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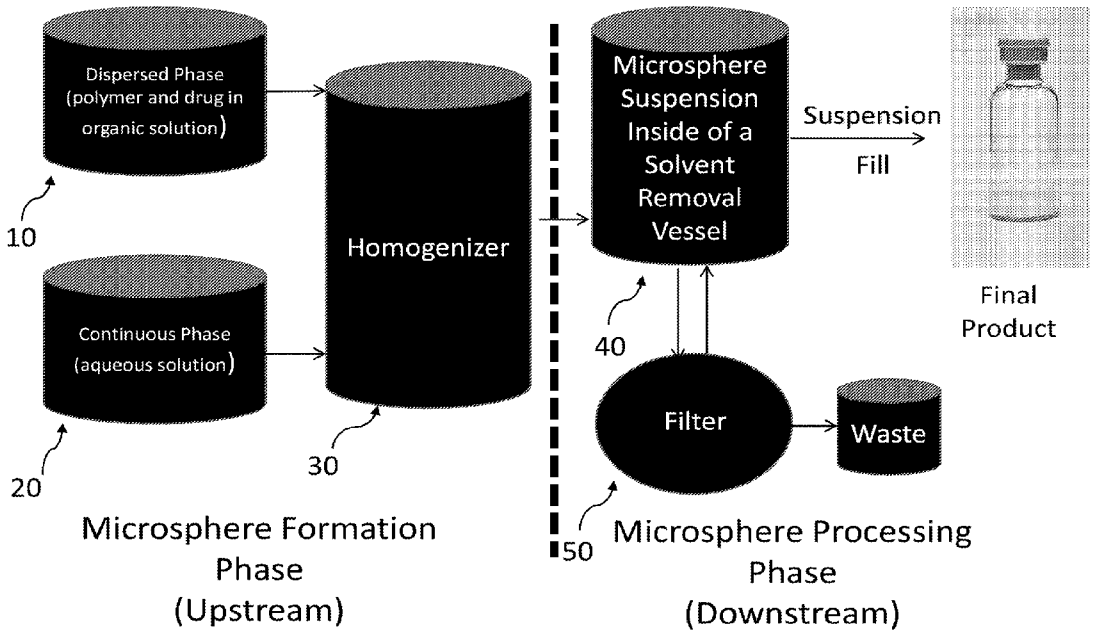

FIG. 1

(57) Abstract: Extended-release, injectable microsphere formulations comprising ketamine are provided. Methods for making and using the microsphere formulations are also provided.

[Continued on next page]

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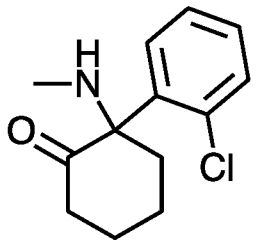
MICROSPHERE FORMULATIONS COMPRISING KETAMINE AND METHODS FOR MAKING AND USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Patent Application No. 63/067,068, filed on August 18, 2020, and U.S. Provisional Patent Application No. 63/149,911, filed on February 16, 2021, each of which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] Ketamine (chemical formula $C_{13}H_{16}ClNO$, IUPAC name 2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one), characterized by the general structure:



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is an N-methyl-D-aspartate ("NMDA") receptor antagonist. Ketamine has primarily been used for anesthesia in humans and animals, as well as for chronic pain and sedation. Ketamine is typically available commercially in liquid form for use as an immediate-acting injection.

[0003] Ketamine is a racemic mixture of two enantiomers, (S)-(+)-ketamine and (R)-(-)-ketamine. The (S)-(+) enantiomer, also known as esketamine, is significantly more potent as an NMDA receptor antagonist and anesthetic than is the (R)-(-) enantiomer, also known as arketamine.

[0004] Ketamine and its enantiomers have also been investigated for treatment of depression. The U.S. Food and Drug Administration ("FDA") has approved esketamine for use, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression ("TRD") and major

depressive disorder ("MDD") in adults. Specifically, the FDA approved Spravato® nasal spray. For the treatment of TRD, the manufacturer recommends that the drug be administered twice per week for the first four weeks, weekly for the next four weeks, then weekly or biweekly.

[0005] Ketamine is also used by recreational drug users and abusers. Ketamine is a Schedule III drug under the U.S. Drug Enforcement Agency's controlled substance classifications under the Controlled Substances Act. In part because of the significant possibility for diversion, Spravato® nasal spray is approved only for administration under the direct supervision of a healthcare provider. This requires a patient to make multiple trips per week to a doctor's office or hospital for the first four weeks, then weekly visits thereafter, making treatment inconvenient for the patient. Patients are also required to stay in the doctor's office or hospital for at least two hours after administration, adding to the patient's inconvenience. Until now, there has been a long felt yet unresolved need for a ketamine formulation that reduces the number of visits a patient needs to make to a provider's office to receive treatment, to reduce cost and inconvenience to the patient and the provider, while maintaining the ability to keep the drug in the hands of the healthcare providers to prevent diversion.

SUMMARY

[0006] Microsphere formulations comprising ketamine are provided. The microsphere formulations comprise polymer microspheres, each polymer microsphere comprising: (i) an active pharmaceutical ingredient ("API") comprising, consisting essentially of, or consisting of ketamine; and (ii) a biodegradable polymer comprising, consisting essentially of, or consisting of a poly(lactide) ("PLA") polymer. Each polymer microsphere may comprise a drug load of between about 10 wt/wt% to about 30 wt/wt%, and the polymer microspheres may have an average particle size of greater than 60 μm (D_{50}), including from about 80 μm (D_{50}) to about 110 μm (D_{50}). In

some aspects, the polymer microspheres are characterized by a plurality of internal emulsions, each emulsion comprising water and a surfactant. In some aspects, the polymer microspheres may be subjected to dehydration, in which case the polymer microspheres are characterized by a plurality of internal macrovoids.

[0007] In some aspects, the polymer microspheres are double emulsified. A method for making double emulsified polymer microspheres is provided, the method comprising: (i) contacting ketamine with a biodegradable PLA polymer in the presence of a solvent to form an organic component and providing the organic component to a first homogenizer; (ii) providing an inner aqueous component comprising water and a first surfactant to the first homogenizer; (iii) homogenizing the organic component with the inner aqueous component to form a primary emulsion; (iv) providing the primary emulsion to a second homogenizer at a first flow rate; (v) providing a continuous phase comprising water and a second surfactant to the second homogenizer at a second flow rate; (vi) homogenizing the primary emulsion and the continuous phase; and (iv) removing the solvent to form the polymer microspheres, wherein each of the formed polymer microspheres incorporates at least a portion of the inner aqueous component in the form of a plurality of emulsions. In some aspects, the polymer microspheres may be subjected to dehydration, in which case the polymer microspheres are characterized by a plurality of internal macrovoids.

[0008] In another aspect, a method for treating depression, including TRD and/or MDD, is provided. The method may comprise administering to a patient in need thereof a microsphere formulation, the microsphere formulation comprising: polymer microspheres, each polymer microsphere comprising: (i) an API comprising, consisting essentially of, or consisting of ketamine; and (ii) a biodegradable polymer comprising, consisting essentially of, or consisting of

a PLA polymer. Each polymer microsphere may comprise a drug load of between about 10 wt/wt% to about 30 wt/wt%, and the polymer microspheres may have an average particle size of greater than 60 μm (D_{50}), including from about 80 μm (D_{50}) to about 110 μm (D_{50}). In some aspects, the microsphere formulation is administered to the patient by intramuscular or subcutaneous injection with a dosing schedule of about every thirty days.

[0009] In another aspect, a method for treating pain is provided. The method may comprise administering by intramuscular or subcutaneous injection to a patient in need thereof a microsphere formulation made according to the methods described herein.

[0010] In another aspect, use is disclosed of a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) an API comprising, consisting essentially of, or consisting of ketamine; and (ii) a biodegradable polymer comprising, consisting essentially of, or consisting of a PLA polymer, wherein each polymer microsphere may comprise a drug load of between about 10 wt/wt% to about 30 wt/wt%, and the polymer microspheres may have an average particle size of greater than 60 μm (D_{50}), including from about 80 μm (D_{50}) to about 110 μm (D_{50}), in the manufacture of a medicament for the treatment of depression.

[0011] In another aspect, a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) an API comprising, consisting essentially of, or consisting of ketamine; and (ii) a biodegradable polymer comprising, consisting essentially of, or consisting of a PLA polymer, wherein each polymer microsphere may comprise a drug load of between about 10 wt/wt% to about 30 wt/wt%, and the polymer microspheres may have an average particle size of greater than 60 μm (D_{50}), including from about 80 μm (D_{50}) to about 110 μm (D_{50}), is provided for use as a medicament for the treatment of depression.

BRIEF DESCRIPTION OF THE FIGURES

[0012] **Figure 1** is a flow chart illustrating an example method for making a single-emulsified microsphere formulation.

[0013] **Figure 2** is a graph showing an example effect of drug load on the amount of ketamine released in vitro over time from a microsphere formulation prepared using a single emulsification technique.

[0014] **Figure 3** is a graph showing an example effect of co-monomer ratio of the biodegradable polymer on the amount of ketamine released in vitro over time from a microsphere formulation prepared using a single emulsification technique.

[0015] **Figure 4** is a graph showing the effect of average polymer microsphere size on the amount of ketamine released in vitro over time from a microsphere formulation prepared using a single emulsification technique.

[0016] **Figure 5** is a graph showing an example effect of the inherent viscosity of the biodegradable polymer and/or choice of solvent on the release of ketamine in vitro over time from three example double emulsified microsphere formulations and one example single emulsified formulation.

[0017] **Figure 6** is a flow chart illustrating an example method for making a double-emulsified microsphere formulation.

[0018] **Figure 7** is a graph showing an amount of ketamine released in vitro over time from an example double emulsified microsphere formulation.

[0019] **Figure 8** is a graph showing example results of a pharmacokinetics study in rats using microsphere formulations as described herein.

[0020] **Figure 9** is a graph showing an amount of ketamine release in vitro over time from several microsphere formulations prepared using a double emulsification technique.

[0021] **Figure 10** is a graph showing an amount of ketamine release in vitro over time versus a linear 30 day release from a microsphere formulation prepared using a double emulsification technique.

[0022] **Figures 11A** and **11B** are two photographs showing a comparison between polymer microspheres prepared using a double emulsion technique (**Figure 11A**) and a single emulsion technique (**Figure 11B**), each prior to dehydration.

DETAILED DESCRIPTION

[0023] Microsphere formulations comprising ketamine are provided. The microsphere formulations comprise polymer microspheres, each polymer microsphere comprising: (i) an API comprising, consisting essentially of, or consisting of ketamine; and (ii) a biodegradable polymer comprising, consisting essentially of, or consisting of a PLA polymer. Each polymer microsphere may comprise a drug load of between about 10 wt/wt% to about 30 wt/wt%, and the polymer microspheres may have an average particle size of greater than 60 μm (D_{50}), including from about 80 μm (D_{50}) to about 110 μm (D_{50}). In some aspects, the polymer microspheres are characterized by a plurality of internal emulsions, each emulsion comprising water and a surfactant. In some aspects, the polymer microspheres may be subjected to dehydration, in which case the polymer microspheres are characterized by a plurality of internal macrovoids.

[0024] In some aspects, the polymer microspheres are double emulsified. A method for making double-emulsified polymer microspheres is provided, the method comprising: (i) contacting ketamine with a biodegradable PLA polymer in the presence of a solvent to form an organic component and providing the organic component to a first homogenizer; (ii) providing an

inner aqueous component comprising water and a first surfactant to the first homogenizer; (iii) homogenizing the organic component with the inner aqueous component to form a primary emulsion; (iv) providing the primary emulsion to a second homogenizer at a first flow rate; (v) providing a continuous phase comprising water and a second surfactant to the second homogenizer at a second flow rate; (vi) homogenizing the primary emulsion and the continuous phase; and (iv) removing the solvent to form the polymer microspheres, wherein each of the formed polymer microspheres incorporates at least a portion of the inner aqueous component in the form of a plurality of emulsions. In some aspects, the polymer microspheres may be subjected to dehydration, in which case the polymer microspheres are characterized by a plurality of internal macrovoids.

API - Ketamine

[0025] In some aspects, the ketamine comprises a racemic mixture. In some aspects, the ketamine may comprise esketamine to the exclusion of arketamine. Alternatively, the ketamine may comprise arketamine to the exclusion of esketamine.

[0026] In some aspects, the ketamine may comprise a pharmaceutically acceptable salt form or a free base form of any of ketamine, esketamine to the exclusion of arketamine, and arketamine to the exclusion of esketamine. Suitable salts may include hydrochloride, sulfate, acetate, phosphate, diphosphate, chloride, maleate, citrate, mesylate, nitrate, tartrate, gluconate, and the like. In other aspects, a complex salt may be used to decrease solubility, such as ketamine palmitate, ketamine benzoic acid, ketamine tosylic acid, ketamine camphor-sulfonic acid, and the like.

[0027] Unless otherwise noted, as used herein, the term “ketamine” is intended to include the racemic mixture as well as both of its individual enantiomers. In some aspects, the ketamine may

be used in its racemic form. Alternatively, the ketamine may be used in its enantiomeric forms, such as in its "S" or "R" forms. An aspect may also include purified forms of the enantiomeric forms. For example, and without limitation, the "S" enantiomer to "R" enantiomer ratio may be from 51:49 up to 100:0 and every range included therein. Alternative aspects may comprise more purified forms of the "R" enantiomer over the "S" enantiomer. For example, and without limitation, the "R" enantiomer to "S" enantiomer ratio may be from 51:49 up to 100:0, and every range included therein. Each enantiomer may also exist in its (+) or (-) forms, such as in S(+) or S(-) forms. An alternative aspect is the use of a purified form of esketamine in which the ratio of S(+) to S(-) may be from 51:49 up to 100:0, and every range included therein. An alternate aspect is the use of a purified form of esketamine in which the ratio of S(-) to S(+) may be from 51:49 up to 100:0, and every range included there.

