IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Plakogiannis; Fotios M.	Confirmation No.:
Serial No.:	17/231553	Group No.:
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Entitled: TRANSDERMAL MICRO-DOSING DELIVERY OF PSYCHEDELICS DERIVATIVES

THIRD-PARTY PRE-ISSUANCE SUBMISSION

Examiner:

The following documents, which are also identified in the Form PTO/SB/429 filed herewith, are submitted for your consideration as being of potential relevance to the examination of the present application:

1. U.S. Pat. App. Pub. No. 2011/0111029 "Composition for transdermal delivery of cationic active agents" (Published 12 May 2011)
2. CARHART-HARRIS (2018) "Psilocybin with psychological support for treatment-resistant depression: six-month follow-up" Psychopharmacology (Berl). 235(2):399-408.
3. ANDERSSON (2017) "Psychoactive substances as a last resort—a qualitative study of self-treatment of migraine and cluster headaches" Harm Reduction Journal. 14(1):1-10.
4. CAMERON (2020) "Psychedelic Microdosing: Prevalence and Subjective Effects" Journal of Psychoactive Drugs. 52(2):113–122.
5. FADIMAN (2018) "Might Microdosing Psychedelics Be Safe and Beneficial? An Initial Exploration" Journal of Psychoactive Drugs. 51(2):118-122.
6. W.I.P.O. Pat. App. No. 2018/135943 "PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES" (Published July 26, 2018)
7. ALPER (2008) "The ibogaine medical subculture" Journal of Ethnopharmacology. 115(1):9-24.
8. GLICK (2006) "18-Methoxycoronaridine (18-MC) and Ibogaine: Comparison of Antiaddictive Efficacy, Toxicity, and Mechanisms of Action" Annals of the New York Academy of Sciences. 914(1)369-386.
9. U.S. Pat. App. No. 2020/0085816 "LSD FOR THE TREATMENT OF ALZHEIMER'S DISEASE" (Published March 19, 2020)
10. POLITO (2019) "A systematic study of microdosing psychedelics" PLoS One. 14(2)1-26.

11. W.I.P.O. Pat. App. No. 2021/003467 "METERED DOSING COMPOSITIONS AND METHODS OF USE OF PSYCHEDELIC COMPOUNDS" (Published January 7, 2021; provisional priority date July 4, 2019)
12. W.I.P.O. Pat. App. No. 2020/123625 "Co-crystals, method and apparatus for forming the same" (Published June 18, 2020; provisional priority date December 11, 2018)
13. BEUG (1982) "Psilocybin and psilocin levels in twenty species from seven genera of wild mushrooms in the Pacific Northwest, U.S.A." Journal of Ethnopharmacology. 5(3):271-285.
14. W.I.P.O. Pat. App. No. 2001/064149 "IMPROVED TRANSDERMAL DRUG PATCH" (Published September 7, 2001)
15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020)
16. W.I.P.O. Pat. App. No. 2008/039179 "COMPOSITIONS FOR THE TREATMENT OF HEPATITIS C AND METHODS FOR USING COMPOSITIONS FOR THE TREATMENT OF HEPATITIS C" (Published April 3, 2008)
17. U.S. Pat. No. 6245347 "Methods and apparatus for improved administration of pharmaceutically active compounds" (Published June 12, 2001)
18. ASI, "Adhesives In Transdermal Drug Delivery Systems" 2005; retrieved https://web.archive.org/web/20161005045648/https://www.adhesivesmag.com/articles/86012-adhesives-in-transdermal-drug-delivery-systems, retrieved October 5, 2016
19. VALENTA (2004) "The use of polymers for dermal and transdermal delivery" European Journal of Pharmaceutics and Biopharmaceutics. 58(2):279-289.
20. SINHA (2000) "Permeation Enhancers for Transdermal Drug Delivery" Drug Development and Industrial Pharmacy. 26(11)1131-1140.
21. U.S. Patent App. No. 2013/0253449 "NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANT-CONTAINING TRANSDERMAL PATCH" (Published September 26, 2013)
22. SMITH (1995) Pcc CRC-Press, ISBN: 0849326052
23. GRODOWSKA (2010) "Organic solvents in the pharmaceutical industry" Acta Poloniae Pharmaceutica – Drug Research. 67(1)3-12.

Attached hereto is a claim chart providing a concise description of the relevance of each reference in the document list to the elements of the presently pending claims.

U.S.S.N. 17/231553 Pending Claims	References
1. A transdermal and/or topical pharmaceutical composition comprising: about 0.1% to about 20% of an active agent selected from the group consisting of psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, derivatives of these compounds, and combinations thereof, about 80% to about 99.9% of an adhesive and/or polymer; optionally, about 0.1% to about 20% of a permeation enhancer; optionally, about 0.1% to about 20% of a solvent, wherein said pharmaceutical composition will have no or minimal hallucinogenic effect in a patient to whom the pharmaceutical composition is applied.	1. U.S. Pat. App. Pub. No. 2011/0111029 "Composition for transdermal delivery of cationic active agents" (Published 12 May 2011) From **claim 1** "A self-adhesive **transdermal patch** composition for iontophoretic transdermal delivery of at least one cationic active agent or a salt thereof, comprising: said at least one cationic active agent or a salt thereof, wherein the total content of said at least one cationic **active agent or a salt thereof amounts to 0.1 to 20%-wt**. relative to the total weight of the transdermal patch composition, and wherein said at least one cationic active agent is selected from the group consisting of cationic indole compounds and salts thereof;" From **claim 9** "The self-adhesive **transdermal patch** composition according to claim 1, wherein said cationic indole compounds comprise N-dimethyltryptamine and **psilocin**, and pharmacologically acceptable salts of said cationic indole compounds." From **claim 13** "The self-adhesive transdermal patch composition according to claim 1, wherein said one or more additive additives is/are selected from the group consisting of solubility enhancers, **skin permeation enhancers** and antimicrobial agents." 6. W.I.P.O. Pat. App. No. 2018/135943 "PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES" (Published July 26, 2018) From **page 14 paragraph 2** "Also encompassed are dosage forms for **transdermal administration**, including creams, lotions, aerosols and/or emulsions. These dosage forms may be included in **transdermal patches of the matrix or reservoir type**, which are generally known in the art. Pharmaceutical preparations dose (for the cannabinoid, terpene and/or the psilocybin/psilocin) may be conveniently prepared in unit dosage form, according to standard procedures of pharmaceutical formulation. The quantity of **active compound(s)** per unit dose may be varied according to the nature of the active compound and the intended dosage regime. Generally **an effective amount shall be used, which may be within the range of from 0.01 mg to 5000 mg**, preferably 0.01-4000 mg, 0.1-3000 mg, 1-2500, 5-1000, or 10-100 mg per unit dose (for the at least one cannabinoid and/or the at least one terpene and/or the **at least one psilocybin and/or the at least one psilocin**)." 9. U.S. Pat. App. No. 2020/0085816 "LSD FOR THE TREATMENT OF ALZHEIMER'S DISEASE" (Published March 19, 2020)

	From **claim 40** "A **transdermal delivery system** comprising a pharmaceutically effective amount of a neuronal growth factor, **2 µg to 30 µg** of **lysergic acid diethylamide** or a pharmaceutically acceptable salt thereof, and a naturally occurring gum." 10. POLITO (2019) "A systematic study of microdosing psychedelics" PLoS One. 14(2)1-26. From **page 1** "Individuals who **microdose** report **minimal acute effects** from these substances yet claim a range of long-term general health and wellbeing benefits." From **page 2** "So, for example, a **microdose of lysergic acid diethylamide (LSD) might be 6–25 micrograms**, or a microdose of **psilocybin might be .1 to .5 grams of dried mushrooms**." 11. W.I.P.O. Pat. App. No. 2021/003467 "METERED DOSING COMPOSITIONS AND METHODS OF USE OF PSYCHEDELIC COMPOUNDS" (Published January 7, 2021; provisional priority date July 4, 2019) From **page 7** "Disclosed are multiple **metered dosing formulations for various corresponding methods of delivery of psychoactive plant and/or fungal compounds for** inhalation, sublingual, nasal, oral (including capsules, gell caps, and tinctures) and **topical use**, which is made up of the following components 1) at least one active compound isolated from psychoactive plants or fungi; b) one of the methods of delivery; and c) a base solution that is appropriate for the chosen method of delivery of the active compound. More specifically the psychoactive plant and/or fungi used will include but not be limited to fundi containing **psilocybin**, baeocystin, and/or **psilocin** and/or plants containing mescaline aka peyote aka 3,4,5-trimethoxyphenethylamine aka DMT." From **page 10** "The embodiments of the present invention contemplate **dosage forms with a total weight of between approximately 0.1mg to 50mg of psychoactive fungal compound(s)**, depending on the formulation of the active compound(s) and method of delivery." From **page 12** "For long-term daily care, **a sub-hallucinogenic regiment of 0.1mg/70kg to 1.5mg/70kg may provide for mood enhancement,** greater empathy and compassion, increased creativity, greater focus and long-term stability in mainlining goals related to preventing intrusive thoughts from PTSD." 13. BEUG (1982) "Psilocybin and psilocin levels in twenty species from seven genera of wild mushrooms in the Pacific Northwest, U.S.A." Journal of Ethnopharmacology. 5(3):271-285.

	From **p. 281**

TABLE 1

Psilocybin and psilocin levels in Pacific Northwest mushrooms as quantified by reversed phase HPLC

Species[1] (Figs. 1 - 20)	Date collected[2]	Psilocybin (mg/g dry weight)	Psilocin (mg/g dry weight)
Conocybe cyanopus (Atk.) Kühner	July 12, 1979	9.3	0
Conocybe tenera (Schaeff. ex Fr.) Kühner	Aug. 22, 1978	0	0
Conocybe sp. (near *lactea* (J. Lange) Métrod)	Aug. 13, 1978	0	0
Pholiotina filaris (Fr.) Singer	Oct. 1979	0	0
Panaeolus campanulatus (Fr.) Quél.	Aug. 13, 1978	0	0
	Sept. 4, 1978	0	0
	Mar. 18, 1980	0	0
Panaeolus acuminatus (Sec.) Quél.	Sept. 4, 1978	0	0
	Mar. 18, 1980	0	0
Panaeolus phalaenarum (Fr.) Quél.	July 23, 1978	0	0
	Cultivated	0	0
Psathyrella foenisecii (Fr.) Smith	June 18, 1978	0	0
	Oct. 4, 1978	0	0
Panaeolus semiovatus (Fr.) Lundell & Nanfeldt	June 28, 1978	0	0
	July 12, 1979 (3 collections)	0	0
Panaeolus subbalteatus (Berk. & Br.) Sacc.	July 3, 1978	3.5	0
	Sept. 5, 1978	6.5	0
	Sept. 3, 1979	1.6	0
Gymnopilus ventricosus (Earle) Hesler (generally identified as *G. spectabilis*)	Oct. 15, 1979	0	0
Stropharia aeruginosa (Fr.) Quél.	Oct. 29, 1979	0	0
Psilocybe semilanceata (Fr.) Quél.	Oct. 1979	6.9	0
	Sept. 4, 1978	10.8	0
	Oct. 22, 1979	12.0	0
	Nov. 5, 1979	6.9	0
	Nov. 27, 1979a	8.4	0
	Nov. 27, 1979b	12.8	0
	Nov. 27, 1979c	9.2	0
	Nov. 27, 1979d	6.6	0
	Nov. 27, 1979e	10.9	0
	Nov. 27, 1979f	8.5	0
Caps only	Nov. 27, 1979g	11.1	0
Stems only	Nov. 27, 1979g	6.2	0
Psilocybe cyanescens Wakefield	Oct. 1978a	4.9	1.7
	Oct. 28, 1979	1.5	9.6
	Nov. 2, 1979	8.2	1.3
	Nov. 6, 1979	11.5	7.6

TABLE 1 *(continued)*

Species[1] (Figs. 1 - 20)	Date collected[2]	Psilocybin (mg/g dry weight)	Psilocin (mg/g dry weight)
Psilocybe cyanescens Wakefield	Nov. 7, 1979a	8.3	2.0
	Nov. 7, 1979b	16.8	2.8
	Nov. 18, 1979a	14.3	2.8
	Nov. 18, 1979b	15.5	2.4
	Nov. 18, 1979c	13.6	2.3
	Nov. 18, 1979d	11.0	2.0
	Nov. 18, 1979e	10.1	1.4
	Nov. 18, 1979f	8.7	1.8
	Nov. 18, 1979g	9.7	2.8
	Nov. 19, 1979	8.4	0.6
Psilocybe stuntzii Guzmán & Ott	Sept. 24, 1978	0	0
	Oct. 27, 1979	3.6	0.6
	Oct. 31, 1979	0.4	0.12
	Nov. 13, 1979	3.6	0.06
Psilocybe baeocystis Singer & Smith	Sept. 1979a	2.04	1.43
	Sept. 1979b	1.96	1.32
	Sept. 1979c	1.92	0.48
	Sept. 1979d	2.04	3.07
	Sept. 5, 1979	8.5	5.9
	Oct. 1979a	2.8	0.8
	Oct. 1979b	1.5	0
Psilocybe coprophila (Bull. ex Fr.) Kummer	June 22, 1979	0	0
Psilocybe montana (Pers. ex Fr.) Kummer	Mar. 18, 1980	0	0
Psilocybe inquilina (Fr. ex Fr.) Bres.	Mar. 18, 1980	0	0
Psilocybe pelliculosa (Sm.) Singer & Smith	Oct. 30, 1979	7.1	0
	Oct. 8, 1979	4.1	0
	Nov. 8, 1979	1.2	0

