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

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 2987909 C 2022/04/26

(11)(21) 2 987 909

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2016/06/27
(87) Date publication PCT/PCT Publication Date: 2017/01/05
(45) Date de délivrance/Issue Date: 2022/04/26
(85) Entrée phase nationale/National Entry: 2017/11/29
(86) N° demande PCT/PCT Application No.: US 2016/039601
(87) N° publication PCT/PCT Publication No.: 2017/003935
(30) Priorité/Priority: 2015/06/27 (US62/185,573)

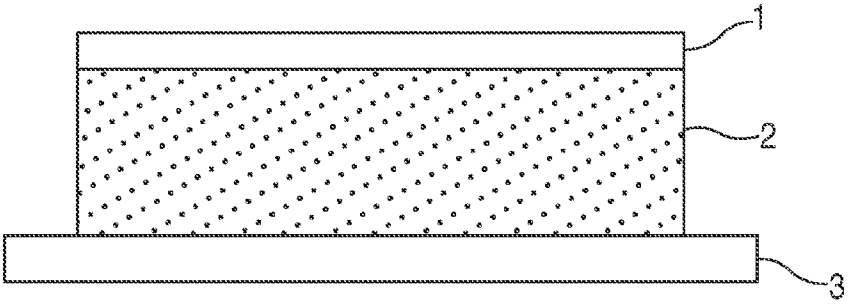
(51) Cl.Int./Int.Cl. *A61K 31/135* (2006.01), *A61K 9/70* (2006.01), *A61P 25/24* (2006.01)

(72) Inventeurs/Inventors:
TANG, HUADONG, US;
TAN, HOCK S., US;
MAYERSOHN, MICHAEL, US

(73) Propriétaire/Owner:
SHENOX PHARMACEUTICALS, LLC, US

(74) Agent: LAVERY, DE BILLY, LLP

(54) Titre : SYSTEME D'ADMINISTRATION TRANSDERMIQUE DE LA KETAMINE
(54) Title: KETAMINE TRANSDERMAL DELIVERY SYSTEM



(57) Abrégé/Abstract:
TThe present invention is directed to a transdermal delivery device comprising ketamine and formulations thereof. The present invention is also directed to a transdermal delivery device comprising ketamine for the treatment of major depressive disorder (MDD) and/or pain. The present invention is further directed to a transdermal delivery device comprising ketamine and abuse deterrent agents.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2017 (05.01.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/003935 A1

(51) International Patent Classification:
A61K 31/135 (2006.01) *A61P 25/24* (2006.01)
A61K 9/70 (2006.01)

(21) International Application Number:
PCT/US2016/039601

(22) International Filing Date:
27 June 2016 (27.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/185,573 27 June 2015 (27.06.2015) US

(71) Applicant: **SHENOX PHARMACEUTICALS, LLC** [US/US]; 675 US Highway One, North Burnswick, New Jersey 08902 (US).

(72) Inventors: **TANG, Huadong**; 640 Prospect Avenue, East Brunswick, New Jersey 080540 (US). **TAN, Hock S.**; 7 Lavender Way, East Brunswick, New Jersey 08816 (US). **MAYERSOHN, Michael**; 4394 W. Butterfly Mountain Drive, Marana, Arizona 85658 (US).

(74) Agents: **CHIARA, Nicholas P.** et al.; Holland & Knight LLP, 10 St. James Avenue, Boston, Massachusetts 02116 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: KETAMINE TRANSDERMAL DELIVERY SYSTEM

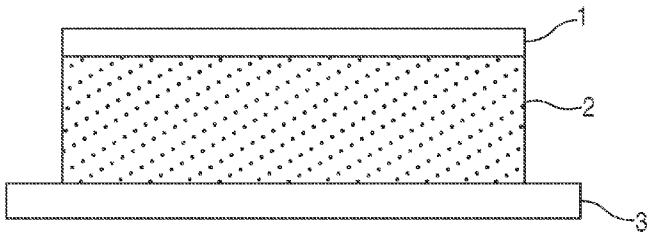


FIG. 1

(57) Abstract: TThe present invention is directed to a transdermal delivery device comprising ketamine and formulations thereof. The present invention is also directed to a transdermal delivery device comprising ketamine for the treatment of major depressive disorder (MDD) and/or pain. The present invention is further directed to a transdermal delivery device comprising ketamine and abuse deterrent agents.

WO 2017/003935 A1

KETAMINE TRANSDERMAL DELIVERY SYSTEM

FIELD OF THE INVENTION

The present invention is directed to transdermal delivery devices comprising ketamine and formulations thereof. The present invention is also directed to transdermal delivery devices comprising ketamine for the treatment of major depressive disorder (MDD) and/or pain. The present invention is further directed to transdermal delivery devices comprising ketamine and abuse deterrent agents.

BACKGROUND OF INVENTION

Major depressive disorder (MDD) is a disabling psychiatric illness. Lifetime prevalence of MDD is approximately 16%. Kessler *et al.*, JAMA, 289(23):3095-105 (2003). There are three primary classes of antidepressants that are commonly prescribed for MDD: (1) monoamine oxidase inhibitors (MAOIs); (2) tricyclics; and (3) serotonin–norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs). There are significant limitations with the use of current antidepressants, including limited efficacy, delayed onset of action, and adverse side effects. Additionally, antidepressants have been found to be only about 20–30% more effective than placebo. The delay of onset varies from weeks to months, which may result in adverse events, including but not limited to increased vulnerability to suicide, decrease in compliance, and increase in social and economic burden. Common side effects of these antidepressants include nausea, insomnia, anxiety, weight-loss/gain, drowsiness, headache, loss of sex drive, and/or blurred vision. *Penn and Tracey*, Ther Adv. Psychopharmacol., 2(5):179–188 (2012).

Pain can present as a disabling physical illness. One type of pain, neuropathic pain, is a complex chronic pain state often accompanied by tissue injury. The occurrence of pain with neuropathic characteristics is about 6.9–10% of the general population. Hecke *et al.*, Pain, 155(4):654-62 (2014). Symptoms of neuropathic pain include spontaneous burning, shooting pain, hyperalgesia, and allodynia. Patients with neuropathic pain often have

Date Reçue/Date Received 2021-06-03

are associated with other significant health issues, including depression, sleep problems, and loss of independence. Bouhassira *et al.*, Pain., 136(3):380-7 (2008). Neuropathic pain can be caused by a variety of mechanisms, including infection, central or peripheral nerve injury, stroke, multiple sclerosis, diabetes mellitus, sarcoidosis, toxic agents (*e.g.*, alcohol or chemotherapy), inherited or genetic neuropathy, and Complex Regional Pain Syndrome (CRPS). CRPS is an intractable form of pain, often resistant to a variety of conventional therapies. Correll *et al.*, Pain Med., 5(3):263-75 (2004). Neuropathic pain is difficult to treat, with only about 40-60% of patients achieving partial relief. Treatment for neuropathic pain includes antidepressants, anticonvulsants, and/or topical pain management medications. Niesters *et al.*, Expert Opin. Drug Metab. Toxicol., 8(11):1409-17 (2012); Dworkin *et al.*, Pain, 132(3):237-51 (2007).

Ketamine is a non-competitive, N-methyl-D-aspartate (NMDA) receptor antagonist, indicated for treatment as an anesthetic, sedative, and analgesic. Ketamine has been demonstrated to be an effective antidepressant, with rapid onset (within about 2 hours of administration) and sustained antidepressant effect (from days to in some cases a week or two after administration). Berman *et al.*, Biol. Psychiatry, 47(4):351-54 (2000). The NMDA receptor pathway plays an important role in pain, including neuropathic pain. Animal studies and human clinical studies have shown the efficacy of ketamine in the treatment of chronic neuropathic pain. Correll *et al.*, Pain Med. 5(3):263-75 (2004); Sigtermans *et al.*, Pain, 145(3):304-11 (2009).

Ketamine is a racemic mixture containing R-ketamine and S-ketamine. It is generally believed that the anesthetic and/or antidepressant effect of ketamine is mainly through the action of S-ketamine because *in vitro* S-ketamine has about a 4-fold greater affinity than the R-ketamine on NMDA receptor binding. However, animal model studies have suggested that R-ketamine is more effective as an antidepressant than S-ketamine. In addition, R-ketamine was shown to be free of psychotomimetic side effects and abuse liability. Yang *et al.*, Transl. Psychiatry, 5(e632):1-11 (2015). The present invention is directed toward administration of the racemic mixture of ketamine; however, embodiments containing the R-ketamine or the S-ketamine enantiomers are within the scope of the present invention.

Ketamine is also a known dissociative anesthetic that has gained popularity as a drug of abuse, and may be referred to illicitly as "K" or "Special K". Ketamine is reported to distort perceptions of sight and sound, and make the user feel disconnected. The 2011 "Monitoring

the Future" (MTF) study reports the annual use of ketamine among 8th, 10th, and 12th graders as being 0.8%, 1.2%, and 1.7%, respectively. Johnston, *et al.*, 2012, *Monitoring the future national results on adolescent drug use: Overview of key findings, 2011*, Ann Arbor: Institute for Social Research, The University of Michigan. Illicit ketamine can be distributed as a dried powder or as a liquid, mixed with beverages, and/or added to smokable materials (such as marijuana or tobacco). As a powder, ketamine can be snorted or pressed into tablets, sometimes in combination with other drugs, including 3,4-methylenedioxymethamphetamine (MDMA, referred to illicitly as "ecstasy"), amphetamine, methamphetamine, cocaine, and/or carisoprodol. On August 12, 1999 ketamine became a Schedule III non-narcotic substance under the Controlled Substances Act. Consequently, there is a need to develop abuse deterrent mechanisms to reduce the risk of ketamine abuse.

IV administration of ketamine presents numerous challenges. First, the patient incurs increased costs to receive IV administration. Second, IV administration is inconvenient for the patient, and may lead to reduced compliance. Third, the rapid initial rise in ketamine plasma concentrations following IV administration to the maximum plasma concentration (C_{max}) can cause adverse side effects, including drug toxicity, psychotomimetic problems, and increased potential for addiction. Moreover, because ketamine has a short half-life (about 2 hours), this immediate release delivery of ketamine by IV administration may result in little to no ketamine remaining in plasma after about 4-8 hours, necessitating frequent and repeated dosing to maintain therapeutic plasma levels. Fourth, without additional safeguards, IV administration of ketamine may be susceptible to abuse.

An intranasal formulation of the S-enantiomer of ketamine, esketamine, is under development and in clinical study by Janssen. US 2013/0236573 A1, Singh *et al.*, Esketamine For The Treatment of Treatment-Refractory Or Treatment-Resistant Depression. However, intranasal delivery of ketamine presents numerous challenges. It suffers from many of the same immediate release issues faced by IV administration of ketamine, namely, rapid onset of maximum concentration (T_{max}), high C_{max}, increased risk of side effects like drug toxicity, and the need for frequent and multiple dosing to maintain therapeutic plasma concentrations. Frequent administration of intranasal ketamine may increase the risk of irritating and damaging the nasal epithelium, which in turn may reduce patient compliance. Also, intranasal administration is associated with high variability in absorption among subjects. Kublik *et al.*, Adv. Drug Deliv. Rev. 29:157-77 (1998). Further, the rapid rise in ketamine plasma concentration following intranasal administration may cause adverse side effects, such as drug

toxicity. Moreover, intranasal delivery of ketamine, without additional safeguards, is highly susceptible to abuse. Other routes of administration of ketamine, including parenteral administration of ketamine (e.g., subcutaneous, intramuscular, etc.) suffer from many of these same challenges.

While oral administration (*i.e.*, tablet or capsule) is typically convenient for the patient, the metabolic and pharmacokinetic properties of ketamine make oral administration less suitable. Ketamine has a high systemic (primarily hepatic) clearance of about 19 ml/min•kg, a rate which approaches liver plasma flow. Thus, ketamine is subject to substantial pre-systemic metabolism, or first-pass effect, in the liver and gut wall by metabolic enzymes, such as cytochrome P450 enzymes (CYP450). Consequently, the absolute oral bioavailability of ketamine in humans is only about 10-20%. Due to this first-pass effect, there is an increased risk for drug-drug interactions (DDI) with drugs that can inhibit or induce CYP450s. Clements *et al.*, J Pharm Sci, 71(5):539-42 (1981); *Fanta, et al.*, Eur. J. Clin. Pharmacol., 71:441–47 (2015); Peltoniemi *et al.*, Basic & Clinical Pharmacology & Toxicology, 111:325–332 (2012). Moreover, ketamine tablets or capsules are easily abused.

SUMMARY OF THE INVENTION

The present invention is directed to transdermal delivery devices comprising ketamine and formulations thereof. The present invention is also directed to transdermal delivery devices comprising ketamine for the treatment of major depressive disorder (MDD) and/or pain. There are long-felt and unmet medical needs for the treatment of MDD and for the treatment of pain, which are fulfilled by the present invention. The controlled, prolonged, and steady ketamine exposure to humans from the transdermal delivery device of the present invention can reduce adverse side effects compared with other routes of ketamine delivery, including but not limited to intravenous (IV) administration and intranasal spray. Because ketamine has high abuse potential, the present invention is further directed to transdermal delivery devices comprising ketamine and abuse deterrent agents.

The present invention has numerous advantages. Formulations of the transdermal delivery device provide excellent ketamine permeability and stability. The inventors discovered, through *in vitro* experiments, that ketamine has excellent transdermal permeability properties, which are very important for efficacious clinical use. Additional *in vitro* experiments demonstrated that adding, for example, crystallization inhibitors to formulations

of the present invention resulted in very stable transdermal delivery devices, which is important when making a pharmaceutical product.