[0028] In one aspect, the API consists or consists essentially of (S)-ketamine base (esketamine base). In one aspect, the microsphere formulation is exclusive of hydromorphone.

Biodegradable Polymers

[0029] PLA may be a suitable biodegradable polymer. In one aspect, the PLA may have an inherent viscosity ("IV") between about 0.30 to about 1.8 dL/g, including from about 0.60 to about 0.70 dL/g, and including about 0.66 dL/g or about 0.67 dL/g. In another aspect, the PLA may have an IV of about 0.67 dL/g. In one aspect, the biodegradable polymer is an Ashland DL 07E PLA polymer have an IV of about 0.67 dL/g.

[0030] As the phrase is used herein, a "poly(lactide) polymer" is to be distinguished from and does not include a poly(lactic-co-glycolic acid) polymer. When a poly(lactic-co-glycolic acid) is intended, it will be explicitly recited. In certain, explicitly recited aspects, suitable biodegradable polymers may include poly(lactic-co-glycolic acid) ("PLGA") copolymers, polyesteramides,

polyanhydrides, polyacetals, polycaprolactones, and polycarbonates. In some aspects, the biodegradable polymer may comprise a PLGA copolymer having a co-monomer ratio for lactide to glycolide content of about 50:50 to about 85:15. In one aspect, the biodegradable polymer may have an average molecular weight from about 30 kDa to about 300 kDa.

[0031] In some aspects, copolymers are specifically excluded. In one aspect, PLGA polymers are specifically excluded. In some aspects, PLGA polymers having a co-monomer ratio for lactide to glycolide content of about 50:50 are specifically excluded.

[0032] In some aspects, the biodegradable polymers are ester end-capped. In some aspects, acid end-capped biodegradable polymers are specifically excluded.

Dispersed Phase/Organic Component - Solvents

[0033] The ketamine and the polymer may be dissolved in a solvent mixture to form a dispersed phase (when using a single emulsion technique) or an organic component (when using a double emulsion technique). Suitable solvents may include methylene chloride (also known as dichloromethane or DCM), ethanol, ethyl acetate, acetic acid, acetone, acetonitrile, acetyl acetone, acrolein, acrylonitrile, allyl alcohol, 1,3-butanediol, 1,4-butanediol, 1-butanol, 2-butanol, tert-butanol, 2-butoxyethanol, n-butyl amine, butyl dioxitol acetate, butyraldehyde, butyric acid, 2-chloroethanol, diacetone alcohol, diacetyl, diethylamine, diethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol monobutyl ether, diethylene glycol monobutyl ether acetate, diethylene glycol monoethyl ether, diethylene glycol monoethyl ether acetate, diethylene glycol monomethyl ether, N,N-diethylnicotinamide, dimethyl sulfoxide, N,N-dimethylacetamide, N,N-dimethylformamide, 1,4-dioxane, 2-ethoxyethanol, 2-ethoxyethyl acetate, ethyl acetate, ethyl formate, ethylene glycol methyl ether acetate, formic acid, furfural, glycofurol, hexylene glycol, isobutanol, isopropyl alcohol, 2,6-lutidine, methyl acetate, methyl

ethyl ketone, methyl isopropyl ketone, methyl propionate, N-methylpyrrolidone, morpholine, tert-pentanol, 2-picoline, 3-picoline, 4-picoline, piperidine, 1-propanol, propionaldehyde, propylene oxide, pyridine, pyrimidine, pyrrolidine, tetrahydrofuran, tetramethylurea, triacetin, triethylene glycol, trimethyl phosphate, and combinations thereof. In some aspects, the solvent comprises DCM, ethanol, ethyl acetate, or a combination of two or all of them. In some aspects, the solvent consists or consists essentially of a combination of DCM and ethanol. In some aspects, the solvent consists or consists essentially of an about 5:1 (by volume) ratio of DCM:ethanol.

Double Emulsified Polymer Microspheres - Inner Aqueous Component

[0034] In one aspect, the organic component is homogenized with an inner aqueous component to form a primary emulsion. In one aspect, the inner aqueous component comprises water. In one aspect, the inner aqueous component comprises water and a surfactant. In one aspect, the surfactant comprises polyvinyl alcohol ("PVA"). In some aspects, the inner aqueous component comprises PVA in an amount of about 0.35% to about 1.0% by weight in water. In some aspects, the inner aqueous component comprises PVA in an amount of about 0.35% by weight in water. In some aspects, the inner aqueous component comprises PVA in an amount of about 1.0% by weight in water.

[0035] **Figures 11A** and **11B** are two photographs showing a comparison between polymer microspheres prepared using a double emulsion technique (**Figure 11A**) and a single emulsion technique (**Figure 11B**), each prior to dehydration. The double emulsified polymer microspheres are characterized in that each of the polymer microspheres incorporates a plurality of emulsions comprising water and the surfactant. In some aspects, the polymer microspheres may be subjected to dehydration, in which case the polymer microspheres are characterized by a plurality of internal macrovoids.

[0036] In one aspect, dehydration may be achieved by freeze drying, including by lyophilization or cryodesiccation, i.e., a low temperature dehydration process that involves freezing the polymer microspheres, lowering pressure, and removing the ice by sublimation. This is in contrast to dehydration methods that evaporate water using heat.

Continuous Phase

[0037] The dispersed phase or the primary emulsion may be homogenized with a continuous phase comprising water and, optionally, a surfactant, such as PVA, to form a secondary emulsion. The surfactant component may be present in the continuous phase in an amount of about 0.35% to about 1.0% by weight in water. In one aspect, the surfactant component comprises PVA in an amount of about 0.35% by weight in water. In one aspect, the surfactant component comprises PVA in an amount of about 1.0% by weight in water. The secondary emulsion may be subjected to solvent removal and washing processes to form the double emulsified polymer microspheres.

[0038] In some aspects, the dispersed phase/primary emulsion flow rate to the homogenizer may from about 10 mL/min to about 30 mL/min, including about 20 mL/min and about 25 mL/min. In some aspects, the continuous phase flow rate to the homogenizer may be about 2L/min. Thus, in one aspect, the continuous phase:dispersed phase/primary emulsion ratio may be from about 66:1 to about 200:1, including about 100:1 and about 80:1.

[0039] The continuous phase may be provided at room temperature or above or below room temperature. In some aspects, the continuous phase may be provided at about 40 °C, about 37 °C, about 35 °C, about 30 °C, about 25 °C, about 20 °C, about 15 °C, about 10 °C, about 5 °C, about 0 °C, and any range or value between any of those values.

Homogenizer

[0040] In some aspects, the homogenization of the organic component and the inner aqueous component may be conducted in a high-speed homogenizer, e.g., in a T25 Ultra-turrax high-speed homogenizer operating, e.g., at 21,500 rpm for 30 seconds to form the primary emulsion. In other aspects, the homogenization of the organic component and the inner aqueous component may be conducted in a sonicator, e.g., a Q700 Sonicator (manufactured by Qsonica), or in a magic LAB® DISPAX-REACTOR® DR (manufactured by IKA).

[0041] In some aspects, the homogenization of the dispersed phase/primary emulsion and the continuous phase may be conducted in an emulsifier or a homogenizer. For brevity, and because the methods are equally applicable to either, the phrase "homogenizer" contemplates a system or apparatus that can homogenize the dispersed phase/primary emulsion and the continuous phase, emulsify the dispersed phase/primary emulsion and the continuous phase, or both, which systems and apparatuses are known in the art. For example, in one aspect, the homogenizer is an in-line Silverson Homogenizer (commercially available from Silverson Machines, Waterside UK) or a Levitronix® BPS-i100 integrated pump system used, e.g., as described in US20210001290, which is incorporated by reference herein in its entirety. In one aspect, the homogenizer is a membrane emulsifier. In one aspect, the homogenizer runs at an impeller speed of about 1,000 to about 4,000 revolutions per minute ("RPM"), including about 1,600 RPM.

Average Particle Size

[0042] The polymer microspheres may be any size that is safely and efficaciously injectable by intramuscular or subcutaneous injection. In one aspect, the polymer microspheres may have an average particle size greater than 60 μm (D_{50}) to about 110 μm (D_{50}), including between about

80 μm (D_{50}) and about 110 μm (D_{50}). In one aspect, particle sizes of 60 μm or less are excluded. In one aspect, particle sizes of less than 80 μm (D_{50}) are excluded.

Drug Load

[0043] The drug load of each polymer microsphere in a drug to polymer ratio, expressed as a percentage, may range from between about 10 wt/wt% to about 50 wt/wt%, from between about 10 wt/wt% to about 30 wt/wt%, or from between about 10 wt/wt% to about 20 wt/wt%.

Extended Release

[0044] The microsphere formulations are characterized in that they have an in vitro (under physiologically relevant conditions) and an in vivo duration of ketamine release of about 30 days. In some aspects, the microsphere formulations are characterized in that the ketamine is released from the polymer microspheres at an average rate of about 2.5% to about 3.5% per day over a 30-day period.

Therapeutic Benefits

[0045] Possible conditions that may be treated using the microsphere formulations include depression, TRD, MDD, conditions involving excitotoxicity including neurodegenerative diseases and benzodiazepine withdrawal, pain, and other diseases or conditions that may be treated by the inhibition of action of the NMDA receptor.

[0046] In one aspect, depression, TRD, or MDD may be treated using the microsphere formulations, wherein the microsphere formulations are administered every about 30 days.

[0047] In another aspect, a method for treating depression, including TRD and/or MDD, is provided. The method may comprise administering to a patient in need thereof a microsphere formulation, the microsphere formulation comprising: polymer microspheres, each polymer microsphere comprising: (i) an API comprising, consisting essentially of, or consisting of

ketamine; and (ii) a biodegradable polymer comprising, consisting essentially of, or consisting of a PLA polymer, wherein each polymer microsphere may comprise a drug load of between about 10 wt/wt% to about 30 wt/wt%, and the polymer microspheres may have an average particle size of greater than 60 μm (D_{50}), including from about 80 μm (D_{50}) to about 110 μm (D_{50}). In some aspects, the microsphere formulation is administered to the patient by intramuscular or subcutaneous injection with a dosing schedule of about every thirty days.

[0048] In another aspect, a method for treating pain is provided. The method may comprise administering by intramuscular or subcutaneous injection to a patient in need thereof a microsphere formulation made according to the methods described herein.

[0049] In another aspect, use is disclosed of a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) an API comprising, consisting essentially of, or consisting of ketamine; and (ii) a biodegradable polymer comprising, consisting essentially of, or consisting of a PLA polymer, wherein each polymer microsphere may comprise a drug load of between about 10 wt/wt% to about 30 wt/wt%, and the polymer microspheres may have an average particle size of greater than 60 μm (D_{50}), including from about 80 μm (D_{50}) to about 110 μm (D_{50}), in the manufacture of a medicament for the treatment of depression.

[0050] In another aspect, a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) an API comprising, consisting essentially of, or consisting of ketamine; and (ii) a biodegradable polymer comprising, consisting essentially of, or consisting of a PLA polymer, wherein each polymer microsphere may comprise a drug load of between about 10 wt/wt% to about 30 wt/wt%, and the polymer microspheres may have an average particle size of greater than 60 μm (D_{50}), including from about 80 μm (D_{50}) to about 110 μm (D_{50}), is provided for use as a medicament for the treatment of depression.

[0051] The microsphere formulations are extended-release, injectable formulations for administration via intramuscular or subcutaneous injection and not intrathecally. In some aspects, the intramuscularly or subcutaneously injectable formulation may further include sodium carboxymethylcellulose, tween 80, and mannitol.

EXAMPLES

Example 1 – General preparation of polymer microspheres comprising ketamine via a single emulsion method

[0052] Microsphere Formation Phase. With reference to **Figure 1**, a dispersed phase ("DP") 10 is formed by dissolving a polymer matrix (such as a PLA or PLGA polymer) in an organic solvent (such as DMC or ethyl acetate), followed by the addition of ketamine with mixing until completely dissolved. The DP 10 is filtered using a 0.2 μm sterilizing PTFE or PVDF membrane filter (such as EMFLON, commercially available from Pall or SartoriousAG) and pumped into a homogenizer 30, such as an in-line Silverson Homogenizer (commercially available from Silverson Machines, Waterside UK) or a Levitronix i100 (as described in US20210001290), at a defined flow rate. A continuous phase ("CP") 20 comprising water and, optionally, PVA is also pumped into the homogenizer 30 at a defined flow rate. The speed of the homogenizer 30 is generally fixed to achieve a desired polymer microsphere size distribution. A representative continuous "upstream" microsphere formation phase is described in U.S. Pat. No. 5,945,126, which is incorporated by reference herein in its entirety.

[0053] Microsphere Processing Phase. The formed or forming microspheres exit the homogenizer 30 and enter a solvent removal vessel ("SRV") 40. Water may be added to the SRV 40 during microsphere formation to minimize the solvent level in the aqueous medium. After the DP 10 has been exhausted, the CP and water flow rates are stopped, and the washing steps are

initiated. Solvent removal is achieved using water washing and a hollow fiber filter (commercially available as HFF from GE Healthcare) 50. A representative "downstream" microsphere processing phase is described in U.S. Pat. No. 6,270,802, which is incorporated by reference herein in its entirety.

[0054] The washed microspheres are collected and freeze-dried overnight in a lyophilizer (Virtis) to remove any moisture. The resulting microspheres are a free-flowing off-white bulk powder.

Example 2 – Preparation of PLGA-based single emulsion microsphere formulation

[0055] Batch No. 1: The DP was formed by dissolving 1.25 g of ester end-capped PLGA Evonik LG 855S polymer (IV = 3.0 dL/g) in 25.5 g DCM, followed by the addition of esketamine (3.75 g) with mixing until completely dissolved. The DP was filtered and pumped at 30 mL/minute into a Silverson L4RT in-line homogenizer operating at 2,000 rpm. A CP comprising water and 0.35% PVA was simultaneously pumped into the homogenizer at 2 L/min to form the single emulsion.