15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020)

From **claim 1** "A method of managing a neurological condition or one or more symptoms thereof in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising:
a) a therapeutically effective amount of one or more 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof; and
b) a pharmaceutically acceptable excipient wherein the therapeutically effective amount of the **5HT receptor agonist o**r a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to the subject in need thereof **in an amount insufficient to provide an adverse side effect, such as hallucinogenic experience.**"

From **claim 4** "The method of any one of the preceding claims, wherein the **5HT receptor agonist** or a pharmaceutically acceptable salt, solvate,

	metabolite, derivative, or prodrug thereof is present in an amount of from about **0.1 mg to about 2 mg**." From **claim 13** "The method of any one of the preceding claims, wherein the **5HT receptor agonist** is **psilocybin** or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof." From **claim 14** "The method of any one of claims 1-12, wherein the 5HT receptor agonist is **psilocin** or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof." From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a spray, aerosol, mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From paragraph [0042] "In certain embodiments, the 5-HT2A agonist provided herein is one of the following classes of 5-HT2A agonists: the ergolines, **tryptamines** and phenethylamines. In specific embodiments, a 5HT (e.g.5HT2A) receptor agonist utilized herein is an ergoline" From paragraph [0047] "Examples of **tryptamines** include serotonin, melatonin, **psilocybin** and N,N-dimethyltryptamine. Additionally, the tryptamine structure may comprise part of a more complex compound, for example: **LSD, ibogaine,** mitragynine, yohimbine, etc." 21. U.S. Patent App. No. 2013/0253449 "NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANT-CONTAINING TRANSDERMAL PATCH" (Published September 26, 2013) From **paragraph [0029]** "The amount of the **adhesive ingredient to be incorporated in the drug-containing layer is from 65 to 98% by mass**, preferably from 70 to 97% by mass relative to the drug-containing layer, in consideration of formation of the drug-containing layer and of sufficient drug releasability."
2. The pharmaceutical composition of claim 1 wherein the adhesive is selected from the group consisting of pressure sensitive adhesives, silicone polymers, bio psa 4302, bio-psa 4202, acrylic pressure sensitive adhesives, duro-tak 87-2156, duro-	1. U.S. Pat. App. Pub. No. 2011/0111029 "Composition for transdermal delivery of cationic active agents" (Published 12 May 2011) From **paragraph [0052]** "Preferably, the polyamine compounds to be used in accordance with the compositions of the invention are present in the form of **polyamine salts**, particularly **water-soluble polyamine salts**. Suitable salts are obtainable by combining or reacting the above-mentioned polyamines with suitable acids, preferably organic acids, by standard procedures."

tak 387-2287, duro-tak 87-9301, duro-tak 387-2051, polyisobutylene, polyisobutylene low molecular weight, polyisobutylene medium molecular weight, polyisobutylene 35000 mw, acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers and combinations thereof.	From **paragraph [0112]** "Adhesiveness can be obtained by incorporating one or more **adhesive polymers** into said compositions. Adhesive polymers suitable for this purpose are generally known to the skilled person. Preferably, a **polyamine or polyamine salt having adhesive properties is used as said adhesive polymer(s).** From **paragraph [0144]** "The anodic reservoir (3) was prepared by applying a solution of said cationic active agent (4%-wt.) in polyamine (**acrylic copolymer**; EUDRAGIT® E 100) onto a non-woven viscose material (coating weight per unit area: 0.1 g/cm2)." 15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 1** "A method of managing a neurological condition or one or more symptoms thereof in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising: a) a therapeutically effective amount of one or more 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof; and b) a pharmaceutically acceptable excipient wherein the therapeutically effective amount of the **5HT receptor agonist o**r a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to the subject in need thereof **in an amount insufficient to provide an adverse side effect, such as hallucinogenic experience.**" From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a spray, aerosol, mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From **paragraph [0132]** "In one non-limiting example, a **mucoadhesive** agent can be, by way of non-limiting example, at least two particulate components selected from titanium dioxide, silicon dioxide, and clay. In some embodiments, when the composition is not further diluted with any liquid prior to administration, the level of silicon dioxide is from about 3% to about 15%, by weight of the composition. In certain embodiments, silicon dioxide is selected from, by way of non- limiting example, fumed silicon dioxide, precipitated silicon dioxide, coacervated silicon dioxide, gel silicon dioxide, and mixtures thereof. In some embodiments, clay is selected from, by way of non-limiting example, kaolin minerals, serpentine minerals, smectites, illite or mixtures thereof. In certain embodiments, clay is selected from, by way of non-limiting example, laponite, **bentonite**, hectorite, saponite, montmorillonites or mixtures thereof."

	From **paragraph [0420]** "[420] Embodiment 107 is the pharmaceutical composition of any one of embodiments 1-38, wherein the composition comprises a patch comprising (i) a support layer and (ii) an adhesive agent layer, wherein the adhesive agent layer comprises (a) a **5HT receptor agonist** or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof, and (b) a **rubber-based adhesive agent** and/or a **silicone-based adhesive agent** 18. ASI, "Adhesives In Transdermal Drug Delivery Systems" 2005; retrieved https://web.archive.org/web/20161005045648/https://www.adhesivesmag.com/articles/86012-adhesives-in-transdermal-drug-delivery-systems, retrieved October 5, 2016 "With many prescription and OTC products already available, there is a steady demand for **bioadhesives**. Currently there are three prevalent types of **pressure-sensitive bioadhesives** in use in the U.S. TDD system market: **polyacrylate copolymers (acrylics), polysiloxanes (silicones) and polyisobutylenes (PIBs)**." 21. U.S. Patent App. No. 2013/0253449 "NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANT-CONTAINING TRANSDERMAL PATCH" (Published September 26, 2013) From **paragraph [0026]** "The rubber-type adhesive ingredient includes one or more selected from styrene-isoprene-styrene block copolymer, **styrene-butadiene-styrene block copolymer**, styrene-butadiene rubber, polyisobutylene, polybutene, butyl rubber, natural rubber and isoprene rubber; and any of these may be used here." From **paragraph [0027]** "The acrylic polymer includes, though not defined thereto, polymers or copolymers containing, as the monomer unit thereof, at least one (meth)acrylate of typically 2-ethylhexyl acrylate, methyl acrylate, butyl acrylate, 2-hydroxyethyl acrylate, 2-ethylhexyl methacrylate or the like. For example, herein usable are adhesives of acrylic polymers and the like that contain acrylic acid/octyl acrylate copolymer, 2-ethylhexyl acrylate/N-vinyl-2-pyrrolidone/1,6-hexaneglycol dimethacrylate copolymer, 2-ethylhexyl acrylate/vinyl acetate copolymer, 2-ethylhexyl acrylate/vinyl acetate/acrylic acid copolymer, 2-ethylhexyl acrylate/2-ethylhexyl methacrylate/dodecyl methacrylate copolymer, methyl acrylate/2-ethylhexyl acrylate copolymer resin emulsion, or acrylic resin alkanolamine liquid; and for example, usable are commercially-available **DURO-TAK™ acrylic adhesive series** (available from Henkel Technologies Japan), GELVA™ acrylic adhesive series (by Monsanto), SK-DYNE MATRIDERM (by Soken Chemical), EUDRAGIT™ series (by Higuchi Shokai), etc."

3. The pharmaceutical composition of claim 1 wherein said polymer is present and is selected from the group consisting of natural polymers, polysaccharides. agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium cargeenan, sodium carageenan, tragacanth, xantham, gum copal, chitosan, resin, semisynthetic polymers, cellulose, methylcellulose, ethyl cellulose, carboxymethyl cellulose, hydroxylpropyl cellulose, hydroxylpropylmethyl cellulose, synthetic polymers, carboxyvinyl polymers, carbomers, carbopol 940, carbopol 934, carbopol 971p NF, polyethylene, clays, silicates, bentonite, silicon dioxide, polyvinyl alcohol, acrylic polymers (eudragit), acrylic acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer, polyvinyl pyrrolidone copolymers, PVP, Kollidon 30, poloxamer, isobutylene, ethyl vinyl acetate	1. U.S. Pat. App. Pub. No. 2011/0111029 "Composition for transdermal delivery of cationic active agents" (Published 12 May 2011) From **paragraph [0094]** "In a further embodiment, the hydrogel compositions may comprise additional gel-forming **polymers** which may be selected e.g. from the group consisting of **polyacrylates** or **cellulose** derivatives such as **hydroxypropylmethyl cellulose, hydroxypropyl cellulose** or hydroxyethyl cellulose." From **paragraph [0144]** "The anodic reservoir (3) was prepared by applying a solution of said cationic active agent (4%-wt.) in polyamine (**acrylic copolymer; EUDRAGIT**® E 100) onto a non-woven viscose material (coating weight per unit area: 0.1 g/cm2)." 19. VALENTA (2004) "The use of polymers for dermal and transdermal delivery" European Journal of Pharmaceutics and Biopharmaceutics. 58(2):279-289. From **page 279** "The use of polymers for skin preparations is manifold. Requirements of such polymers are dependent on the formulation types. The most applied polymers on skin belong to various classes, for example to **cellulose derivatives**, **chitosan**, **carageenan**, **polyacrylates**, **polyvinylalcohol**, **polyvinylpyrrolidone and silicones**." From **page 283** "Another sponge-type was an absorbable sponge, composed of **gelatine and alginate**." From **page 283** "**Collagen** is a **natural substrate** for cellular attachment, growth and differentiation and promotes cellular proliferation. Recently, in an excellent review the effects of collagen matrices on dermal wound healing including a cellular and cell-containing products were discussed in detail." From **page 283** "The most important and already well-known polymers for forming hydrogels are polyacrylic acid derivatives like **Carbomers**®, different cellulose derivatives like hydroxyethyl cellulose, hydroxypropyl cellulose and croscarmellose-sodium." From **page 280** "The novel polymer displayed the lowest incompatibility with multivalent cations as well as with ethanol, and exhibited significantly the best swelling properties among several tested polymers like HPMC, NaCMC, **Carbopol**® and polycarbophil." From **page 283** "Another **synthetic polymer** poly(n-vinylpyrrolidone) was used in a tropical environment. To achieve the thickness, additional additives like **agar** or polyethylene glycol were used."

copolymers, natural rubber, synthetic rubber, and combinations thereof.	From **page 280**"As drug, kojic acid, an antimelanogenic agent was incorporated in different preparations like cream bases of mineral oil with caprylic capric triglyceride (MultiCream) and hydrophilic polymers such as chitosan (ChitoGel), Carbopol®, and **poloxamer** (Pluronics®). Pluronic®-based gels (PluGel) and Carbopol®-based gels (CarboGel) revealed controlled release of drug to some extent, followed by the square root-time kinetics." From **page 281** "One approach is the improvement of the adhesiveness on skin by combining different polymers or by polymer derivatisation. The effect of a combination of the adhesive polymethyl methacrylate (PMMA) with cellulose ethers or **polyvinylpyrrolidone (PVP)** was evaluated by a peel adhesion test." 21. U.S. Patent App. No. 2013/0253449 "NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANT-CONTAINING TRANSDERMAL PATCH" (Published September 26, 2013) From **paragraph [0026]** "The rubber-type adhesive ingredient includes one or more selected from styrene-isoprene-styrene block copolymer, styrene-butadiene-styrene block copolymer, styrene-butadiene rubber, **polyisobutylene**, polybutene, **butyl rubber, natural rubber and isoprene rubber**; and any of these may be used here." From **paragraph [0027]** "The acrylic polymer includes, though not defined thereto, polymers or copolymers containing, as the monomer unit thereof, at least one (meth)acrylate of typically 2-ethylhexyl acrylate, methyl acrylate, butyl acrylate, 2-hydroxyethyl acrylate, 2-ethylhexyl methacrylate or the like. For example, herein usable are adhesives of acrylic polymers and the like that contain acrylic acid/octyl acrylate copolymer, 2-ethylhexyl acrylate/N-vinyl-2-pyrrolidone/1,6-hexaneglycol dimethacrylate copolymer, 2-ethylhexyl acrylate/vinyl acetate copolymer, 2-ethylhexyl acrylate/vinyl acetate/acrylic acid copolymer, 2-ethylhexyl acrylate/2-ethylhexyl methacrylate/dodecyl methacrylate copolymer, methyl acrylate/2-ethylhexyl **acrylate copolymer resin emulsion, or acrylic resin alkanolamine liquid;** and for example, usable are commercially-available DURO-TAK™ acrylic adhesive series (available from Henkel Technologies Japan), GELVA™ acrylic adhesive series (by Monsanto), SK-DYNE MATRIDERM (by Soken Chemical), EUDRAGIT™ series (by Higuchi Shokai), etc." From **paragraph [0042]** "The tackifier includes rosin derivatives such as rosin, rosin glycerin ester, hydrogenated rosin, hydrogenated rosin glycerin ester, etc.; alicyclic saturated hydrocarbon resins, alicyclic hydrocarbon resins, terpene resins, aliphatic saturated hydrocarbon resins, aliphatic hydrocarbon resins, resin maleate, carnauba wax, sodium carmellose, xanthane gum, **chitosan**, glycerin, **magnesium aluminium silicate**, light anhydrous silicic acid, benzyl acetate, talc, hydroxyethyl cellulose,

