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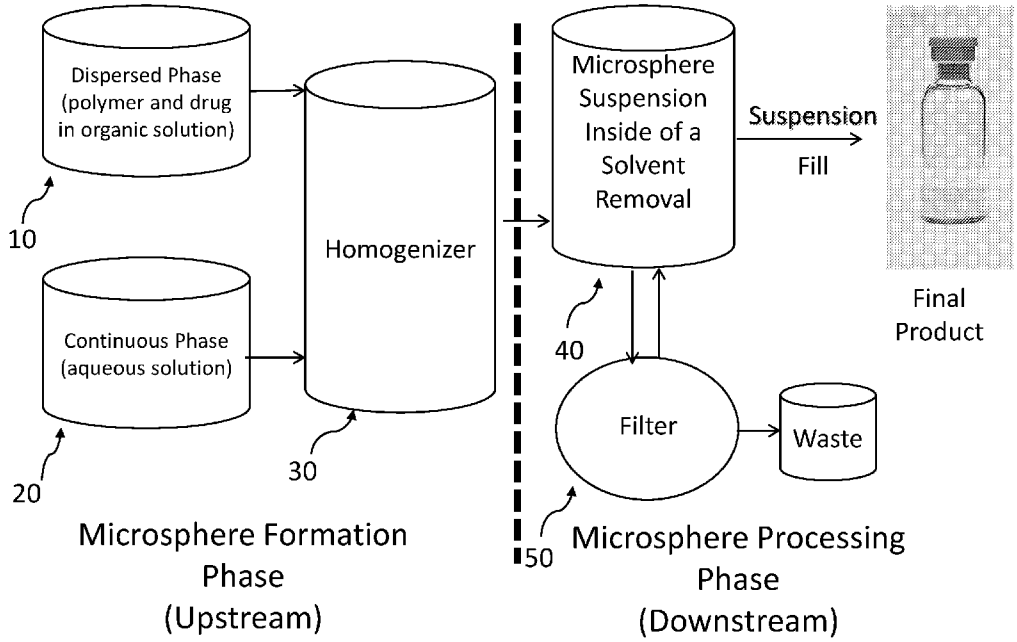

FIG. 1

(57) Abstract: Microsphere formulations comprising naltrexone are provided. The microsphere formulations comprise polymer microspheres, each polymer microsphere comprising: (i) naltrexone; and (ii) a biodegradable polymer comprising a POE or a PLA, wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 25 mm to about 55 mm (D_{50}). Methods for making and using the microsphere formulations are also provided.

[Continued on next page]

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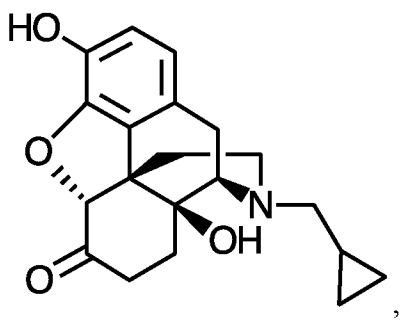
MICROSPHERE FORMULATIONS COMPRISING NALTREXONE AND METHODS FOR MAKING AND USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Patent Application No. 63/266,660, filed on January 11, 2022, U.S. Provisional Patent Application No. 63/161,159, filed on March 15, 2021, and U.S. Provisional Patent Application No. 63/161,187, filed on March 15, 2021, each of which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] Naltrexone (chemical formula $C_{20}H_{23}NO_4$; CAS Number 16590-41-3), characterized by the general structure:



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is a medication used to treat alcohol and opioid dependence. Naltrexone is currently orally administered as a tablet or injected into a muscle (commercially available under the trade name Vivitrol®).

[0003] Vivitrol® is a once-per-month extended-release microsphere formulation wherein naltrexone is encapsulated in a poly(D,L-lactide-co-glycolide), 75:25 polymer matrix, having a drug load of approximately 33.7% and a particle size of approximately 81 μm (D50). Vivitrol® must not be administered intravenously or subcutaneously. Some patients experience side effects from using Vivitrol® and may require another treatment option. Thus, a need exists for an alternative extended-release naltrexone-encapsulating microsphere formulation, especially one

having a high drug load (≥~45 % by weight), small particle size (about 25-55 μm (D50)), long release duration (≥~30, 60, or even 90 days), and a different mode of release.

SUMMARY

[0004] Microsphere formulations comprising naltrexone are provided. The microsphere formulations comprise polymer microspheres, each polymer microsphere comprising: (i) naltrexone; and (ii) a biodegradable polymer comprising either a poly(ortho ester) polymer (a "POE") or a poly(D,L-lactide) polymer (a "PLA"), wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 25 μm to about 55 μm (D_{50}), with the proviso that the biodegradable polymer does not include a poly (D,L-lactide-co-glycolide) (a "PLGA"). In one aspect, the microsphere formulations are characterized in that the naltrexone is released over a period of about 90 days (i.e., 90 days). In other aspects, the microsphere formulations are characterized in that the naltrexone is released over a period of about 30 days (i.e., ±10% of 30 days) or about 60 days (i.e., ±10% of 60 days). In another aspect, the microsphere formulations are characterized in that they have a low initial burst release, that is, not more than 20% of the naltrexone is released within about 24 hours of injection into a subject.

