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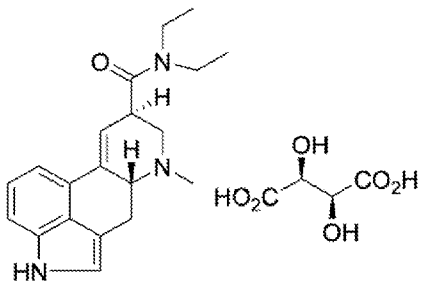
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(54) Title: LYOPHILIZED ORALLY DISINTEGRATING TABLET FORMULATIONS OF D-LYSERGIC ACID DIETHYLAMIDE FOR THERAPEUTIC APPLICATIONS

FIGURE 1



$C_{24}H_{31}N_3O_7$
Mol. Wt.: 473.52

D-LSD D-Tartrate

(57) **Abstract:** A solid oral immediate release formulation of LSD, wherein the composition is produced by lyophilization of a feedstock in a pre-formed mold to form an orally disintegrating tablet. A method of making a solid oral immediate release formulation of LSD by lyophilizing a flash frozen stock solution of LSD and excipients, including a non-gelling matrix former, filler, and binder in a pre-formed mold, and forming an orally disintegrating tablet. A method of treating an individual by administering a solid oral immediate release formulation of LSD, wherein the composition is produced by lyophilization of a feedstock in a pre-formed mold to form an orally disintegrating tablet and treating the individual.

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[Continued on next page]

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Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

LYOPHILIZED ORALLY DISINTEGRATING TABLET FORMULATIONS OF d-LYSERGIC ACID DIETHYLAMIDE FOR THERAPEUTIC APPLICATIONS

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

[0001] The present invention relates to the formulation of drugs. More specifically, the present invention relates to an immediate release formulation for a pharmaceutical formulation of d-lysergic acid diethylamide (LSD).

2. BACKGROUND ART

[0002] Oral solution formulations are convenient for studies in a small number of sites and with a limited number of patients, mainly early phase development studies, but may not be suitable for later phase development studies run in many centers and across wide geographies nor for commercialization due to challenges in product stability and supply chain, such as the potential requirement for cold chain storage.

[0003] Solid oral formulations as tablets or capsules are more common in later phase clinical development and commercially due to advantages in production, supply chain, and patient convenience. Solid oral formulations can be immediate release, dissolving instantaneously in the mouth or stomach, or extended release in which the drug release is prolonged over time.

[0004] Orally disintegrating tablets (ODTs) are another solid dosage form which is formulated with the aim of increasing the dissolution rate of a pharmaceutical product and promoting pre-gastric absorption. In order to achieve rapid disintegration rates, the ODT formulation must provide high porosity, low density, and a low hardness (Berthoumieu et al.,

2010; Bandari et al., 2008). This dosage form can be chosen to modify absorption or for patient populations that have difficulty in swallowing (Lindgren et al., 1993), and is also suitable for use in geriatric and pediatric patients, or for those who suffer from conditions such as dysphagia (Sastry et al., 2000).

[0005] From the perspectives of cost and simplicity, direct compression is a common method for preparing ODTs. However, the disintegration capacity of ODTs produced in this way is limited by the size and hardness of the resulting tablets. An alternative method for preparing ODTs is freeze drying. For example, the Zydis® ODT (orally dissolving tablet) fast-dissolve formulation, is a freeze-dried oral solid dosage form that disperses almost instantly in the mouth with no water required.

[0006] LSD is derived from its German name LysergSäureDiethylamid (Lysergic acid diethylamide). Lysergide belongs to a family of indole alkylamines that includes numerous substituted tryptamines such as psilocin (the active moiety of psilocybin) and N,N-dimethyltryptamine (DMT). The IUPAC name for LSD is 9,10-didehydro-N,N-diethyl-6-methylergoline-8β-carboxamide.