	hydroxypropyl cellulose, hypromellose, polyacrylic acid, sodium polyacrylate, partially-neutralized polyacrylic acid, polyvinyl alcohol, etc." From **paragraph [0043]** "As the support of the transdermal patch of the invention, a drug-impervious elastic or nonelastic support may be used. The support of the type includes, for example, synthetic resin films or sheets or their laminates of **polyethylene**, polypropylene, polybutadiene, ethylene-vinyl acetate copolymer, polyvinyl chloride, polyester (polyethylene terephthalate, etc.), nylon, polyurethane, etc.; porous substances, foams, papers, woven fabrics, nonwoven fabrics, etc."
4. The pharmaceutical composition of claim 1 wherein said permeation enhancer is present, and is selected from the group consisting of dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide, azone, pyrrolidones, N-methyl-2-pyrrolidone, 2-pyrrolidon, esters, fatty acid esters, propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, lauryl lactate, ethyl oleate decyl oleate, glycerol monooleate, glycerol monolaurate, lauryl laurate, fatty acids, capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid, alcohols, fatty alcohols, glycols, oleyl alcohol, nathanol, dodecanol,	1. U.S. Pat. App. Pub. No. 2011/0111029 "Composition for transdermal delivery of cationic active agents" (Published 12 May 2011) From **paragraph [0084]** "**Fatty acids** that may be used in accordance with the present invention include, for instance, hexanoic acid, decanoic acid, **lauric acid**, **myristic acid**, **palmitic acid**, **caprylic acid** and stearic acid; **lauric acid** being preferred." From **paragraph [0106]** "Examples of **permeation enhancers** include, but are not limited to, **dimethylsulfoxide (DMSO)**, **N,N-dimethylacetamide** (DMA), decylmethylsulfoxide (C10 MSO), polyethylene glycol monolaurate (PEGML), **propylene glycol (**PG), **propylene glycol monolaurate** (PGML), **glycerol monolaurate** (GML), lecithin, the 1-substituted alkyl-azacycloalkyl-2-ones, particularly 1-n-dodecylcylazacycloheptan-2-one, **alcohols**, and the like. The permeation enhancer may also be selected from vegetable oils, e.g. safflower oil, cotton seed oil, or corn oil." 20. SINHA (2000) "Permeation Enhancers for Transdermal Drug Delivery" Drug Development and Industrial Pharmacy. 26(11)1131-1140. From **page 1132** "The effect of three **essential oils** (eucalyptus, peppermint, turpentine oil) on the permeation of 5-fluorouracil (5-FU) were studied using excised rat skin. Although all three oils enhanced the **permeation of drug**, their effect was less than that of **azone**." From **page 1132** "**TERPENES, TERPENOIDS, ESSENTIAL OILS**: Terpenes and terpenoids are usually the constituents of volatile oil." From **page 1132** "**Permeation** of haloperidol was increased by both cineole and d-limonene; α-pinene provided no change in its permeation profile. Coapplication of terpenes (1,8-cineole, menthone, limonene, nerolidol) with 5-FU, both at saturation, in a **propylene glycol** (PG)/water cosolvent system increased drug flux significantly (9)."

propylene glycol, glycerol, ethers, alcohol, diethylene glycol monoethyl ether, urea, triglycerides, triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers, brij, sodium lauryl sulfate, tween, polysorbate, terpene, terpenoids, and combinations thereof.	From **page 1133** "**2-Pyrrolidone** and NMP were assessed in enhancing the topical bioavailability of a model steroid betamethasone-17-benzoate, using **dimethylisosorbide** (DMI) as the standard solvent." From **page 1133** "Pyrrolidones and their derivatives have great potential to be used as **transdermal permeation enhancers**. The most common **N-methyl-2-pyrrolidone** (NMP) has been used widely to enhance the skin absorption of many drugs, for example, insulin (19), ibuprofen, and flurbiprofen (20)." From **page 1133** "In general, **2-pyrrolidone enhances the transdermal permeation** of caffeine through polar routes of skin by increasing its diffusivity and reduces the passage through the nonpolar route by decreasing diffusivity and partitioning (28). One of its derivatives, N-dodecyl-2-pyrrolidone, has been shown to increase the permeability coefficient of hydrophilic methyl paraben about seven times while decreasing that of butyl paraben. Perturbation of stratum corneum lipid lamellae seems to be related to the enhancement of absorption of hydrophilic paraben (4). **Fatty acid esters** of N-(2-hydroxyethyl)-2-pyrrolidone (HEP) produced a twofold increase in permeation of hydrocortisone through mouse skin (29)." From **page 1134** "**Azone** (1-dodecylazacycloheptan-2-one) (Fig. 1) forms one of the major classes of percutaneous **permeation enhancers**." From **page 1134** "Azone (2%) in PG promoted the absorption of 5- FU by almost 100-fold, but in combination with **Tween** 20, the effect was less pronounced (33)." From **page 1134** "Azone is less effective than **oleic acid** in increasing the **transdermal permeation** of amino acids through hairless mouse skin (39). But, in the case of insulin, the enhancement is almost double that produced by dodecyl-l-pyroglutamate (19). Compared with **terpenes**, azone is the most effective penetration enhancer for low molecular weight heparin across human skin. The enhancing power of enhancers decreased in the order laurocapram. nerolidol. eucalyptol (11)." From **page 1135** "A large number of **fatty acids and their esters** have been used as **permeation enhancers**." From **page 1135** "**Capric acid, lauric acid,** and neodecanoic acid were tested for their activity on naloxone, testosterone, benzoic acid, indomethacin, 5-FU, and methotrexate (53). All three fatty acids increased the skin diffusivity of naloxone, testosterone, indomethacin, and 5-FU through human skin. **Capric acid** also increased the diffusivity of PG, suggesting that increased solvent penetration could also be involved as a mechanism for increased skin absorption of the drug."

	From **page 1135** "Oleic acid was found to be the most efficient enhancer for piroxicam, followed by **linoleic acid** (50). Sodium oleate was found to be a better **permeation enhancer** than oleyl oleate when tested on indomethacin and urea (10)." From **page 1136** "**Urea** analogues were effective in **enhancing the permeation** of 5-FU only when PG was used as a vehicle (68)." From **page 1136** "ALCOHOLS, **GLYCOLS**, AND GLYCERIDES" From **page 1136** "Of the **fatty alcohols** tested, lauryl alcohol increased the transdermal permeation of propranolol hydrochloride, timolol maleate, ibuprofen, acetaminophen, and 5-FU (50,71,72)." From **page 1136** "Various compounds of category N,N-dimethylamides also possess **penetration-enhancing** power and are also structurally related to sulfoxides. **N,N-Dimethylformamide** promotes absorption through the polar route by increasing both the diffusion and the partitioning of drug." From **page 1137** "Short-chain glycerides are also effective as **permeation enhancers** (e.g., TCP). For instance, glycerin tricaprylate (caprylic acid **triglyceride**) in combination with ethanol is used as a solvent system (22,52)" 21. U.S. Patent App. No. 2013/0253449 "NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANT-CONTAINING TRANSDERMAL PATCH" (Published September 26, 2013) From **paragraph [0031]** "For improving the transdermal absorption of the active ingredient, if desired, a transdermal absorption promoter may be incorporated. The transdermal absorption promoter may be any compound that has heretofore been recognized to exhibit an absorption-promoting effect in transdermal administration, and includes, for example, alkanolamines such as diisopropanolamine, triisopropanolamine, etc., fatty acids or their esters such as lauric acid, oleic acid, **isopropyl myristate**, octyldodecyl myristate, oleic acid glycerol monoester, hexadecyl isostearate, etc.; **alcohols or their esters or ethers** such as **oleyl alcohol**, propylene glycol, propylene glycol monocaprylate, polyethylene glycol monooleate, etc.; sorbitan esters or ethers such as sorbitan monolaurate, sorbitan monooleate, etc.; polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monopalmitate, etc.; phenol ethers such as polyoxyethylene nonylphenyl ether, polyoxyethylene octylphenyl ether, etc.; castor oil or hardened castor oil; ionic surfactants such as oleoyl sarcosine, lauryldimethylaminoacetate betaine, sodium laurylsulfate, etc.; nonionic surfactants such as polyoxyethylene oleyl ether, polyoxyethylene lauryl ether,

	dimethyllaurylamine oxide, etc.; alkylmethyl sulfoxides such as dimethyl sulfoxide, decylmethyl sulfoxide, etc.; pyrrolidones such as **2-pyrrolidone,** 1-methyl-2-pyrrolidone, etc.; azacycloalkanes such as 1-dodecylazacycloheptan-2-one, 1-geranylazacycloheptan-2-one, etc.; terpenes such as menthol, camphor, limonene, etc. Of those, preferred are myristates such as isopropyl myristate, sebacates such as diisopropyl sebacate, etc.; menthol, polyoxyethylene oleyl ether or **Polysorbate** 80™." From **paragraph [0038]** "The plasticizer includes petroleum oils such as paraffinic process oil, naphthenic process oil, aromatic process oil, etc.; liquid fatty acid esters such as **isopropyl myristate**, hexyl laurate, diethyl sebacate, diisopropyl sebacate, isopropyl linoleate, etc.; vegetable oils such as olive oil, camellia oil, castor oil, tall oil, peanut oil, etc.; glycerin, chlorobutanol, vinyl acetate resin, dimethylpolysiloxane-silicon dioxide mixture, D-sorbitol, middle-chain fatty acid triglyceride, **triacetin**, 2-pyrrolidone, phytosterol, propylene glycol, polyethylene glycol, Polysorbate 80™, glycerin monostearate, etc." 22. SMITH (1995) Percutaneous Penetration Enhancers. CRC-Press ISBN: 0849326052 From **page 7**

Table 1 Chemical Penetration Enhancers

Chemical Class	Examples	Ref.
Sulfoxides	Dimethylsulfoxide, decylmethylsulfoxide	17, 18
Alcohols	Alkanol: ethanol, propanol, butanol, pentanol, hexanol, octanol, nonanol, decanol, 2-butanol, 2-pentanol, benzyl alcohol	19, 20
	Fatty alcohol: caprylic, decyl, lauryl, 2-lauryl, myristyl, cetyl, stearyl, oleyl, linoleyl, linolenyl alcohol	21
Fatty acids	Linear: valeric, heptanoic, pelagonic, caproic, capric, lauric, myristic, stearic, oleic, caprylic	21, 22
	Branched: isovaleric, neopentanoic, neoheptanoic, neononanoic, trimethyl hexanoic, neodecanoic, isostearic	21, 22
Fatty acid esters	Aliphatic-isopropyl *n*-butyrate, isopropyl *n*-hexanoate, isopropyl *n*-decanoate, isopropyl myristate, isopropyl palmitate, octyldodecyl myristate	23
	Alkyl: ethyl acetate, butyl acetate, methyl acetate, methylvalerate, methylpropionate, diethyl sebacate, ethyl oleate	24
Polyols	Propylene glycol, polyethylene glycol, ethylene glycol, diethylene glycol, triethylene glycol, dipropylene glycol, glycerol, propanediol, butanediol, pentanediol, hexanetriol	25
Amides	Urea, dimethylacetamide, diethyltoluamide, dimethylformamide, dimethyloctamide, dimethyldecamide	21. 26
	Biodegradable cyclic urea: 1-alkyl-4-imidazolin-2-one	27
	Pyrrolidone derivatives: 1-methyl-2-pyrrolidone, 2-pyrrolidone, 1-lauryl-2-pyrrolidone, 1-methyl-4-carboxy-2-pyrrolidone, 1-hexyl-4-carboxy-2-pyrrolidone, 1-lauryl-4-carboxy-2-pyrrolidone, 1-methyl-4-methoxycarbonyl-2-pyrrolidone, 1-hexyl-4-methoxycarbonyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone, N-cyclohexylpyrrolidone, *N*-dimethylaminopropylpyrrolidone, *N*-cocoalkypyrrolidone, *N*-tallowalkylpyrrolidone	21, 28
	Biodegradable pyrrolidone derivatives: Fatty acid esters of *N*-(2-hydroxyethyl)-2-pyrrolidone	14
	Cyclic amides: 1-dodecylazacycloheptane-2-one (Azone®), 1-geranylazacycloheptan-2-one, 1-farnesylazacycloheptan-2-one, 1-geranylgeranylazacycloheptan-2-one, 1-(3,7-dimethyloctyl)azacycloheptan-2-one, 1-(3,7,11-trimethyldodecyl)azacyclohaptan-2-one, 1-geranylazacyclohexane-2-one, 1-geranylazacyclopentan-2,5-dione, 1-farnesylazacyclopentan-2-one	29, 30
	Hexamethylenelauramide and its derivatives	31
	Diethanolamine, triethanolamine	25
Surfactants	Anionic: Sodium laurate, sodium lauryl sulfate	32, 33
	Cationic: Cetyltrimethyl ammonium bromide, tetradecyltrimethylammonium bromide, benzalkonium chloride, octadecyltrimethylammonium chloride, cetylpyridinium chloride, dodecyltrimethylammonium chloride, hexadecyltrimethylammonium chloride	33–35
	Nonionics: Poloxamer (231, 182, 184), Brij (30, 93, 96, 99), Span (20, 40, 60, 80, 85), Tween (20, 40, 60, 80), Myrj (45, 51, 52), Miglyol 840	21, 36, 37
	Bile salts: Sodium cholate, sodium salts of taurocholic, glycholic, desoxycholic acids	38
	Lecithin	39

