Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3228975 A1 2023/02/23

(21) 3 228 975

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) **Date de dépôt PCT/PCT Filing Date:** 2022/08/17
(87) **Date publication PCT/PCT Publication Date:** 2023/02/23
(85) **Entrée phase nationale/National Entry:** 2024/02/14
(86) **N° demande PCT/PCT Application No.:** US 2022/040653
(87) **N° publication PCT/PCT Publication No.:** 2023/023192
(30) **Priorité/Priority:** 2021/08/19 (US63/234,773)

(51) **Cl.Int./Int.Cl.** ***A61K 9/00*** (2006.01),
A61K 31/48 (2006.01), *A61P 25/28* (2006.01)

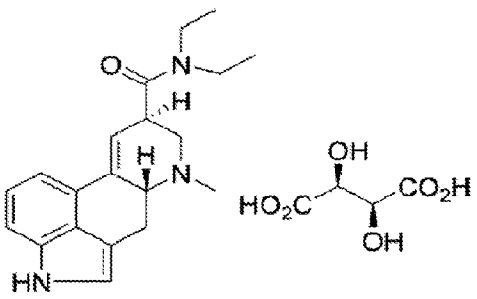
(71) **Demandeur/Applicant:**
MIND MEDICINE, INC., US

(72) **Inventeurs/Inventors:**
MACK, PETER, US;
MELTON, DUSTIN, US;
DOTY, BETHANY AMBER, US;
SCHROEDER, JON, US;
COGHILL, JAMES, GB;
LEVY, DANIEL EMIL, US

(74) **Agent:** SMART & BIGGAR LP

(54) **Titre : FORMULATIONS A LIBERATION IMMEDIATE DE DIETHYLAMIDE DE L'ACIDE D-LYSERGIQUE POUR DES APPLICATIONS THERAPEUTIQUES**
(54) **Title: IMMEDIATE RELEASE 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) **Abrégé/Abstract:**
A solid oral immediate release formulation of LSD, including LSD contained within a dosage form of a capsule, tablet, or orally disintegrating tablet. A method of making a solid oral immediate release formulation of LSD as a free base or in a salt form by granulation, including moisture-activated dry granulation or dry blending. A method of treating an individual, by administering a solid oral immediate release formulation of LSD and treating the individual.

Date Submitted: 2024/02/14

CA App. No.: 3228975

Abstract:

A solid oral immediate release formulation of LSD, including LSD contained within a dosage form of a capsule, tablet, or orally disintegrating tablet. A method of making a solid oral immediate release formulation of LSD as a free base or in a salt form by granulation, including moisture-activated dry granulation or dry blending. A method of treating an individual, by administering a solid oral immediate release formulation of LSD and treating the individual.

IMMEDIATE RELEASE 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] 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.

[0006] 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.

[0007] 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.

[0008] 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).

[0009] 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

[0010] The present invention provides a solid oral immediate release formulation of LSD, including LSD formulations intended for a capsule, tablet, or orally disintegrating tablet dosage form.

[0011] The present invention further provides a method of making a solid oral immediate release formulation of LSD using processes such as granulation and blending that are uniform, chemically stable, and dissolve rapidly.

[0012] The present invention also provides for a method of treating an individual by administering a solid oral immediate release formulation of LSD.

DESCRIPTION OF THE DRAWINGS

[0013] 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:

[0014] FIGURE 1 is a representation of D-LSD D-tartrate salt;

[0015] FIGURE 2 is a graph of LSD content uniformity from a solid oral capsule formulation made by granulation;

[0016] FIGURE 3 is a graph showing the immediate release of LSD from a solid oral capsule formulation made by granulation; and

[0017] FIGURE 4 is a graph showing chemical stability of LSD when blended as a solid drug crystal with lactose, microcrystalline cellulose, or mannitol.

DETAILED DESCRIPTION OF THE INVENTION

[0018] The present invention provides for a formulation of LSD in a quick or immediate release dosage form such as a capsule, tablet, or 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 dissolves relatively quickly once orally ingested. This provides an easy to administer yet anticipated to be effective and efficacious therapeutic effect.

[0019] 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.

[0020] Solid oral formulations typically contain secondary ingredient components known as excipients which can include but are not limited to fillers/bulking agents, binders, absorbents, disintegrants, glidants, lubricants, pH modifiers/buffers, preservatives,

antioxidants, permeation enhancers, coloring agents, and sweeteners / flavoring agents. Examples of each are listed below and some common excipients serve more than one function.

[0021] Examples of fillers used in solid oral formulations 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] Binders, which are polymeric, natural, or synthetic materials that impart cohesive qualities to powdered materials, can also be included. Binders must be non-toxic and must have a good compatibility profile. Materials commonly used as binders include acacia gum, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, tragacanth, polyvinyl pyrrolidone (PVP), starch, etc. Microcrystalline cellulose is also considered a dry binder.