Additionally, the present invention provides improved drug metabolism and pharmacokinetic properties compared with other methods of administering ketamine, such as IV and intranasal administration. First, transdermal delivery avoids the aforementioned first-pass effect. Second, it reduces the aforementioned DDI risk. Third, it delivers a sustained *in vitro* release profile, and therefore, a steadier *in vivo* plasma concentration versus time profile over a longer period of time. In other words, there is no need for frequent, multiple dosing for days or weeks to maintain therapeutic plasma concentrations of ketamine, as may be the case with, for example, IV infusion. Correll *et al.*, Pain Med. 5(3):263-75 (Sept. 2004). Instead, the present invention can meet the desired prolonged drug absorption profile. For example, administration of a single transdermal delivery device of the present invention can deliver a relatively constant ketamine plasma concentration for up to about 7 days. Fourth, the present invention delivers lower C_{max} values for ketamine in the plasma, as well as minimal fluctuation between C_{max} and C_{min}, thereby reducing adverse side effects, including but not limited to toxicity, psychotropic effects, increased potential for addiction, and lack of therapeutic effect.

The transdermal delivery device of the present invention provides flexibility in dose, dosage release rate, patch size, and duration of application to allow for optimization. Transdermal delivery devices according to the present invention include, but are not limited to, transdermals and dermal patches, topical skin applications such as spray, creams, gels, lotions, dressings and liquid solutions, and other transdermal delivery systems and dosage forms known to persons skilled in the art. For example, these flexible parameters can be adjusted by the formulator and/or the clinician to provide the optimal ketamine plasma concentration-time profile for the individual patient that maximizes efficacy and minimizes adverse side effects. Therefore, the ketamine transdermal delivery device of the present invention is particularly effective for the treatment of MDD and pain.

Moreover, the present invention improves convenience and compliance compared with other forms of administering ketamine. For example, administration of the transdermal delivery device once or twice a week is more convenient than, for example, multiple daily doses of immediate release forms of ketamine. Immediate release ketamine or immediate release ketamine formulation means administration of ketamine that is not extended, controlled, delayed or prolonged. Dose equivalent with means that the total dosage of drug

administered between the compared items is the same. Also, the present invention is less invasive and less costly than IV administration. The present invention causes less irritation and is less invasive than intranasal administration. Further, the present invention is less likely to cause drug toxicity than immediate release forms of drug delivery.

The present invention also has advantages with respect to abuse deterrence. The transdermal delivery device itself may serve as an abuse deterrent because it is more difficult to abuse directly, such as by biting or swallowing the device. Specifically, the ketamine is incorporated into a polymeric matrix together with other excipients, including, but not limited to skin permeation enhancers, humectants, plasticizers, buffers, antioxidants, and combinations thereof, each of which may inhibit ketamine extraction for abuse. Nevertheless, specific, additional abuse deterrent agents can be added to formulations of the present invention to further deter abuse.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a ketamine transdermal delivery device without abuse deterrent properties.

Figure 2 is a transdermal delivery device comprising ketamine with abuse deterrent properties.

Figure 3 is an alternate embodiment of a transdermal delivery device comprising ketamine and abuse deterrent agents.

Figure 4 is an alternate embodiment of a transdermal delivery device comprising ketamine and abuse deterrent agents.

Figures 5-7 are ketamine plasma concentration versus time profiles in humans for Example 2 of the present invention using different sizes of the transdermal delivery device. These pharmacokinetic profiles are predicted by known convolution methodology using *in vitro* transdermal permeation data and *in vivo* intravenous plasma concentration data.

Figure 8 is a graph of the *in vitro* skin permeation of ketamine in a Franz Diffusion Cell model for the transdermal delivery device according to Example 2.

Figure 9 is a 6-month stability graph of the present invention prepared in accordance with Example 5.

Figures 10-13 are ketamine plasma concentration versus time profiles in humans corresponding to the transdermal delivery devices of Table 2. These transdermal delivery devices are for the

treatment of MDD. These pharmacokinetic profiles are predicted by known convolution methodology using *in vitro* transdermal permeation data and *in vivo* intravenous plasma concentration data.

Figures 14-17 are graphs of the pharmacokinetic plasma concentrations versus time profiles, corresponding to the transdermal delivery devices of Table 3. These transdermal delivery devices are for the treatment of pain. These pharmacokinetic profiles are predicted by known convolution methodology using *in vitro* transdermal permeation data and *in vivo* intravenous plasma concentration data.

DETAILED DESCRIPTION OF THE INVENTION

The active ingredient in the transdermal delivery device of the present invention is preferably employed at about 1-35% by weight of the final formulation (also referred to as 1-35 weight percent) and most preferably 10-25% by weight of the final formulation. The most preferred active ingredient is ketamine. Additional active ingredients that can be employed in the present invention can be chosen from drugs that counteract the potential adverse effects of ketamine, reduce ketamine addiction potential, and/or enhance ketamine's antidepressant effect and/or pain management effects. All weight percentages provided in the present disclosure are based on the weight of the final formulation, which includes the adhesive-drug layer (or adhesive-drug matrix) and the abuse deterrent layer (or abuse deterrent matrix, which is optional), but not the release liner or the backing film.

The transdermal permeation rate (mg/day) combined with the size of the transdermal delivery device and the duration of application of the transdermal delivery device determines the plasma concentration of the drug. The transdermal permeation rate of the ketamine transdermal delivery device of the present invention will preferably be about 0.1-30 mg/day/cm^2 of the transdermal delivery device, and most preferably about 0.5-5 mg/day/cm^2. The size of transdermal delivery device will preferably be about 5 -300 cm^2. The duration of application of the transdermal devices will preferably be about 8-168 hours. Combinations of these preferred ranges provide prolonged plasma concentrations of ketamine ranging from about 0.4-3850 ng/ml. The plasma concentrations of ketamine will reach near steady-state at about 8 hours after administration and will be sustained for the duration of the application.

Preferred transdermal permeation rates, transdermal delivery device sizes, and durations of applications for the transdermal delivery devices of the present invention are set forth in Table 1.

TABLE 1

Permeation rates ($mg/day/cm^2$)	Transdermal delivery device size (cm^2)	Application Duration (days)	Dosage strength (mg)	Plasma concentrations after about 8 hours (ng/ml)
0.1 - 30	10	1/3	0.33 – 100	0.43 -128
0.1 - 30	300	1/3	10 – 3000	13 – 3850
0.1 - 30	10	1	1 – 300	0.43 -128
0.1 - 30	300	1	30 – 9000	13 – 3850
0.1 - 30	10	7	7 – 2100	0.43 -128
0.1 - 30	300	7	210 – 63000	13 – 3850

The plasma concentrations of ketamine versus time are calculated based on the reported pharmacokinetic parameters of ketamine in humans. Ketamine follows a three-compartment model with the parameters for a 70-kg human as follows: clearance = 79.8 (liter/hour); V1 = 133 liter; and micro constants k_{12} = 0.174 $hour^{-1}$, k_{13} = 1.18 $hour^{-1}$, k_{21} = 0.124 $hour^{-1}$, k_{31} = 1.59 $hour^{-1}$. *Fanta, et al.*, Eur. J. Clin. Pharmacol., 71:441–447 (2015). There is variability among human populations and individuals, such that the pharmacokinetics of each human are not the same, and for certain populations and for some individuals, the pharmacokinetics can deviate significantly. Plasma concentrations provided by any given dosage strength for the transdermal delivery device of the present invention can vary from individual to individual.

For antidepressant effect (*i.e.*, the treatment of MDD) with minimized adverse side effects, the preferred plasma concentration range of ketamine is from about 10-200 ng/ml, and the most preferred plasma concentration range is from about 10-100 ng/ml.

Table 2 provides ranges for the most preferred transdermal permeation rates, transdermal delivery device sizes, and duration of application of the transdermal delivery devices for antidepressant effect (*i.e.*, the treatment of MDD) with minimized adverse side effects. These ranges are chosen to provide prolonged plasma concentrations of ketamine ranging from about 10 -200 ng/ml for about 8-168 hours, and the most preferred plasma concentrations are from about 10-100 ng/ml. Variations on the transdermal delivery devices

comprising ketamine designed for the treatment of MDD will contain from about 8.3-200 mg and be applied for about 8 hours, from about 25-600 mg and be applied for about 24 hours, from about 87.5-2100 mg and be applied for about 84 hours, and from about 175-4200 mg and be applied for about 168 hours.

Transdermal delivery devices for the treatment of MDD are prepared with dosage strengths from about 8.3-200 mg, and are designed to be applied for about 8 hours, which will provide a plasma concentration of ketamine from about 11-257 ng/ml. An alternate embodiment of the present invention for the treatment of MDD is designed to provide reduced adverse side effects. The reduced adverse side effects are provided by a transdermal delivery device according to the present invention prepared with dosage strengths of ketamine from about 8.3-100 mg of ketamine, designed to be applied for 8 hours, and to provide a plasma concentration of ketamine from about 11-128 ng/ml.

Transdermal delivery devices for the treatment of MDD according to the present invention are prepared with dosage strengths from about 25-600 mg and are designed to be applied for about 24 hours, which will provide a plasma concentration of ketamine from about 11-257 ng/ml. An alternate embodiment of the present invention for the treatment of MDD is designed to provide reduced adverse side effects. The reduced adverse side effects are provided by a transdermal delivery device according to the present invention prepared with dosage strengths of ketamine from about 25-300 mg of ketamine, designed to be applied for 24 hours, and to provide a plasma concentration of ketamine from about 11-128 ng/ml.

Transdermal delivery devices for the treatment of MDD according to the present invention are prepared with dosage strengths from about 87.5-2100 mg, and are designed to be applied for about 84 hours, which will provide a plasma concentration of ketamine from about 11-257 ng/ml. An alternate embodiment of the present invention for the treatment of MDD is designed to provide reduced adverse side effects. The reduced adverse side effects are provided by a transdermal delivery device according to the present invention prepared with dosage strengths of ketamine from about 87.5-1050 mg, designed to be applied for about 84 hours, and to provide a plasma concentration of ketamine from about 11-128 ng/ml.

Transdermal delivery devices for the treatment of MDD according to the present invention are prepared with dosage strengths from about 175-4200 mg, and are designed to be applied for about 168 hours, which will provide a plasma concentration of ketamine from about 11-257 ng/ml. An alternate embodiment of the present invention for the treatment of MDD is

designed to provide reduced adverse side effects. The reduced adverse side effects are provided by a transdermal delivery device according to the present invention prepared with dosage strengths of ketamine from about 175-2100 mg, designed to be applied for about 168 hours, and to provide a plasma concentration of ketamine from about 11-128 ng/ml.

TABLE 2

Permeation rates ($mg/day/cm^2$)	Transdermal delivery device size (cm^2)	Application Duration (days)	Dosage strength (mg)	Plasma concentrations after about 8 hours (ng/ml)
1	25 – 300	1/3	8.3 - 100	11 – 128
5	5 –60	1/3	8.3 – 100	11 – 128
5	5 –120	1/3	8.3 – 200	11 – 257
1	25 – 300	1	25 –300	11 – 128
5	5 –60	1	25 – 300	11 – 128
5	5 –120	1	25 – 600	11 – 257
1	25 – 300	3.5	87.5 – 1050	11 – 128
5	5 –60	3.5	87.5 – 1050	11 – 128
5	5 –120	3.5	87.5 – 2100	11 – 257
1	25 – 300	7	175 – 2100	11 – 128
5	5 –60	7	175 – 2100	11 – 128
5	5 –120	7	175 – 4200	11 – 257

For pain management, with minimized adverse events, the preferred plasma concentrations ranges of ketamine are from about 50-1000 ng/ml, and the most preferred plasma concentration is about 500 ng/ml.

Table 3 provides ranges for transdermal permeation rates, transdermal delivery device sizes, and duration of application of the transdermal delivery devices for pain management. These ranges are chosen to provide prolonged plasma concentrations of ketamine ranging from about 50-1000 ng/ml, and for about 8-168 hour, and the most preferred plasma concentration is about 500 ng/ml. Transdermal delivery devices comprising ketamine designed for pain management will contain about 40-500 mg and be applied for about 8 hours, from about 120-1500 mg and be applied for about 24 hours, from about 420-5250 mg and be applied for about 84 hours, and from about 840-10500 mg and be applied for about 168 hours.

Transdermal delivery devices for the treatment of pain according to the present invention are prepared with dosage strengths from about 40-500 mg, are designed to be applied for about 8 hours, and will provide a plasma concentration of ketamine from about 51-642 ng/ml.

Transdermal delivery devices for the treatment of pain according to the present invention are prepared with dosage strengths from about 120-1500 mg, are designed to be applied for about 24 hours, and will provide a plasma concentration of ketamine from about 51-642 ng/ml.

Transdermal delivery devices for the treatment of pain according to the present invention are prepared with dosage strengths from about 420-5250 mg, are designed to be applied for about 84 hours, and will provide a plasma concentration of ketamine from about 51-642 ng/ml.

Transdermal delivery devices for the treatment of pain according to the present invention are prepared with dosage strengths from about 840-10,500 mg, are designed to be applied for about 168 hours, and will provide a plasma concentration of ketamine from about 51-642 ng/ml.