[0005] In one aspect, the microsphere formulations may be made by a method, the method comprising: (A) mixing: (i) the biodegradable polymer comprising a POE or a PLA; (ii) a primary solvent; (iii) naltrexone; and (iv) a co-solvent, to form a dispersed phase; (B) mixing: (i) water; and (ii) a surfactant, to form a continuous phase; and (C) combining the dispersed phase with the continuous phase in a homogenizer.

[0006] In one aspect, a method for treating alcohol and/or opioid dependence 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, wherein the formulation is administered to the patient with a dosing schedule of about every 30, 60, or 90 days.

[0007] In another aspect, use is disclosed of a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) naltrexone; and (ii) a biodegradable polymer comprising a POE or a PLA, wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 25 μm to about 55 μm (D_{50}), in the manufacture of a medicament for the treatment of alcohol and/or opioid dependence.

[0008] In another aspect, a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) naltrexone; and (ii) a biodegradable polymer comprising a POE or a PLA, wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 25 μm to about 55 μm (D_{50}), is provided for use as a medicament for the treatment of alcohol and/or opioid dependence.

[0009] In another aspect, a kit is provided, the kit comprising polymer microspheres, each polymer microsphere comprising: (i) naltrexone; and (ii) a biodegradable polymer comprising a POE or a PLA, wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 25 μm to about 55 μm (D_{50}).

BRIEF DESCRIPTION OF THE FIGURES

[0010] **Figure 1** is a schematic depicting a method for making naltrexone-encapsulated polymer microspheres.

[0011] **Figure 2** is a graph showing naltrexone release over time in dogs from naltrexone-encapsulating PLA-based polymer microspheres in direct comparison to Vivitrol®.

[0012] **Figure 3** is a graph showing naltrexone release over time in dogs from naltrexone-encapsulating POE-based polymer microspheres in direct comparison to Vivitrol®.

DETAILED DESCRIPTION

[0013] Microsphere formulations comprising naltrexone are provided. The microsphere formulations comprise polymer microspheres, each polymer microsphere comprising: (i) naltrexone; and (ii) a biodegradable polymer comprising a POE or a PLA, wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 25 μm to about 55 μm (D_{50}).

[0014] In one aspect, the microsphere formulations may be made by a method, the method comprising: (A) mixing: (i) the biodegradable polymer comprising a POE or a PLA, but not a PLGA; (ii) a primary solvent; (iii) naltrexone; and (iv) a co-solvent, to form a dispersed phase; (B) mixing: (i) water; and (ii) a surfactant, to form a continuous phase; and (C) combining the dispersed phase with the continuous phase in a homogenizer.

Naltrexone

[0015] In one aspect, the naltrexone is a free base supplied by Mallinckrodt Pharmaceuticals. In one aspect, the naltrexone has a dichloromethane ("DCM") solubility of 100 mg/mL, ethyl

acetate ("EA") solubility of 26 mg/mL, and benzyl alcohol ("BA") solubility of >250 mg/mL. In one aspect, the naltrexone has a pKa = 8.4.

[0016] In another aspect, the naltrexone is an HCl salt supplied by Mallinckrodt Pharmaceuticals. In one aspect, the naltrexone HCl salt has a water solubility of about 100 mg/mL.

Biodegradable Polymers

[0017] In one aspect, the biodegradable polymer is a POE. POEs release through surface degradation, as compared to PLGAs, which release by bulk hydrolysis. Suitable POE polymers or co-polymers may include a cyclohexanedimethanol:triethylene glycol (CHDM:TEG) co-polymer, a cyclohexanedimethanol:triethylene glycol:triethylene glycol glycolide (CHDM:TEG:TEG-GL) tri-block polymer, a 3,9-Diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane:triethylene glycol (DETOSU:TEG), or a 3,9-Diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane:triethylene glycol:triethylene glycol glycolide (DETOSU:TEG:TEG-GL). In one aspect, the CHDM:TEG ratio may be about 93:7, with a molecular weight of about 22 kDa. In one aspect, the CHDM:TEG:TEG-GL ratio may be about 88:10:2, with a molecular weight of about 27 kDa. In another aspect, the CHDM:TEG:TEG-GL ratio may be about 70:0:30, with a molecular weight of about 20 kDa.

[0018] In one aspect, the biodegradable polymer is a PLA. The PLA may have an inherent viscosity of about 0.15 dL/g to about 0.75 dL/g, including from about 0.15 dL/g to about 0.25 dL/g, from about 0.26 dL/g to about 0.54 dL/g, including 0.36 dL/g, and from about 0.55 dL/g to about 0.75 dL/g. In one aspect, the PLA comprises Lactel® DL-PLA, ester terminated, IV = 0.36 dL/g, MW = 46 kDa, supplied by Evonik Industries AG ("DL-PLA").

[0019] In one aspect, PLGA polymers are specifically excluded.

Dispersed Phase

[0020] In one aspect, the dispersed phase comprises a primary solvent. In one aspect, the primary solvent comprises DCM. The dispersed phase may also include up to about 50% by weight of a co-solvent capable of optimizing the solubility of naltrexone in the dispersed phase. In one aspect, the co-solvent may be BA, dimethyl sulfoxide, dimethyl formamide, dimethyl acetamide, acetonitrile, ethanol, N-methyl pyrrolidone, EA, or any other solvent that increases the solubility of naltrexone in the dispersed phase. In one aspect, the primary solvent comprises DCM, and the co-solvent comprises BA. In one aspect, the ratio of DCM to BA is about 3:1. The organic solvent is removed from the microspheres in the course of their preparation. A microsphere is considered to be "essentially free" of organic solvent if the microsphere meets the standards set forth in the "ICH Harmonised Guideline, Impurities: Guideline for Residual Solvents Q3C(R8), Current Step 4 version dated 22 April 2021," which is incorporated herein by reference in its entirety.