[0023] Excipients such as starch, colloidal or mesoporous silicon dioxide (i.e. silica), sodium starch glycolate, and microcrystalline cellulose can act as solvent absorbents or disintegrants by absorbing solvents such as water while increasing the formulation wettability. Some of these excipients can be preferred for either absorbent of disintegrant properties but can also include the other property. For example partially pre-gelled starch (e.g., Starch 1500) is often used as a disintegrant, but is also used as an absorbent to scavenge moisture to 'hide' the moisture from drugs that are sensitive to it. When Starch 1500 is used as an absorbent in moisture activated dry granulation (MADG) it loses some of its disintegrant capability, but if it is added after the absorbent stage it can function as a disintegrant. Colloidal (or mesoporous) silicon dioxide can be an excellent absorbent but can be a weak disintegrant. Sodium starch glycolate can be an excellent disintegrant. Microcrystalline cellulose is an excellent absorbent and can have disintegrant properties. Croscarmellose sodium, crospovidone, sodium starch glycolate (which are disintegrants) and starch swell in the presence of aqueous fluids, thereby

CA 03228975 2024-2-14

facilitating tablet disintegration due to the increase in the internal pressure within the tablet matrix.

[0024] Glidants enhance the flowability of a formulation. Typical glidants include magnesium stearate, colloidal silicon dioxide, etc.

[0025] The hydrophobic stearic acid and stearic acid salts e.g., magnesium stearate and sodium stearyl fumarate, are the most widely used lubricants in oral drug formulations. They are typically added at concentrations less than 2% w/w in order to minimize any deleterious effect on formulation matrix disintegration or dissolution. Other examples of lubricants used include polyethylene glycol (PEG), polyoxyethylene stearates, lauryl sulphate salts, talc, glyceryl behenate, glyceryl palmitostearate, calcium stearate, hydrogenated vegetable oils etc.

[0026] 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 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).

[0027] 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, butylatedhydroxy anisole (BHA), and butylated hydroxytoluene (BHT).

[0028] 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. Undue 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). For example, liposomes are microscopic and submicroscopic phospholipid vesicles with a bilayered membrane structure. Photostabilization of the drug substance by entrapment into liposomes is one such way to improve their photostability.

[0029] 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.

[0030] The formulation can also contain permeability enhancers to increase the extent and/or rate of absorption. Examples of such enhancers are sulphoxides (such as dimethyl sulphoxide, 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.

[0031] Coloring agents, sweeteners, and flavoring agents can also be added to solid oral formulations in order to improve patient recognition and acceptability.

[0032] Immediate release formulations produced by granulation can contain but are not limited to the solid oral formulation fillers/bulking agents, binders, absorbents, disintegrants, glidants, and lubricants as described above as well as buffers, antioxidants, absorption

enhancers, and coloring and flavoring agents. One such granulation process is high shear granulation whereby powders (active, dry binders, fillers, etc.) are charged to a closed container which contains mixing/blending components such as an impeller and chopper. In high shear wet granulation, hereafter referred to as wet granulation, the powders are wetted with a binder solution/suspension while mixing allowing for particle cohesion and granule growth. Additional excipients (filler, glidants, disintegrants, lubricants, etc.) can be added and mixed with the granules after the binder solution/suspension addition. Depending on the concentration of the active, it is typically added either as a dry ingredient (higher concentrations of active ingredient typically greater than 1-10% by weight) prior to the binder solution/suspension addition or contained within the binder solution/suspension (lower concentrations of active ingredient typically less than 1-10% by weight) to ensure uniformity. In wet granulation when active is added in solution or suspension the liquid solvent is removed by active drying. Alternatively, with a process called moisture activated dry granulation (MADG) in EXAMPLE 1, the liquid (typically water) content is reduced and taken up by absorbents added to the formulation rather than introducing an active drying step.

[0033] Dry blending of crystalline API, either micronized or not micronized, is an alternative solid oral formulation approach to granulation, further described in EXAMPLE 2. Dry blending can employ similar mixing/blending equipment as granulation or with lower shear mixing and can use similar excipient classes, minimally with a filler. Dry blending formulations can be further processed into tablets including orally disintegrating tablets through direct compression or encapsulated. When forming for direct compression, the composition can also include any of the binders, disintegrants, glidants, and lubricants described above as needed for processing.

[0034] 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.

[0035] 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 humans. 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.

[0036] 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.

[0037] 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.

[0038] 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 a step chosen from 1) granulating with excipients such as fillers, absorbents, binders, disintegrants, glidants, and/or lubricants to encapsulate or form a tablet; or 2) blending with excipients such as fillers, disintegrants, dry binders, glidants, and/or lubricants for direct compression into tablets, including ODTs, or encapsulation. Each approach considers the challenges associated with formulating a low dose product while maintaining content uniformity and chemical integrity of LSD.

[0039] The present invention provides for a method of treating an individual, by administering a solid oral immediate release formulation of LSD and treating the individual.