TABLE 3

Permeation rates ($mg/day/cm^2$)	Transdermal delivery device Size (cm^2)	Application Duration (day)	Dosage strength	Plasma concentrations after about 8 hours (ng/ml)
1	120 - 300	1/3	40 - 100	51 - 128
5	24 - 300	1/3	40- 500	51 - 642
1	120 - 300	1	120 - 300	51 - 128
5	24 - 300	1	120- 1500	51 - 642
1	120 - 300	3.5	420 - 1050	51 - 128
5	24 - 300	3.5	420 - 5250	51 - 642
1	120 - 300	7	840 - 2100	51 - 128
5	24 - 300	7	840 - 10500	51 - 642

Preferably, the transdermal delivery device of the present invention will be administered once a day, twice a week, or once a week. The dosing regimen of the present invention is not limited to the examples provided in Tables 2 and 3 for antidepressant effect and pain management. In accordance with the need of the patient and as determined by the physician, the dose frequencies, device size, and/or dosage strength can be adjusted. For example, the application of the transdermal delivery device can be for a duration shorter than 8 hours, such as 4 hours. The ketamine plasma concentrations at about 4 hours after administration will be about 80% of the plasma concentration at about 8 hours, which can provide effective anti-depressant and/or pain management, depending on the need of the patient.

The plasma drug concentrations profiles in Table 4 and illustrated in Figs. 6-7, are exemplary of the plasma profiles of the present invention. The plasma drug concentration profiles in Tables 2 and 3 and illustrated at least in 10-17, are further exemplary of the plasma profiles of the present invention. These plasma profiles rise slowly and are maintained at a relatively constant level for a prolonged period of time. On the contrary, IV and intranasal ketamine will generally provide a C_{max} approximately 3 to 10 times higher than the C_{max} provided by a transdermal delivery device of the present invention (at equivalent doses), while the area under the curve (AUC) is constant (*e.g.*, Figure 5). Additionally, the prolonged and steady administration of ketamine provided by the transdermal delivery device of the present invention exhibits minimal fluctuations in plasma concentration relative to multiple doses of IV or intranasal administration of ketamine. This reduction or minimization of plasma fluctuations in turn reduces the occurrence of adverse side effects resulting from under and over medication. Consequently, the plasma profile provided by the present invention is improved and may result in better therapeutic outcomes and greater patient compliance.

The structure and packaging of the transdermal delivery device of the present invention are prepared in accordance with methods and techniques known to persons skilled in the art. The primary components are the backing layer, the adhesive-drug layer (or adhesive-drug matrix), the abuse deterrent layer (or abuse deterrent matrix) (optional), and the release liner.

The backing layer may be comprised of polymeric films such as polyester (PET) or polyethylene (PE) films that support the adhesive drug matrix and protect the transdermal delivery device from the environment. The preferred thickness range for the backing film is from about 2-5 mils (1 mil equals 1/1000 of an inch), and the most preferred thickness range of the backing layer is from about 3-4 mils thick.

The adhesive in the adhesive-drug layer may be a pressure sensitive adhesive (PSA). *Tan et al.*, *Pharm Sci. & Tech Today*, 2:60-69 (1999). Useful PSAs in transdermal delivery systems include, but are not limited to, polyisobutylenes (PIB), silicone polymers, and acrylate copolymers, such as acrylic pressure sensitive adhesives, including Duro-Tak 87-2516, 87-2852 and 87-2194, manufactured by Henkel Adhesives. PIBs are elastomeric polymers that are commonly used in PSAs, both as primary-base polymers and as tackifiers. PIBs are homopolymers of isobutylene and feature a regular structure of a carbon–hydrogen backbone with only terminal unsaturation. PIBs are marketed under the trade name Oppanol by BASF. The silicone polymers are a high molecular weight polydimethylsiloxane that contains residual

silanol functionality (SiOH) on the ends of the polymer chains. Silicone PSAs for use in pharmaceutical applications are available from Dow Corning Corporation, for example under the trade name of BIO-PSA. The PSA is preferably employed at about 30-90% by weight of the final formulation, and most preferably about 40-60% by weight of the final formulation.

The release liner can be manufactured in the desired size for the present invention. The release liner may be comprised of silicone or fluoro-polymer coated polyester film. The release liner protects the transdermal delivery device during storage and is removed before its use. Silicone-coated release liners are manufactured by Mylan Corporation, Loparex Corporation, and 3M's Drug Delivery Systems. The fluoro-polymer coated release liners are manufactured and supplied by 3M's Drug Delivery Systems and Loparex. The preferred thickness of the release liner is about 2-10 mils, and most preferably about 3-5 mils.

Additional drugs can be incorporated in the transdermal delivery device to counteract adverse effects, and/or to enhance the antidepressant or pain management effect of ketamine. Examples for enhancing antidepressant effect include, but are not limited to, antagonists of group II metabotropic glutamate receptors, such as LY341495, Podkowa *et al.*, Psychopharmacology (Berl) (Jun 11 2016). Examples for reducing side effects with ketamine, especially psychotomimetic and sympathomimetic, include, but not limited to, co-administration of alpha-2 agonists such as clonidine. *Lenze*, World J Biol Psychiatry, 17(3):230-8 (2016). If an additional drug is employed in the present invention, it is preferably employed at about 0.1-20% by weight of the final formulation, and most preferably about 1-5% by weight of the final formulation.

Additional components can be added to the transdermal delivery device of the present invention to optimize it. Skin permeation enhancers are employed to enhance the skin permeability of the drug through the skin. Skin permeation enhancers that may be employed in the present invention include, but are not limited to, sulphoxides (*e.g.* dimethylsulphoxide, DMSO), Azones (*e.g.* laurocapram), pyrrolidones (*e.g.* 2-pyrrolidone, 2P), alcohols and alkanols (ethanol, or decanol), glycols (*e.g.* propylene glycol (PG)), surfactants and terpenes. *Williams et al.*, Adv Drug Deliv Rev. 27;56(5):603-18 (2004). The skin permeation enhancers are preferably employed at about 1-20% by weight of the final formulation, and most preferably about 4-10% by weight of the final formulation.

Humectants are employed to keep the transdermal delivery device hydrated and/or to reduce the loss of moisture. The humectants that may be employed in the present invention

include, but are not limited to, propylene glycol, glycerol, urea, polyvinylpyrrolidone (PVP), vinylpyrrolidone-vinyl acetate copolymers, and copolymers of PVP (*e.g.*, BASF's Kollidon K30, K12, Kollidon VA 64, or Kollidon CL-M, magnesium silicate, and silica. The humectants are preferably employed at about 2-20% by weight of the final formulation and most preferably about 5-10% by weight of the final formulation.

Plasticizers are employed in transdermal drug delivery systems to obtain desirable mechanical properties, such as to improve the film forming properties and the appearance of the film, to decrease the glass transition temperature of the polymer, to prevent film cracking, and to increase film flexibility. The plasticizers that may be employed in the present invention include, but are not limited to, phthalate esters, phosphate esters, fatty acid esters, and glycol derivatives. The plasticizers are preferably employed at about 2-20% by weight of the final formulation and most preferably about 5-10% by weight of the final formulation. Designing and Characterization of Drug Free Transdermal delivery devices for Transdermal Application, International Journal of Pharmaceutical Sciences and Drug Research, Vol. 2, No. 1, pp. 35-39 Bharkatiya, M.; Nema, R.K. & Bhatnagar, M. (2010) Wypch, G. (2004) and Handbook of Plasticizers, Chem Tec, 437-440, ISBN 1-895198-29-1, Ontario, Canada.

Antioxidants are employed to prevent drug degradation by oxidation. Antioxidants that may be employed in the present invention include, but are not limited to, butylated hydroxyanisole (BHA), butylhydroxy toluene (BHT), *tert*-Butylhydroquinone, ascorbic acid, and tocopherols. The antioxidants are preferably employed at about 0.01-5% by weight of the final formulation and most preferably about 0.1-1.0% by weight of the final formulation.

Anti-irritants are employed to provide alleviation or prevention of skin irritation, and to assist in the release of the active ingredients. Anti-irritants that may be employed in the present invention include, but are not limited to, aloe, arnica, chamomile, cucumber, menthol, mugwort, oat, zinc oxide, drug release modifiers such as chitosan, cellulose-based polymers, silicon dioxides, and polymethacrylates.

Other suitable excipients useful in the preparation of transdermal delivery devices are within the knowledge of those skilled in the art, and can be found in the Handbook of Pharmaceutical Excipients, (7^{th} ed. 2012).

Date Reçue/Date Received 2021-06-03

Figure 1 is an embodiment of the transdermal delivery device in which the backing film (1) is affixed atop the adhesive drug matrix (2), which is supported by a release liner (3). The adhesive drug matrix contains the drug and adhesive, as well as enhancers, humectants, plasticizers, antioxidants, pH modifiers, crystallization inhibitors, and other ingredients that aid in drug release and permeation through skin, and in maintaining drug stability.

Figure 2 is an example of a transdermal delivery device that contains an abuse deterrent agent (4) that is not skin permeable, drug (5) dissolved in the adhesive-drug matrix (2), a transdermal delivery device backing film (1), and a release liner (3).

Figure 3 is a transdermal delivery device that contains a backing film (1), an abuse deterrent layer (6), an adhesive-drug matrix (2), and a release liner (3). The abuse deterrent layer is capable of releasing an abuse deterrent agent upon tampering with the transdermal delivery device. In an embodiment in which the abuse deterrent layer comprises a gel forming agent, the gel forming agent can form a gel solution upon extraction.

Figure 4 is an embodiment of a prolonged use, *e.g.*, 7-day transdermal delivery device, with abuse deterrent agents in a segregated, abuse deterrent layer. Figure 4 shows the backing film (1), and overlay adhesive layer (7), an abuse deterrent layer (6), the adhesive-drug layer (2), and a release liner (3). The overlay adhesive layer extends over the outer edges of the drug-adhesive layer (2) and the abuse deterrent layer (6) to provide added adhesion to the skin for prolonged use. Embodiments of the present invention can be prepared with an overlay adhesive layer (7) with or without an intervening abuse deterrent layer (6).

Table 4 provides estimated plasma concentrations for transdermal delivery devices prepared according to the present invention. The plasma concentration are exemplified in Figs. 5, 6 and 7, which are described below in detail.

TABLE 4

	Fig, 5 IV after 24-hr (ng/ml)		Fig, 6 24-hr Device (ng/ml)			Fig, 7 8-hr Device (ng/ml)		
Time (hr)	IV (0.5 mg/kg)	9.4-cm^2, 24-hr (0.5 mg/kg)	10-cm^2	100-cm^2	300-cm^2	10-cm^2	100-cm^2	300-cm^2
0	0	0	0	0	0	0	0	0
1	110	5.8	6.2	62	186	6.2	62	186
2	62	8.7	9.2	92	276	9.2	92	276
3	43	11	11	113	338	11	113	338
4	31	12	13	127	382	13	127	382

5	23	13	14	138	414	14	138	414
6	17	14	15	146	439	15	146	439
7	14	14	15	153	458	15	153	458
8	11	15	16	158	473	16	158	473
9	8.9	15	16	162	485	10	102	305
10	7.4	16	17	165	495	7.5	75	223
11	6.4	16	17	168	504	5.7	57	169
12	5.5	16	17	170	511	4.4	44	132
13	4.9	16	17	173	518	3.5	35	106
14	4.3	16	17	175	524	2.9	29	87
15	3.9	17	18	176	529	2.4	24	73
16	3.5	17	18	178	534	2.1	21	63
17	3.2	17	18	179	538	1.8	18	54
18	2.9	17	18	181	542	1.6	16	48
19	2.6	17	18	182	546	1.4	14	43
20	2.4	17	18	183	549	1.3	13	38
21	2.2	17	18	184	552	1.2	12	35
22	2.0	17	18	185	554	1.0	10	31
23	1.8	17	19	186	557	0.95	9.5	28
24	1.7	18	19	186	559	0.86	8.6	26
25	1.5	12	13	125	375	0.79	7.9	24
26	1.4	9.0	9.6	96	287	0.72	7.2	21
27	1.3	7.1	7.6	76	227	0.65	6.5	20
28	1.2	5.8	6.1	61	184	0.60	6.0	18
29	1.1	4.8	5.1	51	154	0.55	5.5	16
30	0.97	4.1	4.3	43	130	0.50	5.0	15
31	0.88	3.5	3.8	38	113	0.46	4.6	14
32	0.81	3.1	3.3	33	99	0.42	4.2	13
33	0.74	2.7	2.9	29	88	0.38	3.8	11
34	0.68	2.5	2.6	26	78	0.35	3.5	10
35	0.62	2.2	2.3	23	70	0.32	3.2	9.6
36	0.57	2.0	2.1	21	64	0.29	2.9	8.8
37	0.52	1.8	1.9	19	58	0.27	2.7	8.0
38	0.47	1.6	1.7	17	52	0.24	2.4	7.3
39	0.43	1.5	1.6	16	48	0.22	2.2	6.7
40	0.40	1.4	1.5	15	44	0.21	2.1	6.1
41	0.36	1.2	1.3	13	40	0.19	1.9	5.6
42	0.33	1.1	1.2	12	36	0.17	1.7	5.1
43	0.30	1.0	1.1	11	33	0.16	1.6	4.7
44	0.28	0.95	1.0	10	30	0.14	1.4	4.3
45	0.25	0.87	0.92	9.2	28	0.13	1.3	3.9
46	0.23	0.79	0.85	8.5	25	0.12	1.2	3.6
47	0.21	0.73	0.77	7.7	23	0.11	1.1	3.3
48	0.19	0.66	0.71	7.1	21	0.10	1.0	3.0

Table 5 provides the cumulative amount of ketamine that permeates human skin in the Franz Diffusion Cell model disclosed in Figure 8, as provided by a transdermal delivery device according to Example 2 of the present invention. The total amount of drug in the transdermal delivery device of Example 2 is 4.75 mg. Therefore, the transdermal bioavailability of Example 2 within 24 hours is about 78%.