Continuous Phase

[0021] The dispersed phase may be combined with an aqueous continuous phase that comprises water and, optionally, a surfactant. In one aspect, the continuous phase has a pH of about 6.

[0022] 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 polyvinyl alcohol ("PVA") in a concentration of about 0.35% by weight in water.

[0023] In some aspects, the dispersed phase flow rate to the homogenizer may be 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 ratio may be from about 66:1 to about 200:1, including about 100:1 and about 80:1.

[0024] 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 temperature values.

Homogenizer

[0025] 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 and the continuous phase, emulsify the dispersed phase 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 U.S. Patent No. 11,167,256, 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 1,250 RPM, about 2,000 RPM, about 3,250 RPM, or any value or range between any of those RPM values.

Drug Load

[0026] The drug load of each polymer microsphere in a drug to polymer ratio, expressed as a percentage, may be about 45 wt/wt%, greater than 40 wt/wt%, about 50 wt/wt%, and from about 45 wt/wt% to about 55 wt/wt%.

Particle Size

[0027] The polymer microspheres may be any size that is safely and efficaciously injectable. In one aspect, the polymer microspheres may have an average particle size between about 25 μm (D_{50}) and about 55 μm (D_{50}), between about 25 μm (D_{50}) and about 35 μm (D_{50}), between about 35 μm (D_{50}) and about 45 μm (D_{50}), between about 45 μm (D_{50}) and about 55 μm (D_{50}), less than about 55 μm (D_{50}), and less than about 60 μm (D_{50}).

Extended Release

[0028] Where the polymer is a PLA, the microsphere formulations may be characterized in that they have a duration of release of at least about two weeks and up to about twelve weeks. In some aspects, the microsphere formulations have a duration of release of about three weeks, about four weeks, about five weeks, and about six weeks. In some aspects, the duration of release is about 30 days.

[0029] Where the polymer is a POE comprising CHDM:TEG with a ratio of about 93:7, or the polymer is a POE comprising CHDM:TEG:TEG-GL with a ratio of about 88:10:2, the microsphere formulations may be characterized in that they may have a duration of release of at least about 60 days.

[0030] Where the polymer is a POE comprising CHDM:TEG:TEG-GL with a ratio of about 70:0:30, the microsphere formulations may be characterized in that they have a duration of release of about 90 days.

[0031] The microsphere formulations are further characterized in that they have a low initial burst release, that is, not more than 20% of the naltrexone is released within about 24 hours of injection into a subject.

Therapeutic Benefits

[0032] In one aspect, a method for treating alcohol and/or opioid dependence 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, wherein the formulation is administered to the patient with a dosing schedule of about every 30, 60, or 90 days.

[0033] In another aspect, use is disclosed of a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) naltrexone; and (ii) a biodegradable polymer comprising a POE or a PLA, wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 25 μm to about 55 μm (D_{50}), in the manufacture of a medicament for the treatment of alcohol and/or opioid dependence.

[0034] In another aspect, a microsphere formulation comprising polymer microspheres, each polymer microsphere comprising: (i) naltrexone; and (ii) a biodegradable polymer comprising a POE or a PLA, wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 25 μm to about 55 μm (D_{50}), is provided for use as a medicament for the treatment of alcohol and/or opioid dependence.

[0035] In another aspect, a kit is provided, the kit comprising polymer microspheres, each polymer microsphere comprising: (i) naltrexone; and (ii) a biodegradable polymer comprising a POE or a PLA, wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of about 25 μm to about 55 μm (D_{50}).

EXAMPLES

Example 1 – General preparation of polymer microspheres comprising naltrexone

[0036] Microsphere Formation Phase. With reference to **Figure 1**, a dispersed phase ("DP") 10 is formed by dissolving a polymer matrix (such as a POE or PLA polymer) in an organic solvent system (such as DCM and BA), followed by the addition of naltrexone 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 at a defined flow rate. A continuous phase ("CP") 20 comprising water and surfactant 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.

[0037] 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. See, e.g., U.S. Patent No. 9,017,715, which is incorporated by reference herein in its entirety. 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 Cytiva) 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.

[0038] 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 Naltrexone-Encapsulated PLA Polymer Microspheres – Batch 1

[0039] Following the general procedure described in Example 1, illustrated in **Figure 1**, and detailed in **Table 1**, the DP was formed by dissolving 13.5 g of DL-PLA polymer in 59.4 g of DCM and 19.8 g of BA (DCM/BA (3:1)), followed by addition of naltrexone (16.5 g) with mixing until completely dissolved. The DP was filtered and pumped at a flow rate of 25 mL/min into a Levitronix® BPS-i100 integrated pump system operating at 3,250 RPM. The CP comprising 0.35% PVA was also pumped into the homogenizer at a flow rate of 2 L/min (CP:DP = 80:1).

[0040] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV. 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.