[0040] 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 postpartum 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).

[0041] 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.

[0042] **EXAMPLE 1: Granulating d-LSD D-tartrate with excipients**

[0043] A single pot granulation process called moisture activated dry granulation (MADG) was used for formulating low dose LSD in order to achieve suitable content uniformity and avoid a separate active drying step that would typically be performed with wet granulation. For MADG, the method of making LSD formulations includes: 1) Creating a granulation liquid stock solution of LSD, water (or other suitable solvent), and solubility aids if needed; 2) Blending a filler (i.e. mannitol) and binder (i.e. hydroxypropyl methylcellulose); 3) Spraying the granulation liquid onto the dry mixture and blending to form an agglomeration; 4) Adding a moisture absorbent (i.e. starch) and blending; and finally 5) Adding additional functional excipients such as disintegrants, glidants, and lubricants and blending to form the final granulation powder. In an optimized process there are no lumps in the final granule, so sieving is not required. The final granulation can be encapsulated or formed into tablets.

[0044] TABLE 1 shows 25µg LSD (equivalent to 36.6 µg of d-LSD D-tartrate) formulations developed with microcrystalline cellulose and starch as absorbents in the MADG process. These formulations were encapsulated, placed on stability at 25°C, and tested for total impurities. TABLE 2 shows total impurity results for the microcrystalline cellulose formulation and TABLE 3 shows total impurity results for the starch formulation. In addition, FIGURE 3 shows the dissolution profile for the starch containing formulation, which demonstrates immediate release of LSD or complete dissolution within 15 minutes.

TABLE 1 – Granulation Formulations of d-LSD D-tartrate using a moisture-activated dry granulation process

	Weight % per Capsule	
	Microcrystalline Cellulose Formulation	Starch Formulation
Agglomeration		
d-LSD D-tartrate	< 1%	< 1%
Mannitol	10-90%	10-90%
Hypromellose	1-5%	1-5%
Purified Water	1-5%	1-5%
Absorption and final blend		
Partially pregelled starch		25-50%
Microcrystalline cellulose	20-90%	
Mesoporous Silica	<2%	<2%
Sodium starch glycollate	1-10%	
Croscarmellose Sodium		1-25%
Sodium Stearyl Fumarate	<2%	< 2%

[0045] TABLE 2 shows total impurities data of d-LSD D-tartrate using a MADG formulation with microcrystalline cellulose as the adsorbent.

TABLE 2 – Chemical stability of d-LSD D-tartrate using a MADG formulation with microcrystalline cellulose as the adsorbent

Sample	Total Impurity (% Area)
Initial	1.7
1 Month @ 25°C	1.5
2 Month @ 25°C	2.1

[0046] TABLE 3 shows stability data of d-LSD D-tartrate using a MADG formulation with pregelled starch as the absorbent and FIGURE 3 shows dissolution data.

TABLE 3 – Chemical stability of d-LSD D-tartrate using a MADG formulation with pregelled starch as the absorbent

Time Point	Total Impurity (% Area)
Initial	1.8
1 Month @ 25°C	1.6
3 Month @ 25°C	1.8
6 Month @ 25°C	1.7

[0047] Additional granulation formulations of d-LSD D-tartrate using moisture-activated dry granulation and pregelled starch as the absorbent were made but excluding a lubricant. The composition is comparable to the Starch Formulation in TABLE 1 without sodium stearyl fumarate.

[0048] FIGURE 2 shows content uniformity of the pregelled starch formulation without a lubricant. The process capability based on these results indicates that less than 0.5 parts-per-million (ppm) capsules would be outside the 85%-115% label claim range. The data provides evidence that the uniformity of the final blend was satisfactory.

[0049] TABLE 4 shows the chemical stability data for the pregelled starch formulation without a lubricant at 25°C.

TABLE 4

Time Point	Total Impurity (% Area)
Initial	0.2

1 Month @ 25°C	0.3
3 Month @ 25°C	0.5

[0050] Together these data show that moisture-activated dry granulation can produce a pharmaceutically acceptable uniform, stable, and immediate release formulation of LSD.

[0051] EXAMPLE 2: Dry blending d-LSD D-tartrate drug crystals with excipients

[0052] The method for making dry blend formulations of LSD in a single pot includes adding a minimum filler / carrier excipients, such as mannitol, lactose, and microcrystalline cellulose and d-LSD D-tartrate to a mixing vessel and blending until the drug is uniformly dispersed. The order of addition for the components, or parts of the components, can be adjusted as needed.

[0053] The chemical purity of d-LSD D-tartrate salt (FIGURE 4) when blended as a solid drug crystal with solid excipient in an approximate ratio of 1:100 was assessed over a prolonged period (3 and 6 weeks) at 40°C from the bulk formulation. TABLE 5 shows chromatographic purity results of the three dry blend d-LSD D-tartrate formulations at 40°C demonstrating minimal change in chemical purity for each of the filler / carrier excipients.