[0056] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder with a yield of about 45%.

[0057] Batch No. 1 was tested in an in vitro assay mimicking physiological conditions and resulted in esketamine release over a period of approximately 45 days, which was beyond the desired 30 day release profile.

Example 3 – Preparation of PLA-based single emulsion microsphere formulation

[0058] Batch No. 2: The DP was formed by dissolving 1.25 g of ester end-capped PLA Evonik LG 209S polymer (IV = 2.9 dL/g) in 25.5 g DCM, followed by the addition of esketamine (3.75 g) with mixing until completely dissolved. The DP was filtered and pumped at 30 mL/minute into a Silverson L4RT in-line homogenizer operating at 2,000 rpm. A CP comprising water and 0.35% PVA was simultaneously pumped into the homogenizer at 2 L/min to form the single emulsion.

[0059] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder with a yield of about 36%.

[0060] Batch No. 2 was tested in an in vitro assay mimicking physiological conditions and resulted in esketamine release over a period of approximately 60 days, which was beyond the desired 30 day release profile.

Example 4 – Effect of drug load on ketamine release in PLGA-based single emulsion microsphere formulations

[0061] Batch No. 3: The DP was formed by dissolving 4.5 g of an ester end-capped PLGA Evonik LG 855S polymer (an 85:15 PLGA with ester end-caps and an inherent viscosity of 3.0 dL/g) in 65.0 g DCM, followed by the addition of esketamine (0.5 g) with mixing until completely dissolved. The DP was filtered and pumped at 30 mL/minute into a Silverson L4RT in-line homogenizer operating at 1,000 rpm. A CP comprising water and 0.35% PVA was simultaneously pumped into the homogenizer at 2 L/min to form the single emulsion.

[0062] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved using water

washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder with a yield of about 9%. The drug load was 8.0 wt/wt % (80% drug encapsulation efficiency based on a target drug load of 10 wt/wt%).

[0063] Batch No. 3 was tested in an in vitro assay mimicking physiological conditions and resulted in esketamine release over a period of > 60 days, which was beyond the desired release profile of 30 days. See **Figure 2**.

[0064] Batch No. 4: To test the effect of drug load on ketamine release in PLGA-based single emulsion microsphere formulations, another batch (Batch No. 4) was prepared with a 75 wt/wt% target drug load. Thus, the DP was formed by dissolving 2.5 g of the same 85:15 PLGA as was used in Batch No. 3 in 51.0 g DCM, followed by the addition of esketamine (7.5 g) with mixing until completely dissolved. The DP was filtered and pumped at 30 mL/minute into a Silverson L4RT in-line homogenizer operating at 1,500 rpm. A CP comprising water and 0.35% PVA was simultaneously pumped into the homogenizer at 2 L/min to form the single emulsion.

[0065] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder with a yield of about 34%. The drug load was 48.2 wt/wt % (64% drug encapsulation efficiency based on a target drug load of 75 wt/wt%).

[0066] Batch No. 4 was tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown in **Figure 2**. Batch No. 4 experienced an unacceptable substantial "burst," with >60% release in the first five days and continued to release ketamine beyond the desired 30 day release profile. See **Figure 2**.

Example 5 – Effect of co-monomer ratio on ketamine release in PLGA- and PLA-based single emulsion microsphere formulations

[0067] Batch No. 5: To test the effect of co-monomer ratio, another batch (Batch No. 5) with a 75% drug load was prepared, this time using a PLA polymer. Thus, the DP was formed by dissolving 1.25 g of an ester end-capped Evonik LG 209S polymer (a PLA with IV = 2.9 dL/g) in 26.0 g DCM, followed by the addition of esketamine (3.75 g) with mixing until completely dissolved. The DP was filtered and pumped at 30 mL/minute into a Silverson L4RT in-line homogenizer operating at 2,000 rpm. A CP comprising water and 0.35% PVA was simultaneously pumped into the homogenizer at 2 L/min to form the single emulsion.

[0068] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder with a yield of about 46%. The drug load was 76.0 wt/wt % (101% drug encapsulation efficiency based on a target drug load of 75 wt/wt%). Polymer microspheres in Batch No. 5 had an average particle size of 52 μm (D_{10}), 108 μm (D_{50}), 184 μm (D_{90}).

[0069] Batch No. 5 was tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown in **Figure 3**. Batch No. 5 experienced a much less substantial burst than Batch No. 4, with >30% release in the first five days. However, Batch No. 5 continued to release ketamine beyond the desired 30 day release profile.

Example 6 – Effect of polymer microsphere size on ketamine release in PLGA-based single emulsion microsphere formulations

[0070] Batch Nos. 6 and 6A: The DP for each batch was formed by dissolving 12.75 g of the same 85:15 PLGA polymer as used in Batch Nos. 3 and 4 in 255.0 g DCM, followed by the addition of esketamine (37.5 g) with mixing until completely dissolved. The DP was filtered and pumped at 30 mL/minute into a Silverson L4RT in-line homogenizer. For Batch No. 6, the homogenizer operated at 4,000 rpm. For Batch No. 6A, the homogenizer operated at 3,000 rpm. For each batch, a CP comprising water and 0.35% PVA was simultaneously pumped into the homogenizer at 2 L/min to form the single emulsion.

[0071] For each batch, the formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved using water washing and a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder.

[0072] Batch No. 6 resulted in a yield of about 23%. The drug load was 17.0 wt/wt % (23% drug encapsulation efficiency based on a target drug load of 75 wt/wt%). The particle size was 8 μm (D_{10}), 27 μm (D_{50}), 57 μm (D_{90}).

[0073] Batch No. 6A resulted in a yield of about 29%. The drug load was 32.0 wt/wt % (43% drug encapsulation efficiency based on a target drug load of 75 wt/wt%). The particle size was 24 μm (D_{10}), 60 μm (D_{50}), 113 μm (D_{90}).

[0074] Batch Nos. 6 and 6A were tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time as a function of particle size is shown in **Figure 4**. Batch Nos. 6 and 6A were ultimately deemed deficient because the yields and encapsulation efficiencies were insufficient.

Example 7 – Effect of ethyl acetate as solvent on ketamine release in PLA-based single emulsion microsphere formulations

[0075] Batch No. 7: The DP was formed by dissolving 7.0 g of an ester end-capped PLA Ashland Viatel 07 E polymer (IV = 0.66 dL/g) in 31.5 g of ethyl acetate, followed by the addition of esketamine (3.0 g) with mixing until completely dissolved. The DP was filtered and pumped at 30 mL/minute into a Levitronix i100 (as described in US20210001290) operating at 1,600 rpm. A CP comprising water and 0.35% PVA was simultaneously pumped into the homogenizer at 2 L/min to form the single emulsion.

[0076] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved using water washing and a tangential flow filter. The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder.

[0077] Batch No. 7 resulted in a yield of about 70%. The drug load was 25.6 wt/wt % (85% drug encapsulation efficiency based on a target drug load of 30 wt/wt%).

[0078] Batch No. 7 was tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown in **Figure 5**. Batch No. 7 was ultimately deemed deficient because of an unacceptably large burst (which is even more evident in vivo, as shown in **Figure 8**).

Example 8 – General preparation of microsphere formulations comprising ketamine via a double emulsion method

[0079] Microsphere Formation Phase. Using like numerals for like elements to provide a juxtaposition to the single emulsion method depicted in **Figure 1**, with reference to **Figure 6**, an organic component 12 is formed by dissolving a biodegradeable polymer (such as a PLA polymer)

in an organic solvent (such as DCM, ethanol, or a combination thereof), followed by the addition of ketamine with mixing until completely dissolved. The organic component 12 is homogenized with an inner aqueous component ("IA component") 14 comprising water and, optionally, PVA, in a high-speed homogenizer probe (such as a T25 Ultra-turrax, sonicator, or magic Lab® DISPAX-REACTOR®) 16 to form a primary emulsion ("PE") in place of DP 10. The PE is pumped into a homogenizer 30, such as an in-line Silverson Homogenizer or a Levitronix i100 (as described in US20210001290), at a defined flow rate. The CP 20 comprising water and, optionally, PVA, is also pumped into the homogenizer 30 at a defined flow rate.

[0080] Microsphere Processing Phase. The formed or forming microspheres exit the homogenizer 30 and enter an SRV 40. Water 22 is added to the SRV 40 during microsphere formation to minimize the solvent level. The resulting suspension is mixed in the SRV 40 during the microsphere formation period. After the PE is exhausted, the CP and water flow additions are stopped, and the washing steps are initiated.

[0081] Solvent removal is achieved by washing the microspheres with ambient water 24 (i.e. 25 °C) and hot water (35-39 °C) and filtering them through a hollow fiber filter 50 (commercially available as HFF from GE Healthcare). Excess solvent is removed and discarded, and the filtered microspheres are returned to the SRV until the desired level of solvent is removed from the microsphere formulation.

[0082] The washed microspheres are collected on a filter membrane and freeze-dried overnight in a lyophilizer (Virtis) to remove moisture. The resulting microspheres are a free-flowing off-white bulk powder.

[0083] The double emulsification method consistently resulted in surprisingly high yields compared to the single emulsification method.

Example 9 - Preparation and evaluation of a low inherent viscosity (0.66 dL/g) PLA-based double emulsion microsphere formulation

[0084] Batch No. 8: The organic component was formed by dissolving 7.0 g of an ester end-capped PLA Ashland Viatel 07 E polymer (IV = 0.66 dL/g) in 39 g of DCM and 4.6 g of ethanol (5:1 ratio by volume), followed by the addition of esketamine (3.0 g) with mixing until completely dissolved. The organic component was homogenized with an IA component consisting of 1 mL of de-ionized water in a T25 Ultra-turrax high-speed homogenizer operating at 21,500 rpm for 30 seconds to form the PE.

[0085] The PE was pumped into a Levitronix i100 (as described in US20210001290) operating at 1,600 rpm at a rate of 30 mL/minute, along with a CP comprising water and 0.35% PVA, which was pumped at a rate of 2 L/min, for a CP:PE ratio of 66:1.

[0086] The formed or forming microspheres exited the homogenizer and entered an SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved by washing the microspheres with ambient water (i.e., 25 °C) and hot water (35-39 °C) and filtering them through a hollow fiber filter.

[0087] The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder with a yield of about 59%. The drug load was 16.5 wt/wt % (55% drug encapsulation efficiency based on a target drug load of 30 wt/wt%). The average particle size was 47 μm (D_{10}), 82 μm (D_{50}), 132 μm (D_{90}).

[0088] Batch No. 8 was tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown graphically in **Figure 5** (in comparison to other single and double emulsified batches, as a function of the inherent viscosity of the biodegradable polymer) and in **Figure 7**.

Example 10 - Preparation and evaluation of a low inherent viscosity (0.66 dL/g) PLA-based double emulsion microsphere formulation, comprising PVA in the IA component

[0089] Batch No. 9: The organic component was formed by dissolving 70.0 g of an ester end-capped PLA Ashland Viatel 07 E polymer (IV = 0.66 dL/g) in 388 g of DCM and 46 g of ethanol (5:1 ratio, by volume), followed by the addition of esketamine (30.0 g) with mixing until completely dissolved. The organic component was homogenized with an IA component consisting of 11 mL of a 0.35% PVA solution in a T25 Ultra-turrax high-speed homogenizer operating at 21,500 rpm for 45 seconds to form the PE.

[0090] The PE was pumped into a Levitronix i100 (as described in US20210001290) operating at 1,600 rpm at a rate of 30 mL/minute, along with the CP comprising water and 0.35% PVA, which was pumped at a rate of 2 L/min, for a CP:PE ratio of 66:1.

[0091] The formed or forming microspheres exited the homogenizer and entered an SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved by washing the microspheres with ambient water (i.e., 25 °C) and hot water (35-39 °C) and filtering them through a hollow fiber filter.

[0092] The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder with a yield of about 72%. The drug load was 14.6 wt/wt % (49% drug encapsulation efficiency based on a target drug load of 30 wt/wt%). The average particle size was 38 μm (D_{10}), 75 μm (D_{50}), 123 μm (D_{90}).

[0093] Batch No. 9 was tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown graphically in **Figure 5** (in comparison to other single and double emulsified batches, as a function of the inherent viscosity of the biodegradable polymer).

Example 11 - Preparation and evaluation of a higher inherent viscosity (1.80 dL/g) PLA-based double emulsion microsphere formulation

[0094] Batch No. 10: The organic component was formed by dissolving 7.0 g of an ester end-capped PLA Evonik LG 207S polymer (IV = 1.80 dL/g) in 63 g of DCM and 4.6 g of ethanol (8:1 ratio, by volume), followed by the addition of esketamine (3.0 g) with mixing until completely dissolved. The organic component was homogenized with an IA component consisting of 1 mL of a 0.35% PVA solution in a T25 Ultra-turrax high-speed homogenizer operating at 21,500 rpm for 30 seconds to form the PE.

[0095] The PE was pumped into a Levitronix i100 (as described in US20210001290) operating at 1,600 rpm at a rate of 30 mL/minute, along with the CP comprising water and 0.35% PVA, which was pumped at a rate of 2 L/min, for a CP:DP ratio of 66:1.

[0096] The formed or forming microspheres exited the homogenizer and entered an SRV. Deionized water was added to the SRV at 2L/min. Solvent removal was achieved by washing the microspheres with ambient water (i.e., 25 °C) and hot water (35-39 °C) and filtering them through a hollow fiber filter.

[0097] The bulk suspension was collected via filtration and lyophilized to obtain a free-flowing powder with a yield of about 56%. The drug load was 17.4 wt/wt % (58% drug encapsulation efficiency based on a target drug load of 30 wt/wt%). The average particle size was 27 μm (D_{10}), 67 μm (D_{50}), 136 μm (D_{90}).