[0041] The process parameters and the characterization data for a representative batch (Batch #1) are shown in **Table 1** in comparison to Vivitrol®:

Table 1

Batch #	1	Vivitrol®
Polymer	DL-PLA	PLGA 75:25
Polymer IV (dL/g)	0.36	Unknown
Solvent System	DCM/BA (3:1)	Unknown/BA
Homogenizer RPM	3,250	N/A
Drug Load (%)	47.5	33.7
Residual Solvents (% wt.)	0.1/2.0	N.D./0.6
Particle Size (D_{10})	15	50
Particle Size (D_{50})	31	81

Particle Size (D_{90})	53	129
Microsphere MW (kDa)	41	74

[0042] **Figure 2** is a graph showing naltrexone release over time in dogs from naltrexone-encapsulating PLA polymer microspheres in direct comparison to Vivitrol®.

Example 3 – Preparation of Naltrexone-Encapsulated POE Polymer Microspheres – Batches 2-4

[0043] Following the general procedure described in Example 1, illustrated in **Figure 1**, and detailed in **Table 2**, the DP was formed by dissolving 13.5 g of POE in 59.4 g of DCM and 19.8 g of BA (DCM/BA (3:1)), followed by addition of naltrexone (16.5 g) with mixing until completely dissolved. The DP was filtered and pumped at a flow rate of 25 mL/min into a Levitronix® BPS-i100 integrated pump system operating at 3,250 RPM (Batches 2 and 3) or 4,000 RPM (Batch 4). The CP comprising 0.35% PVA was also pumped into the homogenizer at a flow rate of 2 L/min (CP:DP = 80:1).

[0044] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV. 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.

[0045] The process parameters and the characterization data for three representative batches (Batches 2-4) are shown in **Table 2** in comparison to Vivitrol®:

Table 2

Batch #	2	3	4	Vivitrol®
Polymer (Co-polymer ratio)	CHDM:TEG (93:7)	CHDM:TEG:TEG-GL (88:12:2)	CHDM:TEG:TEG-GL (88:12:2)	PLGA (75:25)
MW (kDa)	22	27	27	Unknown
Solvent System	DCM/BA (3:1)	DCM/BA (3:1)	DCM/BA (3:1)	Unknown/BA
Homogenizer RPM	3,250	3,250	4,000	N/A
Drug Load (% wt)	49.6	49.7	49.1	33.7
Residual Solvents (% wt.)	0.1/3.5	0. 1/3.4	0.1/2.8	N.D./0.6
Particle Size (D_{10})	13	14	13	50
Particle Size (D_{50})	29	30	26	81
Particle Size (D_{90})	52	52	45	129
Microsphere MW (kDa)	22	28	28	74

[0046] **Figure 3** is a graph showing naltrexone release over time in dogs from naltrexone-encapsulating POE polymer microspheres in direct comparison to Vivitrol®.

Example 4 – Preparation of Naltrexone-Encapsulated POE Polymer Microspheres – Batches 5-8

[0047] Following the general procedure described in Example 1, illustrated in **Figure 1**, and detailed in **Table 3**, the DP was formed by dissolving 13.5 g of POE in 59.4 g of DCM and 19.8 g of BA (DCM/BA (3:1)), followed by addition of naltrexone (16.5 g) with mixing until completely dissolved. The DP was filtered and pumped at a flow rate of 25 mL/min into a Levitronix® BPS-i100 integrated pump system operating at 1,250 RPM (Batches 5 and 6) or 3,250 RPM (Batches 7 and 8). The CP comprising 0.35% PVA was also pumped into the homogenizer at a flow rate of 2 L/min (CP:DP = 80:1).

[0048] The formed or forming microspheres exited the homogenizer and entered the SRV. Deionized water was added to the SRV. 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.

[0049] The process parameters and the characterization data for four representative batches (Batches 5-8) are shown in **Table 3.**

Table 3

Batch #	5	6	7	8
Polymer (Co-polymer ratio)	CHDM:TEG:TEG-GL (70:0:30)	CHDM:TEG:TEG-GL (70:0:30)	CHDM:TEG:TEG-GL (70:0:30)	CHDM:TEG:TEG-GL (70:0:30)
MW (kDa)	20	20	20	20

Solvent System	DCM/BA (3:1)	DCM/BA (3:1)	DCM/BA (3:1);	DCM/BA (3:1) 1-hour EtOH 2% solvent treatment*
Homogenizer RPM	1,750	1,750	3,250	3,250
Drug Load (% wt)	50.6	40.7	49.0	48.4
Particle Size (D_{10})	23	18	11	11
Particle Size (D_{50})	43	38	25	20
Particle Size (D_{90})	75	69	52	35

*After the microsphere formation step, the microsphere suspension was dosed with 2% ethanol by volume and stirred for one hour. After stirring, the dosed microsphere suspension was concentrated and subjected to normal washing steps. This is intended to decrease the initial burst of the microspheres in vivo.

[0050] In use, the microspheres may be suspended in a diluent for administration (injection). The diluent may generally contain a thickening agent, a tonicity agent, and a surfactant. The thickening agent may include carboxymethyl cellulose-sodium (CMC-Na) or other suitable compounds. An appropriate viscosity grade and suitable concentration of CMC-Na may be selected so that the viscosity of the diluent is 3 cps or higher. Generally, a viscosity of about 10 cps is suitable; however, a higher viscosity diluent may be preferred for larger microspheres in order to minimize the settling of microspheres in the suspension.