TABLE 5 – Chromatographic Purity results for d-LSD D-tartrate drug crystals blended with various filler excipients, stored at 40°C, and analyzed for chemical stability at T=0, T=3 weeks and T=6 weeks

Excipient	**T=0**	**T= 3 weeks 40°C**	**T= 6 weeks 40°C**

MCC (microcrystalline cellulose)	99.8	99.2	99.2
Mannitol	99.8	99.9	99.9
Lactose	99.8	99.8	99.7

[0054] The results show that d-LSD D-tartrate drug crystals blended with lactose, mannitol, and microcrystalline cellulose are stable. FIGURE 4 shows the % iso-LSD, a known LSD degradation product, versus condition and excipient. 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.

[0055] The invention has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of words of description rather than of limitation.

[0056] 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 chosen from the group consisting of a capsule, tablet, and orally disintegrating tablet.

2. The composition of claim 1, wherein said LSD is in a form chosen from free base and salt.

3. The composition of claim 2, wherein said 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.

4. The composition of claim 1, wherein said LSD is present in an amount of 0.01-1 mg.

5. The composition of claim 1, wherein said LSD is in a form chosen from crystalline and non-crystalline.

6. The composition of claim 1, wherein said composition is produced by granulation.

7. The composition of claim 6, 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.

8. The composition of claim 6, further including a binder chosen from the group consisting of acacia gum, hydroxypropyl methylcellulose, hydroxypropyl cellulose, tragacanth, polyvinyl pyrrolidone (PVP), and starch.

9. The composition of claim 6, further including an absorbent chosen from the group consisting of croscarmellose sodium, starch, mesoporous silicon dioxide, and microcrystalline cellulose.

10. The composition of claim 6, further including a disintegrant chosen from the group consisting of croscarmellose sodium, starch, microcrystalline cellulose, crospovidone, and sodium starch glycolate.

11. The composition of claim 6, further including a glidant chosen from the group consisting of magnesium stearate and colloidal silicon dioxide.

12. The composition of claim 6, further including a lubricant chosen from the group consisting of magnesium stearate, sodium stearyl fumarate, polyethylene glycol (PEG), polyoxyethylene stearates, lauryl sulphate salts, talc, glyceryl behenate, stearic acid, glyceryl palmitostearate, calcium stearate, and hydrogenated vegetable oils.

13. The composition of claim 6, further including an agent for adjusting pH chosen from the group consisting of citrate, phosphate, acetate, sodium hydroxide, and hydrochloric acid.

14. The composition of claim 6, further including an antioxidant chosen from the group consisting of ascorbic acid, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT).

15. The composition of claim 6, further including a photostabilization agent.

16. The composition of claim 6, further including a permeation enhancer chosen from the group consisting of sulphoxides, azones, pyrrolidones, alcohols, alkanols, glycols, surfactants, and terpenes.

17. The composition of claim 6, further including coloring agents, sweeteners, and flavoring agents.

18. The composition of claim 1, wherein said composition is produced by dry blending.

19. The composition of claim 18, further including a filler chosen from the group consisting of lactose, mannitol, dicalcium phosphate, calcium sulfate, starch, cellulose, kaolin, sodium chloride, sorbitol, and sucrose.

20. The composition of claim 18, further including a glidant chosen from the group consisting of magnesium stearate and colloidal silicon dioxide.

21. The composition of claim 18, further including a dry binder of microcrystalline cellulose.

22. The composition of claim 18, further including a disintegrant chosen from the group consisting of croscarmellose sodium, starch, microcrystalline cellulose, crospovidone, and sodium starch glycolate.

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

granulating LSD with excipients of fillers, absorbents, binders, disintegrants, lubricants, and/or glidants; and

encapsulating or compressing to form a tablet of a solid oral immediate release formulation of LSD.

24. The method of claim 23, wherein said granulating step is further defined as moisture activated dry granulation.

25. The method of claim 24, wherein said granulating step includes charging powders of LSD, binders, and fillers to a closed container which contains mixing/blending components, wetting the powders with a binder solution/suspension while mixing allowing for particle cohesion and granule growth, and adding fillers, glidants, disintegrants, and lubricants.

26. The method of claim 23, wherein the LSD is in a form chosen from free base and salt.

27. The method of claim 23, 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.

28. The method of claim 23, wherein the binder is chosen from the group consisting of acacia gum, hydroxypropyl methylcellulose, hydroxypropyl cellulose, tragacanth, polyvinyl pyrrolidone (PVP), and starch.

29. The method of claim 23, wherein the absorbent is chosen from the group consisting of croscarmellose sodium, starch, mesoporous silicon dioxide, and microcrystalline cellulose.

30. The method of claim 23, wherein the disintegrant is chosen from the group consisting of croscarmellose sodium, starch, microcrystalline cellulose, crospovidone, and sodium starch glycolate.