[0007] LSD can be used to assist psychotherapy for many indications including anxiety, depression, addiction, personality disorder, and others and can also be used to treat other disorders such as cluster headache, migraine, and others (Passie et al., 2008; Hintzen et al., 2010; Nichols, 2016; Liechti, 2017). Effects of LSD can include altered thoughts, feelings, awareness of surroundings, dilated pupils, increased blood pressure, and increased body temperature. Therapeutic use of LSD is showing promising results for treating various neurological and behavioral disorders. However, due to its potency there can be challenges in

developing and manufacturing solid oral formulations of LSD that meet pharmaceutically acceptable limits for content uniformity and chemical stability.

[0008] Clinical studies with LSD have focused on oral solution drug product forms. There has been little to no formulation development work with LSD. Oral solutions were used historically and almost all the old studies and anecdotal data are with oral solutions or impregnated papers/cartons.

[0009] There is a need for an LSD dosage form and drug product that is both commercially attractive to a broad patient population and meets regulatory / quality expectations for suitability and robustness. A commercially viable solid oral, immediate release pharmaceutical formulation of d-Lysergic Acid Diethylamide (LSD), as a free base or in a salt form, does not currently exist as a marketed product or reported in literature. With the expected therapeutic dose of LSD to be in the 10's to 100's of micrograms, challenges exist for achieving acceptable drug content uniformity and chemical stability. Furthermore, previous studies have shown LSD in oral solution is not stable at room temperature (Holze et al 2019).

[0010] In addition to achieving a uniform and stable immediate release drug product formulation, the final drug product should be in a form that is easily administered to a broad range of patient populations, including, but not limited to the elderly, pediatrics, and patients with a condition that may limit their ability to swallow.

SUMMARY OF THE INVENTION

[0011] The present invention provides a solid oral immediate release formulation of LSD, including LSD formulations intended for an orally disintegrating tablet dosage form, wherein the composition is produced by lyophilization of a feedstock in a pre-formed mold to form an orally disintegrating tablet.

[0012] The present invention further provides a method of making a solid oral immediate release formulation of LSD by lyophilizing a flash frozen stock solution of LSD and excipients of a non-gelling matrix former, filler, binder, and buffer as well as additional excipients such as antioxidants, photostabilization agents, permeation enhancers and flavoring agents, in a pre-formed mold, and forming an orally disintegrating tablet.

[0013] The present invention also provides for a method of treating an individual by administering a solid oral immediate release formulation of LSD, wherein the composition is produced by lyophilization of a feedstock in a pre-formed mold to form an orally disintegrating tablet and treating the individual.

DESCRIPTION OF THE DRAWINGS

[0014] Other advantages of the present invention are readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings wherein:

[0015] FIGURE 1 is a representation of D-LSD D-tartrate salt; and

[0016] FIGURE 2 is a photograph of Zydis ODT containing LSD.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The present invention provides for a formulation of LSD in a quick or immediate release dosage form such as an orally disintegrating tablet. The term “quick release tablet” is a mechanism that (similar to immediate-release dosage) delivers a drug immediately in contrast with a delay after its administration (delayed-release dosage) or for a prolonged period of time (extended-release (ER, XR, XL) dosage) or to a specific target in the body (targeted-release dosage). Preferably, it refers to minimal time dependent release in oral dose formulations. The present invention provides a composition, preferably including LSD as its active, or one of its

active ingredients, that dissolve relatively quickly once orally ingested. This provides an easy to administer yet anticipated to be effective and efficacious therapeutic effect.

[0018] The LSD can be in a free base form or a salt form as a crystalline or non-crystalline solid. The salt can be, but is not limited to, hydrochloride, hydrobromide, maleate, tartrate (including D-tartrate and meso-tartrate), citrate, phosphate, fumarate, sulfate, mesylate, acetate, oxalate, benzoate, benzensulfonate, xinafoate, 1,5-Napthalene disulfonate, ascorbate, and naphthalene-2-sulfonate. The dose of LSD can preferably be 0.01-1 mg (10-1000 µg). However, dosing can be adjusted depending on indication, age, weight, and other factors affecting the pharmacology, physiology, and drug/drug interactions in a given patient.