TABLE 5

Time (hr)	Cumulative ketamine permeated (mg/cm^2)
2	0.0976
4	0.307
8	1.13
12	1.98
24	3.72

Transdermal delivery devices can be abused. One method of abuse is to place the device in a solvent to separate the drug from the polymeric matrix, followed by separating the drug from any additional components. In order to deter abuse, the present invention is further directed towards a novel transdermal delivery device comprising ketamine and abuse deterrent agents.

Abuse deterrent agents are employed because they have one or more of the following properties: (1) unpalatable bitterness or other repulsive tastes in the mouth (*i.e.*, bittering agents); (2) formation of gel upon mixing with the extraction solvents (*i.e.*, gel forming agents); (3) severe irritation when injected (*i.e.*, irritants); (4) mood depression (*e.g.*, droperidol) or other pronounced central nervous system (CNS) effects; (5) acute gastrointestinal, cardiac or respiratory effects; (6) violent nausea or vomiting; (7) repugnant smells if not used as instructed; (8) sleep inducing, thereby causing the abuser to miss or be made unaware of the euphoria; and/or (9) deactivation or degradation of the active ingredient (*i.e.*, strong oxidation agents (such as hydrogen peroxide), strong acid, or strong base, and/or antagonists) upon attempted extraction. The abuse deterrent agent is employed at about 0.01-10% by weight of the final formulation, preferably about 0.1-4% by weight, and most preferably about 0.1-0.5% by weight.

The abuse deterrent agents can be included in the adhesive drug matrix or in a separate abuse deterrent layer (also referred to as the abuse deterrent matrix). The abuse deterrent layer

may be comprised of a combination of polymer and the abuse deterrent agent. Additionally, the abuse deterrent layer can be the abuse deterrent agent itself because many of the recited polymers also act as gel forming agents. Suitable polymers include, but are not limited to, one or more pharmaceutically acceptable polymers that will undergo an increase in viscosity upon contact with a solvent. Preferred polymers include polyethylene oxide, polyvinyl alcohol, hydroxypropyl methylcellulose, carbomers (carbopol), polyvinylpyrrolidone (PVP), and/or other cellulose polymers. In one embodiment of the present invention the polymer includes polyethylene oxide. The polyethylene oxide can have an average molecular weight ranging from about 300,000-5,000,000, and more preferably from about 600,000-5,000,000, and most preferably at least about 5,000,000. In one embodiment, the polyethylene oxide is a high molecular weight polyethylene oxide. Examples of suitable, commercially available polyethylene oxide polymers include Polyox®, WSRN-1105 and/or WSR coagulant, available from Dow Chemical. The preferred weight range of the polymer is from about 1-40% by weight of the final formulation, and the most preferred range of the polymer is from about 2-10% by weight of the final formulation.

Bittering agents are pharmaceutically acceptable bitter substances that create a bitter taste or effect when administered nasally (snorted), orally, buccally or sublingually, making consumption difficult. The bittering agents that may be employed in the present invention include, but are not limited to, sucrose octaacetate (used as a denaturant for alcohol) (*e.g.*, SD-40), denatonium saccharide, denatonium benzoate, caffeine, quinine (or a quinine salt such as quinine sulfate), bitter orange peel oil, and other botanical extract ingredients, such as pepper extract (cubeb), capsicum, and the like. Preferred bittering agents are sucrose octaacetate, denatonium benzoate (Bitrex), and denatonium saccharide (four times more bitter than denatonium benzoate) because they are extremely bitter even at low concentrations and are essentially non-toxic. The bittering agent is employed at about 0.01-10% by weight of the final formulation, preferably about 0.1-4% by weight, and most preferably about 0.1-0.5% by weight.

Gel forming agents are employed to form a gel structure upon mixing with the extraction solvents and, thus, provide abuse deterrent properties. Specifically, gel forming agents are compounds that upon contact with a solvent (*e.g.*, water or alcohol), absorb the solvent and swell, thereby forming a viscous or semi-viscous substance that significantly reduces and/or minimizes the amount of free solvent which can contain an amount of solubilized drug, and which minimizes what can be drawn into a syringe for injection (*i.e.*, IV

or intramuscular). The gel can also reduce the overall amount of drug extractable with the solvent by entrapping the drug in a gel matrix. In certain embodiments the gel forming agent can be in a segregated abuse deterrent layer laminated to the adhesive drug matrix.

The gel forming agents that may be employed include, but are not limited to, ethyl cellulose, cellulose acetate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, cellulose ether, cellulose ester, cellulose ester ether, acrylic resins comprising copolymers synthesized from acrylic and methacrylic acid esters, the acrylic polymer may be selected from the group consisting of acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethylmethacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), glycidyl methacrylate copolymers, and mixtures thereof. The gel forming agent is preferably employed at about 3-40% by weight of the final formulation, and the most preferably about 5-20% by weight of the final formulation.

In embodiments of the present invention the gel forming agent includes polyvinyl alcohol with a molecular weight ranging from about 20,000-200,000, specific gravity ranging from about 1.19-1.31, and viscosity ranging from about 4-65 cps. The polyvinyl alcohol used in the formulation is preferably a water-soluble synthetic polymer represented by $—(—C_2H_4O—)_n—$, where n can range from about 500-5,000. Examples of suitable, commercially available polyvinyl alcohol polymers include PVA, USP, available from Spectrum Chemical Manufacturing Corporation, New Brunswick, N.J. 08901.

In embodiments of the present invention, the gel forming agent includes hydroxypropyl methyl cellulose (Hypromellose) with a molecular weight ranging from about 10,000-1,500,000, typically from about 5000-10,000 (*i.e.*, low molecular). The specific gravity of the hydroxypropyl methyl cellulose ranges from about 1.19-1.31, with an average specific gravity of about 1.26. Viscosity of the hydroxypropyl methyl cellulose is about 3600-5600 cPs. The hydroxypropyl methylcellulose used in the formulation can be a water-soluble synthetic polymer. Examples of suitable, commercially available hydroxypropyl methylcellulose polymers include Methocel K100 LV and Methocel K4M, available from Dow chemicals.

In other embodiments of the present invention the gel forming agent includes hydrophilic polymers, such as hydrogels, which provides viscosity to the dosage form upon

tampering. In such embodiments, when an abuser crushes and dissolves the dosage form in a solvent (*e.g.*, water or saline), a viscous or semi-viscous gel is formed.

In certain embodiments of the present invention, the gel forming agent can include carbomers, having a molecular weight ranging from 700,000-4,000,000 and viscosity ranging from about 4000-39,400 cPs. Carbomer is preferably employed in the present invention from about 1-40% by weight of the final formulation, and most preferably from about 2-10% by weight. Examples of suitable, commercially available carbomers include carbopol 934P NF, carbopol 974P NF, and carbopol 971P NF, available from Lubrizol.

Irritants are pharmaceutically inert compounds that induce irritation to the mucous membranes of the body (*i.e.*, nasal, mouth, eye, intestine, urinary tract). The irritants that may be employed in the present invention include, but are not limited to surfactants, such as sodium lauryl sulfate (SLS), poloxamer, sorbitan monoesters and glyceryl monooleates, as well as spicy ingredients, and others. The irritants are preferably employed at about 0.01-10% by weight of the final formulation, preferably 0.01-10% by weight, and most preferably about 0.1-5% by weight.

In embodiments of the present invention, the irritant can deter abuse upon tampering with the transdermal delivery device. For example, if an abuser extracts and dries the ketamine, then the irritant is exposed and discourages inhalation of the ketamine mixed with the irritant, as inhalation (*e.g.*, *via* snorting through the nose) will induce pain and/or irritation of the abuser's mucous membrane and/or nasal passageway tissue.

Other suitable excipients useful in the preparation of transdermal delivery devices are within the knowledge of those skilled in the art, and can be found in the Handbook of Pharmaceutical Excipients (7^{th} ed. 2012).

Date Reçue/Date Received 2021-06-03

EXAMPLES

Examples 1-5

The formulation of Examples 1-5 are disclosed below in Table 6.

TABLE 6

Ingredient Class	Ingredient	Ex 1 (wt%)	Ex 2 (wt%)	Ex 3 (wt%)	Ex 4 (wt%)	Ex 5 (wt%)
Active Ingredient	Ketamine	20	25	25	25	25
Pressure-sensitive adhesive	DuroTak 387-2052	70	65		40	
	DuroTak 87-2677			55		
	DuroTak 87-4098					40
Skin permeation enhancer	Oleyloleate	5	5	5		
	Oleyl alcohol				5	5
	Levulinic acid	5	5	5	5	5
	Diethylene glycol monoethyl ether				5	5
Crystallization inhibitors	Polyvinyl pyrrolidone-co-vinyl acetate			10	20	
	Polymethacrylate					20
Total		100	100	100	100	100

The pressure sensitive adhesive (PSA) employed in Examples 1, 2, and 4 was Duro-Tak 387-2052 (supplied by Henkel Adhesives). The PSA employed in Example 3 was Duro-Tak 87-2677 (Henkel Adhesives). The PSA employed in Example 5 was Duro-Tak 87-4098 (Henkel Adhesives). Persons skilled in the art will understand that other known pressure sensitive adhesives can be readily employed with the transdermal delivery devices of the present invention.

The skin permeation enhancer employed in Examples 4 and 5 was diethylene glycol monoethyl ether, sold under the tradename Transcutol P. Persons skilled in the art will understand that other known skin permeation enhancers can be readily employed with the transdermal delivery devices of the present invention.

The crystallization inhibitor in Examples 3 and 4 was polyvinyl pyrrolidone-co-vinyl acetate, sold under the tradename Kollidon VA 64 (BASF Corporation). The crystallization inhibitor employed in Example 5 was polymathacrylate-based polymer, sold under the tradename Plastoid B (Evonik Corporation). Persons skilled in the art will understand that

other known crystallization inhibitor enhancers can be readily employed with the transdermal delivery devices of the present invention.

Figure 5 is a comparison of the plasma concentration-time profile of a 0.5 mg/kg dose of ketamine in a human subject following: (1) a 40-minute single IV administration; and (2) administration of a 24 hour transdermal delivery device of the present invention according Example 2 (a 9.4 cm^2 transdermal delivery device with a 3.75 mg/cm^2 permeation rate). Convolution analysis was applied in accordance with the pharmacokinetic parameters set forth in Fanta, *et al.*, Eur. J. Clin. Pharmacol., 71:441–447 (2015). The transdermal delivery device according to Example 2 exhibits a lower C_{max}, preferably less than about 30%, and more preferably less than about 20%, of the C_{max} from an equivalent IV dosage.

Figure 6 discloses ketamine plasma concentration-time profiles for three sizes (10, 100 and 300 cm^2) of the once-a-day transdermal delivery device of the present invention according to Example 2.

Figure 7 discloses ketamine plasma concentration-time profiles for three sizes (10, 100 and 300 cm^2) of the three times-a-day transdermal delivery device of the present invention according to Example 2.

Skin permeation enhancers are incorporated in the transdermal delivery devices of the present invention to ensure that sufficient ketamine can penetrate through skin. Skin permeation studies were performed on the transdermal delivery devices prepared according to Examples 1-5 using Franz diffusion cells maintained at 37° C. The receptor medium was phosphate buffered saline at pH 7.4, the receptor volume was 12 ml and the permeation area was 1.767 cm^2. Human cadaver skin was used and the tests were performed in triplicate. A 1x1 inch transdermal delivery device was placed onto the donor side of the skin diffusion cells, adhered onto the skin, and the experiment was initiated with the receptor medium being continuously mixed (stirring at 600 rpm). Samples (1.5 ml) of the receptor phase were obtained at 2, 4, 8, 12, 24, 48 and 72 hours. The drug concentrations were quantitated using HPLC. As demonstrated in Table 6, Examples 1-5 of the present invention all provide good skin permeability. The cumulative amounts of ketamine that permeated after 24 hours are shown in Table 7.

TABLE 7

	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5
Ketamine in transdermal delivery device, mg/cm^2	3.56	4.71	5.86	7.51	9.58
24 h Cumulative Permeation, mg/cm^2	1.21	3.72	2.62	1.74	0.73

Figure 8 depicts *in vitro* skin permeability of the transdermal delivery devices of the present invention according to Example 2 as shown by the Franz Diffusion Cell model.

Drug crystallization will retard drug release and skin permeability, reducing the efficacy of the transdermal delivery device. Drug crystals should not be formed in the transdermal delivery device over a period approximating the shelf life, *i.e.*, for about 6 months or greater. Examples 1 and 2 showed instability, *i.e.* drug crystals were formed in the adhesive drug matrix 4-7 days after preparation of the transdermal delivery devices. Examples 3, 4 and 5, were found to be stable for at least 4 weeks, *i.e.* within this period, no crystals were formed. Example 5 was found to be stable for at least 6 months at conditions of 25° C, 60% RH.

Table 8 reports the stability data for the transdermal delivery devices prepared according to Examples 1-5.

Figure 9 depicts the stability of ketamine in a transdermal delivery device according to Example 5 after 0 months and after 6 months.