31. The method of claim 23, wherein the glidant is chosen from the group consisting of magnesium stearate and colloidal silicon dioxide.

32. The method of claim 25, wherein the lubricant is chosen from the group consisting of magnesium stearate, sodium stearyl fumarate, polyethylene glycol (PEG), polyoxyethylene stearates, lauryl sulphate salts, talc, glyceryl behenate, stearic acid, glyceryl palmitostearate, calcium stearate, and hydrogenated vegetable oils.

33. The method of claim 23, 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.

34. A method of making a solid oral immediate release formulation of LSD by dry blending, including the steps of:

blending LSD minimally with filler excipients and additionally a disintegrant, dry binder, glidant and lubricant; and

CA 03228975 2024-2-14

a forming step chosen from the group consisting of directly compressing to form a tablet or orally disintegrating tablet (ODT) of a solid oral immediate release formulation of LSD and encapsulating to form a solid oral immediate release formulation of LSD.

35. The method of claim 34, 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.

36. The method of claim 34, wherein the dry binder is microcrystalline cellulose

37. The method of claim 34, wherein the disintegrant is chosen from the group consisting of croscarmellose sodium, starch, microcrystalline cellulose, crospovidone, and sodium starch glycolate.

38. The method of claim 34, wherein the glidant is chosen from the group consisting of magnesium stearate and colloidal silicon dioxide.

39. The method of claim 34, wherein the lubricant is chosen from the group consisting of magnesium stearate, sodium stearyl fumarate, polyethylene glycol (PEG), polyoxyethylene stearates, lauryl sulphate salts, talc, glyceryl behenate, stearic acid, glyceryl palmitostearate, calcium stearate, and hydrogenated vegetable oils.

40. The method of claim 34, wherein the LSD is in a form chosen from free base and salt.

41. The method of claim 34, 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.

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

administering a solid oral immediate release formulation of LSD chosen from the group consisting of a capsule, tablet, and orally disintegrating tablet; and

treating the individual.

43. The method of claim 42, wherein the individual has trouble swallowing, is elderly, or has dementia.

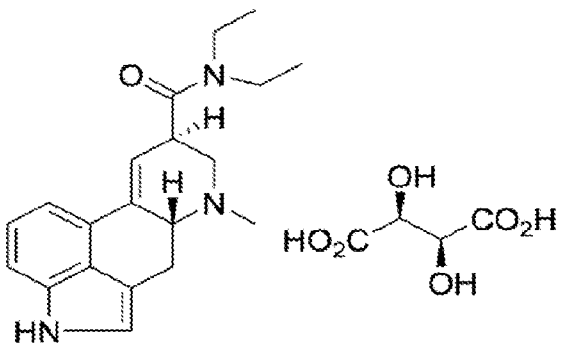
44. The method of claim 42, wherein said treating step is further defined as treating a condition or disease chosen from the group consisting of anxiety disorders, depression, headache disorder, obsessive compulsive disorder (OCD), personality disorders, stress disorders, drug disorders, gambling disorder, eating disorder, body dysmorphic disorder, pain, neurodegenerative disorders, autism spectrum disorder, eating disorders, and neurological disorders.