[0051] Uniform microsphere suspension without particle settling will result in a consistent delivered dose during drug administration by injection. To have a tonicity of the diluent closer to the biological system, about 290 milliosmole (mOsm), solutes such as mannitol, sodium chloride, or any other acceptable salt may be used.

[0052] 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.

[0053] 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.

[0054] 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 API content, if there are 10 polymer microspheres, and two or more of the polymer microspheres have the

particular API content, then that subset of two or more polymer microspheres is intended to meet the limitation.

[0055] The term "about" in conjunction with a number is simply shorthand and 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:

naltrexone; and

a biodegradable polymer comprising a poly(ortho ester) ("POE"),

wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and

wherein the polymer microspheres have an average particle size of between about 25 μm to about 55 μm (D_{50}), with the proviso that the biodegradable polymer does not include poly (D,L-lactide-co-glycolide).

2. The microsphere formulation of claim 1, wherein the naltrexone comprises naltrexone in free base form.

3. The microsphere formulation of claim 1 or 2, wherein the POE comprises a cyclohexanedimethanol:triethylene glycol (CHDM:TEG) co-polymer.

4. The microsphere formulation of any of the preceding claims, wherein the POE comprises a cyclohexanedimethanol:triethylene glycol (CHDM:TEG) co-polymer in a ratio of about 93: about 7.

5. The microsphere formulation of any of claims 1, 2, or 3, wherein the POE comprises a cyclohexanedimethanol:triethylene glycol (CHDM:TEG) co-polymer in a ratio of about 88 to about 12.

6. The microsphere formulation of claim 1 or 2, wherein the POE comprises a cyclohexanedimethanol:triethylene glycol:triethylene glycol glycolide (CHDM:TEG:TEG-GL) tri-block polymer.

7. The microsphere formulation of any of claims 1, 2, or 6, wherein the POE comprises a cyclohexanedimethanol:triethylene glycol:triethylene glycol glycolide (CHDM:TEG:TEG-GL) tri-block polymer in a ratio of about 88: about 10: about 2.

8. The microsphere formulation of any of claims 1, 2, or 6, wherein the POE comprises a cyclohexanedimethanol:triethylene glycol:triethylene glycol glycolide (CHDM:TEG:TEG-GL) tri-block polymer in a ratio of about 70: about 0: about 30.

9. The microsphere formulation of claim 1 or 2, wherein the POE comprises a 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane:triethylene glycol (DETOSU:TEG).

10. The microsphere formulation of claim 1 or 2, wherein the POE comprises a 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane:triethylene glycol:triethylene glycol glycolide (DETOSU:TEG:TEG-GL).

11. The microsphere formulation of any one of the preceding claims, wherein each polymer microsphere comprises a drug load of about 45% to about 55% by weight of the polymer microsphere.

12. The microsphere formulation of any one of the preceding claims, wherein each polymer microsphere comprises a drug load of about 50% by weight of the polymer microsphere.

13. The microsphere formulation of any one of the preceding claims, wherein the polymer microspheres have an average particle size of about 25 μm to about 45 μm (D_{50}).

14. A pharmaceutical composition comprising the microsphere formulation of any one of the preceding claims.

15. A microsphere formulation, comprising:

polymer microspheres, each polymer microsphere comprising:

naltrexone; and

a biodegradable polymer comprising a cyclohexanedimethanol:triethylene glycol:triethylene glycol glycolide (CHDM:TEG:TEG-GL) tri-block polymer in a ratio of about 70: about 0: about 30,

wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and

wherein the polymer microspheres have an average particle size of between about 25 μm to about 55 μm (D_{50}), with the proviso that the biodegradable polymer does not include poly (D,L-lactide-co-glycolide).

16. A microsphere formulation, comprising:

polymer microspheres, each polymer microsphere comprising:

naltrexone; and

a biodegradable polymer comprising a cyclohexanedimethanol:triethylene glycol:triethylene glycol glycolide (CHDM:TEG:TEG-GL) tri-block polymer in a ratio of about 88: about 10: about 2,

wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and

wherein the polymer microspheres have an average particle size of between about 25 μm to about 55 μm (D_{50}), with the proviso that the biodegradable polymer does not include poly (D,L-lactide-co-glycolide).

17. A method for making polymer microspheres comprising naltrexone, the method comprising:

(i) contacting naltrexone with a cyclohexanedimethanol:triethylene glycol:triethylene glycol glycolide (CHDM:TEG:TEG-GL) tri-block polymer in the presence of an organic solvent system comprising dichloromethane and benzyl alcohol to form a dispersed phase;

(ii) combining the dispersed phase with a continuous phase comprising water and surfactant in a homogenizer to form an emulsion;

(iii) removing the organic solvent from the emulsion to form a microsphere formulation essentially free of organic solvent; and

(iv) subjecting the substantially organic solvent-free microsphere formulation to freeze-drying.

18. The method of claim 17, wherein the surfactant comprises polyvinyl alcohol.

19. The method of claim 17 or 18, wherein the surfactant comprises polyvinyl alcohol in a concentration in the continuous phase prior to the combining of about 0.35% by weight.

20. A polymer microsphere formulation made according to the method of any one of preceding claims 17, 18, or 19.

21. A kit, comprising:

polymer microspheres, each polymer microsphere comprising:

(i) naltrexone; and

(ii) a cyclohexanedimethanol:triethylene glycol:triethylene glycol glycolide (CHDM:TEG:TEG-GL) tri-block polymer,

wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of from about 25 μm (D50) to about 55 μm (D50).

