioxide, E171, USP/EP	0.4916%
Hypromellose, USP/EP	QSP 100%

Printing Ink 10A2 Black

The printing ink consists of shellac, E904 US Pharmacopoeia-National Formulary / European Pharmacopoeia (USP-NF/EP), ferric oxide black, E172 (USP-NF), propylene glycol (USP/EP), strong ammonia solution (USP-NF/EP), and potassium hydroxide (USP-NF/EP).

Container Closure System

The container closure system is an aluminum blister pack consisting of cold-formable aluminum laminate and push-through blister lidding foil.

Example 4. Comparative Dissolution Studies.

This protocol describes experiments that can be performed to compare the dissolution profiles obtained for 40 mg MDMA·HCl capsules and 60 mg MDMA·HCl capsules that can be used in Phase III clinical studies manufactured by Sharp Clinical Services versus 40 mg MDMA·HCl (34 mg MDMA on a free base basis) and 60 mg MDMA·HCl (50 mg MDMA on a free base basis) capsules manufactured by Recipharm QB (RQB).

N=12 capsules from each manufacturer can be compared in pH 1.2, 4.5, and 6.8 dissolution media, with all other dissolution and analytical conditions as described in the Dissolution Studies Procedure.

Investigation Strategy

MDMA·HCl capsules (40 mg and 60 mg) and the details of these are listed in Table 5 along with the details of the RQB capsules to be used.

Table 5. MDMA Capsule Details.

Manufacturer	Dose Strength MDMA HCl	Equivalent Dose Strength MDMA freebase	Batch Details
Sharp Clinical Services	40 mg	34 mg	99441B1
RQB	40 mg	34 mg	RQB200601-010A
Sharp Clinical Services	60 mg	50 mg	99441B2
RQB	60 mg	50 mg	RQB200601-010B

The current RQB analytical method has two sampling timepoints (15 and 30 minutes). An initial dissolution can be performed to establish the suitable sampling timepoints.

All testing will be performed using equipment/instruments in the Development Centre at RQB.

Testing to be performed

Dissolution Profile Timepoint Determination

Perform a single dissolution (n=6 capsules) as described in the Dissolution Studies Procedure. Use both strengths of the RQB and Sharp capsules (see Table 5) and sample at the following timepoints: 5, 10, 15, 20, 30, 45, and 60 minutes. Analyse all samples as described in the analytical test method. It is useful to note if coning is observed for either batch of capsules.

Plot the mean % dissolution at each timepoint and use this data to estimate the key timepoints required to describe the dissolution release profile. It may be necessary to interpolate these points. A minimum of 3 timepoints are required. The criteria for the timepoints are:

1) Mean ≤85% dissolution for all but one timepoint
2) CV NMT 20% for timepoints ≤10 minutes
3) CV NMT 10% for timepoints > 10 minutes

The selected timepoints to be used for the dissolution testing need to fulfill these criteria and need to be the same for both strengths and products from both manufacturers. Otherwise, these timepoints must be modified and the analysis repeated based on the profile obtained.

If it is not practical to obtain three timepoints that meet the above criteria i.e., the dissolution is too fast, this must be flagged to the Senior Analyst and next steps will be discussed with the client.

Dissolution Testing

n=12 units of each of both the RQB and Sharp capsule batches in Table 5 is to be tested for dissolution as per the Dissolution Studies Procedure, using each of the media described below and the sampling timepoints established in the Dissolution Studies Procedure.

Standards are to be prepared in the same dissolution media as the samples. Prepare on the day of use.

Media preparation can be scaled as required.

pH 1.2 Dissolution Media Preparation

Prepare 15 L of media as follows: Dissolve 26.3 g NaCl and 111 mL (131.3 g) aqueous hydrogen chloride in 15 L of water. Mix well. Check the pH and report for information.

pH 4.5 Dissolution Media Preparation

Prepare 15 L of media as follows: Dissolve 204.2 g potassium dihydrogen phosphate in 11.2 L water. Adjust the pH with 0.1 M sodium hydroxide or 0.1 M hydrochloric acid as required. Dilute to 15 L with water. Report the pH.

pH 6.8 Dissolution Media Preparation

Prepare 15 L of media as follows: Mix 3750 mL of 0.2 M potassium dihydrogen phosphate with 1680 mL 0.2 M sodium hydroxide and dilute to 15 L with water. Check the pH and report for information.

Calculation of Results

Plot the mean dissolution profile obtained for the Sharp and RQB capsules at each dissolution condition, accounting for the samples removed at the previous timepoints. Compare the mean dissolution profile obtained for the Sharp capsules with the mean dissolution profile obtained for the RQB capsules.

For the comparison of dissolution profiles, where applicable, the similarity factor f2 should be estimated by using the following formula:

$$f2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$$

In the above equation,
f2 is the similarity factor;
n is the number of time points;
R(t) is the mean percent reference drug dissolved at time t after initiation of the study; and
T(t) is the mean percent test drug dissolved at time t after initiation of the study.

Two dissolution profiles are considered similar when the f2 value is ≥50. When both test and reference products demonstrate that ≥85% of the labelled amount of the drug is dissolved in 15 minutes, comparison with an f2 test is unnecessary and the dissolution profiles are considered similar. When the coefficient of variation is too high, f2 calculation is considered inaccurate and a conclusion on similarity in dissolution cannot be made.

If high variability or coning is observed in the paddle apparatus at 50 rpm for both reference and test products, the use of the basket apparatus at 100 rpm is recommended. Additionally, alternative methods where appropriately justified, may be considered to overcome issues such as coning, if scientifically substantiated.

Example 5. Dissolution Studies Procedure.

Introduction

This method describes the procedure for Dissolution Test of MDMA HCI by High Performance Liquid Chromatography – Ultraviolet (HPLC-UV).

Safety

Analysts must ensure that the Alcumus Control of Substances Hazardous to Health (COSHH) forms (ID 4126408) have been read before handling the MDMA HCI formulation. The formulation has been designated as a High Hazard. The potential health hazards include 'Toxic if swallowed', 'Skin - irritation and dermatitis may result from prolonged contact', 'May cause eye irritation' and 'May cause drowsiness or dizziness'. Therefore, the exposure time to the formulation has been established at 30 minutes per shift. Suitable personal protective equipment (PPE) must be worn within the laboratory at all times in order to ensure that chance of contact is kept to the minimum.

Responsibilities

It is the responsibility of analysts within the Development Centre to ensure that the method is followed throughout testing. It is the responsibility of management within the Development Centre to ensure this procedure is followed.

Analytical manager/team leader must ensure that the method in use is correct for the intended purpose. They must also ensure that the operator is suitably trained and comfortable with following this method.

Equipment and Consumables

- Agilent HPLC with Binary pump & UV detector
- Dissolution Bath, Apparatus 2 (Paddle)
- XBridge Phenyl, 3.5µm, 4.6 x 150mm (Cat. No. 186003335, Waters)
- Analytical Balance
- Sonic Bath

- Electronic Pipette (Handystep)
- Grade A glassware
- 0.45 µm GHP membrane filter (Cat. No. WAT200802, Waters)
- 5mL syringe
- Thermometer
- Wire sinkers
- Cannulas, Stainless steel

List of Materials (or equivalent)

Table 6 includes the laboratory reagents that can be used.

Table 6: Laboratory reagents for operation of this method.

Material	Supplier	Product code
Deionized Water	In house supply	N/A
Acetonitrile	Fisher	A/0627/17
Trifluoroacetic Acid (TFA)	VWR	153112E
Hydrochloric Acid (37%)	VWR	20252.335
MDMA Reference Standard	Onyx	TBC

General Statements

Mobile phase preparations may be scaled up or down as long as the required concentration remains the same.

All glassware used in sampling and testing should be Grade A glassware to limit any untoward interactions and must be thoroughly cleaned prior to use.

Agilent HPLC system must be used for the analysis.

Preparation of reagents

Mobile Phase A (Water : TFA – 100 : 0.1)

For every one liter of mobile phase solution, add 1 mL of trifluoroacetic acid (TFA) to 1000 mL of deionized (DI) water, mix thoroughly and sonicate for 15 minutes. Mobile phase can be used for 1 month from the date of preparation.

Mobile Phase A (Acetonitrile : TFA – 100 : 0.1)

For every one liter of mobile phase solution, add 1 mL of TFA to 1000 mL of acetonitrile, mix thoroughly and sonicate for 15 minutes. Mobile phase can be used for 3 months from the date of preparation.

Dissolution Media/ Diluent (0.1 N HCl)

Add 42 mL of 37% hydrochloric acid to 5000 mL of DI water, mix thoroughly and sonicate for 30 minutes. Dissolution media can be used for 1 months from the date of preparation.

Needle wash (Water : Acetonitrile – 50 : 50)

To prepare one liter of needle wash solution, add 500 mL of acetonitrile to 500 mL of DI water, mix thoroughly and sonicate for 15 minutes. This solution can be used for 3 months from the date of preparation.

Preparation of Standard Solution

The standard is 0.1 mg/mL MDMA HCl, and can be prepared in duplicate according to the following steps:

- Accurately weigh about 20 mg MDMA·HCl reference standard into a 50 mL volumetric flask.
- Add diluent (i.e., solvent (e.g., water)) to about two thirds of the volume and dissolve (sonicate if required).
- Dilute to volume with diluent and mix thoroughly to prepare standard stock solution.
- Pipette out 25 mL of Standard Stock solution into 100 mL volumetric flask, dilute to volume with diluent and mix well.