From **page 8**

	Table 1 (continued) Chemical Penetration Enhancers **Chemical Class** / **Examples** / **Ref.** Terpenes — Hydrocarbons: D-Limonene, α-pinene, β-carene; Alcohols: α-Terpineol, terpinen-4-ol, carvol; Ketones: Carvone, pulegone, piperitone, menthone; Oxides: Cyclohexene oxide, limonene oxide, α-pinene oxide, cyclopentene oxide, 1,8-cineole; Oils: Ylang ylang, anise, chenopodium, eucalyptus — 40, 41 Alkanones — *N*-heptane, *N*-octane, *N*-nonane, *N*-decane, *N*-undecane, *N*-dodecane, *N*-tridecane, *N*-tetradecane, *N*-hexadecane — 41 Organic acids — Salicylic acid and salicylates (including their methyl, ethyl, and propyl glycol derivatives), citric and succinic acid — 42
5. The pharmaceutical composition of claim 1 wherein said solvent is present, and is selected from the group consisting of methanol, ethanol, isopropyl alcohol, butanol, propanol, polyhydric alcohols, glycols, propylene glycol, polyethylene glycol, dipropylene glycol, hexylene glycol, butyene glycol, glycerine, derivative of glycols, pyrrolidone, N methyl 2-pyrrolidone, 2 pyrrolidone, sulfoxides, dimethyl sulfoxide, decymethylsulfoxide, dimethylisosorbide, mineral oils, vegetable oils, sesame oil water, polar solvents, semi polar solvents, non polar solvents, volatile chemicals, ethanol, propanol, ethyl acetate, acetone, methanol, dichloromethane, chloroform, toluene, IPA, hexane, acids, acetic acid, lactic acid, levulinic acid, bases,	1. U.S. Pat. App. Pub. No. 2011/0111029 "Composition for transdermal delivery of cationic active agents" (Published 12 May 2011) From **paragraph [0042]** "The term 'aqueous **solvent** mixture' generally includes liquid mixtures containing water and at least one further solvent which is generally selected from polar, water-miscible solvents such as, for instance, alcohols (e.g. **ethanol, isopropanol, glycerol**)." From **paragraph [0042]** "Alternatively, the solubility of the active agent can be achieved by changing its crystal modification. Examples of **solubility enhancers** include, without limitation, **water**; diols such as **propylene glycol** and **glycerol**; monoalcohols such as **ethanol, propanol and higher alcohols**; **dimethylsulfoxide (DMSO)**, **dimethylformamide**, N,N-dimethylacetamide, N-substituted alkyl-azacycloalkyl-2-ones." 21. U.S. Patent App. No. 2013/0253449 "NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANT-CONTAINING TRANSDERMAL PATCH" (Published September 26, 2013) From **paragraph [0031]** "For improving the transdermal absorption of the active ingredient, if desired, a transdermal absorption promoter may be incorporated. The transdermal absorption promoter may be any compound that has heretofore been recognized to exhibit an absorption-promoting effect in transdermal administration, and includes, for example, alkanolamines such as diisopropanolamine, triisopropanolamine, etc., fatty acids or their esters such as lauric acid, oleic acid, isopropyl myristate, octyldodecyl myristate, oleic acid glycerol monoester, hexadecyl isostearate, etc.; alcohols or their esters or ethers such as oleyl alcohol, propylene glycol, propylene glycol monocaprylate, polyethylene glycol monooleate, etc.; sorbitan esters or ethers such as sorbitan monolaurate, sorbitan monooleate, etc.; polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monopalmitate, etc.; phenol ethers such as polyoxyethylene nonylphenyl ether, polyoxyethylene octylphenyl ether, etc.; castor oil or hardened castor oil; ionic surfactants such as oleoyl sarcosine, lauryldimethylaminoacetate

pentane, dimethylformamide, butane, lipids, and combinations thereof.	betaine, sodium laurylsulfate, etc.; nonionic surfactants such as polyoxyethylene oleyl ether, polyoxyethylene lauryl ether, dimethyllaurylamine oxide, etc.; alkylmethyl sulfoxides such as dimethyl sulfoxide, decylmethyl sulfoxide, etc.; **pyrrolidones** such as 2-pyrrolidone, 1-methyl-2-pyrrolidone, etc.; azacycloalkanes such as 1-dodecylazacycloheptan-2-one, 1-geranylazacycloheptan-2-one, etc.; terpenes such as menthol, camphor, limonene, etc. Of those, preferred are myristates such as isopropyl myristate, sebacates such as diisopropyl sebacate, etc.; menthol, polyoxyethylene oleyl ether or Polysorbate 80™." From **paragraph [0038]** "The plasticizer includes petroleum oils such as paraffinic process oil, naphthenic process oil, aromatic process oil, etc.; liquid fatty acid esters such as isopropyl myristate, hexyl laurate, diethyl sebacate, diisopropyl sebacate, isopropyl linoleate, etc.; **vegetable oils such as olive oil, camellia oil, castor oil, tall oil, peanut oil, etc**.; **glycerin**, chlorobutanol, vinyl acetate resin, dimethylpolysiloxane-silicon dioxide mixture, **D-sorbitol,** middle-chain fatty acid triglyceride, triacetin, 2-pyrrolidone, phytosterol, propylene glycol, polyethylene glycol, Polysorbate 80™, glycerin monostearate, etc." From **paragraph [0045]** "There is no specific limitation on the transdermal patch of the invention and it can be produced according to any known production method. Preferred known production methods for the transdermal patch of the invention include a method that comprises, for example, dissolving an active ingredient and an adhesive and optionally a transdermal absorption promoter in an organic solvent of **ethyl acetate, hexane**, toluene or a mixed solvent thereof, then spreading the dissolved matter onto a release liner or a support, evaporating away the solvent from the dissolved matter to form a drug-containing layer, and thereafter sticking a support or a release liner thereto to give a transdermal patch; a method that comprises melting an active ingredient and an adhesive and optionally a transdermal absorption promoter under heat, then spreading the resulting melt onto a release liner or a support to form a drug-containing layer thereon, and thereafter sticking a support or a release liner thereto to give a transdermal patch, etc." 23. GRODOWSKA (2010) "Organic solvents in the pharmaceutical industry" Acta Poloniae Pharmaceutica – Drug Research. 67(1)3-12. From **page 5**

Table 2. Class 2 solvents (2)

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	20.0	2000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
N–methylpyrrolidone	48.4	4840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethylene	0.8	80
Xylene	21.7	2170

From **page 6**

Table 3. Solvents commonly used in chemical industry (6, 7)

Alcohols	Ketones	Halogenated solvents
Ethanol Butanol 2-Ethylhexanol Isobutanol Isopropanol Methanol Propanol Propylene glycol	Acetone Methyl ethyl ketone Methyl isobutyl ketone Methyl isopropyl ketone Mesityl oxide Trichloroethylene	Ethylene bromide Chloroform Ethylene chloride Dichloromethane Tetrachloroethylene Carbon tetrachloride
Amide	Ethers	Sulfur containing
Dimethylformamide	1,4-Dioxane Butyl ether Ethyl ether Diisopropyl ether Tetrahydrofuran *tert*-Butyl methyl ether	Dimethyl sulfoxide
Amine	Nitriles	Esters
Pyridyne	Acetonitrile	Ethyl acetate
Aliphatic hydrocarbons	Water	Aromatic hydrocarbons
Cyclohexane Hexane		Toluene Xylene

6. The pharmaceutical composition of claim 1 formulated as a liquid formulation,	6. W.I.P.O. Pat. App. No. 2018/135943 “PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES” (Published July 26, 2018)

transdermal semisolid formulation, or transdermal polymer matrix formulation, transdermal adhesive matrix formulation, film forming gel formulation, film forming spray formulation.	From **page 14 paragraph 2** "Also encompassed are dosage forms for **transdermal administration**, including creams, lotions, aerosols and/or emulsions. These dosage forms may be included in **transdermal patches of the matrix or reservoir type**, which are generally known in the art. Pharmaceutical preparations dose (for the cannabinoid, terpene and/or the psilocybin/psilocin) may be conveniently prepared in unit dosage form, according to standard procedures of pharmaceutical formulation. The quantity of active compound(s) per unit dose may be varied according to the nature of the active compound and the intended dosage regime. Generally an effective amount shall be used, which may be within the range of from **0.01 mg to 5000 mg, preferably 0.01-4000 mg, 0.1-3000 mg, 1-2500, 5-1000, or 10-100 mg** per unit dose (for the at least one cannabinoid and/or the at least one terpene and/or the at **least one psilocybin and/or the at least one psilocin**)." 9. U.S. Pat. App. No. 2020/0085816 "LSD FOR THE TREATMENT OF ALZHEIMER'S DISEASE" (Published March 19, 2020) From **claim 40** "A **transdermal delivery system** comprising a pharmaceutically effective amount of a neuronal growth factor, **2 µg to 30 µg** of **lysergic acid diethylamide** or a pharmaceutically acceptable salt thereof, and a naturally occurring gum." From **paragraph [0059]** "There are several approaches for providing rate control over the release and **transdermal** permeation of a drug, including: membrane-moderated systems, **adhesive diffusion-controlled systems**, **matrix dispersion-type systems, and microreservoir systems**. A controlled release percutaneous and/or topical composition may be obtained by using a suitable mixture of the above-mentioned approaches." From **paragraph [0060]** "In a membrane-moderated system, the lysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, is present in a reservoir which is totally encapsulated in a shallow compartment molded from a drug-impermeable laminate, such as a metallic plastic laminate, and a rate-controlling polymeric membrane such as a microporous or a non-porous polymeric membrane (e.g., ethylene-vinyl acetate copolymer). The lysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, is only released through the rate-controlling polymeric membrane. In the drug reservoir, the lysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, substance may either be dispersed in a **solid polymer matrix** or suspended in a **viscous liquid medium** such as silicone fluid. On the external surface of the polymeric membrane, a thin layer of an adhesive polymer is applied to achieve an intimate contact of the transdermal system with the skin surface. The adhesive polymer is preferably a hypoallergenic polymer that is compatible with the drug."

	11. W.I.P.O. Pat. App. No. 2021/003467 "METERED DOSING COMPOSITIONS AND METHODS OF USE OF PSYCHEDELIC COMPOUNDS" (Published January 7, 2021; provisional priority date July 4, 2019) From **page 5** "Some of the examples of the methods of use are for particular conditions or therapeutic effect are: **topical fungal extracts** applied behind the ear could help with motion sickness; nasal and inhaled preparations could help with psychotherapy analysis with a small fast-acting dose for psychotherapy session; and sublingual preparations may have more of a muscle relaxing effect than orally administered versions." From **page 7** "Disclosed are multiple **metered dosing formulations for various corresponding methods of delivery of psychoactive plant and/or fungal compounds for** inhalation, sublingual, nasal, oral (including capsules, gel caps, and tinctures) and **topical use**, which is made up of the following components 1) at least one active compound isolated from psychoactive plants or fungi; b) one of the methods of delivery; and c) a base solution that is appropriate for the chosen method of delivery of the active compound. More specifically the psychoactive plant and/or fungi used will include but not be limited to fundi containing **psilocybin**, baeocystin, and/or **psilocin** and/or plants containing mescaline aka peyote aka 3,4,5-trimethoxyphenethylamine aka DMT." 15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 1** "A method of managing a neurological condition or one or more symptoms thereof in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising: a) a therapeutically effective amount of one or more 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof; and b) a pharmaceutically acceptable excipient wherein the therapeutically effective amount of the **5HT receptor agonist o**r a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to the subject in need thereof **in an amount insufficient to provide an adverse side effect, such as hallucinogenic experience.**" From **claim 13** "The method of any one of the preceding claims, wherein the **5HT receptor agonist** is **psilocybin** or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof."