[0019] The preferred solid oral formulation is an orally disintegrating tablet (ODT) such as using ZYDIS® (Catalent, Inc.) technology, described in U.S. Patent No. US 9,192,580 B2, which is herein incorporated by reference. This is further shown in EXAMPLE 1. Typical ZYDIS® ODT formulations include a non-gelling matrix former, filler, binder, and pH modifying agent (i.e. buffer). In addition, antioxidants, photostabilization agents, permeation enhancers, coloring agents, and sweeteners / flavoring agents can be included in ZYDIS® ODT formulations.

[0020] Examples of non-gelling matrix formers used include, but are not limited to, non-gelling gelatin (including fish gelatin), maltodextrin, modified starches, starch ethers, low molecular weight dextrans, and low to intermediate molecular weight cellulose gums (U.S. Patent No. 10,548,839 B2).

[0021] Examples of fillers used include lactose (including anhydrous), mannitol, dicalcium phosphate, calcium sulfate, starch (starch as used herein can include dry or pre-

gelled), cellulose (including microcrystalline cellulose), kaolin, sodium chloride, sorbitol, trehalose, sucrose, etc.

[0022] Examples of binders include acacia gum, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, tragacanth, polyvinyl pyrrolidone (PVP), starch, etc.

[0023] Buffer is added to target the formulation to a specific pH. Currently, three buffers, citrate, phosphate, and acetate, make up the majority of buffers used in parenteral pharmaceuticals approved by the FDA, but less precedented excipients are certainly available to use in commercial dosage forms. The pH of a formulation alternatively can be adjusted with unbuffered acid (i.e. hydrochloric acid) or unbuffered base (i.e. sodium hydroxide).

[0024] Antioxidants can be added to the formulation in order to minimize degradation due to oxidative stress. The term oxidation can be defined as the incorporation of oxygen into the structure of a drug, or as the process of converting one chemical substance into another derivative bearing a smaller number of electrons. Examples of such antioxidants are ascorbic acid, citric acid, butylated hydroxy anisole (BHA), and butylated hydroxyl toluene (BHT).

[0025] Many drugs are sensitive to light and therefore their formulated products can degrade during manufacturing, storage, and administration. The photostability of a drug substance can be defined as the response of the drug or drug product to the exposure to solar, UV, and visible light in the solid, semisolid, or liquid state that leads to a physical or chemical change. Undo light exposure can result in potency loss, altered efficacy, and adverse biological effects. Various additives or encapsulation methods and compositions can be used to protect the active product from light in order to minimize any degradation due to light exposure (i.e. photostabilization agents).

[0026] Photo degradation can also occur in combination with oxygen exposure, resulting in photo-oxidation degradation. Some of the commonly used antioxidants to protect against photo-oxidation are ascorbic acid, α-tocopherol, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), L-histidine, propyl gallate, and sulfur compounds. Ascorbic acid, α-tocopherol, β-carotene, and BHT act as free radical scavengers and singlet oxygen quenchers and thus inhibit the photosensitization reactions. If a drug substance acts as a photosensitizer and initiates a chain reaction in the drug product, some of the excipients can be oxidized, while the drug can be protected from photodegradation.

[0027] The formulation can also contain permeability enhancers to increase the extent and/or rate of absorption. Examples of such enhancers are sulphoxides (such as dimethylsulphoxide, DMSO), azones (e.g. laurocapram), pyrrolidones (for example 2-pyrrolidone, 2P), alcohols and alkanols (ethanol, or decanol), glycols (for example propylene glycol, PG, a common excipient in topically applied dosage forms), surfactants (also common in dosage forms) and terpenes.