Note: Standard solution can be used for 72 hours when standing or stored at ambient temperature.

Dissolution Procedure for Samples

Weigh six capsules separately and prepare dissolution sample with the dissolution parameters shown in Table 7.

Table 7. Dissolution Parameters.

Apparatus Type	Apparatus 2, Paddle
Dissolution Media	0.1N HCl
Media volume	500 mL
Bath Temperature	37 ± 0.5°C
Stir Speed	50 RPM
Filter type	0.45 µm GHP Membrane Filter
Sinker Type	Wire Sinker
Volume pulled per time point	5 mL
Sampling time	15 min, 30 min

Chromatographic Conditions

Table 8 shows the HPLC parameters that can be used.

Table 8: HPLC parameters.

Column	XBridge Phenyl 150 x 4.6mm, 3 µm
Column Oven	30 °C
Injection Volume	10 µL
Autosampler Temperature	Ambient
Flow Rate	1.0 mL/min
Detection	UV 235 nm
Mobile Phase program	MPA:MPB 80:20 Isocratic
Needle Wash	Water : MeCN (50 : 50)
Run Time	10 mins

Guideline injection sequence

The below sequence is a guideline only. An injection sequence may be altered as required. However, the following key points must not be altered:

- Inject the blank solution until a stable baseline is achieved.
- Number of standard solution injections prior to sample analysis.
- Standard solution must be injected in duplicate following a maximum of 6 sample injections (not inclusive of diluent blank injections) and at the end of the sequence.

Table 9 shows an injection sequence that can be used.

Table 9: Example injection sequence.

Solution	Number of Injections
Diluent blank	3

Standard 1	5
Standard 2	1
Standard 1 (Bracketing STD)	2
Sample Solution (Up to 6 samples)	1 per Sample Solution
Standard 1 (Bracketing STD)	2

Column Cleaning

After each use, the column must be thoroughly cleaned to ensure that it is ready for use on a subsequent occasion. Purge the column with a solvent system including 50% water and 50% acetonitrile (CAN) for 30 mins at 0.5 mL/min. Purge the column with a solvent system including 25% water and 75% ACN for 30 mins at 0.5 mL/min. Purge the column with 100% ACN for 1 hour at 0.5 mL/min. Store the column in 100% ACN.

System suitability criteria

- Diluent used in injection prior to the Standard 1 injection must not have significant interferences (> 0.5% of the average area of five injection of STD 1) with the MDMA·HCl peak.
- The percentage relative standard deviation (RSD) of MDMA·HCl peak area for first five STD 1 injection must be < 2.0%
- The United States Pharmacopeia (USP) tailing factor for the MDMA·HCl peak in the first STD 1 injection must be < 3.0.
- The number of USP theoretical plates for the MDMA·HCl peak in the first injection of STD 1 must be > 1500.
- The ratio of check standard solution (STD 2) response to the average response of first five STD 1 injection must be 98.0% - 102.0%.

Calculations

The dissolution calculation for MDMA·HCl is shown below:

$$\% \text{ dissolved} = (PA_{SMP} \times C_{STD} \times VOL_{VES} \times 100) / (PA_{STD} \times LC)$$

where:

PA_{SMP} is sample peak area (MDMA·HCl peak)

VOL_{VES} is volume of dissolution media in the vessel (mL)

C_{STD} is concentration of MDMA·HCl reference standard in the working standard 1 preparation considering the purity of the reference standard (in mg/mL)

PA_{STD} is mean MDMA·HCl peak area of the bracketing assay standard solution 1 injections

LC is labelled claim per capsule (40 mg or 60 mg)

Reporting

Report the % label claim dissolved per vessel to 0 d.p.

Disposal and Cleaning

All samples/standards should be discarded into the appropriate waste containers along with the consumables used to hold/transfer them.

Example 6. Dosage, Administration, and Prescription Information.

Dosage and Administration

Recommended Dosage

The total dosage of MDMA·HCl includes 3 doses in combination with treatment sessions (dose 1: 102 mg; doses 2 and 3: 150 mg each) with interim periods of at least 21 days between doses. The total dose of MDMA·HCl at each of these treatment sessions is provided in an individual package containing 3 capsules. Patients take 2 capsules at the start of the session and take the third capsule 1½ to 2 hours after the first dose. Patients may need to set an alarm to take the second dose.

The MDMA·HCl is for oral use only. The capsules should be swallowed whole and not crushed or chewed. MDMA·HCl may be taken without regard to timing of meals. It is recommended to not exceed 150-mg MDMA·HCl per day.

FIG. 6 shows the schedule of dosing and therapy sessions for MDMA HCl.

Administration Instructions

Instruct patients to follow these administration instructions and read the instructions for use before self-administration. Instruct the patients to take the unopened package with them to the treatment session. At the start of the psychotherapy session, patients should:

- Push 2 capsules through the foil and take with a sip of water.
- Sit or lay down in a comfortable position.
- Protect eyes from bright light.
- Rest and proceed with the treatment session for 1½ to 2 hours
- After 1½ to 2 hours have elapsed, sit up and push remaining capsule through foil. Take 1 capsule with a sip of water.
- Sit or lay down in a comfortable position.
- Protect eyes from bright light.
- Rest and proceed with the treatment session.
- Remain in the facility until effects have worn off.
- Do not engage in potentially hazardous activities such as driving until the next day.

Important Considerations Prior to Initiating and Between MDMA·HCl Treatments

Before initiating treatment, instruct the patient that MDMA·HCl must be self-administered under the direct observation of a health care provider during a treatment session. Also instruct the patient not to engage in potentially hazardous activities, such as driving or operating machinery, until the next day after each treatment.

Blood Pressure Assessment Before Initiating Treatment

- Assess blood pressure prior to prescribing MDMA HCl.
- If baseline blood pressure is elevated (e.g., >140 mm Hg systolic, >90 mm Hg diastolic), consider the risks of short-term increases in blood pressure and benefit of MDMA·HCl treatment in patients with PTSD.

Important Considerations Prior to Prescribing Each MDMA·HCl Dose

- Assess cardiovascular status of patients being considered for treatment with MDMA HCl. Before initiating treatment, conduct a careful history (including assessment for a family

history of sudden death or ventricular arrhythmia) and a physical exam to assess for the presence of cardiac disease with further cardiac evaluation when warranted.

- Before prescribing the second and third doses of MDMA HCl, collect any additional cardiac history to assess for a change in cardiovascular status. Also review concomitant medications to ensure that patients are not taking any contraindicated medications (e.g., monoamine oxidaze inhibitors (MAOIs)) before prescribing each dose of MDMA HCl.

Therapeutic Program

The safety and efficacy of MDMA·HCl were examined in combination with a specific therapeutic program. Physicians should advise patients that each dose of MDMA·HCl must be self-administered under the direct observation of an appropriately-trained health care provider during a treatment session. The prescriber should discuss the following elements of the therapeutic program.

Preparatory Sessions

Preparatory session(s) (talk therapy or psychotherapy) address the patient questions and concerns, as well as to prepare them for upcoming treatment sessions with MDMA HCl. In clinical trials, preparation included multiple preparatory sessions.

Sessions with MDMA HCl

At the beginning of each of the 3 treatment sessions with MDMA HCl, the planned approach and the range of experiences that may occur during the session should be reviewed with the trained health care provider.

Integration Sessions Following Sessions with MDMA HCl

Follow-up contact with the trained health care provider should be conducted to support successful integration. In clinical trials, integration included 3 sessions (talk therapy or psychotherapy) after each session with MDMA HCl.

Post-Administration Observation

During and after MDMA·HCl self-administration at each session, a health care provider should observe the patient for approximately 6 hours from first dose of the split dose. Patients should understand that they should not leave the physical setting while still experiencing effects of MDMA·HCl at treatment sessions. Patients should also understand that additional time may be required beyond the planned length of the sessions, if the patient needs additional support. The patient must also agree to accept transport home from treatment sessions with MDMA HCl.

Missed Treatment Session(s)

If a patient misses treatment session(s), provided there is no evidence of diversion or abuse, the patient should be counseled to re-schedule the missed session and to continue the current psychotherapy schedule. Healthcare providers should reiterate the importance of psychological intervention in combination with MDMA·HCl treatment.

Use of MDMA·HCl with Reversible MAOIs Such as Linezolid or Methylene Blue

Do not start MDMA·HCl in a patient who is being treated with a reversible MAOI such as linezolid or intravenous methylene blue. Drug interactions can increase the risk of hypertensive reactions. In some cases, a patient already receiving psychotherapy with MDMA·HCl may require urgent treatment with MAOIs. MDMA·HCl should not be administered again until 5 to 10 times the half life after the last dose of MAOIs, whichever comes first.

Dosage Forms snd Strengths

MDMA·HCl is supplied as single-dose, foil-wrapped capsules in 2 total dosage strengths:

- 102 mg total dose: midomafetamine (MDMA) HCl 34 mg, 3 Swedish Orange/White, Size 2 capsules imprinted with "MDMA 34".
- 150 mg total dose: midomafetamine HCl 50 mg, 3 Swedish Orange, Size 2 capsules imprinted with "MDMA 50".

Contraindications

MDMA·HCl is contraindicated in patients with:

- The use of MAOIs (intended to treat conditions such as psychiatric disorders or Parkinson's disease) concomitantly with MDMA·HCl or within 14 days of discontinuing treatment with MDMA·HCl is contraindicated. There is an increased risk of hypertensive reactions when MDMA·HCl is used concomitantly with MAOIs. Starting MDMA·HCl in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated.
- Hypersensitivity to MDMA or other components of MDMA HCl.