	From **claim 14** "The method of any one of claims 1-12, wherein the 5HT receptor agonist is **psilocin** or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof." From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a **spray**, aerosol, mist, nebulae, ointment, cream, **gel,** paste, salve, solution, suspension, tincture, **patch**, and atomized vapor."
7. The pharmaceutical composition of claim 1 which is formulated as a transdermal patch.	1. U.S. Pat. App. Pub. No. 2011/0111029 "Composition for transdermal delivery of cationic active agents" (Published 12 May 2011) From **claim 1** "A self-adhesive **transdermal patch** composition for iontophoretic transdermal delivery of at least one cationic active agent or a salt thereof, comprising: said at least one cationic active agent or a salt thereof, wherein the total content of said at least one cationic active agent or a salt thereof amounts to 0.1 to 20%-wt. relative to the total weight of the transdermal patch composition, and wherein said at least one cationic active agent is selected from the group consisting of cationic indole compounds and salts thereof;" From **claim 9** "The self-adhesive **transdermal patch** composition according to claim 1, wherein said cationic indole compounds comprise N-dimethyltryptamine and **psilocin**, and pharmacologically acceptable salts of said cationic indole compounds." 6. W.I.P.O. Pat. App. No. 2018/135943 "PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES" (Published July 26, 2018) From **page 14 paragraph 2** "Also encompassed are dosage forms for **transdermal administration**, including creams, lotions, aerosols and/or emulsions. These dosage forms may be included in **transdermal patches of the matrix or reservoir type**, which are generally known in the art. Pharmaceutical preparations dose (for the cannabinoid, terpene and/or the psilocybin/psilocin) may be conveniently prepared in unit dosage form, according to standard procedures of pharmaceutical formulation. The quantity of active compound(s) per unit dose may be varied according to the nature of the active compound and the intended dosage regime. Generally an effective amount shall be used, which may be within the range of from **0.01 mg to 5000 mg, preferably 0.01-4000 mg, 0.1-3000 mg, 1-2500, 5-1000, or 10-100 mg** per unit dose (for the at least one cannabinoid and/or the at least one terpene and/or the at **least one psilocybin and/or the at least one psilocin**)."
8. The pharmaceutical composition of claim 1	1. U.S. Pat. App. Pub. No. 2011/0111029 "Composition for transdermal delivery of cationic active agents" (Published 12 May 2011)

formulated as a transdermal patch, wherein the transdermal patch is selected from the group such as to reservoir patch, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, extended release transdermal film a liquid reservoir system, a microreservoir patch, a matrix patch, a pressure sensitive adhesive patch, a film forming gel, a film forming spray, a micro-dosing patch, a mucoadhesive patch, and combinations thereof.	From **claim 1** "A **self-adhesive transdermal patch** composition for iontophoretic transdermal delivery of at least one cationic active agent or a salt thereof, comprising: said at least one cationic active agent or a salt thereof, wherein the total content of said at least one cationic active agent or a salt thereof amounts to 0.1 to 20%-wt. relative to the total weight of the transdermal patch composition, and wherein said at least one cationic active agent is selected from the group consisting of cationic indole compounds and salts thereof;" From **claim 9** "The self-adhesive **transdermal patch** composition according to claim 1, wherein said cationic indole compounds comprise N-dimethyltryptamine and **psilocin**, and pharmacologically acceptable salts of said cationic indole compounds." From **claim 14** "The composition according to claim 1, wherein said composition is a **liquid or aqueous composition**." From **claim 30** "Use of a composition according to claim 1 as a component of a **transdermal patch**." From **claim 45** "The use of a composition according to claim 30 as a component of an active **substance reservoir** of a transdermal patch." 6. W.I.P.O. Pat. App. No. 2018/135943 "PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES" (Published July 26, 2018) From **page 14 paragraph 2** "Also encompassed are dosage forms for **transdermal administration**, including creams, lotions, aerosols and/or emulsions. These dosage forms may be included in **transdermal patches of the matrix or reservoir type**, which are generally known in the art. Pharmaceutical preparations dose (for the cannabinoid, terpene and/or the psilocybin/psilocin) may be conveniently prepared in unit dosage form, according to standard procedures of pharmaceutical formulation. The quantity of active compound(s) per unit dose may be varied according to the nature of the active compound and the intended dosage regime. Generally an effective amount shall be used, which may be within the range of from 0.01 mg to 5000 mg, preferably 0.01-4000 mg, 0.1-3000 mg, 1-2500, 5-1000, or 10-100 mg per unit dose (for the at least one cannabinoid and/or the at least one terpene and/or the at least one **psilocybin and/or the at least one psilocin**)." 9. U.S. Pat. App. No. 2020/0085816 "LSD FOR THE TREATMENT OF ALZHEIMER'S DISEASE" (Published March 19, 2020)

	From **claim 40** "A **transdermal delivery system** comprising a pharmaceutically effective amount of a neuronal growth factor, **2 µg to 30 µg** of **lysergic acid diethylamide** or a pharmaceutically acceptable salt thereof, and a naturally occurring gum." From **section [0061]** "In an **adhesive diffusion-controlled system**, **a reservoir of the lysergic acid diethylamide**, or a pharmaceutically acceptable salt thereof, is formed by directly dispersing the drug in an adhesive polymer and then spreading the adhesive containing the drug onto a flat sheet of substantially drug-impermeable metallic plastic backing to form a thin drug reservoir layer." 15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 1** "A method of managing a neurological condition or one or more symptoms thereof in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising: a) a therapeutically effective amount of one or more 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof; and b) a pharmaceutically acceptable excipient wherein the therapeutically effective amount of the **5HT receptor agonist o**r a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to the subject in need thereof **in an amount insufficient to provide an adverse side effect, such as hallucinogenic experience.**" From **claim 4** "The method of any one of the preceding claims, wherein the **5HT receptor agonist** or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is present in an amount of from about **0.1 mg to about 2 mg**." From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a **spray**, aerosol, mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From **paragraph [0123]** "Often, **mucoadhesive drug delivery systems** interact with the mucus layer covering the mucosal epithelial surface to increase the residence time of the dosage form at the site of absorption. In some instances, a **composition or formulation provided herein comprises a mucoadhesive agent**, such as, by way of non-limiting example, a soluble PVP, a carbopol, a crosslinked poly(acrylic acid) (e.g. Carbopol 974P), a carbomer homopolymer, a carbomer copolymer, a water-swellable, but

	water-insoluble, fibrous, cross-linked carboxy-functional polymer, a mucoadhesive polysaccharide (e.g. a hydrophilic polysaccharide gum), one or more maltodextrin, alginate, a cross-linked aliginate gum gel, a water-dispersible polycarboxylated vinyl polymer. In some embodiments, the mucoadhesive agent is a carbopol."
9. The pharmaceutical composition of claim 1 further comprising carriers or ingredients in effective amount selected from the group consisting of solvents, gelling agents, polymers, pressure sensitive adhesive, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, tackifier, diluetns, surfactants, antioxidants, oxidants, and combinations thereof.	1. U.S. Pat. App. Pub. No. 2011/0111029 "Composition for transdermal delivery of cationic active agents" (Published 12 May 2011) From **claim 1** "A self-adhesive **transdermal patch** composition for iontophoretic transdermal delivery of at least one cationic active agent or a salt thereof, comprising: said at least one cationic active agent or a salt thereof, wherein the total content of said at least one cationic **active agent or a salt thereof amounts to 0.1 to 20%-wt**. relative to the total weight of the transdermal patch composition, and wherein said at least one cationic active agent is selected from the group consisting of cationic indole compounds and salts thereof;" From **claim 13** "The self-adhesive transdermal patch composition according to claim 1, wherein said one or more additive additives is/are selected from the group consisting of **solubility enhancers**, **skin permeation enhancers** and antimicrobial agents." From **paragraph [0100]** "As described above, the compositions of the present invention are formulated as aqueous compositions, particularly as **hydrogel compositions**. In a further embodiment, the said aqueous compositions have a pH of 3 to 8, preferably 5.5 to 7, or most preferably about 6." From **paragraph [0101]** "Generally, it is preferred to adjust and maintain the pH in said water-containing compositions such they do not substantially affect the ph of the skin, when the compositions are applied to the skin (e.g. during transdermal or iontophoretic administration). In a further embodiment, the pH of the skin changes about ±4.0 or less, about ±3.5 or less, about ±3.0 or less, about ±2.5 or less, about ±2.0 or less, about ±1.5 or less, about ±1.0 or less, or about ±0.5 or less. Substances and **buffers suitable for pH adjustment** are known to the skilled person." From **paragraph [0144]** "The anodic reservoir (3) was prepared by applying a solution of said cationic active agent (4%-wt.) in polyamine (**acrylic copolymer**; EUDRAGIT® E 100) onto a non-woven viscose material (coating weight per unit area: 0.1 g/cm2)." 15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE,

	BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **paragraph [0079]** "In some embodiments, the pharmaceutically acceptable excipient is selected from the group consisting of fillers, binders, **suspending agents**, disintegrants, lubricants, and combinations thereof." From **paragraph [0149]** "In some instances, the pharmaceutical formulations further include **diluent** which are used to stabilize a 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof because they provide a more stable environment." From **paragraph [0153]** "**Plasticizers** include compounds used to soften the microencapsulation material or film coatings to make them less brittle. Suitable plasticizers include, e.g. PEGs such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, triethyl cellulose and triacetin. Plasticizers also function as **dispersing agents** or wetting agents." From **paragraph [0155]** "**Stabilizers** include compounds such as any **antioxidation agents, buffers**, acids, preservatives and any combination thereof." From **page [0157]** "**Surfactants** include compounds such as sodium lauryl sulfate, sodium docusate, Tween 60 or 80, triacetin, vitamin E TPGS, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g. Pluronic® (BASF), and any combination thereof. Additional surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g. polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g. octoxynol 10, octoxynol 40. Sometimes, surfactants are included to enhance physical stability or for other purposes." 21. U.S. Patent App. No. 2013/0253449 "NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANT-CONTAINING TRANSDERMAL PATCH" (Published September 26, 2013) From **paragraph [0037]** "If desired, the **transdermal patch** of the invention may contain any other additional ingredients such as a **plasticizer**, a crosslinking agent, a colorant, a UV absorbent, **a tackifier**, etc.
10. The pharmaceutical composition of claim 1 indicated for the treatment and/or	2. CARHART-HARRIS (2018) "Psilocybin with psychological support for treatment-resistant depression: six-month follow-up" Psychopharmacology (Berl). 235(2):399-408.

prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient.	From **page 399** "Here, we report on safety and efficacy outcomes for up to 6 months in an open-label trial of **psilocybin** for **treatment-resistant depression**." From **page 399** "Twenty patients (six females) with (mostly) severe, unipolar, treatment-resistant **major depression** received two oral doses of **psilocybin** (10 and 25 mg, 7 days apart) in a supportive setting." From **page 399** "Psilocybin has shown promise in the treatment of **obsessive compulsive disorder** (Moreno et al. 2006), **alcohol** (Bogenschutz et al. 2015) and **tobacco addiction** (Johnson et al. 2014) and **anxiety related to terminal diagnoses** (Griffiths et al. 2016; Ross et al. 2016; Grob et al. 2011)." 3. ANDERSSON (2017) "Psychoactive substances as a last resort—a qualitative study of self-treatment of migraine and cluster headaches" Harm Reduction Journal. 14(1):1-10. From **page 1** "Primarily, **psilocybin, lysergic acid diethylamide, and related psychedelic tryptamines** were reportedly **effective for both prophylactic and acute treatment of cluster headache and migraines**." 4. CAMERON (2020) "Psychedelic Microdosing: Prevalence and Subjective Effects" Journal of Psychoactive Drugs. 52(2): 113–122. From **page 113** "Psychedelic compounds, such as **lysergic acid diethylamide (LSD)**, **psilocybin**, and N,N-dimethyltryptamine (DMT), have been used for centuries by many cultures for religious and/or medicinal reasons (Ott 1993). More recently, they have shown promise as experimental therapeutics in the clinic for **treating depression, anxiety, and substance use disorder**" 5. FADIMAN (2018) "Might Microdosing Psychedelics Be Safe and Beneficial? An Initial Exploration" Journal of Psychoactive Drugs. 51(2):118-122. From **page 120** "Many participants reported that they wanted to microdose for their diagnosed ADHD, or for their self-diagnosed attention issues, or simply to be more productive or creative. Most reported that **microdosing** was helpful for their productivity, as they procrastinated less and were able to see the parts of a project through to completion. Though **LSD or psilocybin** may affect different neuroreceptors than other stimulant therapies for **ADHD**, they are still stimulants, and perhaps the change in attention was due to stimulation, no matter what receptor."

	6. W.I.P.O. Pat. App. No. 2018/135943 "PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES" (Published July 26, 2018) From **claim 15** "**Psilocybin and/or psilocin** in combination with at least one cannabinoid and/or at least one terpene for use in the prevention and/or treatment of **ADHD**, ADD, anorexia nervosa, antisocial personality disorder, autism, **addiction**, avoidant personality disorder, bipolar disorder, bulimia nervosa, borderline personality disorder, catatone schizophrenia, chronic motor or vocal tic disorder, conversion disorder, cyclothymia, dependent personality disorder, delier, dementia, depersonalization disorder, **depression**, Dhat syndrome, dissociative amnesia, dissociative fugue, dissociative identity disorder, dissociative disorder, dissociative disorder, not otherwise specified, dysthymic disorder, Da Costa's syndrome, ephobophilia, exhibitionism, **generalized anxiety disorder**, grandiose delusions, hypochondria, hoarding disorder, intermittent explosive disorder, jealousy, kleptomania, KICiver-Bucy syndrome, maternity psychosis, mental retardation, monomania, MCinchhausen syndrome, misophony, narcissistic personality disorder, **obsessive-compulsive disorder**, oniomania, organic personality disorder, phobia, paranoid personality disorder, paranoid delusions, passive-aggressive personality, pathological gambling, pathological lying, personality disorder not otherwise defined (PDNOS), pervasive developmental disorder, pica, pain disorder, post encephalitic syndrome, postpartum depression, posttraumatic stress disorder, psychosis, psychotic disorder due to substance use, pyromania, querulant delusions, ruminational disorder, schizophrenia, schizoaffective disorder, schizoid, personality disorder, schizotypal personality disorder, separation anxiety, social phobia, somatisation disorder, somatic delusion, somatoform disorder, syndrome of Capgras, syndrome of Cotard, syndrome of Ganser, syndrome of Gilles de la Tourette, selective mutism, theatrical personality disorder, trichotillomania, or undifferentiated somatoform disorder" From **page 14 paragraph 2** "Also encompassed are dosage forms for **transdermal administration**, including creams, lotions, aerosols and/or emulsions. These dosage forms may be included in transdermal patches of the matrix or reservoir type, which are generally known in the art. Pharmaceutical preparations dose (for the cannabinoid, terpene and/or the psilocybin/psilocin) may be conveniently prepared in unit dosage form, according to standard procedures of pharmaceutical formulation. The quantity of active compound(s) per unit dose may be varied according to the nature of the active compound and the intended dosage regime. Generally an effective amount shall be used, which may be within the range of from 0.01 mg to 5000 mg, preferably 0.01-4000 mg, 0.1-3000 mg, 1-2500, 5-1000, or 10-100 mg per unit dose (for the at least one cannabinoid and/or the at least one terpene and/or the at least one psilocybin and/or the at least one psilocin)."