TABLE 8

	Ex 1	Ex 2	Ex 3	Ex 4	Ex 5
Crystallization Inhibitors	None	None	10% Kollidon VA 64	20% Kollidon VA 65	20% Plastoid B
Stability at 25° C /65% RH	Crystals formed at Day 10	Crystals formed at Day 10	Crystals formed at Month 3	Crystals formed at Month 3	No crystals formed up to Month 6

Example 6:

Transdermal Delivery Device With Non-segregated Abuse Deterrent Agents

Example 5 was modified to prepare a transdermal delivery device that contains 5 mg of denatonium benzoate and 200 mg of ketamine in the adhesive drug matrix. *In vitro* skin permeation studies showed that no denatonium benzoate permeated the skin (because of its

large molecular weight (447 DA) and the high melting point (170° C). Nevertheless, ketamine showed excellent skin permeability (0.8 mg/cm^2 in 24 hours), indicating that incorporation of an abuse deterrent agent, such as denatonium benzoate did not affect the skin permeation of ketamine.

In an extraction study to simulate attempted drug-abuse, transdermal delivery devices prepared according to Example 6 were soaked for 60 minutes in 100 ml of three different media: (1) 40% ethanol; (2) 70% isopropyl alcohol; and (3) acetone. All three media were assayed for ketamine and denatonium benzoate using HPLC. More than 50% of the original ketamine and more than 50% of the denatonium benzoate were found in the media (*i.e.*, the bittering agent extracted proportionally to the amount of ketamine extracted), indicating the effectiveness of using denatonium benzoate as an abuse deterrent agent in the present invention.

Example 7:

Transdermal Delivery Device with Abuse Deterrent Agents in a Segregated Layer

Example 7 comprises a transdermal delivery device with an abuse deterrent agent in a segregated layer. The abuse deterrent agent employed in Example 7 is a gelling agent which reacts with common solvents (*e.g.*, water and alcohol) used to extract and abuse the ketamine in the transdermal delivery device. The thickness of the adhesive-drug layer and the abuse deterrent layer are both about 2 to about 5 mils. The transdermal delivery device according to Example 7 is prepared in a two-step process.

Step 1. Preparation of the Abuse Deterrent Layer

PolyOx 1105, propylene glycol, and PEG 4000 were mixed to form the abuse deterrent layer. The three ingredients were dissolved in a water/ethanol solvent, followed by casting of the wet film directly on a sheet of backing layer, *e.g.*, 3M's polyethylene film, Scotpak 1012. The wet film is then dried at 60° C for 30 min in a convective-air drying oven. The coating thickness of the abuse deterrent layer is about 3 mils. An example of a suitable abuse deterrent layer composition is disclosed in Table 9.

TABLE 9

Ingredient	gm	Wt %
PolyOx WSR N-10	7.20	46.2%
PolyOx 1105	3.60	23.1%
PEG 4000	2.80	17.9%
Propylene Glycol	2.00	12.8%
Ethanol Anhydrous*	28.00	0.00%
Purified Water*	57.00	0.00%
Total	100.60	100%

*evaporated during processing.

An abuse deterrent agent, such as Bitrex and sodium lauryl sulfate (SLS), may be incorporated into the abuse deterrent layer, preferably from about 0.01-5% by weight of the final formulation, and most preferably from about 0.05-0.5% by weight of the final formulation.

Step 2. Preparation of Adhesive Drug Matrix Layer:

The adhesive drug matrix layer is prepared by casting the adhesive drug matrix mix directly on the abuse deterrent layer (prepared in step 1), or onto a release liner and then laminated to the abuse deterrent layer.

DuroTak 87-4098 is weighed into a 100 ml beaker, and then mixed at low speed. Next, the Kollidon VA 64 and the ketamine are added to the mixer. The batch is mixed until all ingredients are dissolved. Then wet films are prepared at 3 mils thickness using a film casting applicator on release liner, such as 3M's 9744. The wet coating is air dried for 1 hour, and then oven dried at 60° C for 10 min. Finally, the laminate is dried onto the abuse deterrent layer, which was subsequently coated on 3M's backing Scotpak 1012.

The laminated sheet can be die-cut into transdermal delivery devices of various sizes, such as 10 cm^2, 20 cm^2, 100 cm^2, 300 cm^2 to obtain the desired dosages of the drug.

An exemplary composition of the adhesive drug matrix is given in Table 10.

TABLE 10

Ingredients	Wt %
Ketamine	15%
vinylpyrrolidone-vinyl acetate copolymers (Kollidon VA 64)	20%
DuroTak 87-4098	65%
Total	100%

Example 8

A transdermal delivery device according to Examples 7 is prepared with apomorphine, an emetic, in the abuse deterrent layer. After solvent extraction by an abuser, the emetic can cause severe nausea if injected, snorted, or inhaled. Apomorphine is preferably employed in the present invention from about 0.05-5% by weight of the final formulation, and most preferred from about 0.1-2% by weight.

Example 9

Example 9 was prepared in accordance with Example 7, with the exception that the abuse deterrent agent is capsaicin. After being dissolved in solvents by an abuser, the ketamine solution containing capsaicin will cause a torturous burning sensation if snorted or inhaled, thereby reducing the abuse potential of the transdermal drug delivery device.

Examples 10

Table 11 provides additional techniques by which the abuse deterrent agents can be employed in the transdermal delivery device of the present invention.

TABLE 11

Potential Route of Manipulation/Abuse	Abuse Deterrent Agents
Extraction with drinkable solvent (alcohol), followed by drinking	Denatonium released when abused, co-precipitates with ketamine, and bitters the drinkable solvent
Extraction with injectable medium, followed by injection	Gel forming agent will dissolve in medium, forming viscous liquid, which deters injection
Extraction with solvent, evaporation, followed by snorting	SLS will co-precipitate with ketamine, and cause nasal mucosal irritation upon snorting
Extraction with solvent, evaporation, followed by mixing with liquid and drinking	Denatonium released when abused, co-precipitates and dries with ketamine, and bitters the subsequent drinking liquid

Example 11

In an embodiment of the present invention is prepared according to Example 7, in which the adhesive-drug layer comprises an adhesive and 200 mg of ketamine, and the abuse deterrent layer comprises a gel forming agent comprising 7 mg of SLS and 5 mg of denatonium benzoate.

The foregoing description and examples have been set forth merely to illustrate the present invention and are not intended to be limiting. Since modifications of the described embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art, the invention should be construed broadly to include all variations within the scope of this application.

Date Reçue/Date Received 2021-09-24

Claims

1. A transdermal delivery device comprising a backing layer, an adhesive-drug layer, an optional abuse deterrent layer, and a release liner, wherein the adhesive-drug layer comprises ketamine of 10-25% by weight, a crystallization inhibitor, a skin permeation enhancer, and a pressure sensitive adhesive, wherein the transdermal delivery device provides a ketamine permeation rate of 0.1-5 mg/day/cm^2 for about 8 hours to about 168 hours, wherein the crystallization inhibitor comprises polyvinyl pyrrolidone-co-vinyl acetate or polymethacrylate, the skin permeation enhancer comprises oleyl oleate, oleyl alcohol, levulinic acid, diethylene glycol monoethyl ether or any combination thereof; and the pressure sensitive adhesive comprises an acrylic pressure sensitive adhesive.

2. The transdermal delivery device according to claim 1, comprising about 40 to about 60 weight percent of pressure sensitive adhesive, about 1 to about 10 weight percent of skin permeation enhancer, and about 5 to about 40 weight percent of crystallization inhibitor.

3. The transdermal delivery device according to claim 1 or 2, further comprising about 0.01 to about 10 weight percent of the abuse deterrent agent.

4. The transdermal delivery device according to any one of claims 1 to 3, wherein the abuse deterrent agent is capsaicin, apomorphine, denatonium, sodium laurel sulfate, a gel forming agent, or any combinations thereof.

5. The transdermal delivery device according to any one of claims 1 to 4, wherein the transdermal delivery device is for administration once a day, twice a week, or once a week for treating major depressive disorders.

6. The transdermal delivery device according to claim 5, wherein the transdermal delivery device is for administration once a day.

7. The transdermal delivery device according to claim 5, wherein the transdermal delivery device is for administration twice a week.

8. The transdermal delivery device according to claim 5, wherein the transdermal delivery device is for administration once a week.

Date Reçue/Date Received 2021-09-24

9. The transdermal delivery device according to any one of claims 1 to 8, wherein said transdermal delivery device has a size of about 10 to about 300 cm^2.

10. The transdermal delivery device according to claim 9, wherein said transdermal delivery device has a size of about 100 to about 300 cm^2.

11. The transdermal delivery device according to claim 9, wherein said transdermal delivery device has a size of about 10 to about 100 cm^2.

12. The transdermal delivery device according to any one of claims 1 to 11, wherein said ketamine is racemic.

13. The transdermal delivery device according to any one of claims 1 to 11, wherein said ketamine is the R-enantiomer.

14. The transdermal delivery device according to any one of claims 1 to 11, wherein said ketamine is the S-enantiomer.

15. The transdermal delivery device according to any one of claims 1 to 14, wherein the skin permeation enhancer comprises a combination of oleyl oleate and levulinic acid.

16. The transdermal delivery device according to any one of claims 1 to 14, wherein the skin permeation enhancer comprises a combination of oleyl alcohol, levulinic acid, and diethylene glycol monoethyl ether.