45. The method of claim 42, wherein the LSD is in a form chosen from free base and salt.

46. The method of claim 45, 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.

47. The method of claim 42, 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

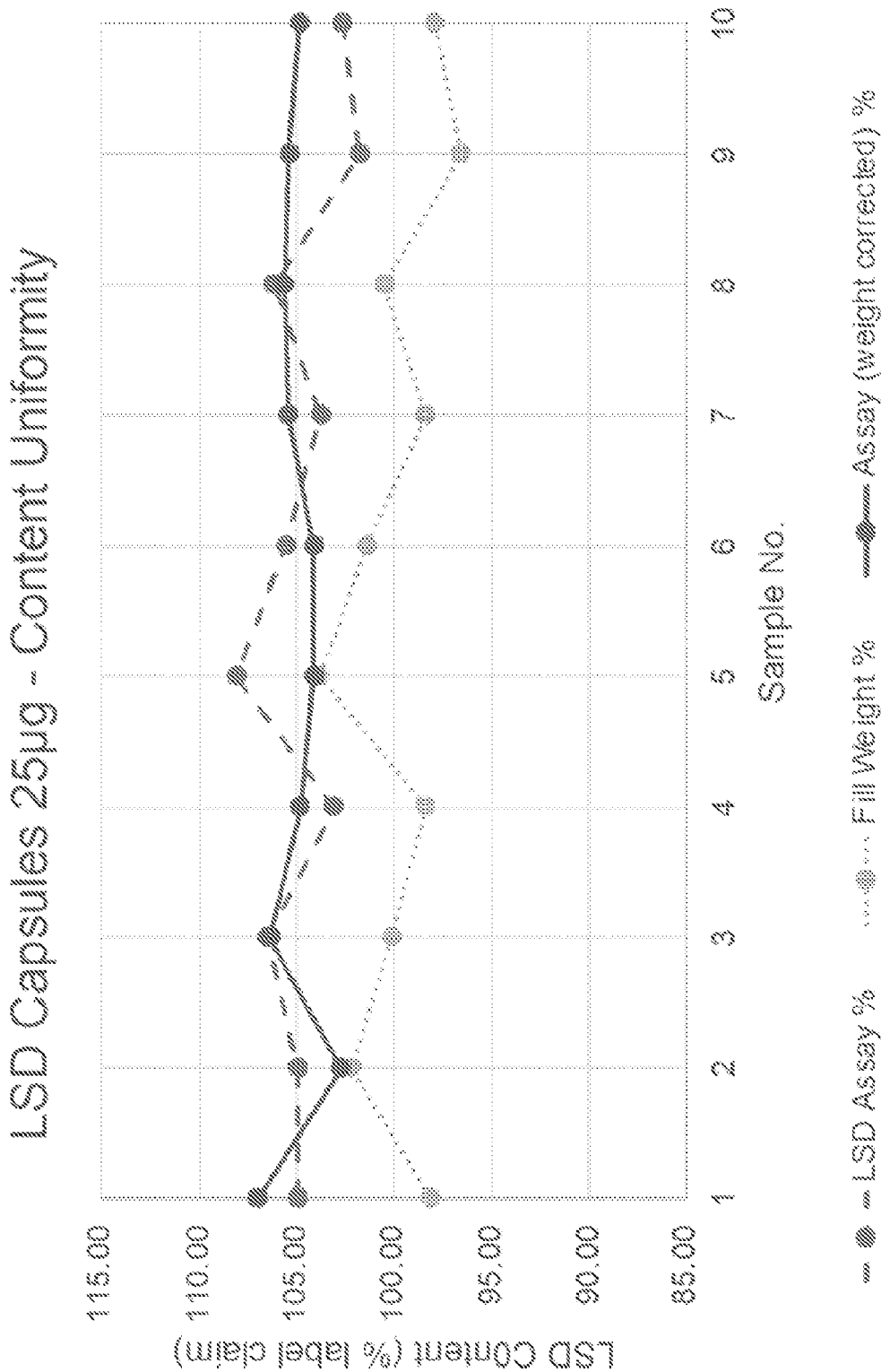

LSD Capsules 25µg - Content Uniformity
LSD Content (% label claim)
115.00
110.00
105.00
100.00
95.00
90.00
85.00
1
2
3
4
5
6
7
8
9
10
Sample No.
LSD Assay %
Fill Weight %
Assay (weight corrected) %