[0098] Batch No. 10 was tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown graphically in **Figure 5** (in comparison to other single and double emulsified batches, as a function of the inherent viscosity of the biodegradable polymer).

Example 12 – Pharmacokinetics Study in Rats of Batch Nos. 7, 9, and 10

[0099] The pharmacokinetic profile of ketamine following a subcutaneously injected dose of time-released ketamine formulation in male Sprague-Dawly rats was studied. The rats received a 50 mg/kg dose of the indicated Batch No., having a ketamine concentration of 33.33 mg/mL and a volume of 1.5 mL/kg. Microsphere suspension concentrations (mg/mL) were as follows: (a) Batch No. 7: 130.21; (b) Batch No. 9: 228.31; and (c) Batch No. 10: 191.57. Blood was collected at 0.5, 1, 2, 4, 24, 48, 168, 264, 360, 480, 600, 720, 840, 960, 1080, and 1200 hours. **Figure 8** is a graph showing the measured mean blood concentration (ng/mL) of ketamine as a function of time for Batches Nos. 7 (Example 7), 9 (Example 10), and 10 (Example 11).

Example 13 – Low inherent viscosity (0.67 dL/g) PLA-based double emulsion microsphere formulations, with a CP:PE ratio of 100:1

[00100] Batch Nos. 11A and 11B: An organic component was formed by dissolving 14.0 g of an ester end-capped PLA Ashland DL Viatel 07 E polymer (IV = 0.67 dL/g) in 77.58 g of DCM and 9.2 g of ethanol (5:1 ratio, by volume), followed by the addition of esketamine (6.0 g) with mixing until completely dissolved. The organic component was homogenized with an IA component consisting of 2.18 g of 0.35% PVA solution in a T25 Ultra-turrax high-speed homogenizer operating at 21,500 rpm for 30 seconds to form the PE having an organic:IA component ratio of about 49:1 (on a mass basis).

[00101] The primary emulsion was pumped into a Levitronix i100 (as described in US20210001290) operating at 1,600 rpm at a rate of 20 mL/minute, along with a CP comprising water and 0.35% PVA, which was pumped at a rate of 2 L/min, for a CP:PE ratio of 100:1.

[00102] The formed or forming microspheres exited the homogenizer and a portion (Batch No. 11A) of the suspension entered a first SRV, wherein the microspheres were subjected immediately

to deionized water at 2L/min. Solvent removal was achieved by washing the microspheres with ambient water (i.e., 25 °C) and hot water (35-39 °C) and filtering them through a hollow fiber filter. The bulk suspension was collected via filtration and lyophilized to yield 6.6 g of a free-flowing powder. The drug load was 23.0 wt/wt % (77% drug encapsulation efficiency based on a target drug load of 30 wt/wt%). The average particle size was 53 μm (D_{10}), 94 μm (D_{50}), 152 μm (D_{90}).

[00103] A second portion of the suspension (Batch No. 11B) entered a second SRV, wherein it was held for four hours. At the conclusion of the four hour hold, the microspheres were washed, filtered, and lyophilized as described with respect to Batch No. 11A to yield 6.7 g of a free-flowing powder. The drug load was 9.2 wt/wt % (31% drug encapsulation efficiency based on a target drug load of 30 wt/wt%). The mean particle size was 50 μm (D_{10}), 90 μm (D_{50}), 143 μm (D_{90}). The total yield of Batch Nos. 11A and 11B was 66.3%.

[00104] Batch Nos. 11A and 11B were tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown graphically in **Figure 9**.

Example 14 – Low inherent viscosity (0.67 dL/g) PLA-based double emulsion microsphere formulations, with a CP:PE ratio of 80:1.

[00105] Batch Nos. 12A and 12B: An organic component was formed by dissolving 10.5 g of an ester end-capped PLA Ashland DL 07 E polymer (IV = 0.67 dL/g) in 58.19 g of DCM and 6.9 g of ethanol (5:1 ratio, by volume), followed by the addition of esketamine (4.5 g) with mixing until completely dissolved. The organic component was homogenized with an IA component consisting of 1.64 g of 0.35% PVA solution in a T25 Ultra-turrax high-speed homogenizer

operating at 21,500 rpm for 30 seconds to form the PE having an organic:IA component ratio of about 49:1 (on a mass basis).

[00106] The PE was pumped into a Levitronix i100 (as described in US20210001290) operating at 1,600 rpm at a rate of 25 mL/minute, along with a CP comprising water and 0.35% PVA, which was pumped at a rate of 2 L/min, for a CP:PE ratio of 80:1.

[00107] The formed or forming microspheres exited the homogenizer and a portion (Batch No. 12A) of the suspension entered a first SRV, wherein the microspheres were subjected immediately to deionized water at 2L/min. Solvent removal was achieved by washing the microspheres with ambient water (i.e., 25 °C) and hot water (35-39 °C) and filtering them through a hollow fiber filter.

[00108] The bulk suspension was collected via filtration and lyophilized to yield 0.89 g of a free-flowing powder. The drug load was 24.8 wt/wt % (83% drug encapsulation efficiency based on a target drug load of 30 wt/wt%). The mean particle size was 57 μm (D_{10}), 111 μm (D_{50}), 189 μm (D_{90}).

[00109] A second portion (Batch No. 12B) of the suspension entered a second SRV, wherein it was held for four hours. At the conclusion of the four hour hold, the microspheres were washed, filtered, and lyophilized as described with respect to Batch No. 12A to yield 7.2 g of a free-flowing powder. The drug load was 17.4 wt/wt % (58% drug encapsulation efficiency based on a target drug load of 30 wt/wt%). The mean particle size was 54 μm (D_{10}), 99 μm (D_{50}), 161 μm (D_{90}). The total yield of Batch Nos. 12A and 12B was 54%.

[00110] Batch Nos. 12A and 12B were tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown graphically in **Figure 9**.

Example 15 – Low inherent viscosity (0.67 dL/g) PLA-based double emulsion microsphere formulations, with a CP:PE ratio of 80:1

[00111] Batch Nos. 13A and 13B: An organic component was formed by dissolving 10.5 g of an ester end-capped PLA Ashland DL 07 E polymer (IV = 0.67 dL/g) in 58.19 g of DCM and 6.9 g of ethanol (5:1 ratio, by volume), followed by the addition of esketamine (4.5 g) with mixing until completely dissolved. The organic component was homogenized with an IA component consisting of 1.64 g of 0.35% PVA solution in a T25 Ultra-turrax high-speed homogenizer operating at 21,500 rpm for 30 seconds to form the PE having an organic:IA component ratio of about 49:1 (on a mass basis).

[00112] The PE was pumped into a Levitronix i100 (as described in US20210001290) operating at 1,600 rpm at a rate of 25 mL/minute, along with a CP comprising water and 0.35% PVA, which was pumped at a rate of 2 L/min, for a CP:DP ratio of 80:1.

[00113] The formed or forming microspheres exited the homogenizer and a portion (Batch No. 13A) of the suspension entered a first SRV, wherein the microspheres were subjected immediately to deionized water at 2L/min. Solvent removal was achieved by washing the microspheres with ambient water (i.e., 25 °C) and hot water (35-39 °C) and filtering them through a hollow fiber filter.

[00114] The bulk suspension was collected via filtration and lyophilized to yield 2.99 g of a free-flowing powder. The drug load was 29.4 wt/wt % (98% drug encapsulation efficiency based on a target drug load of 30 wt/wt%). The mean particle size was 46 μm (D_{10}), 104 μm (D_{50}), 190 μm (D_{90}).

[00115] A second portion (Batch No. 13B) of the suspension entered a second SRV, wherein it was held for four hours. At the conclusion of the four hour hold, the microspheres were washed,

filtered, and lyophilized as described with respect to Batch No. 13A to yield 7.09 g of a free-flowing powder. The drug load was 26.4 wt/wt % (88% drug encapsulation efficiency based on a target drug load of 30 wt/wt%). The mean particle size was 52 μm (D_{10}), 99 μm (D_{50}), 162 μm (D_{90}). The total yield of Batch Nos. 13A and 13B was 67%.

[00116] Batch Nos. 13A and 13B were tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown graphically in **Figure 9**.

Example 16 – Low inherent viscosity (0.67 dL/g) PLA-based double emulsion microsphere formulations, with CP (1.0% PVA) and a CP:PE ratio of 80:1

[00117] Batch Nos. 14A and 14B: An organic component was formed by dissolving 12.45 g of an ester end-capped PLA Ashland DL 07 E polymer (IV = 0.67 dL/g) in 70.74 g of DCM and 8.39 g of ethanol (5:1 ratio, by volume), followed by the addition of esketamine (2.55 g) with mixing until completely dissolved. The organic component was homogenized with an IA component consisting of 1.64 g of 0.35% PVA solution in a T25 Ultra-turrax high-speed homogenizer operating at 21,500 rpm for 30 seconds to form the PE having an organic:IA component ratio of about 57:1 (on a mass basis).

[00118] The PE was pumped into a Levitronix i100 (as described in US20210001290) operating at 1,600 rpm at a rate of 25 mL/minute, along with a CP comprising water and 1.0% PVA, which was pumped at a rate of 2 L/min, for a CP:PE ratio of 80:1.

[00119] The formed or forming microspheres exited the homogenizer and a portion (Batch No. 14A) of the suspension entered a first SRV, wherein the microspheres were subjected immediately to deionized water at 2L/min. Solvent removal was achieved by washing the microspheres with

ambient water (i.e., 25 °C) and hot water (35-39 °C) and filtering them through a hollow fiber filter.

[00120] The bulk suspension was collected via filtration and lyophilized to yield 2.99 g of a free-flowing powder. The drug load was 14.5 wt/wt % (85% drug encapsulation efficiency based on a target drug load of 17 wt/wt%). The mean particle size was 32 μm (D_{10}), 87 μm (D_{50}), 149 μm (D_{90}).

[00121] A second portion (Batch No. 14B) of the suspension entered a second SRV, wherein it was held for four hours. At the conclusion of the four hour hold, the microspheres were washed, filtered, and lyophilized as described with respect to Batch No. 14A to yield 6.95 g of a free-flowing powder. The drug load was 13.7 wt/wt % (81% drug encapsulation efficiency based on a target drug load of 17 wt/wt%). The mean particle size was 37 μm (D_{10}), 88 μm (D_{50}), 148 μm (D_{90}). The total yield of Batch Nos. 14A and 14B was 75%.

[00122] Batch Nos. 14A and 14B were tested in an in vitro assay mimicking physiological conditions. The cumulative percent release of ketamine over time is shown graphically in **Figure 10** compared to an ideal 30 day release profile.

[00123] The aspects disclosed herein are not intended to be exhaustive or to be limiting. A skilled artisan would acknowledge that other aspects or modifications to instant aspects can be made without departing from the spirit or scope of the invention. The aspects of the present disclosure, as generally described herein and illustrated in the figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are contemplated herein.

[00124] Unless otherwise specified, “a,” “an,” “the,” “one or more of,” and “at least one” are used interchangeably. The singular forms “a”, “an,” and “the” are inclusive of their plural forms.

The recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.). The terms "comprising" and "including" are intended to be equivalent and open-ended. The phrase "consisting essentially of" means that the composition or method may include additional ingredients and/or steps, but only if the additional ingredients and/or steps do not materially alter the basic and novel characteristics of the claimed composition or method. The phrase "selected from the group consisting of" is meant to include mixtures of the listed group.

[00125] When reference is made to the term "each," it is not meant to mean "each and every, without exception." For example, if reference is made to microsphere formulation comprising polymer microspheres, and "each polymer microsphere" is said to have a particular ketamine content, if there are 10 polymer microspheres, and two or more of the polymer microspheres have the particular ketamine content, then that subset of two or more polymer microspheres is intended to meet the limitation.

[00126] The term "about" in conjunction with a number is intended to include ±10% of the number. This is true whether "about" is modifying a stand-alone number or modifying a number at either or both ends of a range of numbers. In other words, "about 10" means from 9 to 11. Likewise, "about 10 to about 20" contemplates 9 to 22 and 11 to 18. In the absence of the term "about," the exact number is intended. In other words, "10" means 10.

CLAIMS

What is claimed is:

1. A microsphere formulation, comprising:

polymer microspheres, each polymer microsphere comprising:

(i) esketamine; and

(ii) a biodegradable poly(lactide) polymer having an inherent viscosity of about 0.6 dL/g to about 0.7 dL/g,

wherein each polymer microsphere has a ketamine drug load of about 12 wt/wt% to about 17 wt/wt%;

wherein the polymer microspheres have an average particle size of about 80 μm (D_{50}) to about 110 μm (D_{50}); and

wherein the polymer microspheres are characterized in that each of the polymer microspheres comprises a plurality of internal macrovoids.

2. The microsphere formulation of claim 1, wherein the polymer microspheres are characterized in that the esketamine exhibits an in vivo average release rate from the polymer microspheres of from about 2.5% to about 3.5% per day over a 30 day period in a human.

3. A microsphere formulation, comprising:

polymer microspheres, each polymer microsphere comprising:

(i) ketamine; and

(ii) a biodegradable poly(lactide) polymer;

wherein each polymer microsphere has a ketamine drug load of about 10 wt/wt% to about 30 wt/wt%, and

wherein the polymer microspheres have an average particle size greater than 60 μm (D_{50}).

4. The microsphere formulation of claim 3, wherein the polymer microspheres have an average particle size of about 80 μm (D_{50}) to about 110 μm (D_{50}).

5. The microsphere formulation of claim 3, wherein the ketamine comprises a free base form of esketamine.

6. The microsphere formulation of claim 3, wherein each polymer microsphere has a ketamine drug load of between about 12 wt/wt% to about 17 wt/wt%.

7. The microsphere formulation of claim 3, wherein the biodegradable poly(lactide) polymer has an inherent viscosity from about 0.6 dL/g to about 0.7 dL/g.