[0028] Coloring agents, sweeteners, and flavoring agents can also be added to solid oral formulations in order to improve patient recognition and acceptability.

[0029] The compound of the present invention is administered and dosed considering the clinical condition of the individual patient, the site and method of administration, scheduling of administration, patient age, sex, body weight and other factors known to medical practitioners. The pharmaceutically "effective amount" for purposes herein is thus determined by such considerations as are known in the art. The amount must be effective to achieve improvement including but not limited to improved survival rate or more rapid recovery, or

improvement or elimination of symptoms and other indicators as are selected as appropriate measures by those skilled in the art.

[0030] In the method of the present invention, the compound of the present invention can be administered in various ways. It should be noted that it can be administered as the compound and can be administered alone or as an active ingredient in combination with pharmaceutically acceptable carriers, diluents, adjuvants, and vehicles. The patient being treated is a warm-blooded animal and, in particular, mammals including man. The pharmaceutically acceptable carriers, diluents, adjuvants, and vehicles generally refer to inert, non-toxic solid or liquid fillers, diluents or encapsulating material not reacting with the active ingredients of the invention.

[0031] The doses can be single doses or multiple doses over a period of several days. The treatment generally has a length proportional to the length of the disease process and drug effectiveness and the patient species being treated.

[0032] Absorption of the active drug can be targeted. Drug absorption is determined by the drug's physicochemical properties, formulation, and route of administration. Dosage forms (e.g., tablets, capsules, solutions), consisting of the drug plus other ingredients, are formulated to be given by various routes (e.g., oral, buccal, sublingual, rectal, parenteral, topical, inhalational). Regardless of the route of administration, drugs must be in solution to be absorbed. Thus, solid forms (e.g., tablets, capsules) must be able to disintegrate and deaggregate. Solid oral tablets and capsule formulations typically have gastric absorption, whereas an ODT formulation can be formulated to target pre-gastric or buccal absorption which can further enhance bioavailability.

[0033] The present invention provides for a method of making a solid oral immediate release formulation of LSD, as a free base or in a salt form, by lyophilizing a flash frozen stock solution of drug and excipients in a pre-formed mold to form an orally disintegrating tablet. This approach considers the challenges associated with formulating a low dose product while maintaining content uniformity and chemical integrity of LSD.

[0034] The present invention provides for a method of treating an individual, by administering a solid oral immediate release formulation of LSD, wherein the composition is produced by lyophilization of a feedstock in a pre-formed mold to form the orally disintegrating tablet and treating the individual.

[0035] The condition or disease being treated can include, but is not limited to, anxiety disorders (including anxiety in advanced stage illness e.g. cancer, as well as generalized anxiety disorder), depression (including post partum depression, major depressive disorder and treatment-resistant depression), headache disorder (including cluster headaches and migraine headache), obsessive compulsive disorder (OCD), personality disorders (including conduct disorder), stress disorders (including adjustment disorders and post-traumatic stress disorder), drug disorders (including alcohol dependence or withdrawal, nicotine dependence or withdrawal, opioid dependence or withdrawal, cocaine dependence or withdrawal, methamphetamine dependence or withdrawal), other addictions (including gambling disorder, eating disorder, and body dysmorphic disorder), pain, neurodegenerative disorders (such as dementia, Alzheimer's Disease, Parkinson's Disease), autism spectrum disorder, eating disorders, or neurological disorders (such as stroke).

[0036] The invention is further described in detail by reference to the following experimental examples. These examples are provided for the purpose of illustration only and

are not intended to be limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

[0037] EXAMPLE 1: Lyophilization of d-LSD D-tartrate stock solution to formulate an orally disintegrating tablet

[0038] Solid oral formulations of d-LSD D-tartrate in a fast dispersing orally disintegrating tablet (ODT) were produced the following method: A) Generating a formula stock solution containing d-LSD D-tartrate, a non-gelling matrix forming excipient, a filler excipient, and a binding agent fully dissolved in water; B) Dosing the stock solution in pre-formed molds; and C) Lyophilizing the dosed formulations to remove water by sublimation. Formulation compositions are provided in TABLE 1. Images for Formulation 1 are shown in FIGURE 2. All formulations disintegrated in less than 60 seconds demonstrating immediate release.