FIGURE 3

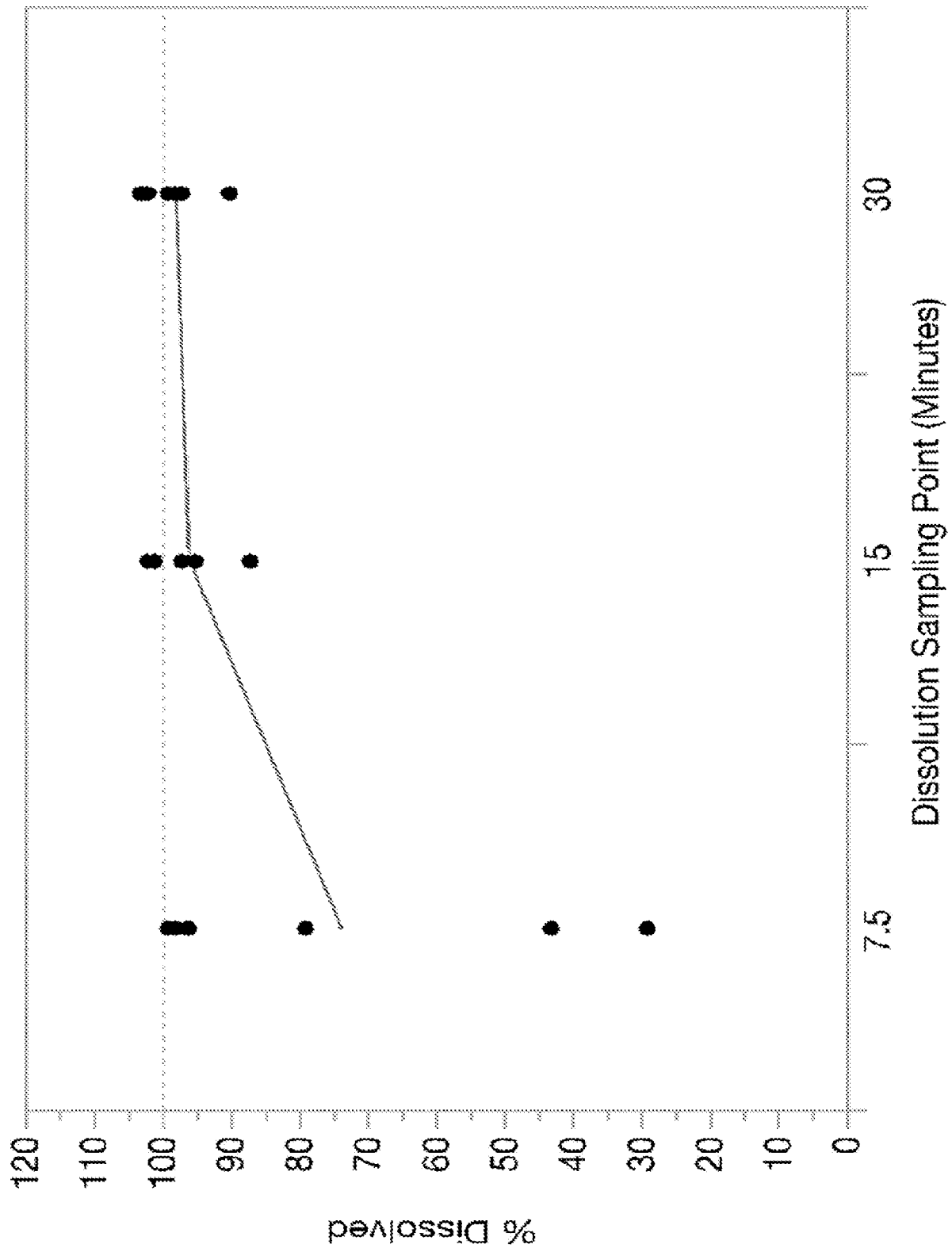

% Dissolved
120
110
100
90
80
70
60
50
40
30
20
10
0
7.5
15
30
Dissolution Sampling Point (Minutes)