22. The kit of claim 21, wherein the co-polymer is present in a ratio of either about 88: about 10: about 2 or about 70: about 0: about 30.

Sheet 1 of 3

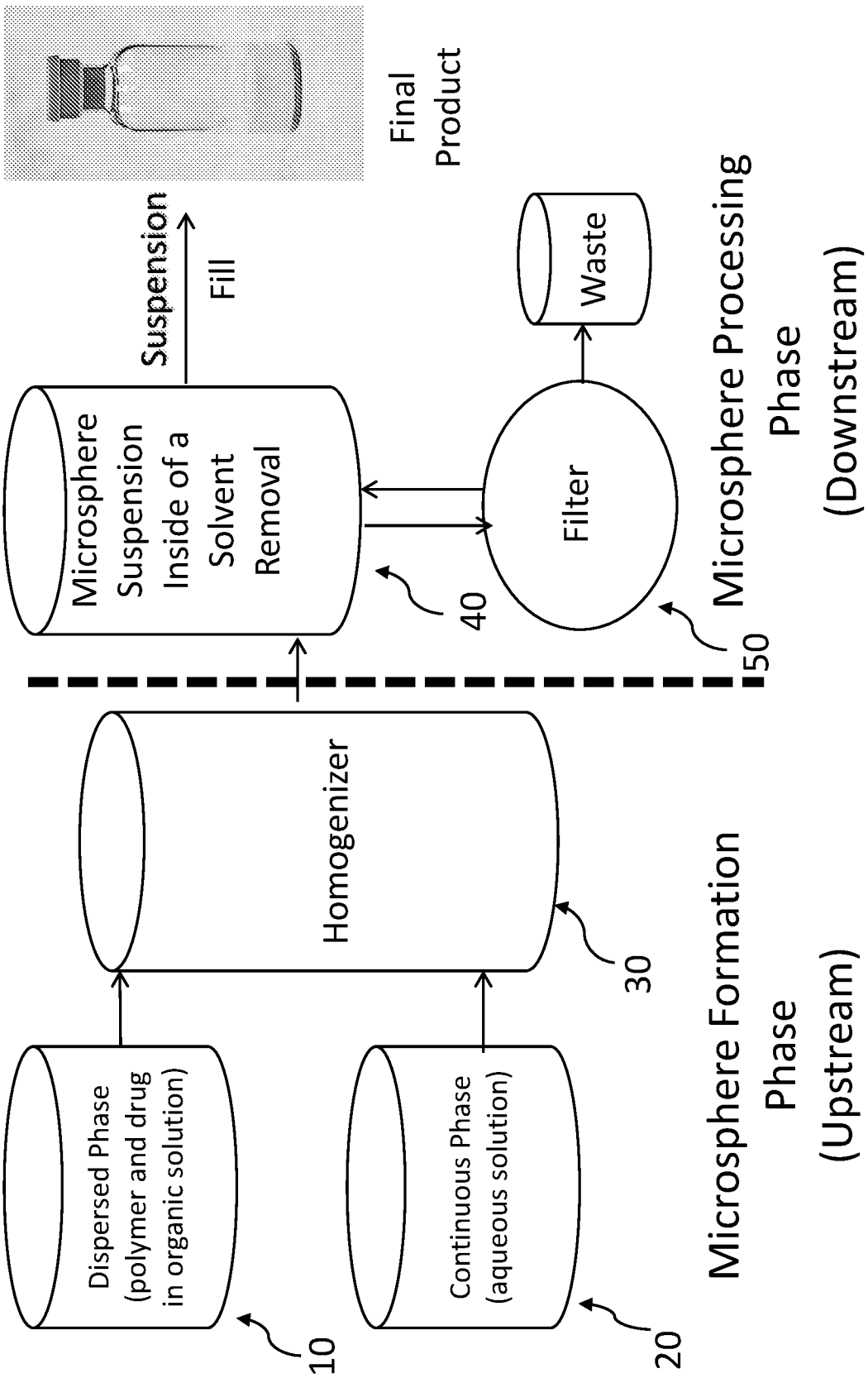

FIG. 1

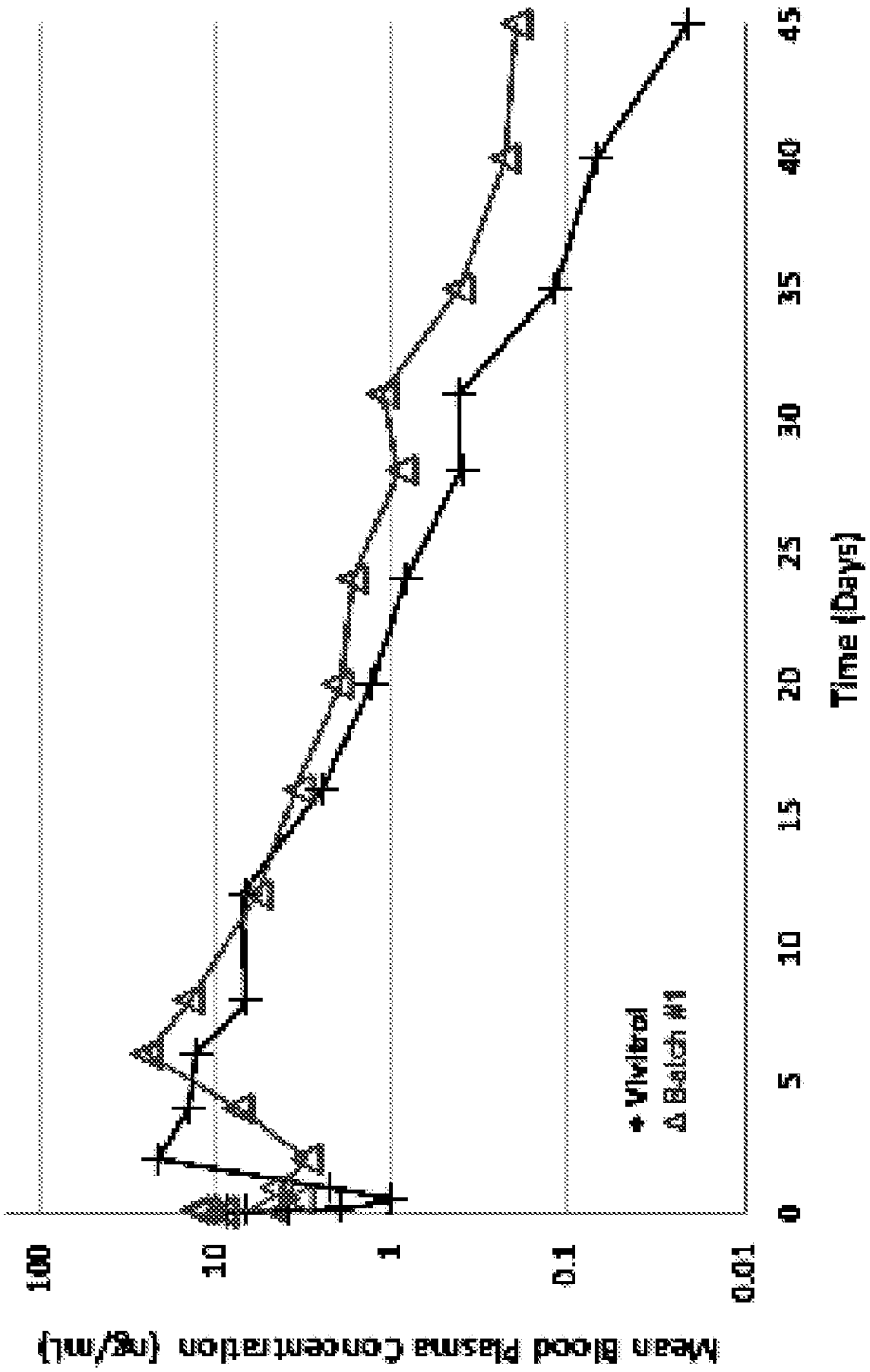
Mean Blood Plasma Concentration (ng/mL)