8. The microsphere formulation of claim 3, characterized in that the ketamine exhibits an in vivo average release rate from the polymer microspheres of from about 2.5% to about 3.5% per day over a 30 day period in a human.

9. The microsphere formulation of claim 3, characterized in that each of the polymer microspheres comprises a plurality of internal emulsions comprising water and a surfactant.

10. The microsphere formulation of claim 3, characterized in that each of the polymer microspheres comprises a plurality of internal macrovoids.

11. A method for making polymer microspheres, the method comprising:

(i) contacting ketamine with a biodegradable poly(lactide) polymer in the presence of a solvent to form an organic component and providing the organic component to a first homogenizer;

(ii) providing an inner aqueous component comprising water and a first surfactant to the first homogenizer;

(iii) homogenizing the organic component with the inner aqueous component to form a primary emulsion;

(iv) providing the primary emulsion to a second homogenizer at a first flow rate;

(v) providing a continuous phase comprising water and a second surfactant to the second homogenizer at a second flow rate;

(vi) homogenizing the primary emulsion and the continuous phase; and

(iv) removing the solvent to form the polymer microspheres,

wherein each of the formed polymer microspheres incorporates at least a portion of the inner aqueous component in the form of a plurality of emulsions.

12. The method of claim 11, further comprising dehydrating the polymer microspheres, wherein the dehydrated polymer microspheres are characterized in that each of the polymer microspheres comprises a plurality of internal microvoids.

13. The method of claim 11, wherein the biodegradable poly(lactide) polymer has an inherent viscosity of about 0.6 dL/g to about 0.7 dL/g.

14. The method of claim 11, wherein the first surfactant comprises polyvinyl alcohol in an amount of about 0.35% by weight in the water.

15. The method of claim 11, wherein the biodegradable poly(lactide) polymer comprises between about 10% and about 15% of the organic component.

16. The method of claim 11, wherein the solvent comprises a mixture of methylene chloride and ethanol.

17. The method of claim 11, wherein the solvent comprises a mixture of methylene chloride and ethanol in a 5:1 volumetric ratio.

18. The method of claim 11, wherein the ketamine comprises between about 3.3% and about 5.5% of the organic component.

19. The method of claim 11, wherein the second surfactant comprises polyvinyl alcohol in an amount of about 0.35% to about 1.0% by weight in the water.

20. The method of claim 11, wherein the second surfactant comprises polyvinyl alcohol in an amount of about 1.0% by weight in water.

21. The method of claim 11, wherein a ratio of the continuous phase flow rate to the primary emulsion flow rate is from about 66:1 to about 200:1.

22. A method for treating depression, the method comprising intramuscularly or subcutaneously injecting a patient in need thereof with a therapeutically effective amount of a microsphere formulation, the microsphere formulation comprising:

polymer microspheres, each polymer microsphere comprising:

(i) esketamine; and

(ii) a biodegradable poly(lactide) polymer;

wherein each polymer microsphere has a ketamine drug load of between about 10 wt/wt% to about 30 wt/wt%, and

wherein the polymer microspheres have an average particle size greater than 60 μm (D_{50}).

23. The method of claim 22, wherein the polymer microspheres have an average particle size of about 80 μm (D_{50}) to about 110 μm (D_{50}).

24. The method of claim 22, wherein each polymer microsphere has a ketamine drug load of between about 12 wt/wt% and about 17 wt/wt%.

25. The method of claim 22, wherein the biodegradable poly(lactide) polymer has an inherent viscosity of about 0.6 dL/g to about 0.7 dL/g.

26. The method of claim 22, characterized in that the ketamine exhibits an in vivo average release rate from the polymer microspheres of from about 2.5% to about 3.5% per day over a 30 day period.

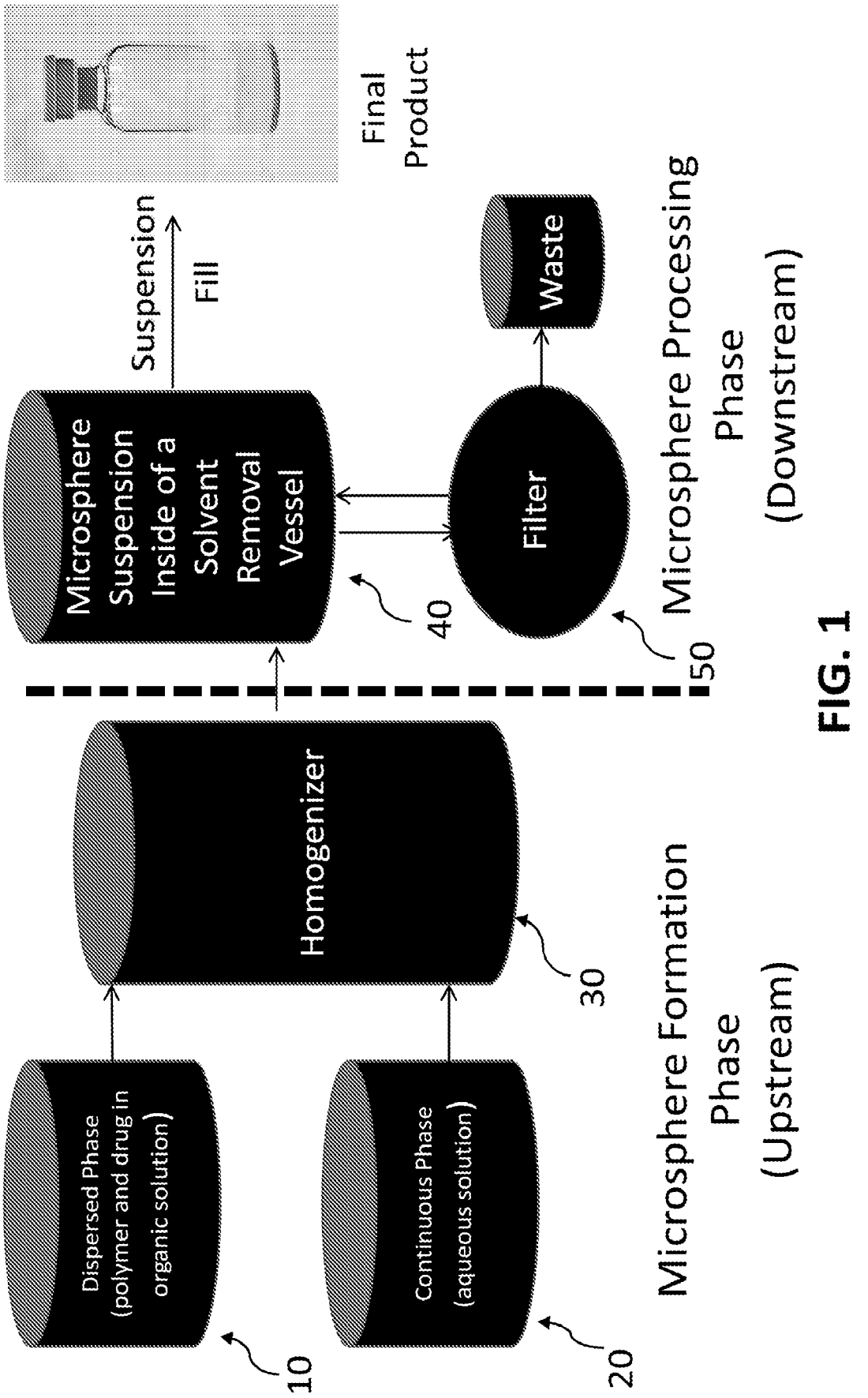

Dispersed Phase (polymer and drug in organic solution)
Continuous Phase (aqueous solution)
Homogenizer
Microsphere Suspension Inside of a Solvent Removal Vessel
Filter
Waste
Suspension
Fill
Final Product
10
20
30
40
50
Microsphere Formation Phase (Upstream)
Microsphere Processing Phase (Downstream)

FIG. 1

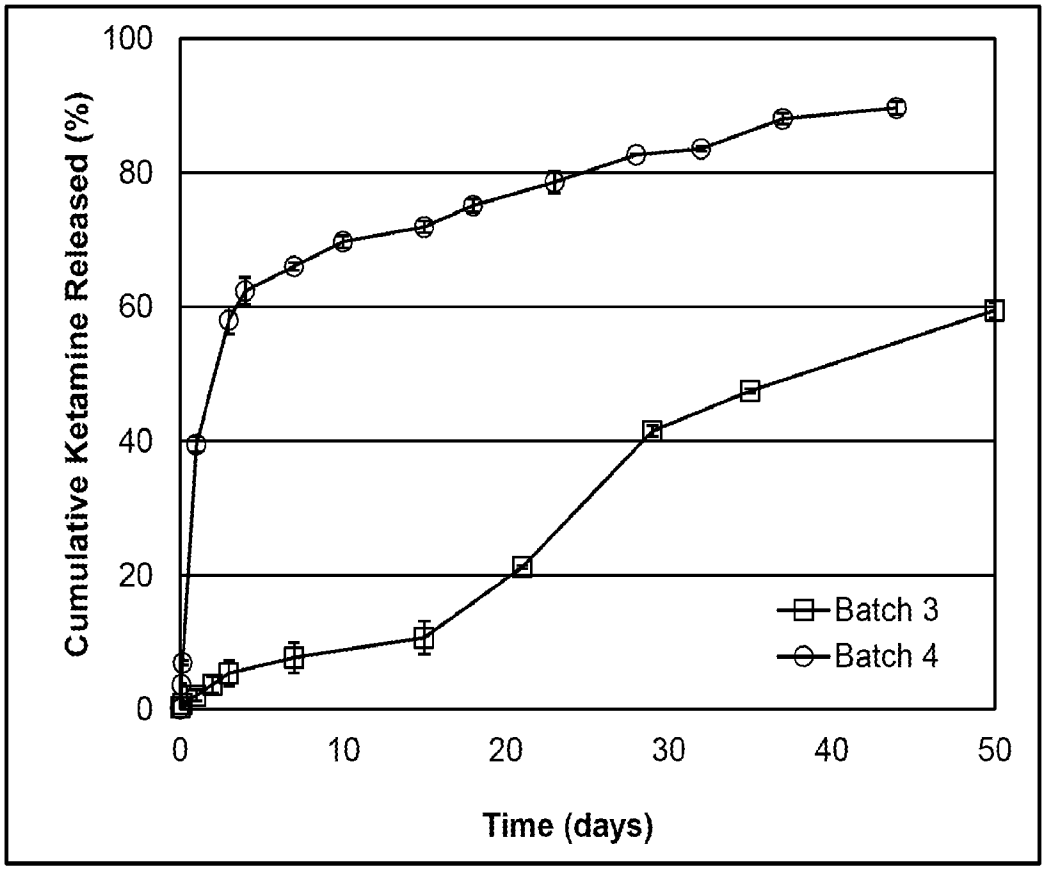

Cumulative Ketamine Released (%)
100
80
60
40
20
0
0
10
20
30
40
50
Time (days)
Batch 3
Batch 4

FIG. 2

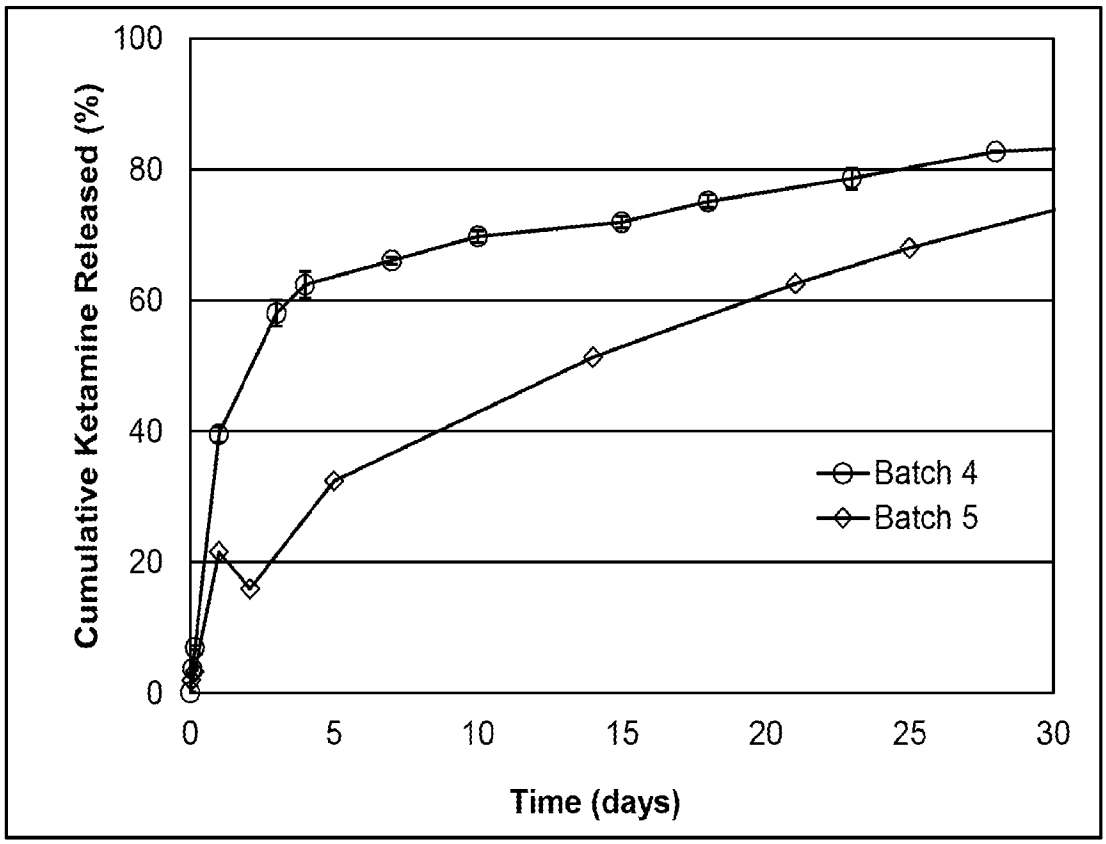

Cumulative Ketamine Released (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (days)
Batch 4
Batch 5