[0039] TABLE 1 - d-LSD D-tartrate formulations lyophilized to form orally disintegrating tablets

Component	**Formulation 1**	**Formulation 2**	**Formulation 3**	**Approximate Wt%**
Drug	d-LSD D-tartrate			< 1%
Non-gelling matrix	Fish Gelatin	Maltodextrin		2-10%
Binder		Methylcellulose		1-5%
Filler	Mannitol	Mannitol	Trehalose	2-10%
Solvent	Water			qs to 100%

[0040] These formulations were protected from moisture ingress, set on stability at 40°C, and after one month tested for chemical degradation. The total chemical impurities are presented in TABLE 2. These results show minor changes in total impurities after one month stored at accelerated conditions, demonstrating the suitability of lyophilized ODT formulations of d-LSD D-tartrate.

[0041] TABLE 2 - Total Impurities of lyophilized d-LSD D-tartrate formulations after one month storage at 40°C.

Time point	Formulation 1	Formulation 2	Formulation 3
T = 0	0.9	0.3	0.7
T = 1 mo @ 40°C	1.6	0.2	0.5

[0042] Throughout this application, various publications, including United States patents, are referenced by author and year and patents by number. Full citations for the publications are listed below. The disclosures of these publications and patents in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

[0043] The invention has been described in an illustrative manner, and it is to be understood that the terminology, which has been used is intended to be in the nature of words of description rather than of limitation.

[0044] Obviously, many modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood that within the scope of the appended claims, the invention can be practiced otherwise than as specifically described.

CLAIMS

What is claimed is:

1. A composition of a solid oral immediate release formulation of LSD, comprising LSD contained within an immediate release dosage form of an orally disintegrating tablet, wherein said composition is produced by lyophilization of a feedstock in a pre-formed mold to form the orally disintegrating tablet.

2. The composition of claim 1, further including a non-gelling matrix former chosen from the group consisting of non-gelling gelatin, maltodextrin, modified starches, starch ethers, low molecular weight dextrans, and low to intermediate molecular weight cellulose gums.

3. The composition of claim 1, further including a filler chosen from the group consisting of lactose, mannitol, dicalcium phosphate, calcium sulfate, starch, cellulose, kaolin, sodium chloride, sorbitol, trehalose, and sucrose.

4. The composition of claim 1, further including a binder chosen from the group consisting of acacia gum, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, tragacanth, polyvinyl pyrrolidone (PVP), and starch.

5. The composition of claim 1, further including a buffer chosen from the group consisting of citrate, phosphate, and acetate.

6. The composition of claim 1, further including an antioxidant chosen from the group consisting of ascorbic acid, butylated hydroxy anisole (BHA), and butylated hydroxyl toluene (BHT).

7. The composition of claim 1, further including a photostabilization agent.

8. The composition of claim 1, further including a permeation enhancer chosen from the group consisting of sulphoxides, azones, pyrrolidones, alcohols, alkanols, glycols, surfactants, and terpenes.

9. The composition of claim 1, further including coloring agents, sweeteners, and flavoring agents.

10. A method of making a solid oral immediate release formulation of LSD, including the steps of:

lyophilizing a flash frozen stock solution of LSD and excipients of a non-gelling matrix former, filler, binder, and buffer in a pre-formed mold; and

forming an orally disintegrating tablet.

11. The method of claim 10, wherein the non-gelling matrix former is chosen from the group consisting of non-gelling gelatin, maltodextrin, modified starches, starch ethers, low molecular weight dextrans, and low to intermediate molecular weight cellulose gums.