Warnings and Precautions

Perceptual Changes

Known effects of MDMA·HCl include perceptual changes such as difficulty concentrating and impaired judgment, and physiological effects such as dizziness, impaired gait/balance, and blurred vision. Other known effects of MDMA·HCl include an altered state that may include a range of emotions, thoughts, and physical sensations. Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that effects of MDMA·HCl have dissipated (e.g., impaired judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, until the day after taking MDMA HCl.

Abuse and Misuse

MDMA·HCl contains the hydrochloride salt of 3,4-methylenedioxymethamphetamine (MDMA) and a schedule II controlled substance (CII), and may be subject to abuse and misuse. Assess each patient's risk for abuse or misuse prior to prescribing MDMA·HCl and monitor all patients receiving MDMA·HCl for the development of these behaviors or conditions, including drug-seeking behavior, while taking MDMA HCl. Prescribe and dispense MDMA·HCl with appropriate precautions to minimize risk of misuse or abuse. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence. Patients should not be prescribed more than 3 doses of MDMA. Contact local state

professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of MDMA HCl.

MDMA·HCl is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of MDMA HCl.

MDMA·HCl Risk Evaluation and Mitigation Strategy (REMS)

MDMA·HCl is available only through a restricted program under a REMS called the MDMA·HCl REMS because of the risks of serious adverse outcomes from abuse and overdose. Important requirements of the MDMA·HCl REMS include the following:
Healthcare settings must be certified in the program and ensure that MDMA·HCl is:

- Only dispensed by certified pharmacies.
- Self-administered by patients enrolled in the program.
- Administered by patients under the direct observation of a health care professional.
- Patients are to be monitored by a health care professional for at least 6 hours after administration of MDMA HCl.
- Pharmacies must be certified in the REMS and must only dispense MDMA·HCl to patients enrolled in the program.

Increase in Blood Pressure and Heart Rate

MDMA·HCl causes transient dose-dependent increases in systolic and/or diastolic blood pressure (BP) and heart rate at all recommended doses. A substantial increase in blood pressure and/or heart rate could occur after any dose even if smaller blood pressure or heart rate effects were observed with previous administrations. Assess blood pressure and control hypertension before initiating treatment with MDMA HCl. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. In patients whose BP is elevated (as a general guide: >140/90 mm Hg) a decision to delay MDMA·HCl should take into account the balance of benefit and risk in individual patients. Exercise caution when treating patients at higher risk of major adverse cardiovascular events (including stroke, myocardial infarction, and cardiovascular death), particularly patients with known cardiovascular

and cerebrovascular disease, preexisting hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Treatment with MDMA·HCl should be discontinued in patients who develop hypertensive crisis or hypersensitive encephalopathy. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain or shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness, or focal neurological deficits) immediately for emergency care.

Suicidal Thoughts and Behaviors in Patients with PTSD

Patients with psychiatric disorders, including PTSD, are at increased risk of suicide. Monitor all PTSD patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially at times of any dosing changes preceding MDMA·HCl treatment and after psychotherapy sessions where MDMA·HCl was self-administered. Council family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing MDMA HCl, in patients who are experiencing emergent suicidal thoughts or behaviors that are not resolved with psychological intervention. The effectiveness of MDMA·HCl in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of MDMA·HCl does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of MDMA HCl.

Psychiatric Symptoms

Psychiatric adverse reactions have been observed in clinical trials with MDMA HCl, including anxiety, insomnia, and irritability. MDMA·HCl has not been evaluated in patients with psychosis or bipolar affective disorder Type 1. Exercise caution when treating patients with MDMA·HCl who have a history of psychosis or bipolar disorders. Patients treated with MDMA·HCl should be observed for the possible emergence or exacerbation of psychiatric symptoms. If serious or severe psychiatric symptoms develop in association with the administration of MDMA HCl, consider discontinuation of MDMA HCl.

Serotonin Syndrome

Monoamine reuptake inhibitors, including MDMA HCl, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs. Serotonin syndrome can also occur when these drugs are used alone.

Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of MDMA·HCl with MAOIs is contraindicated. In addition, do not initiate MDMA·HCl in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking MDMA HCl, discontinue MDMA·HCl before initiating treatment with the MAOI.

Monitor all patients taking MDMA·HCl for the emergence of serotonin syndrome. Discontinue treatment with MDMA·HCl and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of MDMA·HCl with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

Drug Interactions

Drugs Metabolized by CYP2D6

Midomafetamine HCl is a strong CYP2D6 inhibitor. Therefore, coadministration of MDMA·HCl with drugs that are primarily metabolized by CYP2D6 may increase the exposures of those drugs. Such drugs include certain antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone and flecainide). When used concomitantly with MDMA HCl, it may be necessary to decrease the dose of these CYP2D6 substrates or temporarily halt administration, particularly for drugs with a narrow therapeutic index.

Drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen and codeine) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as MDMA HCl. Patients treated concomitantly with MDMA·HCl and such drugs may require temporarily increased doses of the drug.

Psychostimulants

Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of MDMA·HCl with psychostimulants.

Monoamine Oxidase Inhibitors (MAOIs)

Concomitant use of MDMA·HCl and other monoamine oxidase inhibitors (MAOIs) within 14 days is contraindicated because of an increased risk of causing hypertensive reactions. At least 14 days should elapse between discontinuation of an MAOI and treatment with MDMA HCl. Conversely, at least 14 days should be allowed after taking MDMA·HCl before starting an MAOI.

Serotonergic Drugs

Co-administration with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) may eliminate or greatly attenuate the effects of MDMA HCl, and these medications should be tapered in line with the prescriber's clinical judgment.

Use in Specific Populations

Geriatric Use

Clinical studies of MDMA·HCl did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

Hepatic Impairment

MDMA·HCl has not been studied in patients with hepatic impairment. Use in this population is not recommended.

Drug Abuse and Dependence

Controlled Substance

MDMA·HCl contains the hydrochloride salt of 3,4 methylenedioxymethamphetamine (MDMA), a Schedule II Substance under the Controlled Substances Act.

Drug Abuse

MDMA·HCl produces dose-dependent central nervous system effects, including positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Illicit MDMA has been extensively abused and/or misused. Because illicit use of MDMA has been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of illicit MDMA

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of MDMA HCl. Careful consideration is advised prior to use of individuals with a history of substance use disorder.

All patients treated with MDMA·HCl require careful monitoring for signs of abuse. Proper assessment of the patient, proper prescribing practices and proper handling and storage of the medication are appropriate measures that help to limit abuse or misuse of MDMA HCl. MDMA·HCl may produce a variety of symptoms broadly characterized as positive reinforcing effects. Monitoring for signs of abuse and misuse is recommended.

Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or significant dosage reduction of a drug.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

As MDMA·HCl administration is limited to 3 individual doses administered at least 21 days apart, dependence and tolerance is not expected to develop when MDMA·HCl is used as prescribed.

Overdosage

Clinical Presentation

The prescription unit is restrictive to prevent overdose and therefore is unlikely to occur. The manifestations of acute overdose with illicit MDMA in excess of the recommended dose range may include hyperthermia, hyponatremia, rhabdomyolysis, acute renal failure, seizure, cardiovascular adverse events, disseminated intravascular coagulation, hemorrhage, and death.

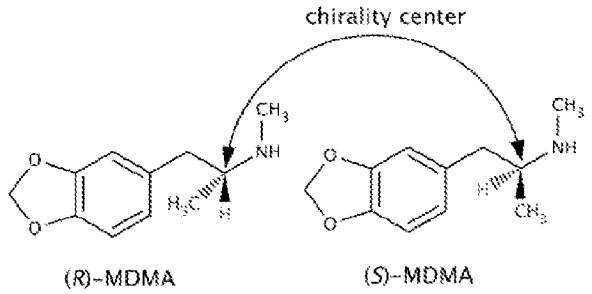
Management of Overdosage

There is no specific antidote for MDMA overdose. In the case of overdose, the possibility of multiple drug involvement should be considered, and supportive care should be provided.

Contact a Certified Poison Control Center for the most up to date information on the management of overdosage.

11 DESCRIPTION

MDMA·HCl contains the racemic anhydrous hydrochloride salt of 3,4-methylenedioxymethamphetamine (MDMA), a triple monoamine reuptake releaser and inhibitor. MDMA is a ring-substituted phenethylamine. The chemical name is (RS)-1-(benzo[d][1,3]dioxol-5-yl)-N-methylpropan-2-amine hydrochloride. Its molecular formula is $C_{11}H_{15}NO_2$.HCl and its molecular weight is 229.70. The structural formula is shown below:



MDMA is a white crystalline powder that is freely soluble in freely soluble in water and chloroform, soluble in ethanol, and slightly soluble in acetone. MDMA·HCl is intended for oral administration and is available at 2 dosage strengths, 34 and 50 mg of MDMA hydrochloride. Each capsule also contains hydroxypropylmethylcellulose (HPMC) with mannitol and magnesium stearate.

Clinical Pharmacology

Mechanism of Action

MDMA·HCl is an Entactogen. The mechanism of action of MDMA·HCl in the treatment of PTSD is not known. MDMA·HCl is a serotonin and other monoamine (norepinephrine and dopamine) reuptake inhibitor as well as a modulator of monoamine transport. MDMA HCl, in combination with psychological intervention, leads to the modulation of DNA methylation in genes controlling the hypothalamic pituitary adrenal access (resulting in epigenetic malleability).

MDMA·HCl increases the release of monoamines such as serotonin, dopamine and norepinephrine into the extraneuronal space.