FIG. 3

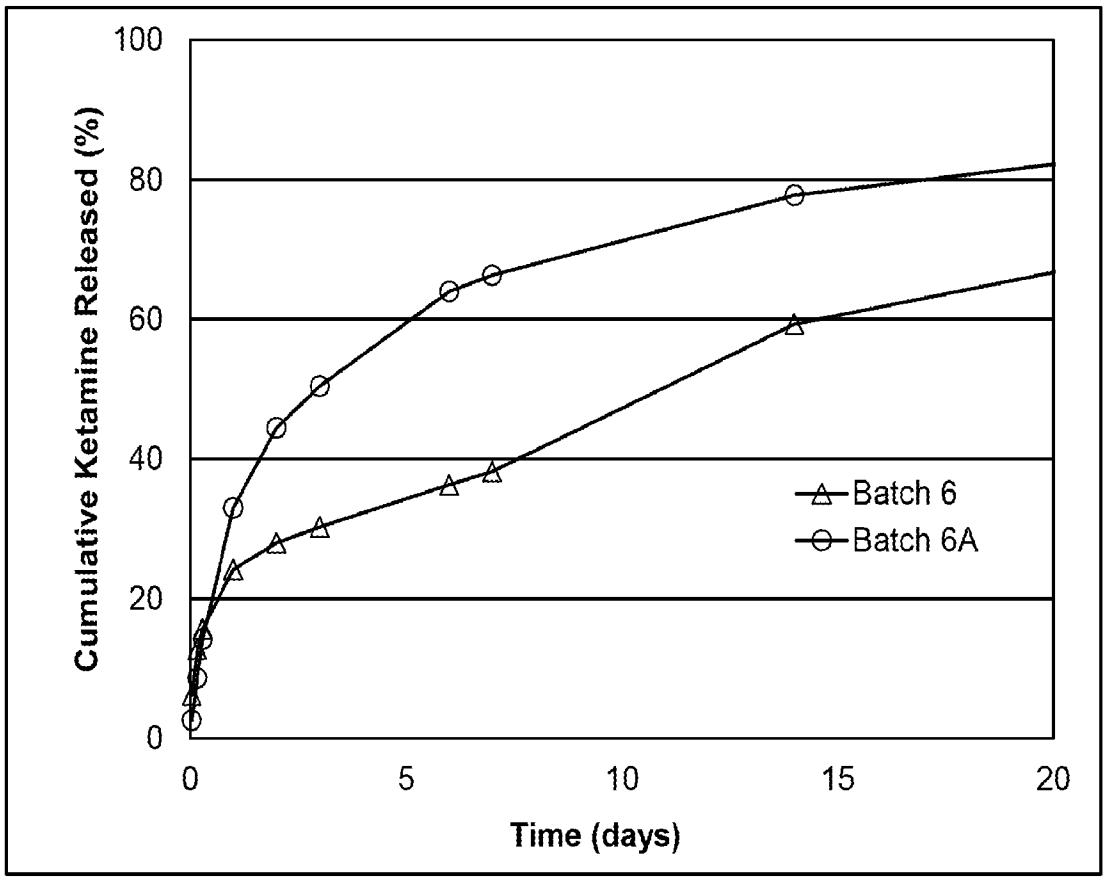

Cumulative Ketamine Released (%)
100
80
60
40
20
0
0
5
10
15
20
Time (days)
Batch 6
Batch 6A

FIG. 4

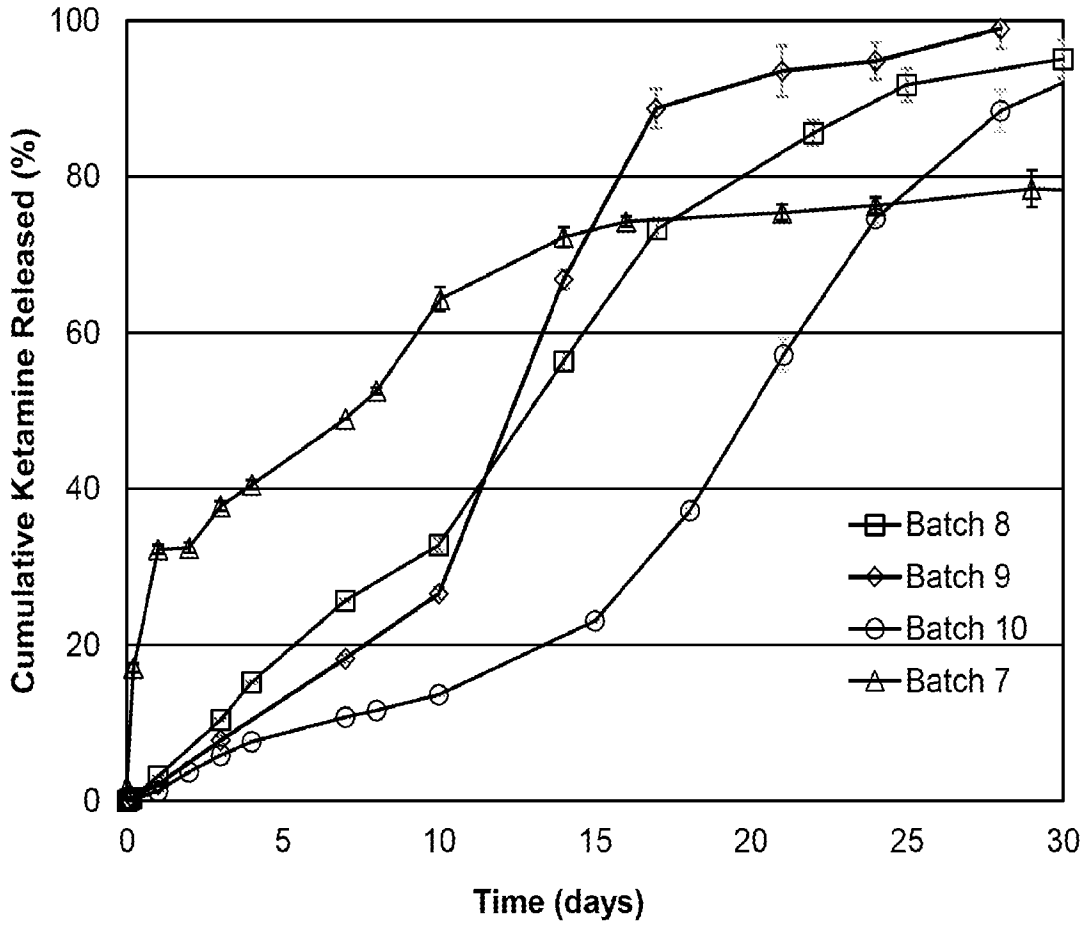

Cumulative Ketamine Released (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (days)
Batch 8
Batch 9
Batch 10
Batch 7

FIG. 5

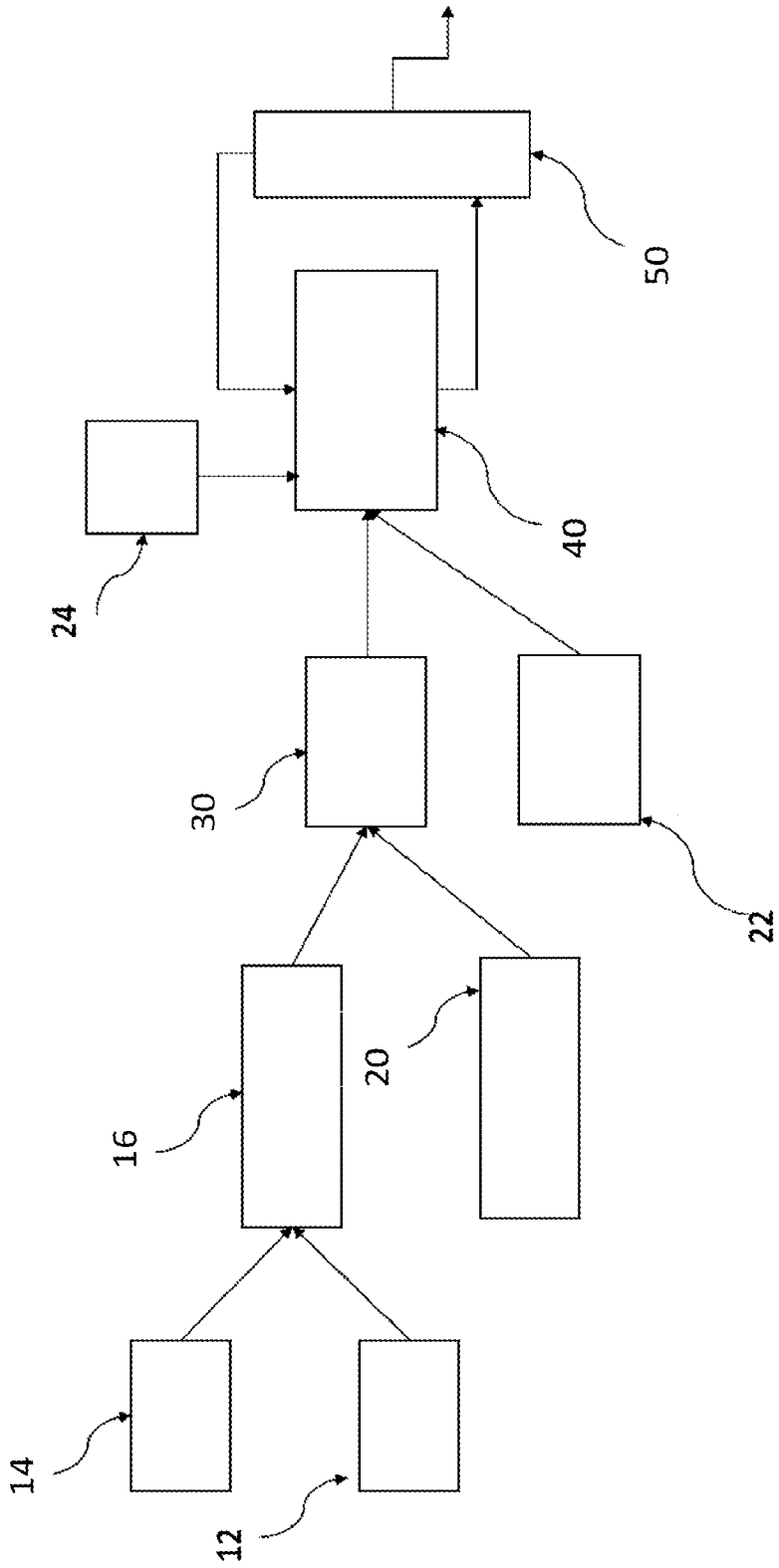


FIG. 6

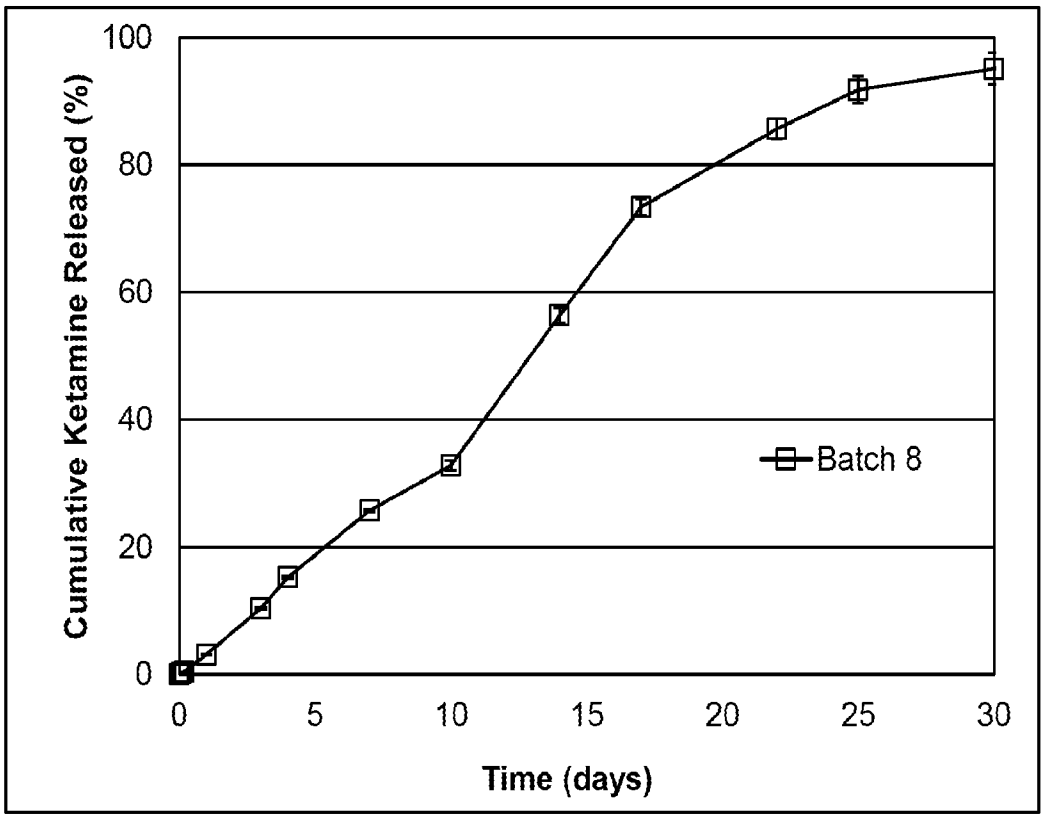

Cumulative Ketamine Released (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (days)
Batch 8