	7. ALPER (2008) "The ibogaine medical subculture" Journal of Ethnopharmacology. 115(1):9-24 From **page 9** "**Ibogaine** is a naturally occurring psychoactive indole alkaloid that is used to treat **substance-related disorders** in a global medical subculture, and is of interest as an ethnopharmacological prototype for experimental investigation and possible rational pharmaceutical development." 8. GLICK (2006) "18-Methoxycoronaridine (18-MC) and Ibogaine: Comparison of Antiaddictive Efficacy, Toxicity, and Mechanisms of Action" Annals of the New York Academy of Sciences. 914(1)369-386. "Like **ibogaine** (40 mg/kg), 18-MC (40 mg/kg) **decreases** the intravenous self-administration of **morphine and cocaine** and the oral self-administration of **ethanol and nicotine** in rats; unlike ibogaine, 18-MC does not affect responding for a nondrug reinforcer (water)." 15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 1** "A method of managing a neurological condition or one or more symptoms thereof in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising: a) a therapeutically effective amount of one or more 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof; and b) a pharmaceutically acceptable excipient wherein the therapeutically effective amount of the **5HT receptor agonist o**r a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to the subject in need thereof **in an amount insufficient to provide an adverse side effect, such as hallucinogenic experience.**" From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a spray, aerosol, mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From **claim 39** "The method of any one of the preceding claims, wherein the neurological condition is an addictive disorder." From **claim 40** "The method of claim 39, wherein the **addictive disorder** is **alcohol abuse, substance abuse, smoking,** or obesity."

	From **claim 43** "The method of any one of claims 1-38, wherein the neurological condition is **depression**, bipolar disorder, **anxiety**, social anxiety, **post-traumatic stress disorder (PTSD)**, panic disorder, phobia, schizophrenia, psychopathy, or antisocial personality disorder." From **claim 44** "The method of any one of claims 1-38, wherein the neurological condition is an impulsive disorder." From **claim 45** "The method of claim 44, wherein the impulsive disorder is **attention deficit hyperactivity disorder (ADHD), attention deficit disorder (ADD)**, Tourette's syndrome or autism." From **claim 46** "The method of any one of claims 1-38, wherein the neurological condition is a compulsive disorder." From **claim 47** "The method of claim 46, wherein the compulsive disorder is **obsessive compulsive disorder (OCD)**, gambling, or aberrant sexual behavior."
11. The pharmaceutical composition of claim 1 which is formulated as the transdermal formulation which can be administered in a dosage regimen selected from the group consisting of once daily, twice daily, three times a day, once in 1-8 hrs, once in 1-24 hrs, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in a 8 to about 13 days, once in two weeks, once in 15 days to about 30 days.	9. U.S. Pat. App. No. 2020/0085816 "LSD FOR THE TREATMENT OF ALZHEIMER'S DISEASE" (Published March 19, 2020) From **claim 40** "A **transdermal delivery system** comprising a pharmaceutically effective amount of a neuronal growth factor, **2 µg to 30 µg of lysergic acid diethylamide** or a pharmaceutically acceptable salt thereof, and a naturally occurring gum." From **claim 43** "A method of treating Alzheimer's disease in a subject, said method comprising administering to the subject a pharmaceutical composition comprising lysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, in an amount sufficient to treat said Alzheimer's disease." From **claim 52** "The method of claim 43, wherein said lysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, is administered in a dosing regimen from **once daily to once weekly.**" 15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 1** "A method of managing a neurological condition or one or more symptoms thereof in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising:

	a) a therapeutically effective amount of one or more 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof; and b) a pharmaceutically acceptable excipient wherein the therapeutically effective amount of the **5HT receptor agonist o**r a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to the subject in need thereof **in an amount insufficient to provide an adverse side effect, such as hallucinogenic experience.**" From **claim 30** "The method of any one of the preceding claims, wherein the pharmaceutical composition is administered to a subject in need thereof **once a day, every alternate day, three times a week, twice a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month or three times per month.** From **claim 31** "The method of any one of the preceding claims, wherein the pharmaceutical composition is administered **about once a day.**" From **paragraph [0138]** "These pharmaceutical compositions might also be formulated for transmucosal administration, buccal administration, for administration by inhalation, for parental administration, for **transdermal administration**, and rectal administration"
12. The pharmaceutical composition of claim 1 which may be formulated as microneedles.	12. W.I.P.O. Pat. App. No. 2020/123625 "Co-crystals, method and apparatus for forming the same" (Published June 18, 2020; provisional priority date December 11, 2018) From **claim 14** "The method of any one of claims 1 -13, wherein the organic compound is selected from the group consisting of caffeine, carbamazepine, 5-methoxy sulfadiazine, ethenzamide, nalidixic acid, isoniazid, furosemide, sulfadimidine, celecoxib, temozolamide, piroxicam, **tryptamine**, chlorzoxazone, p-coumaric, itraconazole, fluoxetine, telaprevir, sildenafil, theophylline, aceclofenac, 5-nitrouracil, indomethacin, aripiprazole, and atorvastatin, or a mixture thereof." From **claim 38** "The method of any one of claims 1 -37, wherein the substrate is a medical device." From **claim 39** "The method of claim 38, wherein the medical device is selected from the group consisting of a stent, needle, **microneedle**, probe, syringe, cannula, catheter, sponge, clip, mesh, bandage, gauze, dressing, tape, swab, burn dressing, staple, implant, contact lens, medical tubing, **adhesive patches**, artificial tissue, endoscopic device." From **paragraph [0073]** "The disclosure also provides a co-crystal-coated needle (see e.g. FIG. 7) coating a needle or **microneedle patch** with a co-crystal prior to insertion into the skin, rather that direct injection, can enable

	a new route of treatment that does not require deep insertion, alleviating patient discomfort.”
13. The pharmaceutical composition of claim 1 wherein said psilocybin, psilocin, lysergic acid diethylamine (LSD), and/or ibogaine, derivatives of these compounds, and combinations thereof is produced by a natural route or a synthetic route.	1. U.S. Pat. App. Pub. No. 2011/0111029 “Composition for transdermal delivery of cationic active agents” (Published 12 May 2011) From **claim 1** “A self-adhesive **transdermal patch** composition for iontophoretic transdermal delivery of at least one cationic active agent or a salt thereof, comprising: said at least one cationic active agent or a salt thereof, wherein the total content of said at least one cationic **active agent or a salt thereof amounts to 0.1 to 20%-wt**. relative to the total weight of the transdermal patch composition, and wherein said at least one cationic active agent is selected from the group consisting of cationic indole compounds and salts thereof;” From **claim 9** “The self-adhesive **transdermal patch** composition according to claim 1, wherein said cationic indole compounds comprise N-dimethyltryptamine and **psilocin**, and pharmacologically acceptable salts of said cationic indole compounds.” 6. W.I.P.O. Pat. App. No. 2018/135943 “PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES” (Published July 26, 2018) From **page 14 paragraph 2** “Also encompassed are dosage forms for **transdermal administration**, including creams, lotions, aerosols and/or emulsions. These dosage forms may be included in **transdermal patches of the matrix or reservoir type**, which are generally known in the art. Pharmaceutical preparations dose (for the cannabinoid, terpene and/or the psilocybin/psilocin) may be conveniently prepared in unit dosage form, according to standard procedures of pharmaceutical formulation. The quantity of active compound(s) per unit dose may be varied according to the nature of the active compound and the intended dosage regime. Generally an effective amount shall be used, which may be within the range of from 0.01 mg to 5000 mg, preferably 0.01-4000 mg, 0.1-3000 mg, 1-2500, 5-1000, or 10-100 mg per unit dose (for the at least one cannabinoid and/or the at least one terpene and/or the at **least one psilocybin and/or the at least one psilocin**).” 9. U.S. Pat. App. No. 2020/0085816 “LSD FOR THE TREATMENT OF ALZHEIMER'S DISEASE” (Published March 19, 2020) From **claim 40** “A **transdermal delivery system** comprising a pharmaceutically effective amount of a neuronal growth factor, **2 µg to 30 µg of lysergic acid diethylamide** or a pharmaceutically acceptable salt thereof, and a naturally occurring gum.”

	16. W.I.P.O. Pat. App. No. 2008/039179 "COMPOSITIONS FOR THE TREATMENT OF HEPATITIS C AND METHODS FOR USING COMPOSITIONS FOR THE TREATMENT OF HEPATITIS C" (Published April 3, 2008) From **claim 7** "A method for treating hepatitis C or hepatitis C-related complications which comprises administering a pharmaceutically effective amount of a composition comprising **ibogaine**, ibogamine, tabernanthine, their nontoxic salts and/or the converted principal metabolite noribogaine to a human or mammal." From **claim 9** "The method of claim 7, wherein said composition is administered in a tablet, capsule, pharmacological carrier, parenteral solution, **transdermal technology**, suppository, or liquid."
14. The pharmaceutical composition of claim 1 co-administered with at least one additional active agent.	9. U.S. Pat. App. No. 2020/0085816 "LSD FOR THE TREATMENT OF ALZHEIMER'S DISEASE" (Published March 19, 2020) From **claim 40** "A **transdermal delivery system** comprising a pharmaceutically effective amount of a **neuronal growth factor**, 2 μg to 30 μg of **lysergic acid diethylamide** or a pharmaceutically acceptable salt thereof, and a naturally occurring gum." From **claim 43** "A method of treating Alzheimer's disease in a subject, said method comprising **administering to the subject a pharmaceutical composition comprising lysergic acid diethylamide**, or a pharmaceutically acceptable salt thereof, in an amount sufficient to treat said Alzheimer's disease." From **claim 54** "The method of claim 43, **further comprising administering to said subject a neuronal growth factor, a neuronal survival factor, a neuronal trophic factor, a cholinergic modulator, an adrenergic modulator, a nonadrenergic modulator, a dopaminergic modulator, a glutaminergic modulator or an agent that modulates PKC, PKA, GABA, NMDA, cannabinoid, AMPA, kainite modulator, phosphodiesterase (PDE), CREB or nootropic pathways** within 1-30 days of administering said lysergic acid diethylamide, or a pharmaceutically acceptable salt thereof."
15. A method for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive	2. CARHART-HARRIS (2018) "Psilocybin with psychological support for treatment-resistant depression: six-month follow-up" Psychopharmacology (Berl). 235(2):399-408. From **page 399** "Here, we report on safety and efficacy outcomes for up to 6 months in an open-label trial of **psilocybin** for **treatment-resistant depression**."

disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient comprising: selecting a patient in need of treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress; topically applying the transdermal pharmaceutical composition of claim 1, wherein said patent experiences no or minimal hallucinogenic effects from said transdermal pharmaceutical composition.	From **page 399** "Twenty patients (six females) with (mostly) severe, unipolar, treatment-resistant **major depression** received two oral doses of **psilocybin** (10 and 25 mg, 7 days apart) in a supportive setting." From **page 399** "Psilocybin has shown promise in the treatment of **obsessive compulsive disorder** (Moreno et al. 2006), **alcohol** (Bogenschutz et al. 2015) and **tobacco addiction** (Johnson et al. 2014) and **anxiety related to terminal diagnoses** (Griffiths et al. 2016; Ross et al. 2016; Grob et al. 2011)." 3. ANDERSSON (2017) "Psychoactive substances as a last resort—a qualitative study of self-treatment of migraine and cluster headaches" Harm Reduction Journal. 14(1):1-10. From **page 1** "Primarily, **psilocybin, lysergic acid diethylamide, and related psychedelic tryptamines** were reportedly **effective for both prophylactic and acute treatment of cluster headache and migraines**." 4. CAMERON (2020) "Psychedelic Microdosing: Prevalence and Subjective Effects" Journal of Psychoactive Drugs. 52(2): 113–122. From **page 113** "Psychedelic compounds, such as **lysergic acid diethylamide (LSD)**, **psilocybin**, and N,N-dimethyltryptamine (DMT), have been used for centuries by many cultures for religious and/or medicinal reasons (Ott 1993). More recently, they have shown promise as experimental therapeutics in the clinic for **treating depression, anxiety, and substance use disorder**" 5. FADIMAN (2018) "Might Microdosing Psychedelics Be Safe and Beneficial? An Initial Exploration" Journal of Psychoactive Drugs. 51(2):118-122. From **page 120** "Many participants reported that they wanted to microdose for their diagnosed ADHD, or for their self-diagnosed attention issues, or simply to be more productive or creative. Most reported that **microdosing** was helpful for their productivity, as they procrastinated less and were able to see the parts of a project through to completion. Though **LSD or psilocybin** may affect different neuroreceptors than other stimulant therapies for **ADHD**, they are still stimulants, and perhaps the change in attention was due to stimulation, no matter what receptor." 6. W.I.P.O. Pat. App. No. 2018/135943 "PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES" (Published July 26, 2018) From **claim 15** "**Psilocybin and/or psilocin** in combination with at least one cannabinoid and/or at least one terpene for use in the prevention and/or

	treatment of **ADHD**, ADD, anorexia nervosa, antisocial personality disorder, autism, **addiction**, avoidant personality disorder, bipolar disorder, bulimia nervosa, borderline personality disorder, catatone schizophrenia, chronic motor or vocal tic disorder, conversion disorder, cyclothymia, dependent personality disorder, delier, dementia, depersonalization disorder, **depression**, Dhat syndrome, dissociative amnesia, dissociative fugue, dissociative identity disorder, dissociative disorder, dissociative disorder, not otherwise specified, dysthymic disorder, Da Costa's syndrome, ephobophilia, exhibitionism, **generalized anxiety disorder**, grandiose delusions, hypochondria, hoarding disorder, intermittent explosive disorder, jealousy, kleptomania, KICiver-Bucy syndrome, maternity psychosis, mental retardation, monomania, MCinchhausen syndrome, misophony, narcissistic personality disorder, **obsessive-compulsive disorder**, oniomania, organic personality disorder, phobia, paranoid personality disorder, paranoid delusions, passive-aggressive personality, pathological gambling, pathological lying, personality disorder not otherwise defined (PDNOS), pervasive developmental disorder, pica, pain disorder, post encephalitic syndrome, postpartum depression, posttraumatic stress disorder, psychosis, psychotic disorder due to substance use, pyromania, querulant delusions, ruminational disorder, schizophrenia, schizoaffective disorder, schizoid, personality disorder, schizotypal personality disorder, separation anxiety, social phobia, somatisation disorder, somatic delusion, somatoform disorder, syndrome of Capgras, syndrome of Cotard, syndrome of Ganser, syndrome of Gilles de la Tourette, selective mutism, theatrical personality disorder, trichotillomania, or undifferentiated somatoform disorder" From **page 14 paragraph 2** "Also encompassed are dosage forms for **transdermal administration**, including creams, lotions, aerosols and/or emulsions. These dosage forms may be included in transdermal patches of the matrix or reservoir type, which are generally known in the art. Pharmaceutical preparations dose (for the cannabinoid, terpene and/or the psilocybin/psilocin) may be conveniently prepared in unit dosage form, according to standard procedures of pharmaceutical formulation. The quantity of active compound(s) per unit dose may be varied according to the nature of the active compound and the intended dosage regime. Generally an effective amount shall be used, which may be within the range of from **0.01 mg to 5000 mg, preferably 0.01-4000 mg, 0.1-3000 mg, 1-2500, 5-1000, or 10-100 mg** per unit dose (for the at least one cannabinoid and/or the at least one terpene and/or the at **least one psilocybin and/or the at least one psilocin**)." 7. ALPER (2008) "The ibogaine medical subculture" Journal of Ethnopharmacology. 115(1):9-24 From **page 9** "**Ibogaine** is a naturally occurring psychoactive indole alkaloid that is used to treat **substance-related disorders** in a global

	medical subculture, and is of interest as an ethnopharmacological prototype for experimental investigation and possible rational pharmaceutical development." 8. GLICK (2006) "18-Methoxycoronaridine (18-MC) and Ibogaine: Comparison of Antiaddictive Efficacy, Toxicity, and Mechanisms of Action" Annals of the New York Academy of Sciences. 914(1)369-386. "Like **ibogaine** (40 mg/kg), 18-MC (40 mg/kg) **decreases** the intravenous self-administration of **morphine and cocaine** and the oral self-administration of **ethanol and nicotine** in rats; unlike ibogaine, 18-MC does not affect responding for a nondrug reinforcer (water)." 10. POLITO (2019) "A systematic study of microdosing psychedelics" PLoS One. 14(2)1-26. From **page 1** "Individuals who **microdose** report **minimal acute effects** from these substances yet claim a range of long-term general health and wellbeing benefits." From **page 2** "So, for example, a **microdose of lysergic acid diethylamide (LSD) might be 6–25 micrograms**, or a **microdose of psilocybin might be .1 to .5 grams of dried mushrooms**." From **page 11** "Participants reported significant improvements in mood: specifically, **Depression** ($t = -3.97$, $p = .001$) and **Stress** ($t = -3.36$, $p = .004$) decreased during the study period, indicating participants experienced improvements in their mental health after microdosing. Mind Wandering decreased significantly during the study period ($t = -2.49$, $p = .047$) indicating that participants were better able **maintain focus** after microdosing." 11. W.I.P.O. Pat. App. No. 2021/003467 "METERED DOSING COMPOSITIONS AND METHODS OF USE OF PSYCHEDELIC COMPOUNDS" (Published January 7, 2021; provisional priority date July 4, 2019) From **page 7** "Disclosed are multiple **metered dosing formulations for various corresponding methods of delivery of psychoactive plant and/or fungal compounds for** inhalation, sublingual, nasal, oral (including capsules, gell caps, and tinctures) and **topical use**, which is made up of the following components 1) at least one active compound isolated from psychoactive plants or fungi; b) one of the methods of delivery; and c) a base solution that is appropriate for the chosen method of delivery of the active compound. More specifically the psychoactive plant and/or fungi used will include but not be limited to fundi containing **psilocybin**,

	baeocystin, and/or **psilocin** and/or plants containing mescaline aka peyote aka 3,4,5-trimethoxyphenethylamine aka DMT." From **page 10** "The embodiments of the present invention contemplate dosage forms with a total weight of between **approximately 0.1mg to 50mg of psychoactive fungal compound(s)**, depending on the formulation of the active compound(s) and method of delivery." From **page 12** "For **anxiety and depression related to end-of-life concerns due to terminal illness**, a range of 1mg/70kg to 30mg/kg dosing may decrease **depressed mood** and **anxiety** with improved attitudes about life and self, mood, relationships, and spirituality." From **page 12** "For long-term daily care, **a sub-hallucinogenic regiment of 0.1mg/70kg to 1.5mg/70kg** may provide for **mood enhancement,** greater empathy and compassion, increased creativity, greater focus and long-term stability in mainlining goals related to preventing intrusive thoughts from **PTSD**." 13. BEUG (1982) "Psilocybin and psilocin levels in twenty species from seven genera of wild mushrooms in the Pacific Northwest, U.S.A." Journal of Ethnopharmacology. 5(3):271-285. From **p. 281**

TABLE 1

Psilocybin and psilocin levels in Pacific Northwest mushrooms as quantified by reversed phase HPLC

Species[1] (Figs. 1 - 20)	Date collected[2]	Psilocybin (mg/g dry weight)	Psilocin (mg/g dry weight)
Conocybe cyanopus (Atk.) Kühner	July 12, 1979	9.3	0
Conocybe tenera (Schaeff. ex Fr.) Kühner	Aug. 22, 1978	0	0
Conocybe sp. (near *lactea* (J. Lange) Métrod)	Aug. 13, 1978	0	0
Pholiotina filaris (Fr.) Singer	Oct. 1979	0	0
Panaeolus campanulatus (Fr.) Quél.	Aug. 13, 1978	0	0
	Sept. 4, 1978	0	0
	Mar. 18, 1980	0	0
Panaeolus acuminatus (Sec.) Quél.	Sept. 4, 1978	0	0
	Mar. 18, 1980	0	0
Panaeolus phalaenarum (Fr.) Quél.	July 23, 1978	0	0
	Cultivated	0	0
Psathyrella foenisecii (Fr.) Smith	June 18, 1978	0	0
	Oct. 4, 1978	0	0
Panaeolus semiovatus (Fr.) Lundell & Nanfeldt	June 28, 1978	0	0
	July 12, 1979 (3 collections)	0	0
Panaeolus subbalteatus (Berk. & Br.) Sacc.	July 3, 1978	3.5	0
	Sept. 5, 1978	6.5	0
	Sept. 3, 1979	1.6	0
Gymnopilus ventricosus (Earle) Hesler (generally identified as *G. spectabilis*)	Oct. 15, 1979	0	0
Stropharia aeruginosa (Fr.) Quél.	Oct. 29, 1979	0	0
Psilocybe semilanceata (Fr.) Quél.	Oct. 1979	6.9	0
	Sept. 4, 1978	10.8	0
	Oct. 22, 1979	12.0	0
	Nov. 5, 1979	6.9	0
	Nov. 27, 1979a	8.4	0
	Nov. 27, 1979b	12.8	0
	Nov. 27, 1979c	9.2	0
	Nov. 27, 1979d	6.6	0
	Nov. 27, 1979e	10.9	0
	Nov. 27, 1979f	8.5	0
Caps only	Nov. 27, 1979g	11.1	0
Stems only	Nov. 27, 1979g	6.2	0
Psilocybe cyanescens Wakefield	Oct. 1978a	4.9	1.7
	Oct. 28, 1979	1.5	9.6
	Nov. 2, 1979	8.2	1.3
	Nov. 6, 1979	11.5	7.6

TABLE 1 *(continued)*

Species[1] (Figs. 1 - 20)	Date collected[2]	Psilocybin (mg/g dry weight)	Psilocin (mg/g dry weight)
Psilocybe cyanescens	Nov. 7, 1979a	8.3	2.0
Wakefield	Nov. 7, 1979b	16.8	2.8
	Nov. 18, 1979a	14.3	2.8
	Nov. 18, 1979b	15.5	2.4
	Nov. 18, 1979c	13.6	2.3
	Nov. 18, 1979d	11.0	2.0
	Nov. 18, 1979e	10.1	1.4
	Nov. 18, 1979f	8.7	1.8
	Nov. 18, 1979g	9.7	2.8
	Nov. 19, 1979	8.4	0.6
Psilocybe stuntzii	Sept. 24, 1978	0	0
Guzmán & Ott	Oct. 27, 1979	3.6	0.6
	Oct. 31, 1979	0.4	0.12
	Nov. 13, 1979	3.6	0.06
Psilocybe baeocystis	Sept. 1979a	2.04	1.43
Singer & Smith	Sept. 1979b	1.96	1.32
	Sept. 1979c	1.92	0.48
	Sept. 1979d	2.04	3.07
	Sept. 5, 1979	8.5	5.9
	Oct. 1979a	2.8	0.8
	Oct. 1979b	1.5	0
Psilocybe coprophila (Bull. ex Fr.) Kummer	June 22, 1979	0	0
Psilocybe montana (Pers. ex Fr.) Kummer	Mar. 18, 1980	0	0
Psilocybe inquilina (Fr. ex Fr.) Bres.	Mar. 18, 1980	0	0
Psilocybe pelliculosa	Oct. 30, 1979	7.1	0
(Sm.) Singer & Smith	Oct. 8, 1979	4.1	0
	Nov. 8, 1979	1.2	0

15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020)

From **claim 1** "A method of **managing a neurological condition** or one or more symptoms thereof in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising:
a) a therapeutically effective amount of one or more 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof; and
b) a pharmaceutically acceptable excipient wherein the therapeutically effective amount of the **5HT receptor agonist o**r a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to the subject in need thereof **in an amount insufficient to provide an adverse side effect, such as hallucinogenic experience.**"

From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a spray, aerosol,

	mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From **claim 39** "The method of any one of the preceding claims, wherein the neurological condition is an addictive disorder." From **claim 40** "The method of claim 39, wherein the **addictive disorder** is **alcohol abuse, substance abuse, smoking,** or obesity." From **claim 43** "The method of any one of claims 1-38, wherein the neurological condition is **depression**, bipolar disorder, **anxiety**, social anxiety, **post-traumatic stress disorder (PTSD)**, panic disorder, phobia, schizophrenia, psychopathy, or antisocial personality disorder." From **claim 44** "The method of any one of claims 1-38, wherein the neurological condition is an impulsive disorder." From **claim 45** "The method of claim 44, wherein the impulsive disorder is **attention deficit hyperactivity disorder (ADHD), attention deficit disorder (ADD)**, Tourette's syndrome or autism." From **claim 46** "The method of any one of claims 1-38, wherein the neurological condition is a compulsive disorder." From **claim 47** "The method of claim 46, wherein the compulsive disorder is **obsessive compulsive disorder (OCD)**, gambling, or aberrant sexual behavior."
16. The method of claim 15 wherein the topical application of a transdermal pharmaceutical composition for the treatment and/or prevention and/or control of severe depression (treatment resistant), major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, opioid addiction, anxiety	9. U.S. Pat. App. No. 2020/0085816 "LSD FOR THE TREATMENT OF ALZHEIMER'S DISEASE" (Published March 19, 2020) From **claim 40** "A **transdermal delivery system** comprising a pharmaceutically effective amount of a neuronal growth factor, 2 μg to 30 μg of **lysergic acid diethylamide** or a pharmaceutically acceptable salt thereof, and a naturally occurring gum." From **claim 43** "A method of treating Alzheimer's disease in a subject, said method comprising administering to the subject a pharmaceutical composition comprising lysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, in an amount sufficient to treat said Alzheimer's disease." From **claim 52** "The method of claim 43, wherein said lysergic acid diethylamide, or a pharmaceutically acceptable salt thereof, is administered in a dosing regimen from **once daily to once weekly.**"

(stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient, wherein the transdermal patch is applied at a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.	From **section [0007]** "In particular embodiments, the AD-associated neuropsychiatric condition is **depression, anxiety,** agitation, apathy, irritability, and/or aggression." 11. W.I.P.O. Pat. App. No. 2021/003467 "METERED DOSING COMPOSITIONS AND METHODS OF USE OF PSYCHEDELIC COMPOUNDS" (Published January 7, 2021; provisional priority date July 4, 2019) From **page 7** "Disclosed are multiple **metered dosing formulations for various corresponding methods of delivery of psychoactive plant and/or fungal compounds for** inhalation, sublingual, nasal, oral (including capsules, gel caps, and tinctures) and **topical use**, which is made up of the following components 1) at least one active compound isolated from psychoactive plants or fungi; b) one of the methods of delivery; and c) a base solution that is appropriate for the chosen method of delivery of the active compound. More specifically the psychoactive plant and/or fungi used will include but not be limited to fundi containing **psilocybin**, baeocystin, and/or **psilocin** and/or plants containing mescaline aka peyote aka 3,4,5-trimethoxyphenethylamine aka DMT." From **page 10** "The embodiments of the present invention contemplate dosage forms with a total weight of between **approximately 0.1mg to 50mg of psychoactive fungal compound(s)**, depending on the formulation of the active compound(s) and method of delivery." From **page 12** "For **anxiety and depression related to end-of-life concerns due to terminal illness**, a range of 1mg/70kg to 30mg/kg dosing may decrease **depressed mood** and **anxiety** with improved attitudes about life and self, mood, relationships, and spirituality." From **page 12** "For long-term daily care, **a sub-hallucinogenic regiment of 0.1mg/70kg to 1.5mg/70kg** may provide for **mood enhancement,** greater empathy and compassion, increased creativity, greater focus and long-term stability in mainlining goals related to preventing intrusive thoughts from **PTSD**." 14. W.I.P.O. Pat. App. No. 2001/064149 "IMPROVED TRANSDERMAL DRUG PATCH" (Published September 7, 2001) From **claim 37** "The formulation for providing **transdermal drug delivery at a consistent rate** comprising: **a drug**, said drug being capable of transdermal absorption, a solvent, said solvent having a predesigned solubility such that said drug formulation has a substantially constant concentration of dissolved drug, when excess amount of said drug is present in said formulation."

	From **page 5, paragraph 1** "In other words, the patch can keep a **constant delivery rate for more than 10 days**." 15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 1** "A method of **managing a neurological condition** or one or more symptoms thereof in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising: a) a therapeutically effective amount of one or more 5HT receptor agonist or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof; and b) a pharmaceutically acceptable excipient wherein the therapeutically effective amount of the **5HT receptor agonist o**r a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to the subject in need thereof **in an amount insufficient to provide an adverse side effect, such as hallucinogenic experience.**" From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a spray, aerosol, mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From **claim 30** "The method of any one of the preceding claims, wherein the pharmaceutical composition is administered to a subject in need thereof **once a day, every alternate day, three times a week, twice a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month or three times per month.** From **claim 31** "The method of any one of the preceding claims, wherein the pharmaceutical composition is administered **about once a day.**" From **claim 39** "The method of any one of the preceding claims, wherein the neurological condition is an addictive disorder." From **claim 40** "The method of claim 39, wherein the **addictive disorder** is **alcohol abuse, substance abuse, smoking,** or obesity." From **claim 43** "The method of any one of claims 1-38, wherein the neurological condition is **depression**, bipolar disorder, **anxiety**, social anxiety, **post-traumatic stress disorder (PTSD)**, panic disorder, phobia, schizophrenia, psychopathy, or antisocial personality disorder."

	From **claim 44** "The method of any one of claims 1-38, wherein the neurological condition is an impulsive disorder." From **claim 45** "The method of claim 44, wherein the impulsive disorder is **attention deficit hyperactivity disorder (ADHD), attention deficit disorder (ADD)**, Tourette's syndrome or autism." From **claim 46** "The method of any one of claims 1-38, wherein the neurological condition is a compulsive disorder." From **claim 47** "The method of claim 46, wherein the compulsive disorder is **obsessive compulsive disorder (OCD)**, gambling, or aberrant sexual behavior."
17. The method of claim 15 further providing a constant rate of delivery of the active components of the transdermal patch over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.	14. W.I.P.O. Pat. App. No. 2001/064149 "IMPROVED TRANSDERMAL DRUG PATCH" (Published September 7, 2001) From **claim 37** "The formulation for providing **transdermal drug delivery at a consistent rate** comprising: **a drug**, said drug being capable of transdermal absorption, a solvent, said solvent having a predesigned solubility such that said drug formulation has a substantially constant concentration of dissolved drug, when excess amount of said drug is present in said formulation." From **page 5, paragraph 1** "In other words, the patch can keep a **constant delivery rate for more than 10 days**." 15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a spray, aerosol, mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From **claim 30** "The method of any one of the preceding claims, wherein the pharmaceutical composition is administered to a subject in need thereof **once a day, every alternate day, three times a week, twice a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month or three times per month.** From **paragraph [0138]** "These pharmaceutical compositions might also be formulated for transmucosal administration, buccal administration, for

	administration by inhalation, for parental administration, for **transdermal administration**, and rectal administration"
18. The method of claim 15 further providing a steady absorption rates of the active components of the transdermal patch over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.	15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a spray, aerosol, mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From **claim 30** "The method of any one of the preceding claims, wherein the pharmaceutical composition is administered to a subject in need thereof **once a day, every alternate day, three times a week, twice a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month or three times per month.** From **paragraph [0138]** "These pharmaceutical compositions might also be formulated for transmucosal administration, buccal administration, for administration by inhalation, for parental administration, for **transdermal administration**, and rectal administration" 17. U.S. Pat. No. 6245347 "Methods and apparatus for improved administration of pharmaceutically active compounds" (Published June 12, 2001) From claim 1 "A method of **controlling the rate of absorption of a drug** in a target area of a human body comprising: initiating the **transdermal administration of a drug** to a portion of the body; activating a controlled temperature modification apparatus proximate the drug being administered by exposing to oxygen an oxygen-activated exothermic medium disposed within the controlled temperature modification apparatus; and varying the amount of oxygen to which the exothermic medium is exposed to vary a rate of reaction of the exothermic medium and thereby adjusting the temperature of said target area of the body with said controlled temperature modification apparatus."
19. The method of claim 15 further achieving a constant blood serum levels of the active components of the transdermal patch over a time	15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020)

period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.	From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a spray, aerosol, mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From **claim 30** "The method of any one of the preceding claims, wherein the pharmaceutical composition is administered to a subject in need thereof **once a day, every alternate day, three times a week, twice a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month or three times per month.**" From **paragraph [0138]** "These pharmaceutical compositions might also be formulated for transmucosal administration, buccal administration, for administration by inhalation, for parental administration, for **transdermal administration**, and rectal administration" From **paragraph [0020]** "In some embodiments, the therapeutically effective amount of 5HT receptor agonist (e.g., psilocin) or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to a subject in need thereof in an amount and/or formulation to provide a **plasma concentration** of (e.g. active form of the) 5HT receptor agonist (e.g., **psilocin**) or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof of **at least 0.1 ng/mL** (e.g. at least 0.2 ng/mL, at least 0.3 ng/mL, at least 0.5 ng/mL, or the like) after **at least 6 hours (e.g. at least 12 hours, at least 24 hours, at least 36 hours, at least 48 hours, at least 72 hours, at least 96 hours, at least 120 hours, at least 144 hours, or the like)**" From **paragraph [0221]** "In certain embodiments controlled release dosage forms are designed to provide a quick increase in the **plasma concentration of the drug which remains substantially constant within the therapeutic range of the drug** for a period of time (e.g. 24-hour period)."
20. The method of claim 15 further achieving a reduced variability in dosage of the active components of the transdermal patches over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a	11. W.I.P.O. Pat. App. No. 2021/003467 "METERED DOSING COMPOSITIONS AND METHODS OF USE OF PSYCHEDELIC COMPOUNDS" (Published January 7, 2021; provisional priority date July 4, 2019) From **paragraph 3, page 7** "Similarly, the associated method may also include one or more of the following steps: a) oral or nasal inhalation; b) sublingual delivery; or c) oral delivery; d) nasal spray; or e) **topical delivery**." From **paragraph 4, page 7** "The disclosed formulations are unique because they provide (a) **consistent dosing**; (b) metered dosing; and (c) multiple methods of delivery."

week, once in ten days, and once in fifteen days.	15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 17** "The method of any one of the preceding claims, wherein the pharmaceutical composition is in a form selected from a spray, aerosol, mist, nebulae, **ointment, cream, gel, paste, salve,** solution, suspension, tincture, **patch**, and atomized vapor." From **claim 30** "The method of any one of the preceding claims, wherein the pharmaceutical composition is administered to a subject in need thereof **once a day, every alternate day, three times a week, twice a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month or three times per month.**" From **paragraph 55** "Provided herein are methods for managing disorders or conditions, and treating symptoms of disorders or conditions, comprising administering one or more 5HT receptor agonists, or pharmaceutically acceptable salts, solvates, metabolites, derivatives, or prodrugs thereof. The methods provide **improved dosage and administration**, enabling enhanced bioavailability and efficacy to subjects in need thereof."
21. The method of claim 15 further providing a plasma concentration of the active components of the transdermal patch in a therapeutic range over a time period selected from the group consisting of once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in ten days, and once in fifteen days.	15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **claim 30** "The method of any one of the preceding claims, wherein the pharmaceutical composition is administered to a subject in need thereof **once a day, every alternate day, three times a week, twice a week, once a week, every other week, two weeks per month, three weeks per month, once a month, twice a month or three times per month.**" From **paragraph [0138]** "These pharmaceutical compositions might also be formulated for transmucosal administration, buccal administration, for administration by inhalation, for parental administration, for **transdermal administration**, and rectal administration" From **paragraph [0020]** "In some embodiments, the therapeutically effective amount of 5HT receptor agonist (e.g., psilocin) or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to a subject in need thereof in an amount and/or formulation to provide a **plasma concentration** of (e.g. active form of the) 5HT receptor agonist (e.g., **psilocin**) or a pharmaceutically acceptable salt,

	solvate, metabolite, derivative, or prodrug thereof of **at least 0.1 ng/mL** (e.g. at least 0.2 ng/mL, at least 0.3 ng/mL, at least 0.5 ng/mL, or the like) after **at least 6 hours (e.g. at least 12 hours, at least 24 hours, at least 36 hours, at least 48 hours, at least 72 hours, at least 96 hours, at least 120 hours, at least 144 hours, or the like)**"
22. The method of claim 15 further providing a plasma concentration of the active components of the transdermal patch in a therapeutic range of about 0.01 ng/mL to about 500 ng/mL.	15. W.I.P.O. Pat. App. No. 2020/157569 "METHODS AND COMPOSITIONS COMPRISING A 5HT RECEPTOR AGONIST FOR THE TREATMENT OF PSYCHOLOGICAL, COGNITIVE, BEHAVIORAL, AND/OR MOOD DISORDERS" (Published August 6, 2020) From **paragraph [0138]** "These pharmaceutical compositions might also be formulated for transmucosal administration, buccal administration, for administration by inhalation, for parental administration, for **transdermal administration**, and rectal administration" From **paragraph [0020]** "In some embodiments, the therapeutically effective amount of 5HT receptor agonist (e.g., psilocin) or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof is provided to a subject in need thereof in an amount and/or formulation to provide a **plasma concentration** of (e.g. active form of the) **5HT receptor agonist (e.g., psilocin)** or a pharmaceutically acceptable salt, solvate, metabolite, derivative, or prodrug thereof of **at least 0.1 ng/mL** (**e.g. at least 0.2 ng/mL, at least 0.3 ng/mL, at least 0.5 ng/mL, or the like**) after at least 6 hours (e.g. at least 12 hours, at least 24 hours, at least 36 hours, at least 48 hours, at least 72 hours, at least 96 hours, at least 120 hours, at least 144 hours, or the like)"

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First Named Inventor/Applicant Name:	Fotios M. Plakogiannis
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Warnings:					
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2	Third-Party Submission Under 37 CFR 1.290	Third-party-preissuance-submission.pdf	57074 2f982ebf61e33e7072a6daaf716b65174d540e20	no	3
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4	Concise Description of Relevance	Claims_Chart.pdf	1751418 392e649f5f6b4884eab2ff6622ff343e77dd3226	no	48
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Warnings:					
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6	Non Patent Literature	22-SMITH.pdf	1041919 cf9bb41e2c1c69583317ccddd64c91f2bb3bf34a	no	7
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7	Non Patent Literature	23-GRODOWSKA.pdf	9372353 6e9116f8ed33986701dd672331c2cc1694a36f2e	no	10
Warnings:					
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8	Fee Worksheet (SB06)	fee-info.pdf	37709 61a14e2f5456f7d21fd2ef6abe81fbadd0cb4cbf	no	2
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