Pharmacodynamics

Cardiac Electrophysiology

The effect of MDMA·HCl on the QTc interval was evaluated in a randomized, crossover study in N healthy subjects. A large increase in heart rate (i.e., >10 bpm) was observed with MDMA HCl. The totality of evidence from the nonclinical and clinical data indicates a lack of clinically relevant QTc prolongation at the therapeutic dose of MDMA HCl.

Pharmacokinetics

MDMA·HCl is a racemic mixture. Both enantiomers are pharmacologically active. 3,4-methylendioxyampetamine (MDA) is a metabolite of MDMA and is also pharmacologically active. Peak plasma levels and $AUC_{0\text{-}inf}$ of MDA are less than 10% of the corresponding parameters for MDMA. MDA may contribute to the pharmacological effects of MDMA HCl. The pharmacokinetics of MDMA are non-linear with higher than dose proportional increases in plasma concentration due to auto-inhibition of CYP2D6. The elimination half life of a single 120 mg dose of MDMA·HCl was 9 hours.

Absorption

The absolute bioavailability of MDMA·HCl in humans is not known because pharmacokinetic studies have not been conducted following intravenous (iv) administration of MDMA HCl. MDMA·HCl exhibits high solubility and permeability and appears to be well absorbed. In humans, following a single 120 mg dose of MDMA HCl, peak plasma concentration of MDMA was generally achieved within 2 hours and C_{max} was 261 ng/mL. The $AUC_{0\text{-}inf}$ of MDMA was 3890 h*ng/mL following a single 120 mg dose of MDMA HCl. Peak plasma levels (C_{max}) of MDA were 13.3 ng/mL and occurred at 6 hours post dose. The $AUC_{0\text{-}inf}$ of MDA was 374 h*ng/mL following a single 120 mg dose of MDMA HCl.

Table 10. Pharmacokinetics of MDMA and MDA following a single 120 mg dose of MDMA·HCl administered to fasting healthy males and females

PK Parameter	MDMA	MDA
C_{max} ng/mL (CV%)	261 (27.0)	13.3 (27.6)
T_{max} h (min, max)	2.00 (2.00, 8.00)	6.00 (2.00, 8.00)
AUC_{0-inf} h*ng/mL (CV%)	3890 (39.1)	374 (38.1)
$t_{1/2}$ h (CV%)	9.10 (19.6)	12.8 (19.2)

Effect of Food

The C_{max} and AUC data from a food-effect study involving administration of MDMA·HCl to healthy volunteers under fasting conditions and with a high-fat meal indicated that exposure to the drug is not affected by food. A high fat meal had no effect on the pharmacokinetics of a single 120 mg dose of MDMA·HCl in healthy males and females.

Distribution

In vitro studies have demonstrated that MDMA is X% bound to human plasma proteins at concentrations up to Y. MDMA is not a substrate of BCRP, MDR1, OATP1B1, or OATP1B3. A single 120 mg dose of MDMA·HCl resulted in a volume of distribution of 430 L.

Elimination

Metabolism

MDMA is extensively metabolized in humans. Several parallel metabolic pathways contribute to the metabolism of MDMA including CYP2D6, CYP1A2, CYP3A4, CYP2C19, and CYP2B6. MDMA is a strong inhibitor of CYP2D6 and thus auto-inhibits its own metabolism, leading to higher than dose proportional pharmacokinetics of MDMA.

N-demethylation of MDMA forms an active metabolite, 3,4-methylenedioxyamphetamine (MDA). The parent compound and MDA are further O-demethylated to 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA), respectively. Both HHMA and HHA are subsequently O-methylated mainly to 4-hydroxy-3-methoxymethamphetamin (HMMA) and 4-hydroxy-3-methoxyamphetamine (HMA).

MDMA is a strong inhibitor of CYP2D6 and thus auto-inhibits its own metabolism, leading to higher than dose proportional pharmacokinetics of MDMA.

Excretion

Formal ADME studies evaluating the recovery of labeled MDMA have not been conducted. The percentage of unchanged MDMA excreted in urine following orally administered doses of 1.0 and 1.6 mg/kg MDMA was 8% and 11%, respectively. The majority of the dose recovered in the urine was conjugated metabolites.

Specific Populations

Patients with Renal Impairment

The pharmacokinetics of MDMA·HCl in subjects with renal impairment have not been studied. The percentage of unchanged MDMA excreted in urine following orally administered doses of 1.0 and 1.6 mg/kg MDMA was 8% and 11%, respectively (Schwaninger 2011). Therefore, renal impairment is unlikely to alter the pharmacokinetics of MDMA·HCl in a clinically meaningful way.

Patients with Hepatic Impairment

The pharmacokinetics of MDMA·HCl in subjects with hepatic impairment have not been studied. MDMA·HCl is extensively metabolized by hepatic enzymes.

Drug Interaction Studies

Potential for Other Drugs to Affect MDMA HCl

MDMA·HCl is metabolized via several parallel Cytochrome P450 (CYP) pathways. Therefore, the potential that inhibition of any one pathway will impact the pharmacokinetics of MDMA·HCl in a clinically meaningful way is minimized. The effect of the CYP2D6 inhibitors paroxetine and bupropion have been evaluated in clinical studies with MDMA (Segura 2005, Schmid 2015). Paroxetine administered 20 mg a day for three days to 7 healthy males increased the $AUC_{0\text{-}inf}$ of a single 100 mg dose of MDMA by 27% and C_{max} by 17% (Segura 2005).

Bupropion 150 mg per day for three days followed by 300 mg a day for four days administered to 16 healthy male and female Caucasian subjects increased the $AUC_{0\text{-}24hr}$ of a single 125 mg dose of MDMA by 33% and C_{max} by 14% (Schmid 2015).

Potential for MDMA·HCl to Affect Other Drugs

MDMA·HCl is a strong CYP2D6 inhibitor. Therefore, when administered in combination with sensitive CYP2D6 substrates, MDMA·HCl may cause significant increase in the plasma levels of those drugs. The effect of MDMA on the plasma pharmacokinetics of dextromethorphan and paroxetine has been evaluated in clinical studies (Yubero-Lahoz 2011, O'Mathuna 2008 and Sequra 2005). A single 1.5 mg/kg dose of MDMA administered to 15 healthy males 4 hours before 30 mg dextromethorphan (Days 1, 2, 3, 4, 5 and 8) increased the $AUC_{0\text{-}8hr}$ of dextromethorphan 9.5-fold and C_{max} 8.5-fold (O'Mathuna 2008). A single 1.5 mg/kg dose of midomafetamine HCl administered 4 hours before 30 mg dextromethorphan (Days 1, 2, 5, 8 and 11) to 12 healthy Caucasian females increased the $AUC_{0\text{-}inf}$ of dextromethorphan 13.6-fold and C_{max} 8.3-fold (Yubero-Lahoz 2011). A single 100 mg dose of MDMA administered to 7 healthy males increased the $AUC_{0\text{-}8hr}$ of paroxetine (20 mg) 3-fold and increased C_{max} 2.5-fold (Segura 2005). MDMA·HCl is not an inducer of CYPs and did not inhibit CYPs other than CYP2D6 in a clinically meaningful manner.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Based on negative in vivo and in vitro genotoxicity studies, the carcinogenic risk of MDMA·HCl is low. No tumors were reported after daily 28-day repeated dose toxicology studies of MDMA in rats (0, 10, 50, or 100 mg/kg/day) or dogs (0, 3, 9, or 15 mg/kg/day).

Mutagenesis

MDMA was not mutagenic with or without metabolic activation in the in vitro bacterial reverse mutation assay (Ames test). Additionally, MDMA showed no signs of chromosomal aberrations in CHO-WBL cells with and without metabolic activation.

Oral MDMA was shown to have no signs of genotoxicity in male rats in doses up to 100 mg/kg day over two days. No statistically significant differences in micronucleated polychromatic erythrocytes or bone marrow cytotoxicity were observed across all dose levels.

Impairment of Fertility

MDMA (0, 2.5, 5, and 10 mg/kg/day) was orally administered to male and female rats before mating. Males were dosed once daily for 28 days prior to pairing and dosing continued until euthanasia. Females were dosed once daily for 21 days prior to pairing and dosing continued though gestational day seven. Mean prostate gland weights decreased in all MDMA-treated males relative to controls, however this did not affect fertility or overall health of the animals. No effect on fertility and reproductive performance was observed up to the highest dose evaluated (10 mg/kg/day).

Animal Toxicology and/or Pharmacology

In 28-day repeat-dose toxicity studies, MDMA was well tolerated with no mortality or significant toxicologic findings after weekly, oral administration to rats ($\leq$ 20 mg/kg) and dogs ($\leq$ 4 mg/kg). No morphologic changes, based on neurohistopathology examination, were evident in the brains of rats or dogs treated with MDMA at any dose. The relevance of these findings to humans is unknown.

How Supplied/Storage and Handling

MDMA·HCl is available as 34-mg or 50-mg capsules.

Storage

Store at ambient temperature, 15° to 25°C (59° to 77°F); excursions permitted from 5° to 30°C (41° to 86°F).

Disposal

MDMA·HCl oral capsules must be handled with adequate security, accountability, and proper disposal, per facility procedure for a Schedule II drug product, and per applicable federal, state, and local regulations.

Example 7. Clinical Pharmacokinetics of MDMA from Study MPKF and the National Institute on Drug Abuse (NIDA) Study.