FIG. 7

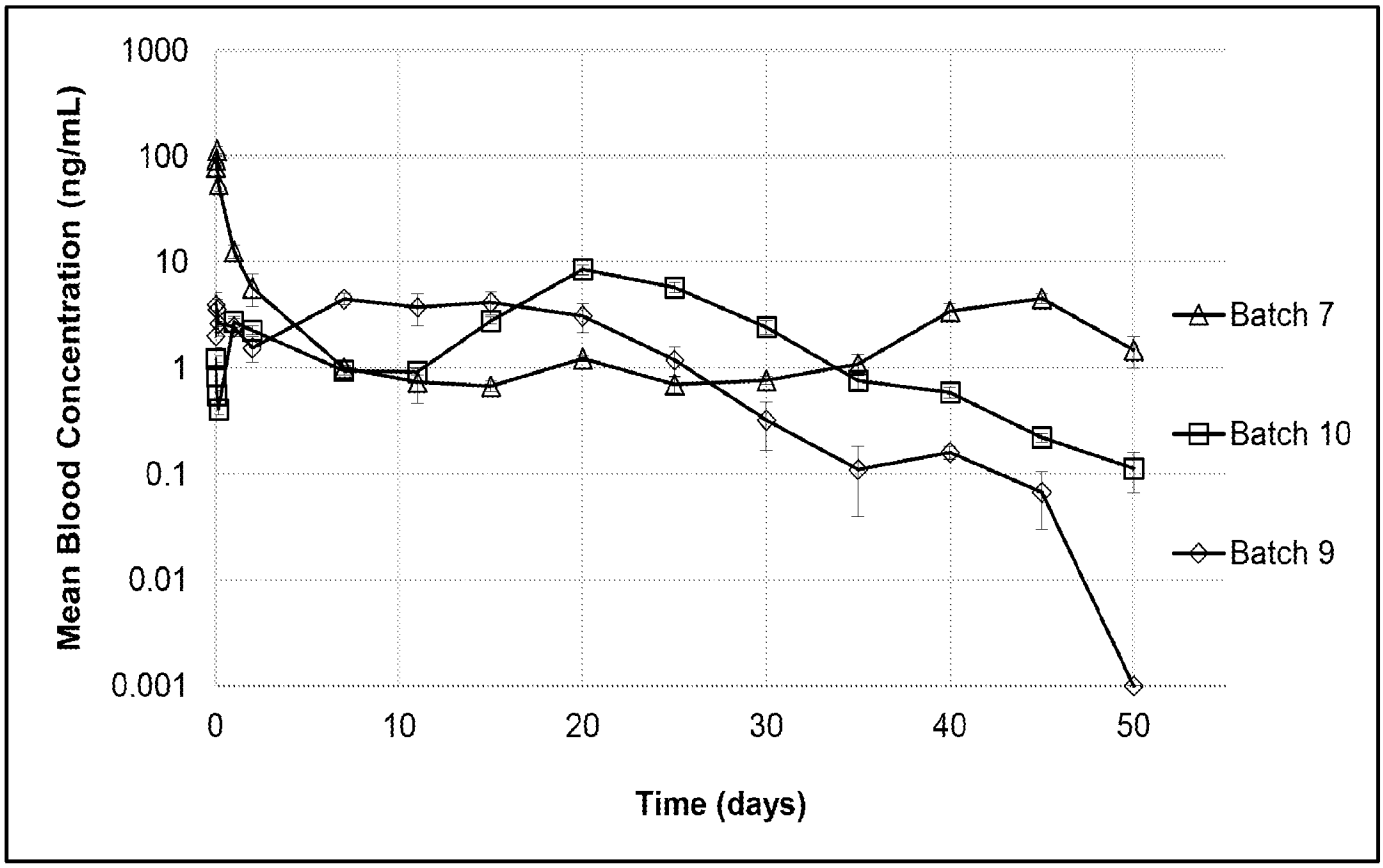

Mean Blood Concentration (ng/mL)
1000
100
10
1
0.1
0.01
0.001
0
10
20
30
40
50
Time (days)
Batch 7
Batch 10
Batch 9

FIG. 8

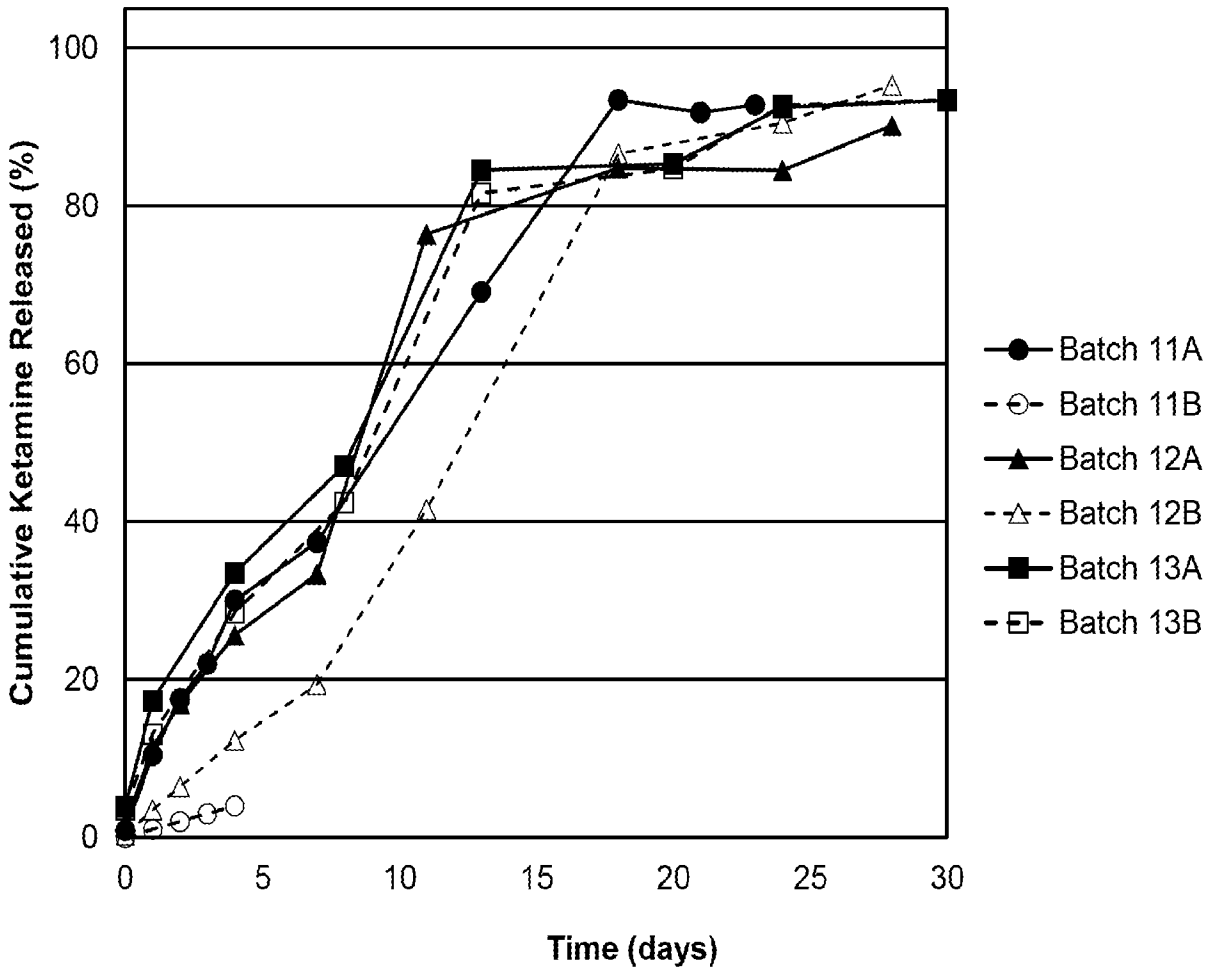

Cumulative Ketamine Released (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (days)
Batch 11A
Batch 11B
Batch 12A
Batch 12B
Batch 13A
Batch 13B

FIG. 9

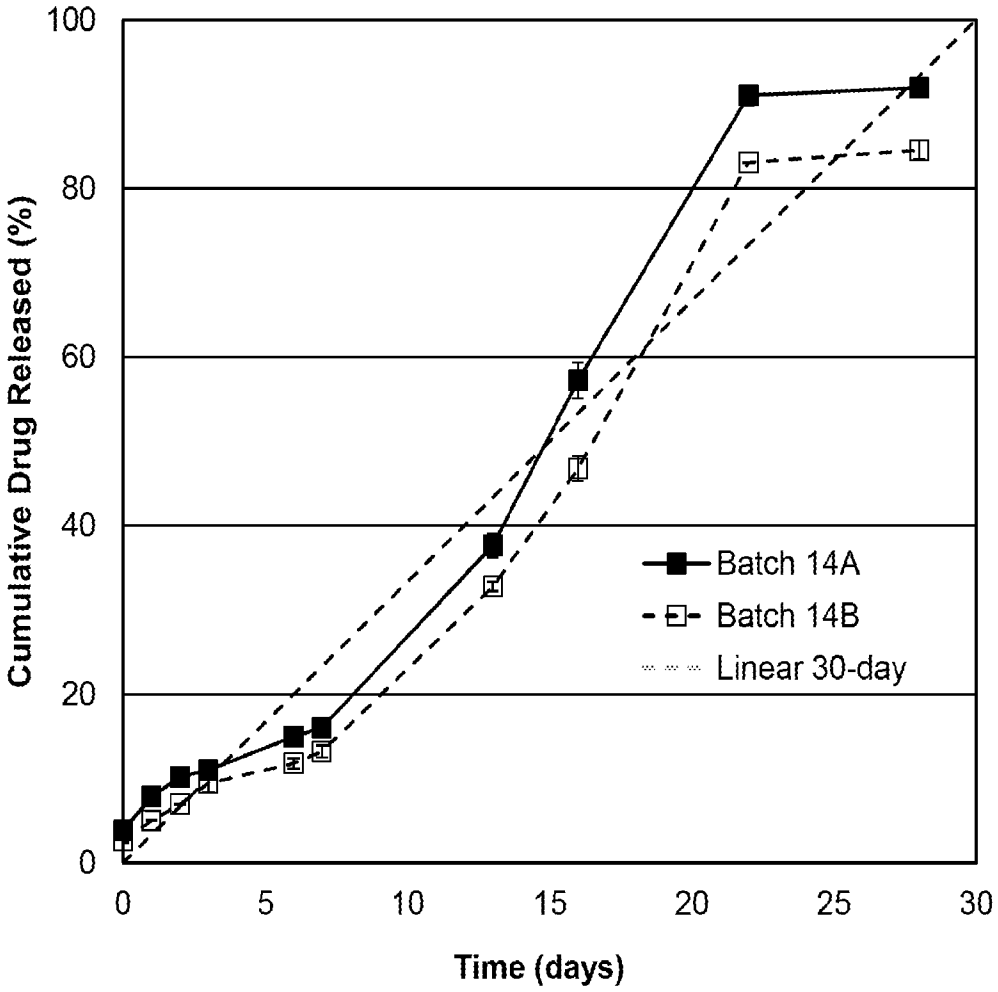

100
80
60
40
20
0
Cumulative Drug Released (%)
0
5
10
15
20
25
30
Time (days)
Batch 14A
Batch 14B
Linear 30-day

FIG. 10

FIG. 11A

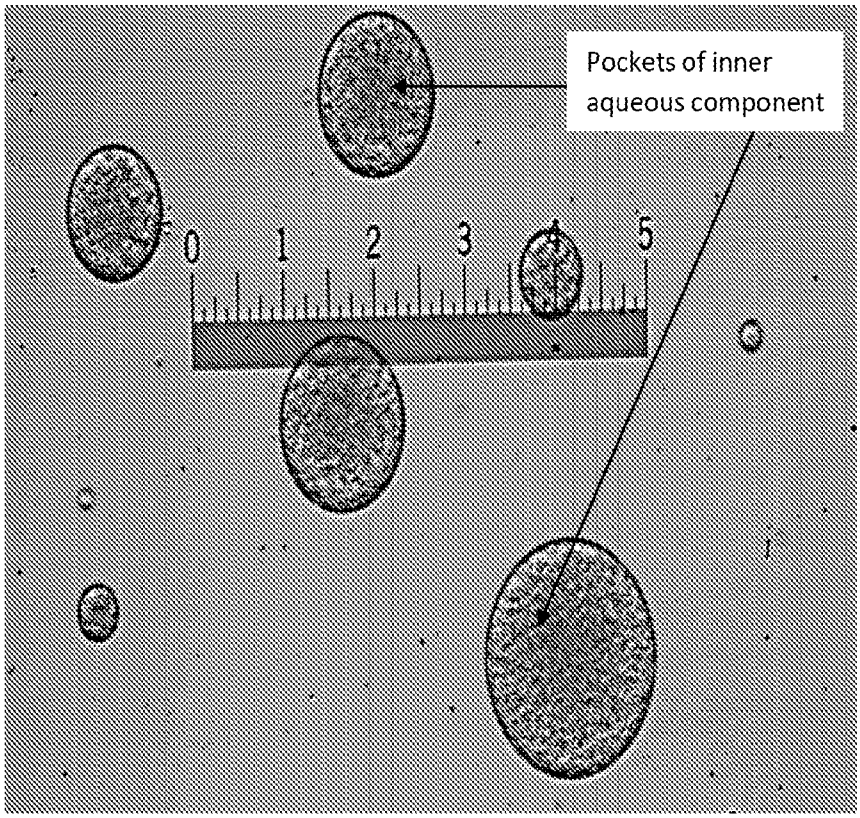
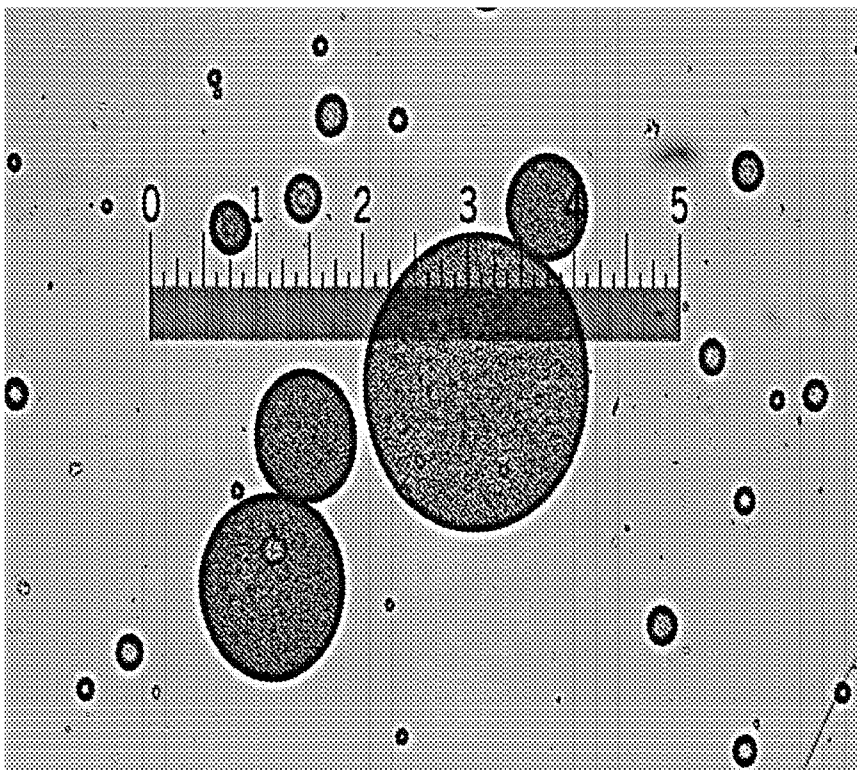