12. The method of claim 10, wherein the filler is chosen from the group consisting of lactose, mannitol, dicalcium phosphate, calcium sulfate, starch, cellulose, kaolin, sodium chloride, sorbitol, trehalose, and sucrose.

13. The method of claim 10, wherein the binder is chosen from the group consisting of acacia gum, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, tragacanth, polyvinyl pyrrolidone (PVP), and starch.

14. The method of claim 10, wherein the buffer is chosen from the group consisting of citrate, phosphate, and acetate.

15. The method of claim 10, wherein the LSD is in a form chosen from free base and salt.

16. The method of claim 10, wherein the LSD is in a salt form and the salt is chosen from the group consisting of hydrochloride, hydrobromide, maleate, tartrate, citrate, phosphate, fumarate, sulfate, mesylate, acetate, and oxalate.

17. A method of treating an individual, including the steps of:

administering a solid oral immediate release formulation of LSD of an orally disintegrating tablet, wherein the composition is produced by lyophilization of a feedstock in a pre-formed mold to form the orally disintegrating tablet; and

treating the individual.

18. The method of claim 17 wherein the individual has trouble swallowing, is elderly, or has dementia.

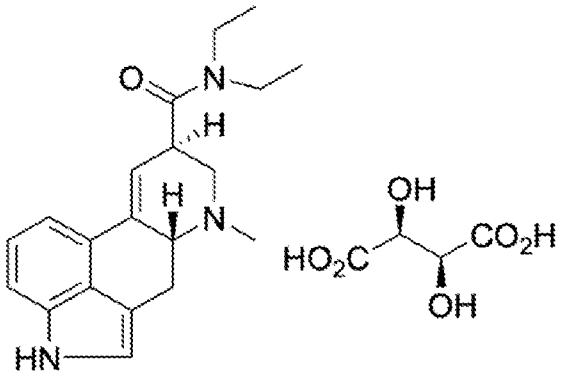
19. The method of claim 17, wherein said treating step is further defined as treating a condition or disease chosen from the group consisting of anxiety disorders, depression, headache disorder, obsessive compulsive disorder (OCD), personality disorders, stress disorders, drug disorders, gambling disorder, eating disorder, body dysmorphic disorder, pain, neurodegenerative disorders, autism spectrum disorder, eating disorders, and neurological disorders.

20. The method of claim 17, wherein the LSD is in a form chosen from free base and salt.

21. The method of claim 17, wherein the LSD is in a salt form and the salt is chosen from the group consisting of hydrochloride, hydrobromide, maleate, tartrate, citrate, phosphate, fumarate, sulfate, mesylate, acetate, and oxalate.

22. The method of claim 17, wherein said administering step is further defined as administering 0.01-1 mg of LSD.

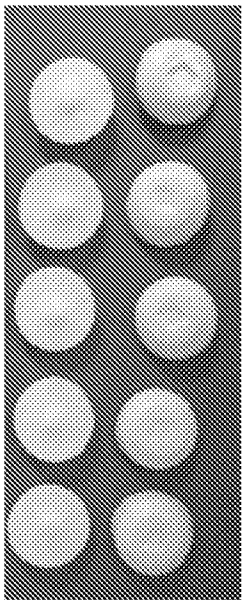
FIGURE 1



$C_{24}H_{31}N_3O_7$
Mol. Wt.: 473.52

D-LSD D-Tartrate

FIGURE 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/40636

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/48, A61K 9/19, A61K 9/00, F26B 5/06 (2022.01)
ADD. A61P 25/28 (2022.01)