Introduction:

The MPKF is a Phase 1, open-label, randomized sequence, multi-dose, 2-period crossover food effect study in 16 healthy individuals. The MPKF study evaluated plasma concentrations of both MDMA and the active metabolite 3,4-methylenedioxyamphetamine (MDA). Summary PK Parameters of the preliminary data was based on interim analysis are presented in Table 12, and Table 13 for MDMA and MDA, respectively.

The NIDA study 7 days of individual-level blood plasma data were collected for 46 participants receiving a low MDMA dose (1.0 mg/kg) and 41 participants receiving a high MDMA dose (1.6 mg/kg, 150 mg maximum).

Materials and methods:

The MPKF study:

Formulation: d,l-MDMA HCl (50/50 racemic mixture) encapsulated with excipients listed in Table 11. The API, synthesized by Onyx Scientific, was a white crystalline powder of pharmaceutical quality, made according to current Good Manufacturing Practices for human use. This formulation is the highest dosage strength equivalent to the formulation intended for marketing.

Participants: Sixteen healthy individuals were recruited for the study.

Intervention: The study was conducted as a Phase 1, open-label, randomized sequence, multi-dose, 2-period crossover food effect study. Each participant received multiple doses of MDMA, and plasma concentrations of both MDMA and the active metabolite MDA were measured.

Sample Collection: Blood samples were collected at various time points up to 72 hours after dosing. The samples were analyzed using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

Pharmacokinetic Analysis: Plasma pharmacokinetic parameters, such as area under the concentration-time curve from time 0 to the last quantifiable concentration (AUC0-t), area under the concentration-time curve from time 0 to 72 hours (AUC0-72), area under the concentration-time curve from time 0 to infinity (AUC0-inf), maximum concentration (Cmax), time to maximum concentration (Tmax), elimination half-life (t1/2), lag time (Tlag), clearance (CL/F), and volume of distribution (Vd/F) were calculated using non-compartmental methods.

Data Analysis: The summary PK parameters were presented in Table 12 for MDMA and Table 13 for MDA. The data were analyzed using descriptive statistics, and the mean and standard deviation were calculated. The results were compared between the two periods and analyzed for food effects. Statistical analyses were performed using appropriate methods, such as analysis of variance (ANOVA) and paired t-tests. A p-value of less than 0.05 was considered statistically significant. Results are shown in table 12 and 13.

Table 11. 60 mg MDMA HCl Formulation Used in Study MPKF.

Component	**Amount (mg) MPKF Capsules**	**Proportion relative to core weight (% w/w) MPKF Capsules**
MDMA HCl	59.5[1]	50.0%
Mannitol (filler)	58.31	49.0%
Mg Stearate (lubricant)	1.19	1.0%
Total	**119.00**	**100.0%**

[1] equivalent to 50 mg MDMA free base

The NIDA study:

Formulation: d,l-MDMA HCl (50/50 racemic mixture) encapsulated without excipients. The API, synthesized by Lipomed; Arlesheim, Switzerland, was a white crystalline powder of pharmaceutical quality, made according to current Good Manufacturing Practices for human use.

Participants: Healthy adult volunteers were recruited for each study.

Intervention: A single oral dose of MDMA (1.0 mg/kg (low), or 1.6 mg/kg (high))) was administered to participants.

Sample collection: Blood samples were collected at various time points up to 3 hours after dosing. Urine samples were collected at various time points up to 120 hours after dosing.

Pharmacokinetic Analysis: The samples were analyzed using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods to determine the plasma pharmacokinetic parameters, such as AUC-0, Cmax, and Tmax. The samples were analyzed using validated gas chromatography-mass spectrometry (GC-MS) and LC-MS/MS methods to determine the % of oral MDMA dose excreted in urine over the 0-120 hour period post-dose.

Data Analysis: The results show a comprehensive understanding of the disposition of MDMA and its metabolites in blood and urine. The data were analyzed using descriptive statistics, and the mean and standard deviation were calculated. Statistical analyses were performed using appropriate methods, such as ANOVA and paired t-tests. A p-value of less than 0.05 was considered statistically significant. Results are shown in table 14 and 15.

Table 12. Preliminary Plasma PK Parameters of MDMA Following a Single 120 mg Oral Dose of MDMA HCl Under Fasting or Fed Conditions (Study MPKF).

		120 mg MDMA Treatment	
MDMA PK Parameters[a]	**Units**	**Fasted N = 11**	**Fed N = 11**
AUC_{0-t}	h*ng/mL	3670 (43.2);11	3550 (54.4);11
AUC_{0-72}	h*ng/mL	3880 (38.2);11	3800 (48.5);11
AUC_{0-inf}	h*ng/mL	3890 (39.1);11	3800 (50.7);11
C_{max}	ng/mL	261 (27.0);11	242 (24.2);11
T_{max}[b]	h	2.00 (2.00, 8.00);11	4.00 (4.00, 6.00);11
$t_{1/2}$	h	9.10 (19.6);11	8.36 (28.3);11
Tlag[b]	h	0.50 (0.00, 1.00);11	0.50 (0.00, 1.00);11
CL/F	L/h	34.5 (33.7);11	37.5 (39.8);11
Vd/F	L	430 (18.7);11	412 (20.4);11

[a] Arithmetic Mean (Arithmetic CV%);N
[b] Median (Min; Max);N

Table 13. Preliminary Plasma PK Parameters of MDA Following a Single 120 mg Oral Dose of MDMA HCl Under Fasting or Fed Conditions (Study MPKF).

	120 mg MDMA Treatment

MDA PK Parameters[a]	**Units**	**Fasted N = 13**	**Fed N = 13**
AUC_{0-t}	h*ng/mL	324 (41.4);13	287 (50.5);13
AUC_{0-72}	h*ng/mL	342 (36.3);13	308 (42.9);13
AUC_{0-inf}	h*ng/mL	374 (38.1);10	388 (37.1);8
C_{max}	ng/mL	13.3 (27.6);13	12.2 (23.9);13
T_{max}[b]	h	6.00 (2.00, 8.00);13	8.00 (4.00, 12.00);13
$t_{1/2}$	h	12.8 (19.2);10	13.2 (25.8);8
Tlag[b]	h	0.50 (0.00, 1.00);13	1.00 (0.00, 1.00);13
CL/F	L/h	368 (41.6);10	339 (29.4);8
Vd/F	L	6510 (31.0);10	6140 (22.8);8

[a] Arithmetic Mean (Arithmetic CV%);N
[b] Median (Min; Max);N

Table 14. Summary Plasma PK Parameters of MDMA Following a Single Oral Dose of MDMA (1.0 or 1.6 mg/kg) in the NIDA study.

		1.0 mg/kg		**1.6 mg/kg**	
PK Parameters	**Units**	**Blood**	**Plasma**	**Blood**	**Plasma**
AUC_{0-3h}[a]	h*ng/mL	248.9 [120.0-536.4] n = 45	220.7 [98.7-480.7] n = 45	419.0 [20.0-831.7] n = 40	352.7 [16.2-846.3] n = 42
Cmax[a]	ng/mL	144.9 [90.3-358.2] n =46	126.3 [66.9-276.1] n = 46	241.6 [58.5-461.9] n = 41	205.1 [46.3-465.3] n = 41
Tmax[a]	h	2.5 [1.5-3.0] n = 46	2.5 [1.5-3.0] n = 46	2.5 [1.0-3.0] n = 41	2.5 [1.0-3.0] n = 42
% of oral MDMA Dose Excreted in Urine (0-120 h post-dose)[b]	%	10.4 [6.3-17.5] n = 5		17.0 [9.0-25.4] n = 9	
% of oral MDMA Dose Excreted in Urine (0-120 h post-dose)[c]	%	8.1, n = 10		11.2, n = 10	

Data presented as median [range] n
[a] Plasma PK data from (Hartman RL, Desrosiers NA, Barnes AJ, et al. 3,4-Methylenedioxymethamphetamine (MDMA) and metabolites disposition in blood and plasma following controlled oral administration. Anal Bioanal Chem. 2014;406(2):587-99).
[b] Urine PK data from (Abraham TT, Barnes AJ, Lowe RH, et al. Urinary MDMA, MDA, HMMA, and HMA excretion following controlled MDMA administration to humans. Journal of analytical toxicology.2009;33(8):439-46).

[c] Urine PK data from (Schwaninger AE, Meyer MR, Barnes AJ, et al. Urinary excretion kinetics of 3,4- methylenedioxymethamphetamine (MDMA, ecstasy) and its phase I and phase II metabolites in humans following controlled MDMA administration. Clinical chemistry. 2011;57(12):1748-56) (range not available).

Table 15. Summary Plasma PK Parameters of MDA Following a Single Oral Dose of MDMA (1.0 or 1.6 mg/kg) in the NIDA study.