Date Reçue/Date Received 2021-09-24

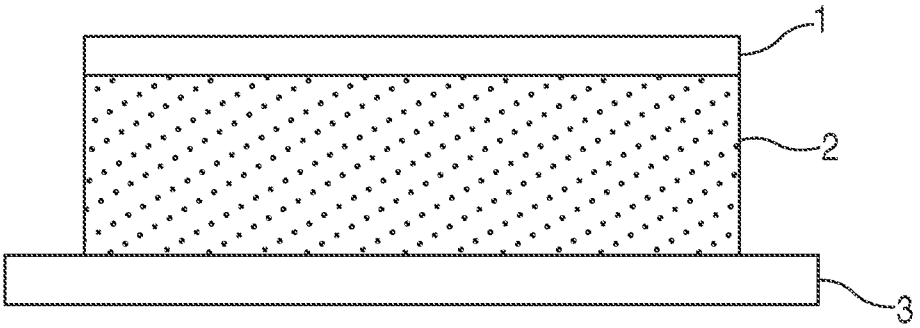


FIG. 1

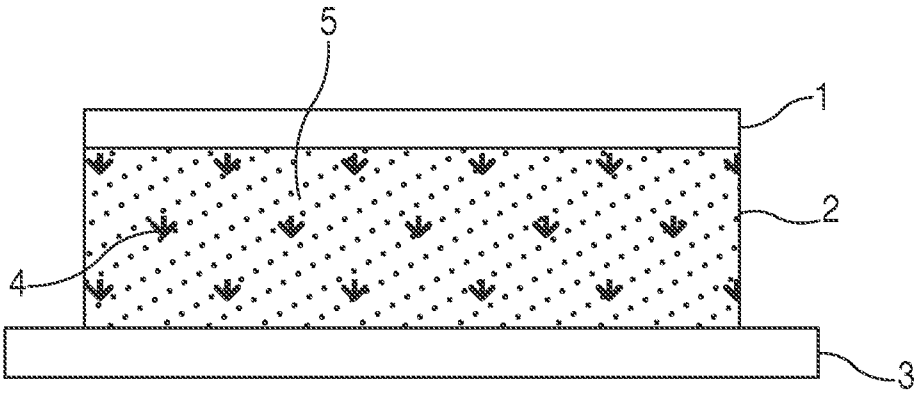


FIG. 2

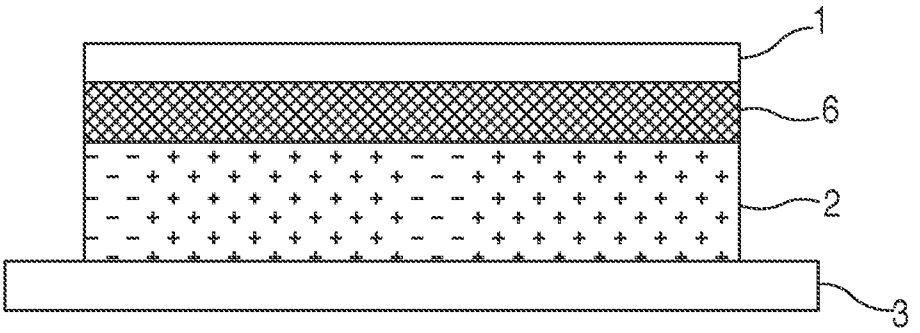


FIG. 3

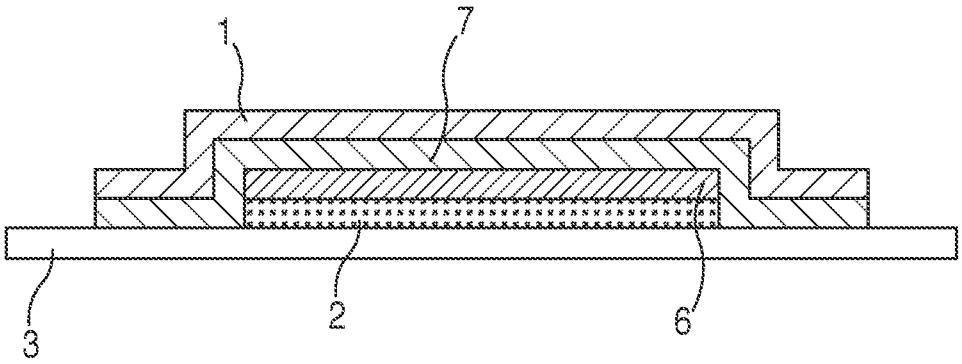

1
7
3
2
6

FIG. 4

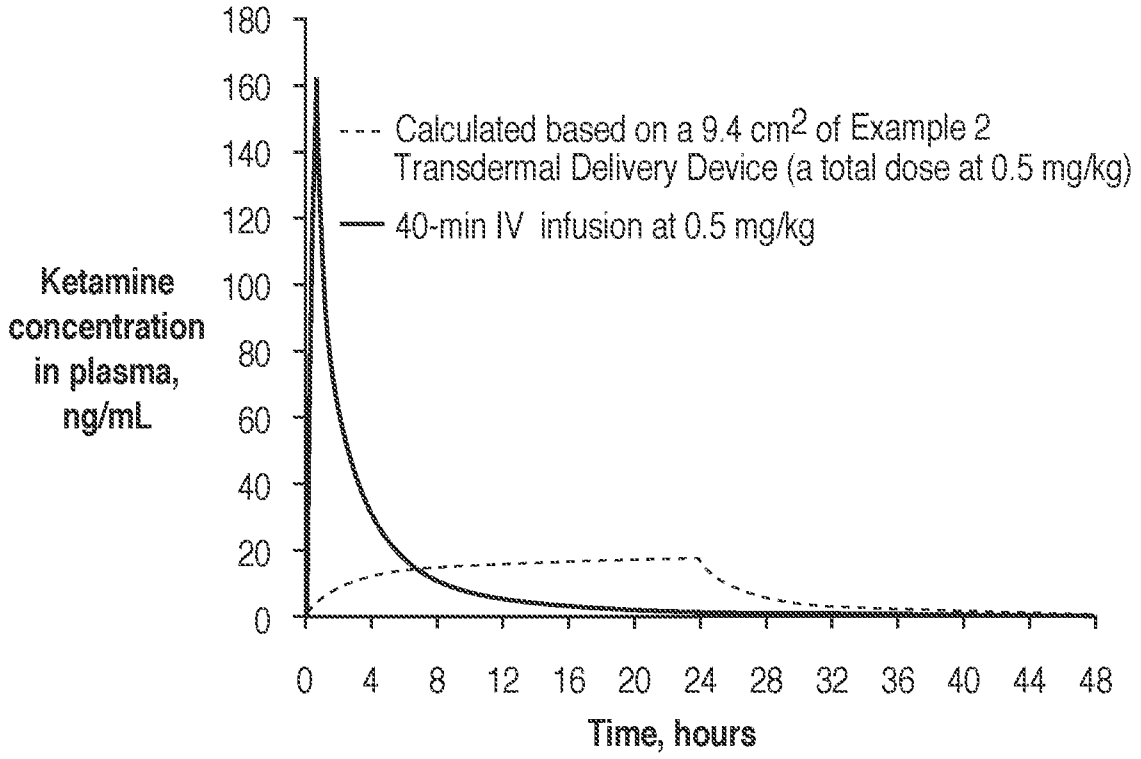

Ketamine concentration in plasma, ng/mL
180
160
140
120
100
80
60
40
20
0
Calculated based on a 9.4 cm2 of Example 2 Transdermal Delivery Device (a total dose at 0.5 mg/kg)
40-min IV infusion at 0.5 mg/kg
0 4 8 12 16 20 24 28 32 36 40 44 48
Time, hours

FIG. 5

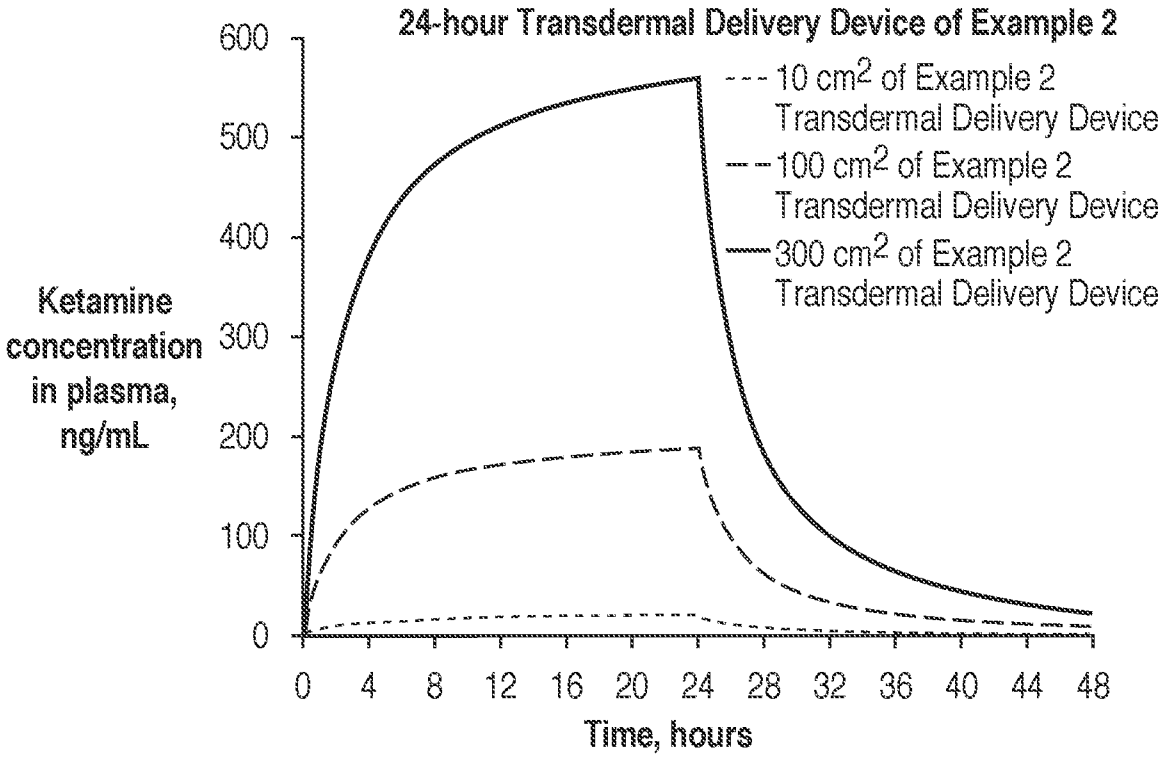

24-hour Transdermal Delivery Device of Example 2
10 cm2 of Example 2 Transdermal Delivery Device
100 cm2 of Example 2 Transdermal Delivery Device
300 cm2 of Example 2 Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
600
500
400
300
200
100
0
0 4 8 12 16 20 24 28 32 36 40 44 48
Time, hours

FIG. 6

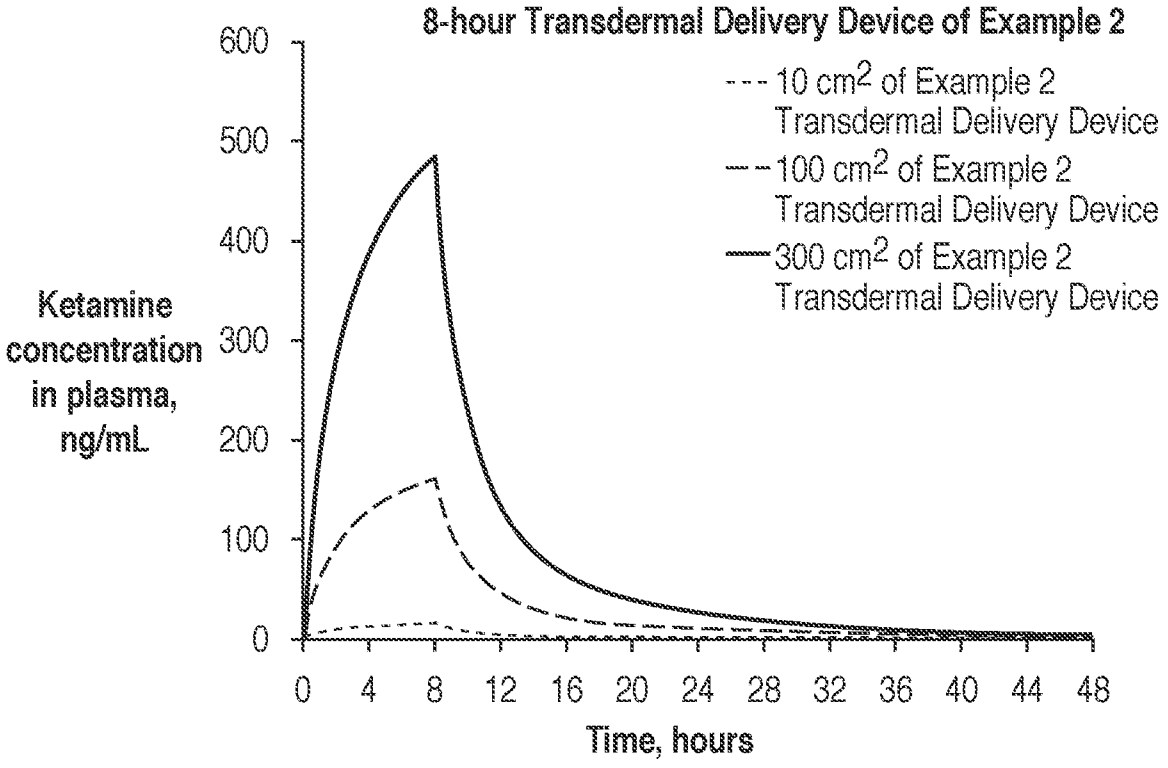

8-hour Transdermal Delivery Device of Example 2
10 cm2 of Example 2 Transdermal Delivery Device
100 cm2 of Example 2 Transdermal Delivery Device
300 cm2 of Example 2 Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
600
500
400
300
200
100
0
0 4 8 12 16 20 24 28 32 36 40 44 48
Time, hours

FIG. 7

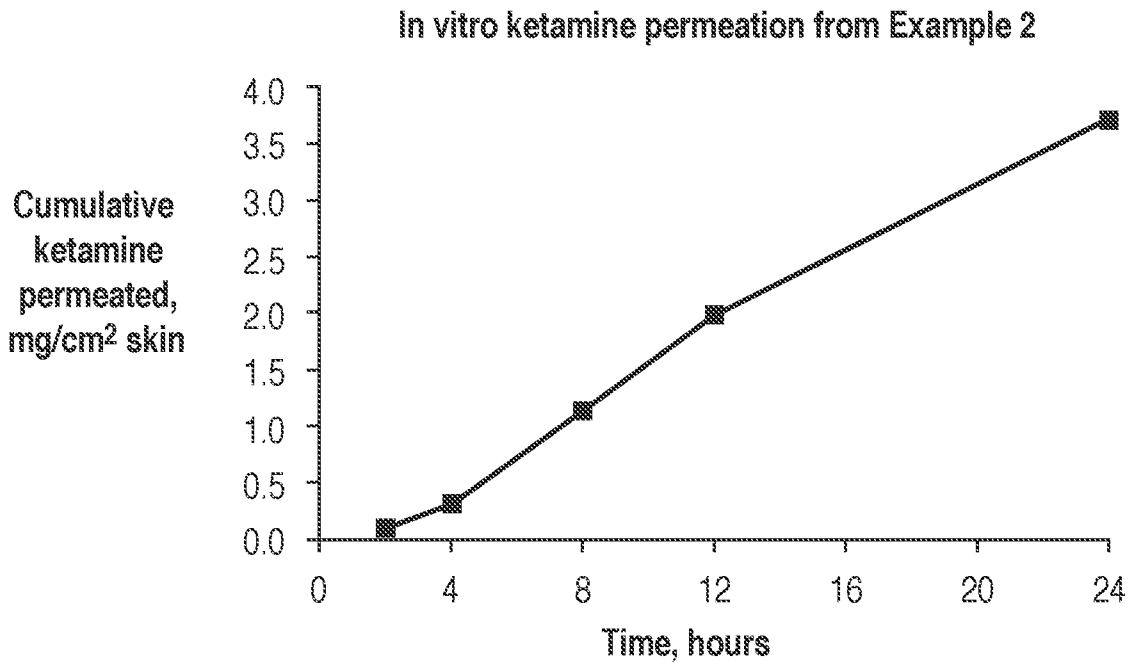

In vitro ketamine permeation from Example 2
Cumulative ketamine permeated, mg/cm2 skin
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
4
8
12
16
20
24
Time, hours

FIG. 8

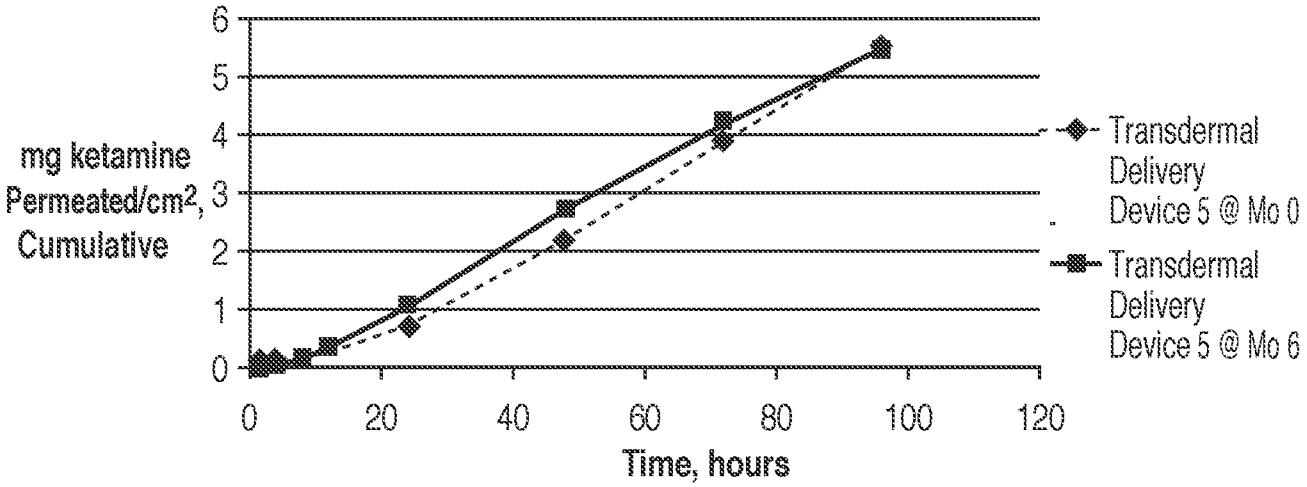

mg ketamine Permeated/cm2, Cumulative
6
5
4
3
2
1
0
0
20
40
60
80
100
120
Time, hours
Transdermal Delivery Device 5 @ Mo 0
Transdermal Delivery Device 5 @ Mo 6