FIGURE 4

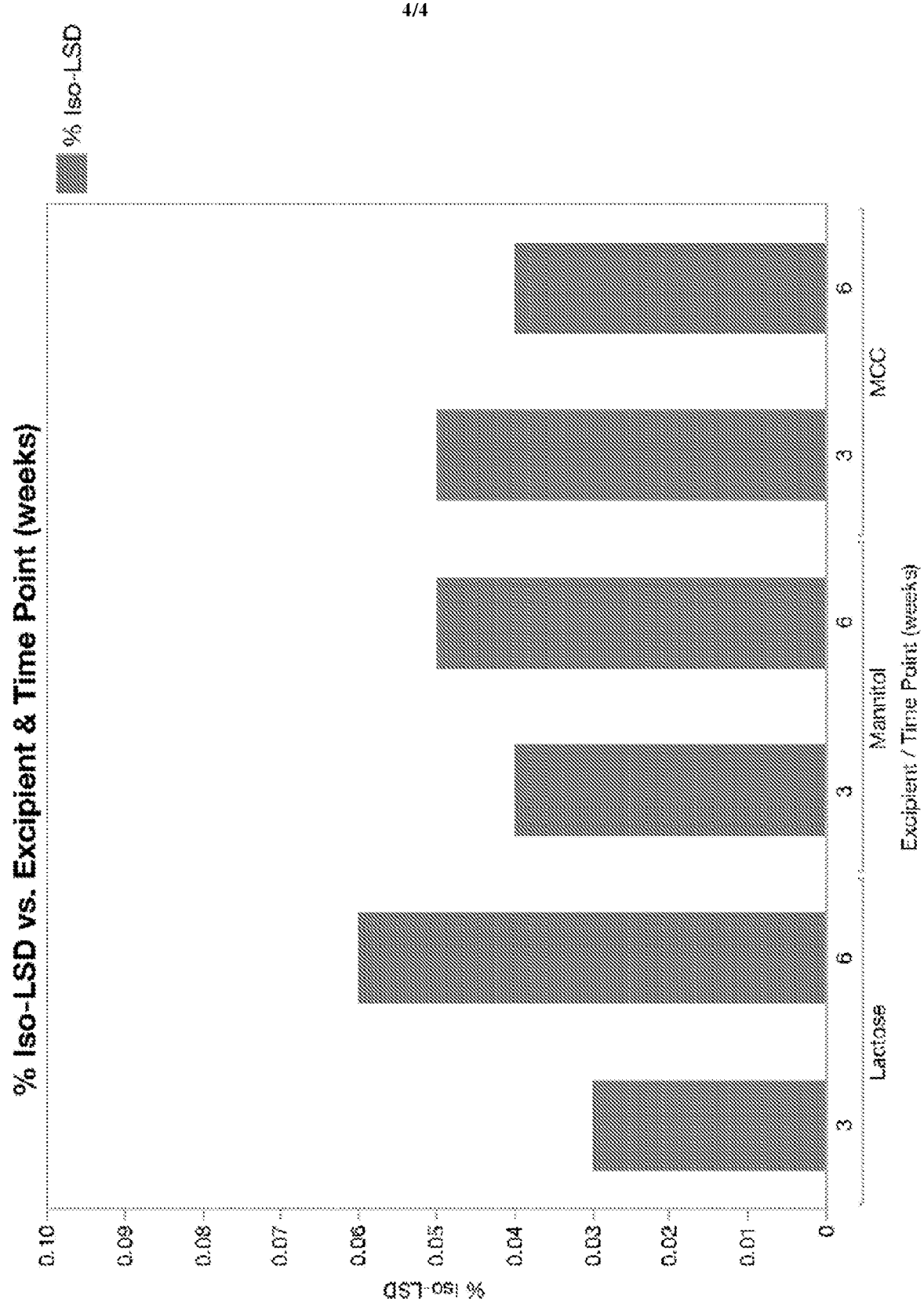
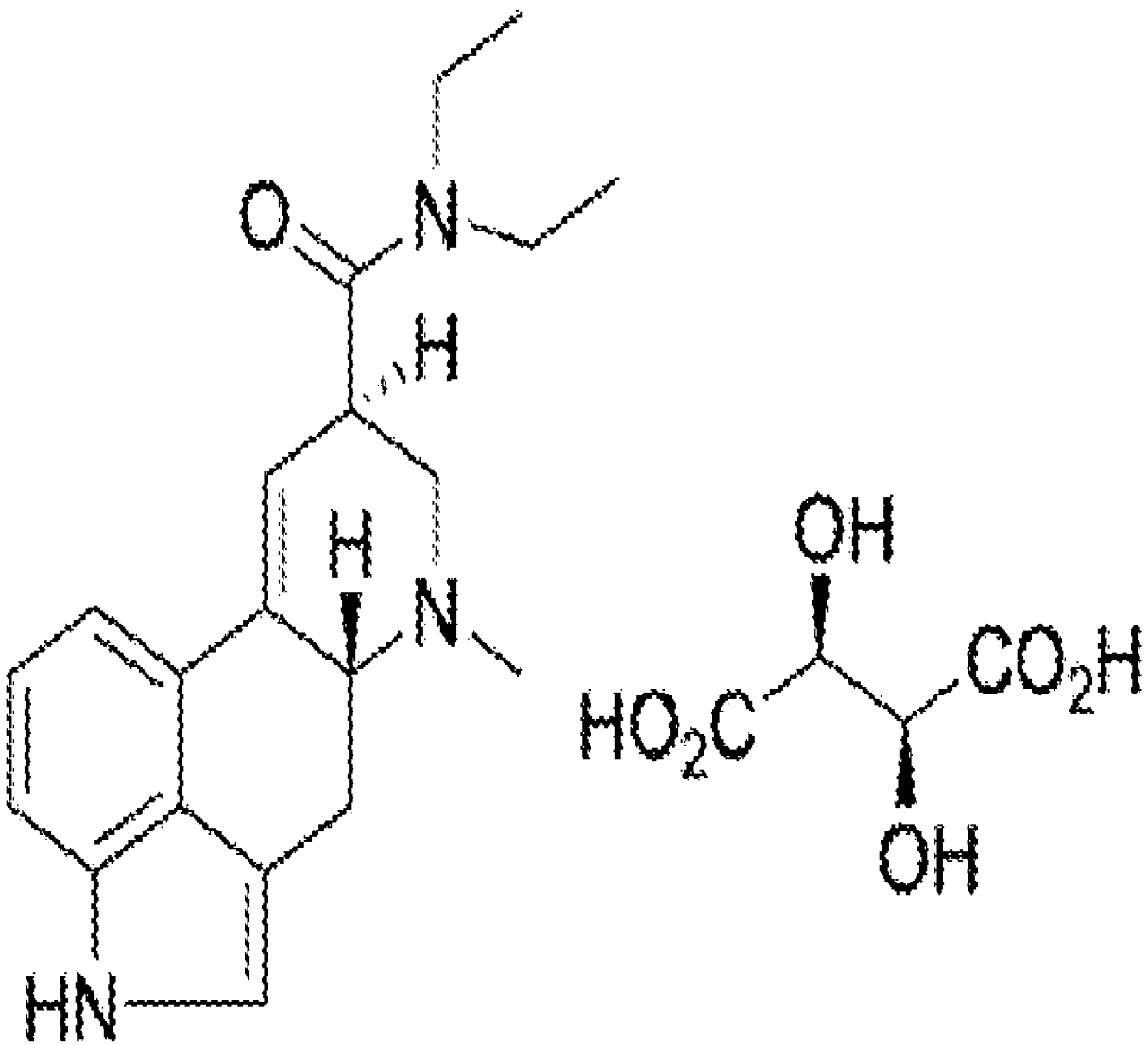

% Iso-LSD vs. Excipient & Time Point (weeks)
% Iso-LSD
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
% Iso-LSD
3
6
3
6
3
6
Lactose
Mannitol
MCC
Excipient / Time Point (weeks)

FIGURE 1



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

D-LSD D-Tartrate