		1.0 mg/kg		**1.6 mg/kg**	
PK Parameters	**Units**	**Blood**	**Plasma**	**Blood**	**Plasma**
AUC_{0-3h}[a]	h*ng/mL	12.9 [4.1-26.4] n = 45	8.8 [2.5-15.2] n = 45	19.4 [0.8-43.6] n = 40	11.9 [0.5-36.6] n = 42
Cmax[a]	ng/mL	8.0 [4.0-18.3] n = 46	5.5 [2.3-11.3] n = 46	13.0 [3.0-24.1] n = 41	8.6 [2.0-21.0] n = 42
Tmax[a]	h	3.0 [1.5-3.0] n = 45	3.0 [2.0-3.0] n = 46	3.0 [1.5-3.0] n = 41	3.0 [2.0-3.0] n = 42
% of oral MDMA Dose Excreted in Urine (0-120 h post-dose)[b]	%	0.9 [0.6-2.2] n = 5		1.6 [0.9-2.7] n = 9	
% of oral MDMA Dose Excreted in Urine (0-120 h post-dose)[c]	%	0.6, n = 10		1.2, n = 10	

Data presented as median [range] n
[a] Plasma PK data from (Hartman et al, 2014)
[b] Urine PK data from (Abraham et al, 2009)
[c] Urine PK data from (Schwaninger et al, 2011) (range not available)

Discussion:

MDMA exhibits high PK variability. The unbound maximum concentration (C_{max}) of MDMA following a single 120 mg dose is estimated to be 0.66 µM, based on the PK data from the MPKF study demonstrating a C_{max} of 261 ng/ml following a single 120 mg dose of MDMA, and literature reporting that in humans MDMA is 51% bound to plasma proteins (Wan Aasim WR, Tan SC, Gan SH. Interspecies In Vitro Evaluation of Stereoselective Protein Binding for 3, 4-Methylenedioxymethamphetamine. Journal of Chemistry. 2017;2017).

Example 8. Population PK (PopPK) Analysis

Introduction:

PopPK analyses of MPKF and NIDA concentration-time data will be carried out according to the FDA Guidances for Industry: *Population Pharmacokinetics* (February 2022) and *Exposure-Response Relationships Study Design, Data Analysis, and Regulatory Applications* (May 2003) and European Medicines Agency (EMA) Guideline on *Reporting the Results of Population Pharmacokinetic Analyses* (Jan 2008). The objectives will include development of population PK models for MDMA and MDA, characterization of the extrinsic and intrinsic factors affecting the exposure of MDMA and MDA, and simulate the dosing scenarios to inform the development of prescribing information in the product label. Table 7 shows the data from MPKF and the NIDA studies (see Example 7) that will be included in the population PK analysis of MDMA and MDA.

Table 16. Clinical Studies that will be included in the population PK analysis.

Study Design	**Number of Subjects**	**Drug Dose and Regimen**	**PK Sampling**
NIDA: Placebo-controlled, double-blind, crossover study in healthy volunteers	N = 50 unique participants with PK data N = 46 1.0 mg/kg MDMA N = 41 1.6 mg/kg MDMA N = 17 completers (all 3 dosing sessions)	Participants received 3 dosing sessions: 1.0mg/kg MDMA, 1.6 mg/kg MDMA, and placebo in randomized order	–0.25 (Pre-dose), 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 7.0, 9.0, 11, 13, 15, 23, 29, 34, 39, 47, 71, 95, 119, 143, and 167 hour Predose through 47-hour specimens were collected from all participants; the exact number of later collections depended on the length of residential stay.
MPKF: Single-center, open label, randomized sequence, 2-period cross-over study to determine the effect of food on the relative BA of MDMA oral formulation in healthy volunteers	N = 16 evaluable unique participants with PK data N = 14 participants completed both study periods.	A dose of 100 mg MDMA (equivalent to 120 mg MDMA HCl) for each dosing session. Total cumulative dose is 200 mg.	Pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 hour for each dosing session

Data Analysis:

Nonlinear mixed-effects modeling software (NONMEM®; version 7.3 or higher; ICON, Hanover, MD, US) or Phoenix NLME version 8.0 or higher (Certara, Princeton, NJ, US) will be used for popPK analysis. NONMEM, Phoenix, and/or R (version 3.3.0 or higher) will be used for simulations. SAS or R will be used for data preparation, graphical analysis, model diagnostics, and statistical summaries. Xpose®, Perl-speaks-NONMEM (PsN; Department of Pharmacy, Uppsala University, Uppsala, Sweden), and/or Pirana (Certara, Princeton, NJ, US) may also be used for model diagnostics and facilitation of tasks such as model running and covariate testing.

Modeling will proceed in a stepwise manner with additional model complexity added as indicated by the data. Separate or sequential models of MDA may be developed. The models will include inter-individual random effects and residual error. The covariates listed in Table 8 may be evaluated for effects on the PK of MDMA and MDA, as data allow.

Table 17. Description of Covariates and Associated Derivation Methods.

Covariate (Abbreviation)	**MDMA Parameters**	**MDA Parameters**
Body size (e.g., body weight, LBM, body surface area, and BMI)	Clearance and central volume of distribution	
Age		
Race		
Clearance and central volume of distribution		
Albumin		
Hepatic impairment/liver function tests (e.g., AST, ALT, serum bilirubin, or NCI liver dysfunction category)	Clearance	
Renal function (eGFR and CrCl)		
Fasting status	Absorption constant rate	NA

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; LBM = lean body mass; NA=not applicable; NCI = National Cancer Institute;

Model evaluation and selection will proceed by inspecting change in objective function value, condition number, goodness-of-fit plots, plausibility, and precision of model parameters, among other measures. A nonparametric bootstrap and visual predictive checks of the final model will be conducted to evaluate the stability and predictive ability of the model.

The final popPK models will be used to simulate rich concentration-time profiles for MDMA and MDA based on subject-level posterior Bayes estimates of the PK parameters. Dosing regimens tested in Phase 2 and 3 studies as well as the proposed clinical dosing regimen

may be simulated. Exposure metrics, such as AUC, C_{min}, and C_{max} at steady state will be derived based on these concentration-time profiles. Descriptive statistics will be derived, and results summarized. Results will also be summarized within subgroups based on clinically important covariates that were identified during the covariate analysis.

Foreseeable limitations to the population PK analysis are listed in Table 18. Namely these limitations pertain to formulation differences between MPKF and NIDA studies (confounded by study and subject population), carryover effects of CYP2D6 enzyme inhibition (due to potential insufficient washout period of 7 days for prior therapies/drug use or MDMA administration within the study), and differences in food intake during dosing days between MPKF and NIDA. Published PK parameters from the NIDA study (Table 14 and Table 15) show several fold range in both AUC and C_{max}, demonstrating high variability in this dataset.

Table 18. Comparison of Design Elements Impacting PopPK Analysis.

Design Element	**MPKF**	**NIDA**	**PopPK Limitation**
Formulation	120 mg MDMA HCl	d,l-MDMA HCl (Lipomed, Arlesheim, Switzerland)	Formulation is confounded by study and subject population (MDMA-naïve, vs. drug users and MDMA users).
Population	MDMA-naïve	**Non-drug users** (n = 18): no cannabis usage in the prior 2 years; lifetime cannabis usage not to exceed 10 times **Drug (cannabis) users/non-MDMA** (n = 18): self-reported drug use and confirmation blood/urine test. **MDMA users** (n = 18): participants must have a positive test for amphetamine or MDMA within 90 days of the first dose	Prior drug use within 10 days of study drug administration may result in altered CL due to CYP2D6 inhibition.
Design	Group 1: fasted followed by a fed treatment Group 2: fed followed fasted treatment. A minimum of 14 days between	Participants received low (1.0 mg/kg, ~70 mg) and high dose (1.6 mg/kg, ~112 mg) MDMA and placebo capsules during 3 dosing sessions. Administration of the 3	Washout period in NIDA study may be insufficient for CYP2D6 activity to return to baseline and may result in carry-over effects between dosing occasions. Altered CL due to CYP2D6

	treatments	doses was randomized and balanced with a minimum of 7 days between sessions.	inhibition is likely.
Controlled Fed/Fasted Dosing	Yes	No	Food consumption immediately prior to dosing was not specified in the NIDA protocol.

Example 9. Evaluation of MDMA tolerability in subjects with moderate Hepatic Impairment Compared to Matched Control Subjects with Normal Hepatic Function.

Introduction:

This study aims to evaluate the effect of moderate hepatic impairment on the PK of oral MDMA and its active metabolite, MDA, and to assess the safety and tolerability of oral MDMA in individuals over the age of 18 with moderate hepatic impairment compared to matched control subjects with normal hepatic function. It is a Phase I, open-label study that will enroll a total of 16 eligible participants, with 8 participants who meet the diagnosis of moderate hepatic impairment (class B according to Child-Pugh's criteria), and 8 participants with normal hepatic function.

Materials and Methods:

Participants will be administered a single oral dose of 125mg MDMA. Blood samples will be collected at pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose. The plasma concentrations of MDMA and MDA will be analyzed using validated analytical methods. Safety and tolerability will be evaluated by monitoring adverse events, vital signs, and electrocardiograms (ECGs).

Data Analysis:

The primary objective of the study is to compare the PK parameters of MDMA and MDA in participants with moderate hepatic impairment versus matched control subjects with normal hepatic function. The PK parameters that will be evaluated include Cmax, time to reach Tmax, AUC, and t1/2. The PK parameters will be compared between the two groups using analysis of

variance (ANOVA) or non-parametric tests, as appropriate. Safety and tolerability will be assessed by comparing the incidence and severity of adverse events between the two groups. The data will be summarized using descriptive statistics, and statistical analyses will be performed using appropriate methods. Statistical tests will be two-sided, and a p-value of less than 0.05 will be considered statistically significant. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Example 10. 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 11. Evaluation of an open-label, multi-site phase 2 study of the safety and feasibility of MDMA-Assisted therapy for eating disorders.

Introduction:

This study will aim to evaluate the safety and feasibility of open-label MDMA-assisted therapy with a flexible dose of MDMA and adjunctive caregiver support in reducing eating disorder symptoms for 16 participants over the age of 18 with Anorexia Nervosa, Restricting-Type (AN-R), or Binge Eating Disorder (BED). The protocol will be amended to update the IMP packaging in alignment with new standards and to allow a lower supplemental dose regimen of 34 mg MDMA for participants who receive an initial dose of 100 mg MDMA. Supplemental doses for any eating disorder participant (ED-P) will not exceed half of the initial dose.