FIG. 9

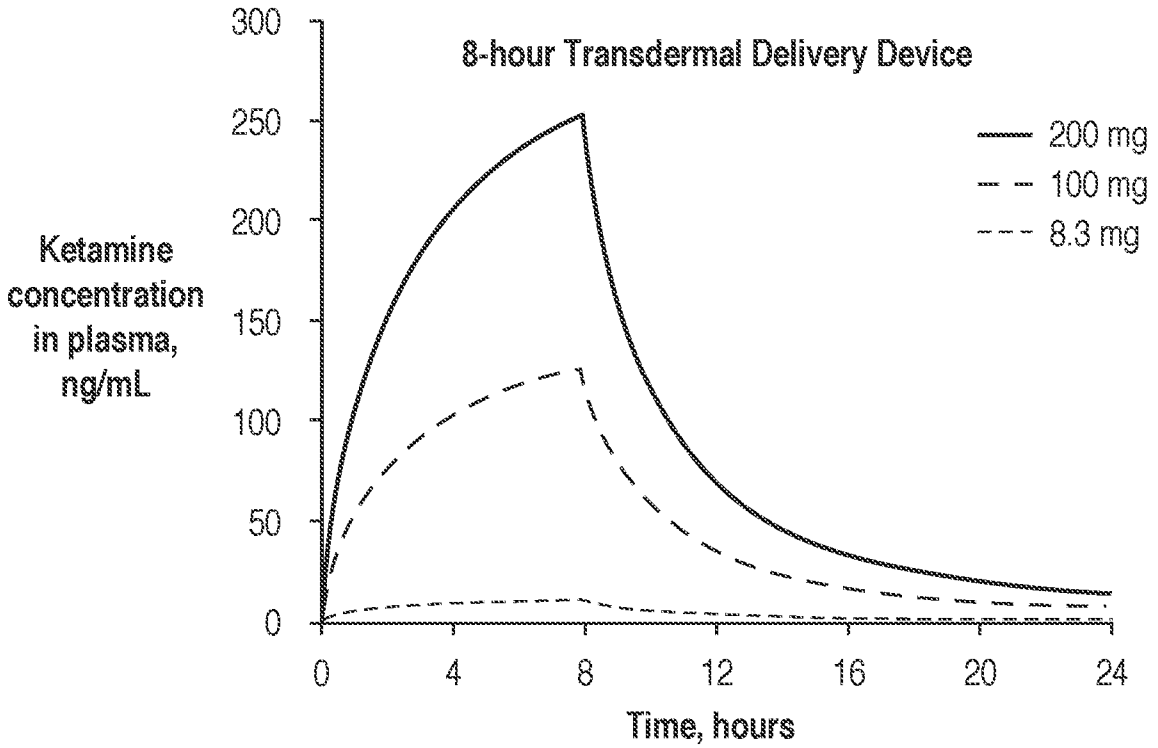

8-hour Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
300
250
200
150
100
50
0
0
4
8
12
16
20
24
Time, hours
200 mg
100 mg
8.3 mg

FIG. 10

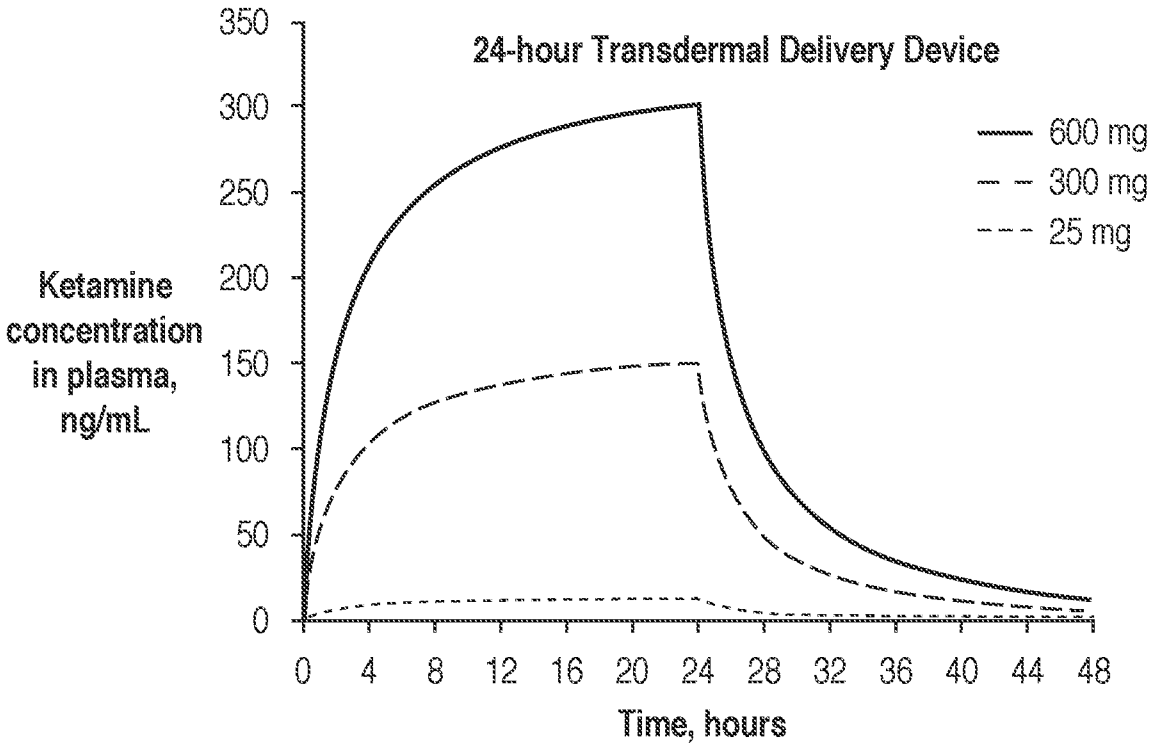

24-hour Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
350
300
250
200
150
100
50
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Time, hours
600 mg
300 mg
25 mg

FIG. 11

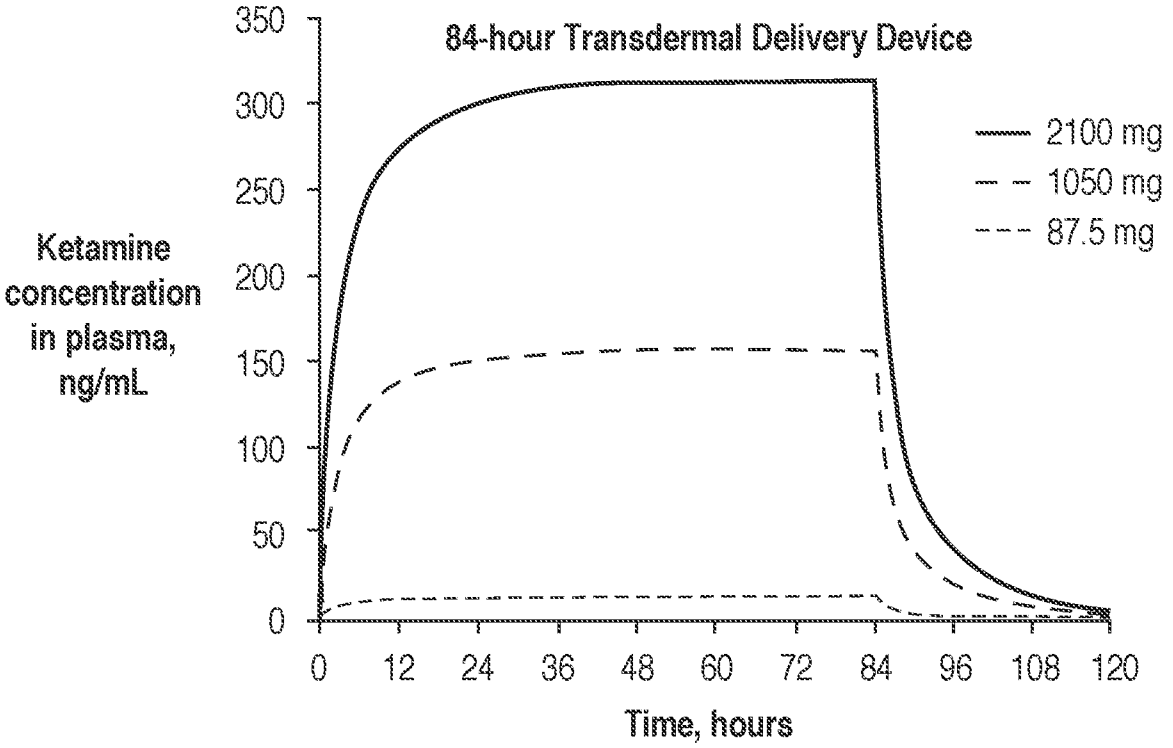

84-hour Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
350
300
250
200
150
100
50
0
0 12 24 36 48 60 72 84 96 108 120
Time, hours
2100 mg
1050 mg
87.5 mg

FIG. 12

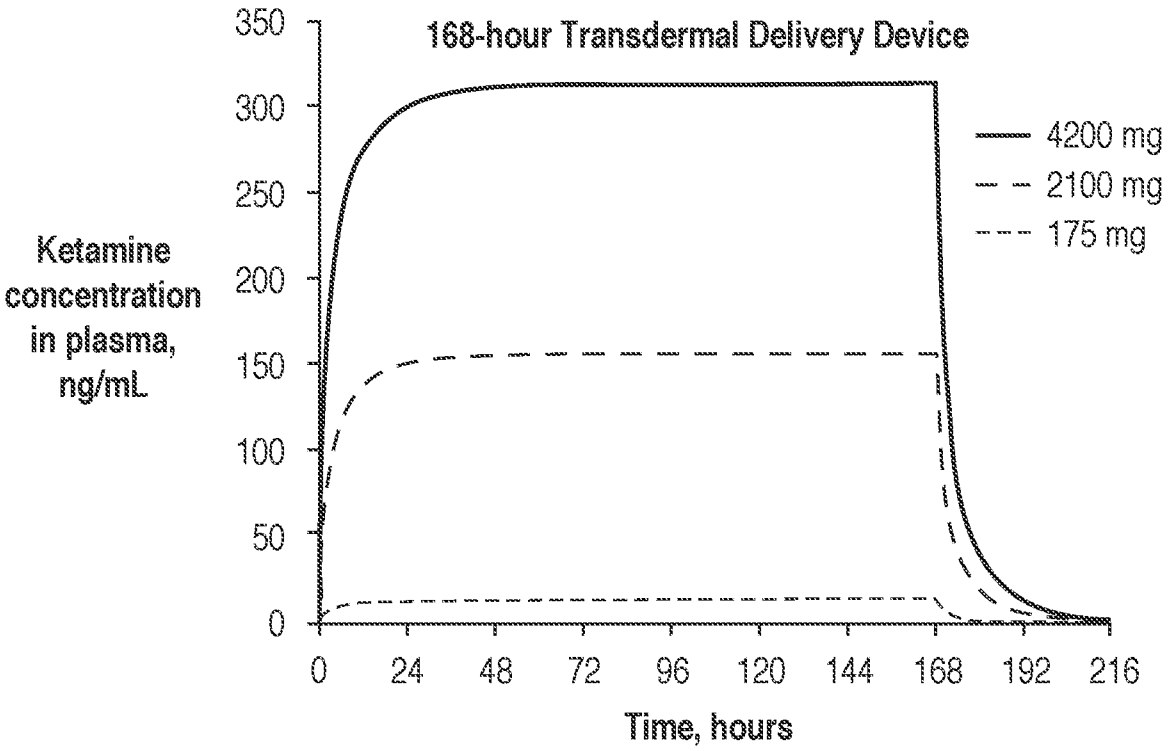

168-hour Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
350
300
250
200
150
100
50
0
0 24 48 72 96 120 144 168 192 216
Time, hours
4200 mg
2100 mg
175 mg