CPC - INV. A61K 31/48, A61K 9/19, A61K 9/0056, F26B 5/06
ADD. A61P 25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2020/0085816 A1 (Eleusis Benefit Corporation, PBC) 19 March 2020 (19.03.2020); entire document, especially abstract, [0007], [0039], [0043], [0046], [0057], [0061]	1-22
Y	PharmaTech, "Is Spray Drying a Viable Alternative to Lyophilization?", 15 December 2009 (15.12.2009), retrieved on 05 October 2022 from https://www.pharmtech.com/view/spray-drying-viable-alternative-lyophilization; entire document, especially pg 1 para 1-2	1-9, 17-22
Y	US 2007/0248652 A1 (Barzilay et al.) 25 October 2007 (25.10.2007); entire document, especially abstract, [0057]	10-16
A	US 2002/0028942 A1 (Jacewicz et al.) 07 March 2002 (07.03.2002); entire document	1-22
A	US 2010/0105783 A1 (Lee et al.) 29 April 2010 (29.04.2010); entire document	1-22

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 November 2022	DEC 29 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/40636

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-9 and 17-22, directed to a formulation of LSD and use thereof.

Group II: Claims 10-16, directed to a method of making a formulation of LSD.

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

****See Supplemental Box****

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

Continuation of Box III Observations where unity of invention is lacking

Special Technical Features:

Group II requires lyophilizing a flash frozen stock solution of LSD and excipients of a non-gelling matrix former, filler, binder, and buffer in a pre-formed mold; not required by group I.

Common Technical Features:

Groups I and II share the technical feature of a composition of a solid oral immediate release formulation of LSD, comprising LSD contained within an immediate release dosage form of an orally disintegrating tablet, wherein said composition is produced by lyophilization of a feedstock in a pre-formed mold to form the orally disintegrating tablet. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is obvious over US 2020/0085816 A1 to Eleusis Benefit Corporation, PBC (hereinafter "Eleusis") in view of document titled "*Is Spray Drying a Viable Alternative to Lyophilization?*" to PharmaTech (hereinafter "PharmaTech"). Eleusis teaches a composition of a solid oral immediate release formulation of LSD (para [0039], "Pharmaceutical compositions according to the invention may be formulated to release the lysergic acid diethylamide, or a *pharmaceutically acceptable salt thereof, substantially immediately upon administration*"; para [0043], "Formulations for oral use include tablets containing the lysergic acid diethylamide"), comprising LSD contained within an immediate release dosage form of an orally disintegrating tablet (para [0039], "Pharmaceutical compositions according to the invention may be formulated to release the lysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, substantially immediately upon administration"; para [0043], "Formulations for oral use include tablets containing the lysergic acid diethylamide... These excipients may be, for example... disintegrating agents..."), wherein said composition is produced by spray drying of a feedstock in a pre-formed mold to form the orally disintegrating tablet (para [0046], "Formulations for oral use may also be presented as chewable tablets, or as hard gelatin capsules wherein the lysergic acid diethylamide... Powders and granulates may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment..."; para [0061], "A matrix dispersion-type system is characterized in that a reservoir of the drug substance is formed by substantially homogeneously dispersing the drug substance in a hydrophilic or *lipophilic polymer matrix and then molding the drug-containing polymer into a disc with a* substantially well-defined surface area and thickness"); but does not teach wherein said composition is produced by lyophilization of the feedstock. However, in a document relating to spray drying alternatives, PharmaTech teaches lyophilization as a comparable alternative *to spray drying* (*PharmaTech* pg 1 para 1-2, "Lyophilization, or freeze drying, is the most common processing method for removing moisture from biopharmaceuticals, and it can increase the stability, temperature tolerance, and shelf life of these products... Spray drying is an alternative technique for preserving biopharmaceuticals"). Therefore, it would have been obvious to one of ordinary skill in the art to combine these references and incorporate the Lyophilization method by routine experimentation to optimize the stability of the composition in Eleusis (PharmaTech pg 1 para 1-2, "Lyophilization, or freeze drying, is the most common processing method for removing moisture frombiopharmaceuticals, and it can increase the stability, temperature tolerance, and shelf life of these products...").

As the shared technical features were known in the art at the time of the invention, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-II lack unity under PCT Rule 13.