Materials and Methods

The study will enroll 16 participants over the age of 18 with AN-R or BED, of which 12 participants who meet DSM-5 criteria for AN-R, and 6 participants who meet DSM-5 criteria for BED are eligible to enroll. Participants will receive a flexible dose of MDMA (75-125mg) in conjunction with psychotherapy for three sessions. If required, supplemental doses of up to half of the initial dose may be administered, with a maximum of 50 mg MDMA (equivalent to 60 mg MDMA HCl) per supplemental dose. Participants will be assessed at baseline, post-treatment, and 6-month follow-up using various measures, including the eating disorder questionnaire and depression inventory questionnaires. Adverse events will be monitored and recorded throughout the study.

Data Analysis:

Descriptive statistics will be used to summarize demographic and clinical characteristics of the sample. Mixed-effects regression models will be used to explore the effects of MDMA-assisted therapy on primary and secondary outcomes, accounting for site as a random effect. Adverse events will be tabulated and reported.

Example 12. 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 19 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 19. 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 20 below.

Table 20. 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 13. 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 comprise particles that 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 HCl 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

FIG. 1

FIG. 2

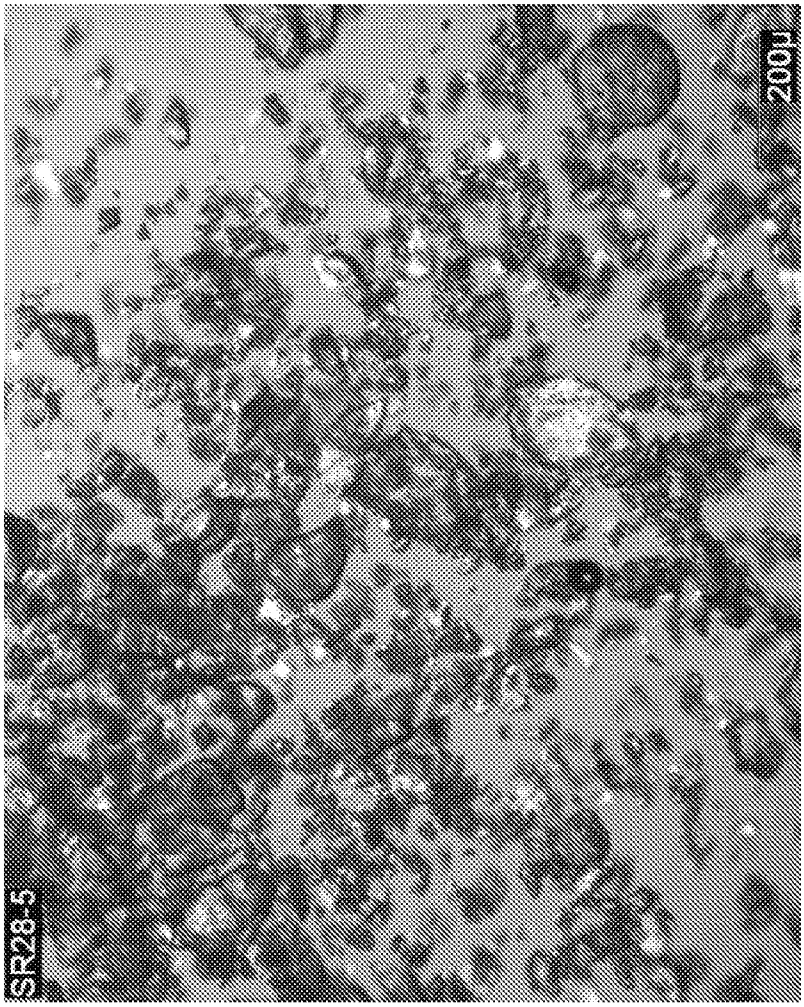


FIG. 3

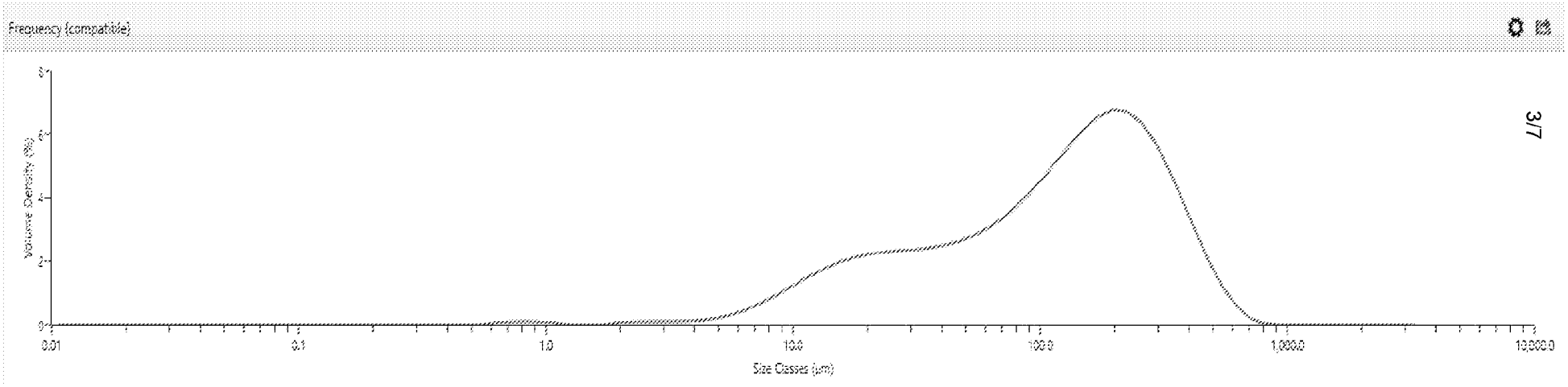

Frequency (compatible)
Volume Density (%)
0
2
4
6
8
0.01
0.1
1.0
10.0
100.0
1,000.0
10,000.0
Size Classes (µm)

FIG. 4

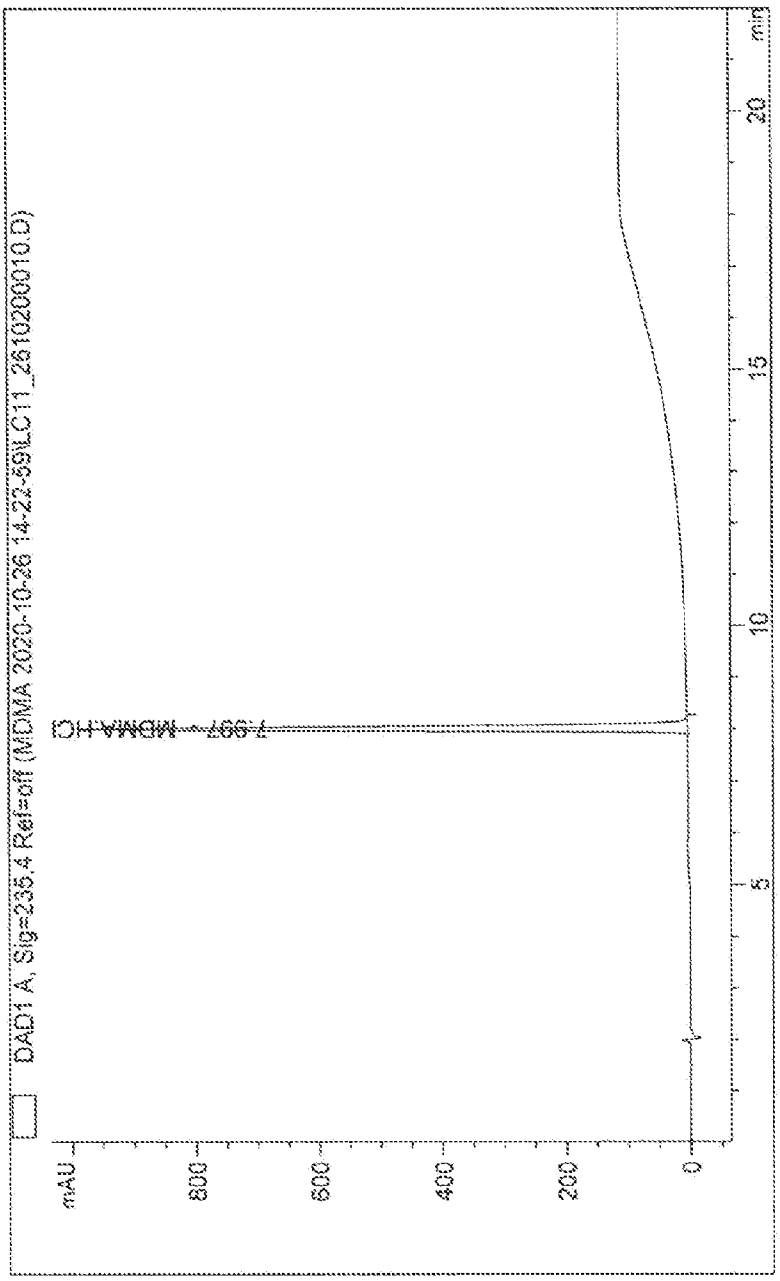
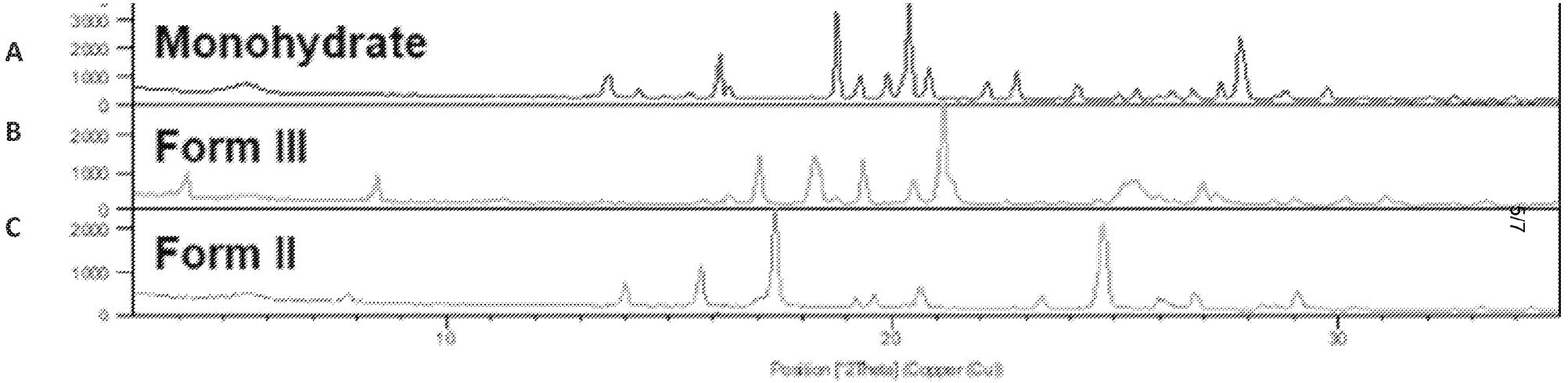