FIG. 11B



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/46220

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/167; A61K 31/485; A61K 31/573 (2021.01)

CPC - A61K 31/167; A61K 31/485; A61K 31/573

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2015/0250719 A1 (AURIS MEDICAL AG) 10 September 2015 (10.09.2015) - entire document especfically para [0020], [0028], [0029], [0032], [0052], [0081]	1-10
Y	US 2011/0027331 A1 (HOBOT) 3 February 2011 (03.02.2011) - entire document especially para [0156], [0162], [0052], [0183], [0059], [0133], [0161], [0043], [0073], [0055], [0012], [0181]	1-13
Y	WO 2019/054948 A1 (AGENCY FOR SCIENCE, TECHNOLOGY AND RESEARCH) 21 March 2019 (21.03.2019) - entire document especially abstract and pg 6, 7, 21, 23, 25, 28, 35, 36, 41	11-21
A	WO 2005/107706 A2 (HUGHES ET AL.) 17 November 2005 (17.11.2005) - entire document	1-10
A	WO 02/089767 A1 (ADAMIS ET AL.) 14 November 2002 (14.11.2002) - entire document	1-10
A	WO 2007/082061 A2 (STOCKMAN ET AL.) 19 July 2007 (19.07.2007) - entire document	1-10
A	US 6,291,013 B1 (GIBSON ET AL.) 18 September 2001 (18.09.2001) - entire document	11-21
A	US 2005/0260272 A1 (FIGUEIREDO ET AL.) 24 November 2005 (24.11.2005) - entire document	11-21

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 2021	JAN 05 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/46220

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

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

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

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

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

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

This International Searching Authority found multiple inventions in this international application, as follows:
see extra sheet

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

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

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-21

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

Remark on Protest

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

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

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/46220

Continuation of Box No. III (Observations where unity of invention is lacking)

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

Group I: Claims 1-10 are directed towards a microsphere formulation, comprising: polymer microspheres, each polymer microsphere comprising: (i) esketamine; and (ii) a biodegradable poly(lactide) polymer having an inherent viscosity of about 0.6 dL/g to about 0.7 dL/g, wherein each polymer microsphere has a ketamine drug load of about 12 wt/wt% to about 17 wt/wt%; wherein the polymer microspheres have an average particle size of about 80 micrometers (D5o) to about 110 micrometers (D5o); and wherein the polymer microspheres are characterized in that each of the polymer microspheres comprises a plurality of internal macrovoids.

Group II: Claims 11-21 are directed towards a method for making polymer microspheres, the method comprising: (i) contacting ketamine with a biodegradable poly(lactide) polymer in the presence of a solvent to form an organic component and providing the organic component to a first homogenizer; (ii) providing an inner aqueous component comprising water and a first surfactant to the first homogenizer; (iii) homogenizing the organic component with the inner aqueous component to form a primary emulsion; (iv) providing the primary emulsion to a second homogenizer at a first flow rate; (v) providing a continuous phase comprising water and a second surfactant to the second homogenizer at a second flow rate; (vi) homogenizing the primary emulsion and the continuous phase; and (iv) removing the solvent to form the polymer microspheres, wherein each of the formed polymer microspheres incorporates at least a portion of the inner aqueous component in the form of a plurality of emulsions.

Group III: Claims 22-26 are directed towards a method for treating depression, the method comprising intramuscularly or subcutaneously injecting a patient in need thereof with a therapeutically effective amount of a microsphere formulation, the microsphere formulation comprising: polymer microspheres, each polymer microsphere comprising: (i) esketamine; and (ii) a biodegradable poly(lactide) polymer; wherein each polymer microsphere has a ketamine drug load of between about 10 wt/wt% to about 30 wt/wt%, and wherein the polymer microspheres have an average particle size greater than 60 micrometers (D5o).

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

Special Technical Features:

Group I requires a microsphere formulation comprising polymer microspheres wherein each polymer microsphere comprises esketamine, a biodegradable poly(lactide) polymer having an inherent viscosity of about 0.6 dL/g to about 0.7 dL/g, and wherein the polymer microspheres are characterized in that each of the polymer microspheres comprises a plurality of internal macrovoids, not required by Group II and III.

Group II requires a method for making polymer microspheres, the method comprising: (i) contacting ketamine with a biodegradable poly(lactide) polymer in the presence of a solvent to form an organic component and providing the organic component to a first homogenizer; (ii) providing an inner aqueous component comprising water and a first surfactant to the first homogenizer; (iii) homogenizing the organic component with the inner aqueous component to form a primary emulsion; (iv) providing the primary emulsion to a second homogenizer at a first flow rate; (v) providing a continuous phase comprising water and a second surfactant to the second homogenizer at a second flow rate; (vi) homogenizing the primary emulsion and the continuous phase; and (iv) removing the solvent to form the polymer microspheres, wherein each of the formed polymer microspheres incorporates at least a portion of the inner aqueous component in the form of a plurality of emulsions, not required by Group III.

Group III requires a method for treating depression, the method comprising intramuscularly or subcutaneously injecting a patient in need thereof with a therapeutically effective amount of a microsphere formulation, not required by Group II.

Shared Technical Features:

Groups I-II share the common technical features of polymer microspheres comprising ketamine and a biodegradable poly(lactide) polymer. However, these shared technical features do not represent a contribution over prior art, because the shared technical features are anticipated by US 2015/0250719 A1 to Auris Medical Ag (hereinafter "Auris"). Auris teaches polymer microspheres (para [0032], the biocompatible polymer used in the composition preferably can form gels which may be microsphere-based; para [0052], it is also possible to combine the embodiments described above allowing the controlled release of the active agent, for example by creating a gel holding microspheres. There, the release of the active agent may be controlled by the gel system as well as by the microspheres suspended in the polymer gel system) comprising ketamine (para [0020], any derivative, analogue, and/or enantiomeric form of ketamine may be used as active agent in the inventive composition; para [0081], S-(+)-Ketamine hydrochloride was dissolved at a concentration of 2% (weight/weight) equivalent 73 mM. S-(+)-Ketamine is esketamine; see instant specification para [0003], The (S)-(+) enantiomer, also known as esketamine) and a biodegradable poly(lactide) polymer (para [0028], in order to be used in medical compositions the biodegradable polymer must be biocompatible and preferably meet other criteria, such as being biomaterial-processable, sterilizable and capable of controlled stability or degradation in response to biological conditions; para [0029], poly(esters) based on polylactide (PLA), polyglycolide (PGA), polycaprolactone (PCL) and their copolymers are useful polymers in pharmaceutical compositions. Degradation of these materials yields the corresponding hydroxy acids, making them safe for in vivo use).

--see next page--

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/46220

Continuation of Box No. III (Observations where unity of invention is lacking)

Groups I-III share the common technical features of a microsphere formulation comprising polymer microspheres, wherein each polymer microsphere comprises esketamine, a biodegradable poly(lactide) polymer, wherein each polymer microsphere has a ketamine drug load of between about 10 wt/wt% to about 30 wt/wt%, and wherein the polymer microspheres have an average particle size greater than 60 micrometers (D5o). However, these shared technical features do not represent a contribution over prior art, because the shared technical features are anticipated by US 2015/0250719 A1 to Auris Medical Ag (hereinafter "Auris") and US 2011/0027331 A1 to Hobot (hereinafter "Hobot"). Auris teaches a microsphere formulation (para [0032], the biocompatible polymer used in the composition preferably can form gels which may be microsphere-based; para [0052], it is also possible to combine the embodiments described above allowing the controlled release of the active agent, for example by creating a gel holding microspheres. There, the release of the active agent may be controlled by the gel system as well as by the microspheres suspended in the polymer gel system) comprising polymer microspheres (para [0032], the biocompatible polymer used in the composition preferably can form gels which may be microsphere-based; para [0052], it is also possible to combine the embodiments described above allowing the controlled release of the active agent, for example by creating a gel holding microspheres. There, the release of the active agent may be controlled by the gel system as well as by the microspheres suspended in the polymer gel system), wherein each polymer microsphere comprises esketamine (para [0020], any derivative, analogue, and/or enantiomeric form of ketamine may be used as active agent in the inventive composition; para [0081], S-(+)-Ketamine hydrochloride was dissolved at a concentration of 2% (weight/weight) equivalent 73 mM. S-(+)-Ketamine is esketamine; see instant specification para [0003], The (S)-(+) enantiomer, also known as esketamine), a biodegradable poly(lactide) polymer (para [0028], in order to be used in medical compositions the biodegradable polymer must be biocompatible and preferably meet other criteria, such as being biomaterial-processable, sterilizable and capable of controlled stability or degradation in response to biological conditions; para [0029], poly(esters) based on polylactide (PLA), polyglycolide (PGA), polycaprolactone (PCL) and their copolymers are useful polymers in pharmaceutical compositions. Degradation of these materials yields the corresponding hydroxy acids, making them safe for in vivo use), but does not specifically teach wherein each polymer microsphere has a ketamine drug load of between about 10 wt/wt% to about 30 wt/wt% and wherein the polymer microspheres have an average particle size greater than 60 micrometers (D5o). In a similar invention, Hobot teaches a microsphere formulation (para [0161], in various embodiments, rather than directly admixing the therapeutic agents into the gel, microspheres may be dispersed within the gel, the microspheres being loaded with at least one analgesic agent and/or at least one anti-inflammatory agent. In one embodiment, the microspheres provide for a sustained release of the at least one analgesic and/or anti-inflammatory agent) wherein each polymer microsphere has a ketamine drug load of about 15% by weight of the formulation (para [0039], in some embodiments, local administration of the drug depot at or near the target tissue site allows for a lower dose of the analgesic, muscle relaxant and/or the anti-inflammatory agent to be used than the usual oral, intravenous, or intramuscular dose. For example, local administration of the drug depot can be accomplished with daily doses that are 15% of the usual oral, intravenous or intramuscular dose; para [0043], analgesic refers to an agent that can reduce, relieve or eliminate pain, analgesic agents include ketamine hydrochloride. 15 wt% falls within the range of 12-17 wt%). Hence, it would have been obvious to one of skill in the art to combine both references to teach wherein each polymer microsphere has a ketamine drug load of about 15% by weight of the formulation to improve the release kinetics of the formulation (see US 2015/0250719 to Auris, para [0087], the drug load had also a significant influence on release kinetics, using as high a loading factor as possible will help extend the release kinetics). In the same invention discussed earlier, Hobot also teaches wherein the polymer microspheres have an average particle size of about 10 micrometers to about 200 micrometers (para [0162], the diameter of the microspheres range from about 10 microns to about 200 microns in diameter. Diameter is interpreted as "average particle size", and 80 micrometers to 110 micrometers falls within this range). It would have been obvious to one of skill in the art to combine both references to teach wherein each microsphere has an average particle size or diameter of about 10 micrometers to about 200 micrometers to optimize release relates of the active agent (see US 2015/0250719 A1 to Auris, para [0053], active agent release rates depend very strongly on the size of the microspheres containing the active agent, larger microspheres may generally release encapsulated compounds more slowly and over longer time periods. To achieve a delivery of the active agent at a constant rate it might be useful to mix microspheres of different sizes to generate a constant rate of release over a prolonged period of time).

Groups II-III share the common technical features of polymer microspheres comprising ketamine and a biodegradable poly(lactide) polymer. However, these shared technical features do not represent a contribution over prior art, because the shared technical features are anticipated by US 2015/0250719 A1 to Auris Medical Ag (hereinafter "Auris"). Auris teaches polymer microspheres (para [0032], the biocompatible polymer used in the composition preferably can form gels which may be microsphere-based; para [0052], it is also possible to combine the embodiments described above allowing the controlled release of the active agent, for example by creating a gel holding microspheres. There, the release of the active agent may be controlled by the gel system as well as by the microspheres suspended in the polymer gel system) comprising ketamine (citation) and a biodegradable poly(lactide) polymer (para [0028], in order to be used in medical compositions the biodegradable polymer must be biocompatible and preferably meet other criteria, such as being biomaterial-processable, sterilizable and capable of controlled stability or degradation in response to biological conditions; para [0029], poly(esters) based on polylactide (PLA), polyglycolide (PGA), polycaprolactone (PCL) and their copolymers are useful polymers in pharmaceutical compositions. Degradation of these materials yields the corresponding hydroxy acids, making them safe for in vivo use).

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