100
10
1
0.1
0.01
0
5
10
15
20
25
30
35
40
45
Time (Days)
◆ Vivitrol
△ Batch #1

FIG. 2

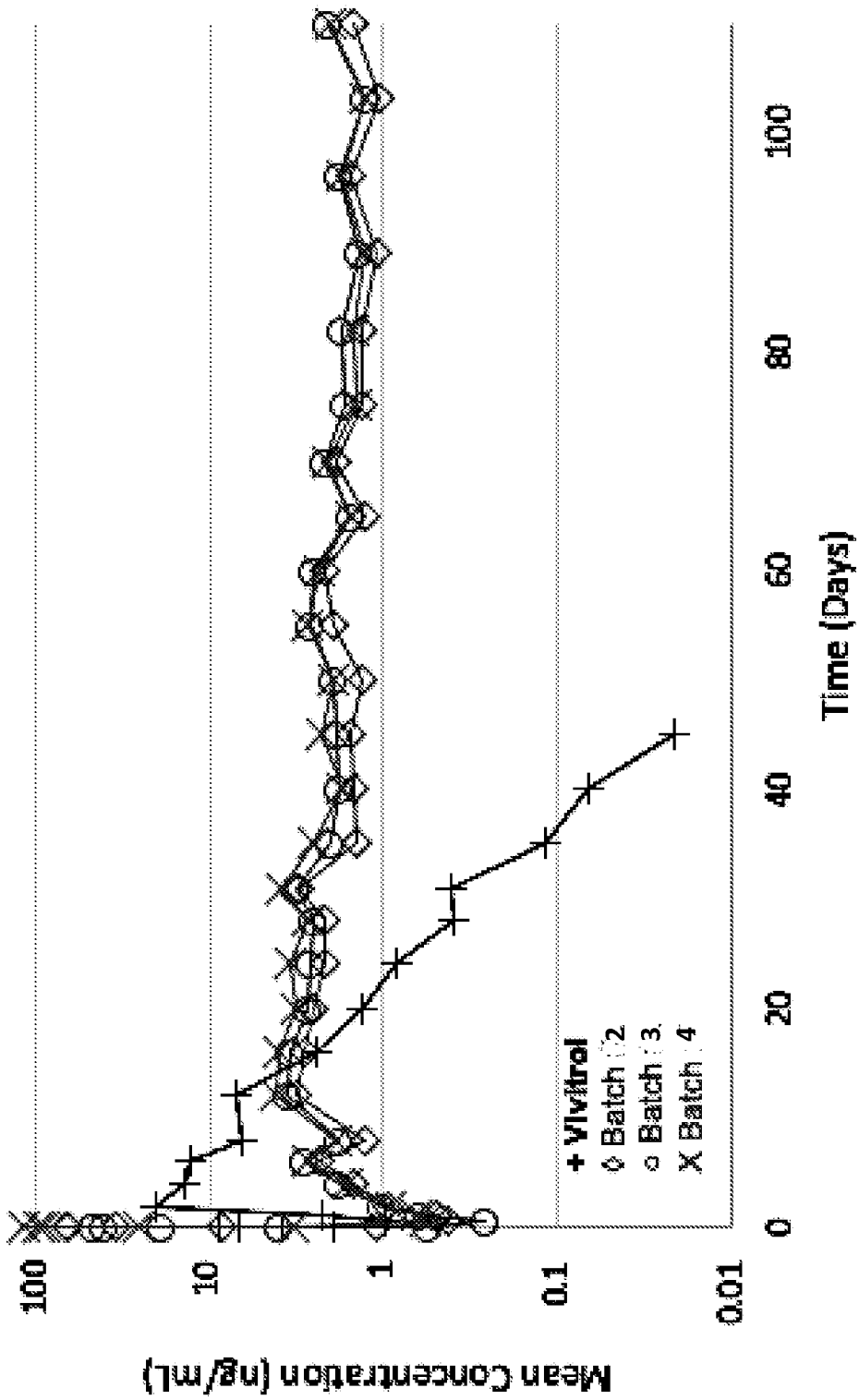
Mean Concentration (ng/mL)
100
10
1
0.1
0.01
0
20
40
60
80
100
Time (Days)
+ Vivitrol
◊ Batch 2
○ Batch 3
X Batch 4