DAD1 A, Sig=235,4 Ref=off (MDMA 2020-10-26 14-22-59\LC11_26102000010.D)
mAU
800
600
400
200
0
7.997 - MDMA-HCl
5
10
15
20
min

FIG. 5



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

FIG. 6

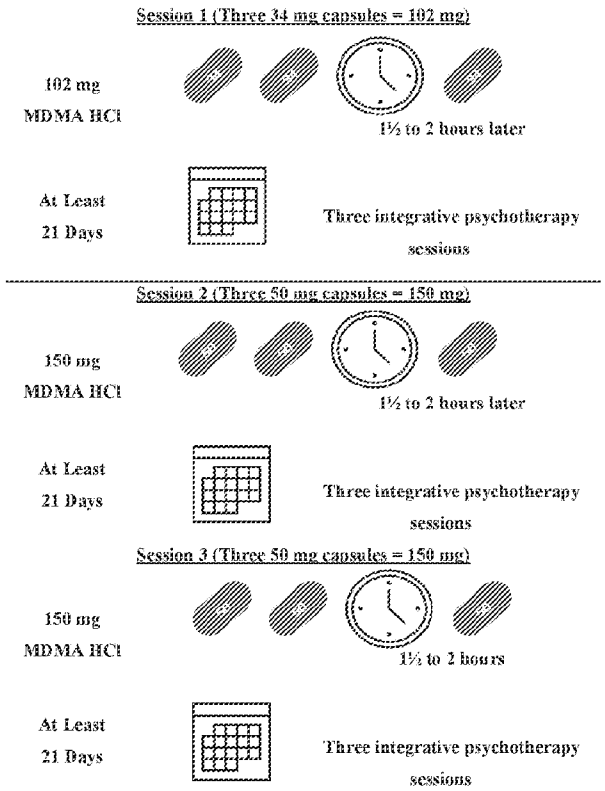
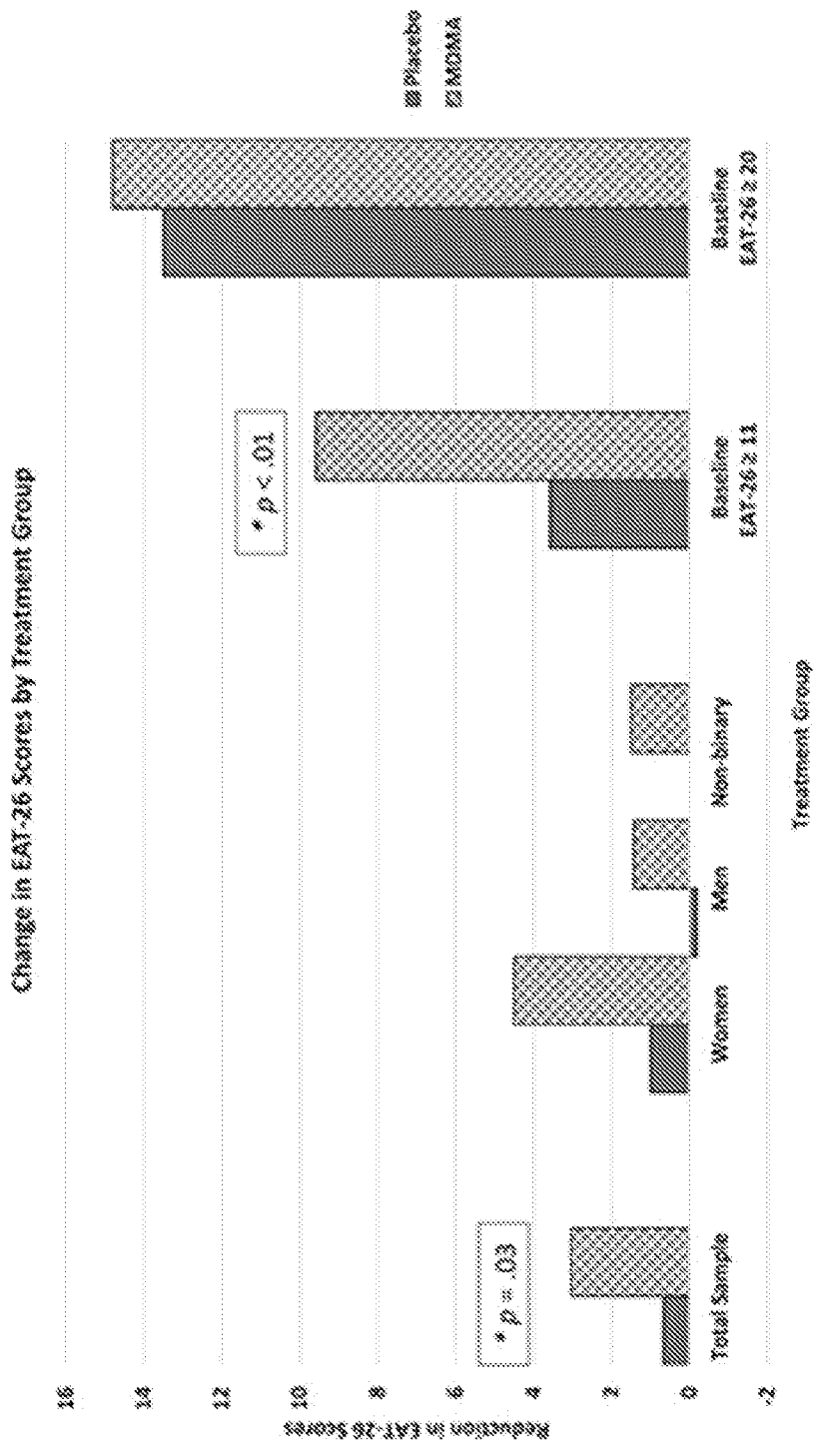

Session 1 (Three 34 mg capsules = 102 mg)
102 mg
MDMA HCl
1½ to 2 hours later
At Least
21 Days
Three integrative psychotherapy sessions
Session 2 (Three 50 mg capsules = 150 mg)
150 mg
MDMA HCl
1½ to 2 hours later
At Least
21 Days
Three integrative psychotherapy sessions
Session 3 (Three 50 mg capsules = 150 mg)
150 mg
MDMA HCl
1½ to 2 hours
At Least
21 Days
Three integrative psychotherapy sessions

FIG. 7


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

Electronic Acknowledgement Receipt

EFS ID:	47931284
Application Number:	63463170
International Application Number:	
Confirmation Number:	3887
Title of Invention:	METHODS OF TREATING EATING DISORDERS
First Named Inventor/Applicant Name:	. .
Customer Number:	26191
Filer:	William Turner Spencer III/Kristine McGuirk
Filer Authorized By:	William Turner Spencer III
Attorney Docket Number:	54925-0009P02
Receipt Date:	01-MAY-2023
Filing Date:	
Time Stamp:	15:50:56
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$120
RAM confirmation Number	E202351F51416750
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Provisional Cover Sheet (SB16)	54925_0009P02_Transmittal.pdf	134197 75f049f07d7ed76130df930118a32c68bcb1c0f7	no	2
Warnings:					
This is not a USPTO supplied Provisional Cover Sheet SB16 form.					
Information:					
2	Application Data Sheet	54925_0009P02_ADS.pdf	2225619 41729b30fbd7c97ec4826661362373fb34e9b80e	no	8
Warnings:					
Information:					
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3		54925_0009P02_Specification.pdf	773457 d7ef7d263667f045fe1deca2ed5b0068e6fadd31	yes	97

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	91
Claims	92	96
Abstract	97	97

Warnings:					
Information:					
4	Drawings-other than black and white line drawings	54925_0009P02_Figs.pdf	1716887 4fd680a25f34348710cdd7e92174150b492b8638	no	7
Warnings:					

Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	37249 1730c548cb47914e14d91adc2a69311bda6c20ee	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4887409	

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New International Application Filed with the USPTO as a Receiving Office

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