FIG. 13

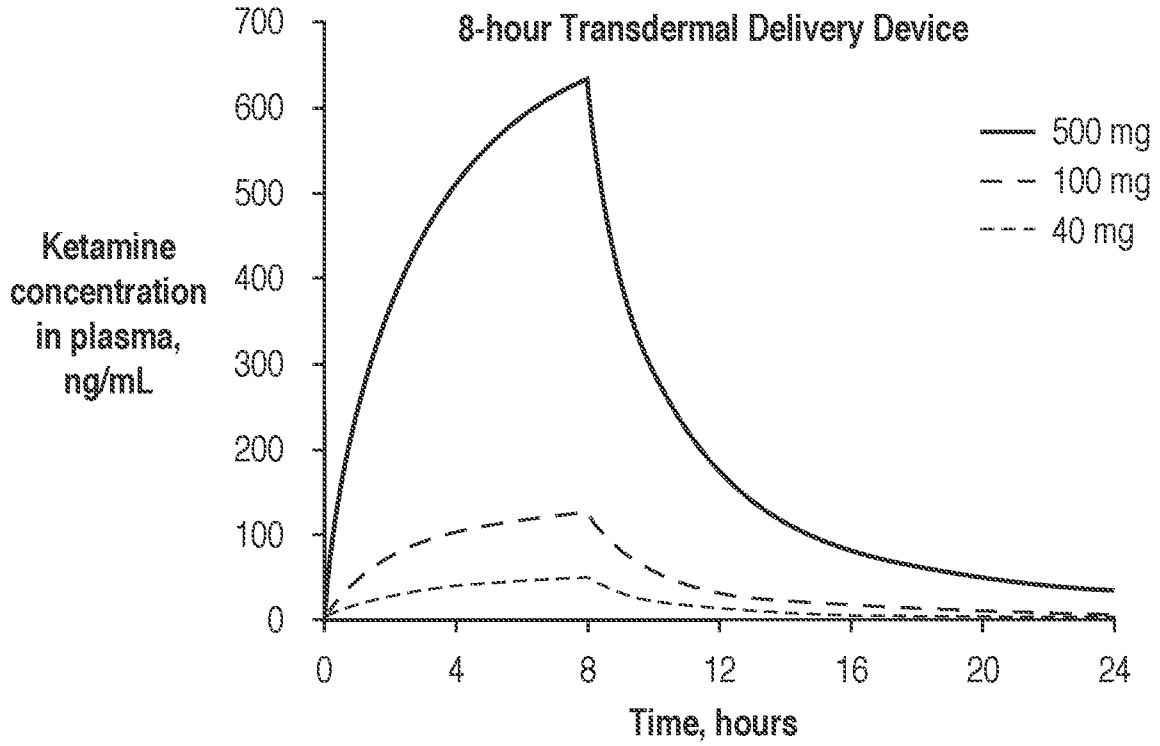

8-hour Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time, hours
500 mg
100 mg
40 mg

FIG. 14

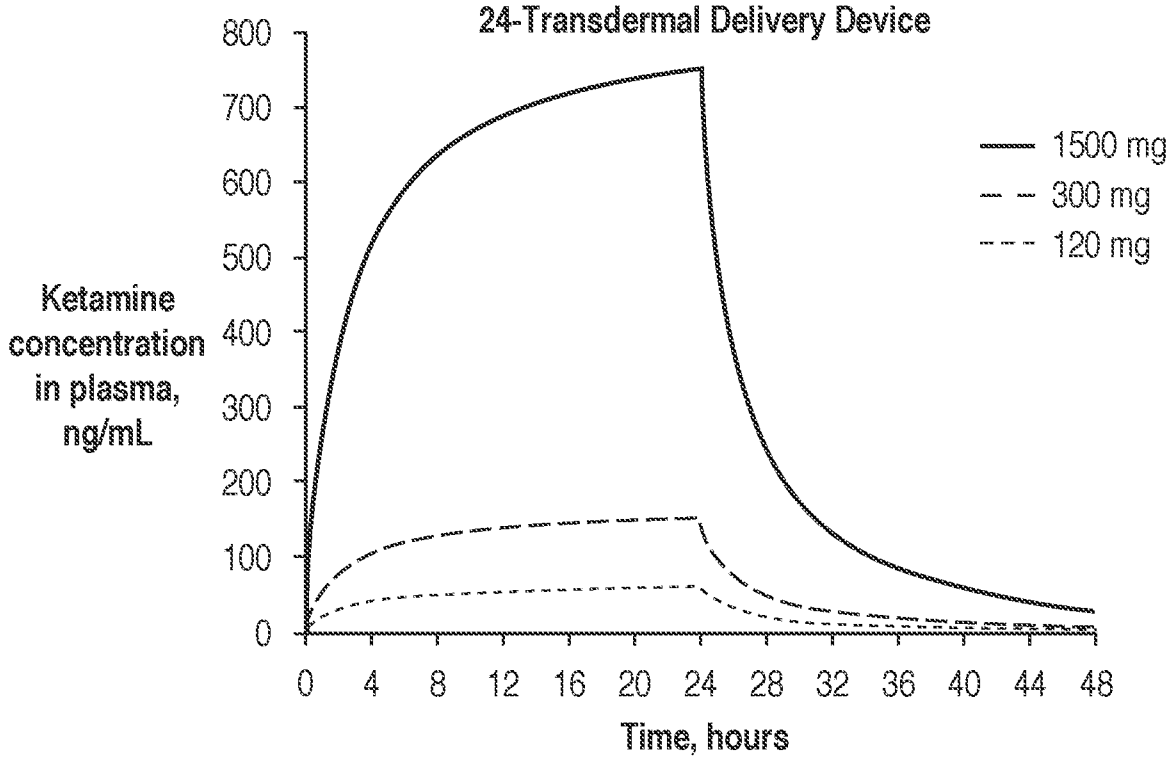

24-Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
800
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Time, hours
1500 mg
300 mg
120 mg

FIG. 15

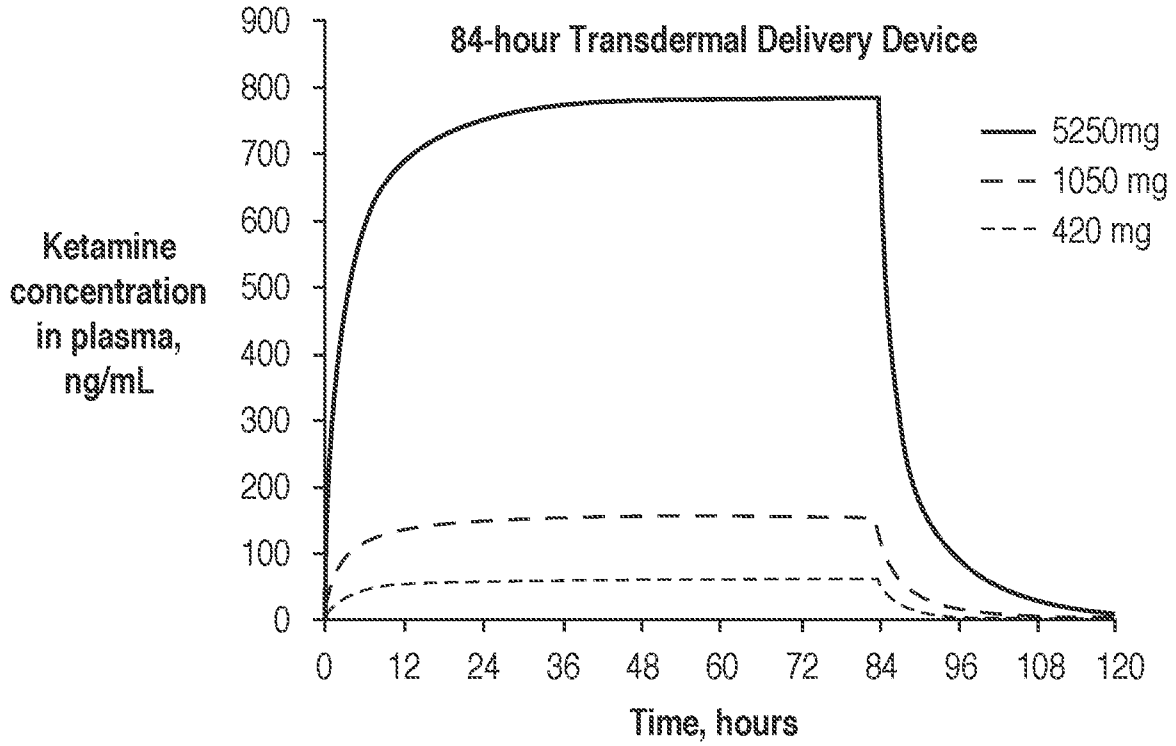

84-hour Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
900
800
700
600
500
400
300
200
100
0
0 12 24 36 48 60 72 84 96 108 120
Time, hours
5250mg
1050 mg
420 mg

FIG. 16

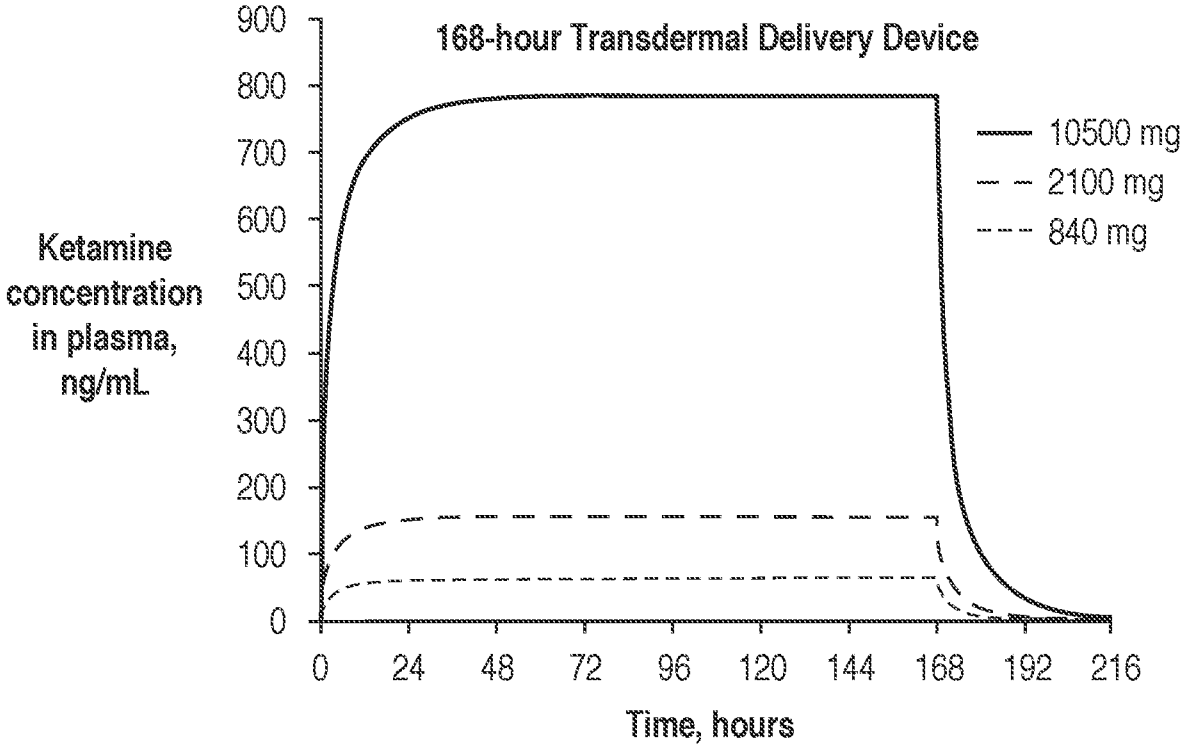
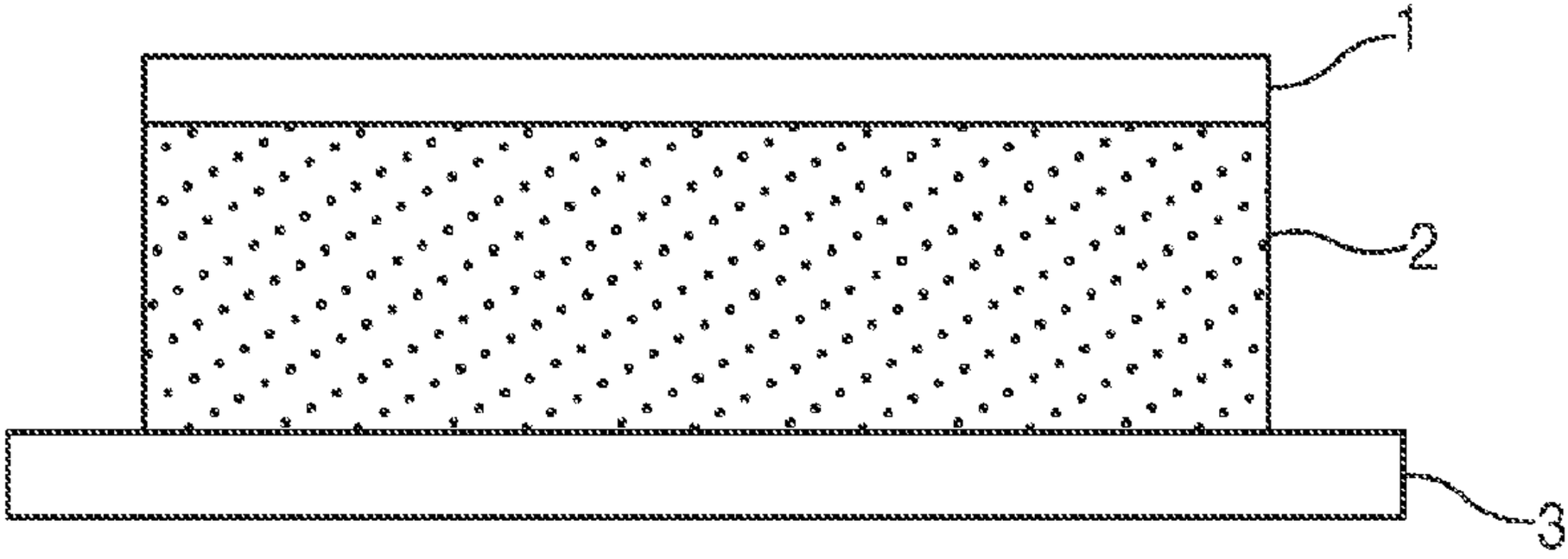

168-hour Transdermal Delivery Device
Ketamine concentration in plasma, ng/mL
900
800
700
600
500
400
300
200
100
0
0 24 48 72 96 120 144 168 192 216
Time, hours
10500 mg
2100 mg
840 mg

FIG. 17


1
2
3