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/70941

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/337; A61K 31/485; A61K 31/513 (2022.01)

CPC - 61K 31/337; A61K 31/485; A61K 31/513

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.
X	Heller et al. "Poly(ortho esters) - their development and some recent applications" European Journal of Pharmaceutics and Biopharmaceutics 50 (2000) 121-128, pg 124, right col, para 1, Figure 4, pg 121, right col, para 4, Figure 7, Figure 9, abstract	1-3, 6, 9-10, 15-16, 21-22
A	Maa et al. "Controlled Release of Naltrexone Pamoate From Linerar Poly(Ortho Esters)" Journal of Controlled Release, 14 (1990) 21-28, entire document	1-3, 6, 9-10, 15-16, 21-22
A	US 2003/0107149 A1 (Yang et al.) 12 June 2003 (12.06.2003), entire document	1-3, 6, 9-10, 15-16, 21-22
A	US 2008/0293695 A1 (Bristol et al.) 27 November 2008 (27.11.2008), entire document	1-3, 6, 9-10, 15-16, 21-22
A	US 2020/0297650 A1 (Allergan, Inc.) 24 September 2020 (24.09.2020), entire document	1-3, 6, 9-10, 15-16, 21-22

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 2022	JUN 27 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/70941

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.: 4-5, 7-8, 11-14, 20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

Group I: Claims 1-3, 6, 9-10, 15-16, 21-22 are directed towards a microsphere formulation.

Group II: Claims 17-19 are directed towards a method for making polymer microspheres comprising naltrexone

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

Special Technical Features

---Continued on Supplemental Box---

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 6, 9-10, 15-16, 21-22

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

---Continuation of Box No. III: Observations where Unity of Invention is Lacking---

Group I requires a microsphere formulation wherein each polymer microsphere comprises a drug load of naltrexone of at least 40% by weight of the polymer microsphere, and wherein the polymer microspheres have an average particle size of between about 25 um to about 55 um (D50), with the proviso that the biodegradable polymer does not include poly (D,L-lactide-co-glycolide) not required by Group II.

Group II requires a method for making polymer microspheres, the method comprising: (i) contacting naltrexone with a cyclohexanedimethanol:triethylene glycol:triethylene glycol glycolide (CHDM:TEG:TEG-GL) tri-block polymer in the presence of an organic solvent system comprising dichloromethane and benzyl alcohol to form a dispersed phase; (ii) combining the dispersed phase with a continuous phase comprising water and surfactant in a homogenizer to form an emulsion; (iii) removing the organic solvent from the emulsion to form a microsphere formulation essentially free of organic solvent; and (iv) subjecting the substantially organic solvent-free microsphere formulation to freeze drying not required by Group I.

Shared Common Features

Groups I-II share the common technical feature of a polymer microsphere comprising naltrexone and a poly(ortho ester). However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by the document entitled "Poly(ortho esters) - their development and some recent applications" to Heller et al. (hereinafter Heller)..

Heller teaches a polymer microsphere (Figure 4 ...poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane and trans-cyclohexanedimethanol/triethylene glycol/ triethylene glycol diglycolide (35/25/40). Microspheres, average size , 100 um, bupivacaine loading 60 wt%, n =5...) comprising naltrexone (pg 121, right col, para 4 ...The polymer has been used ...in the delivery of the narcotic antagonist naltrexone...) and a poly(ortho ester) (Figure 4 ...poly(ortho ester) prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane and trans-cyclohexanedimethanol/triethylene glycol/ triethylene glycol diglycolide (35/25/40). Microspheres, average size , 100 um, bupivacaine loading 60 wt%, n =5...).

As the shared technical features were known in in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I-II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding technical feature.

*Item 4 (contd): Claims 4-5, 7-8, 11-14, 20 are determined unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).