

**ANTIPSYCHOTIC INJECTABLE EXTENDED-RELEASE COMPOSITION****FIELD OF THE INVENTION**

**[001]** The present patent application relates to an injectable extended-release composition for use in administering the antipsychotic drug risperidone and for use in treating a risperidone or paliperidone responsive disorder. The composition is particularly suitable for forming intramuscular administration and forms *in situ* an implant that releases risperidone over a period of about 28 days or more. The composition exhibits reduced agglomeration during reconstitution and reduced time for reconstitution and comprises particularly advantageous grades of PLGA defined by its particle size distribution.

**BACKGROUND OF THE INVENTION**

**[002]** Risperidone, and its primary active metabolite 9-OH-risperidone (paliperidone), are indicated for the treatment of psychotic disorders such as schizophrenia, schizoaffective disorder, bipolar disorder, and bipolar mania. Risperidone can be administered orally in commercially available tablet, solution, or orally disintegrating tablet dosage forms.

**[003]** LAI depot compositions are known: US 8,221,778 to Siegel et al. (corresponding to WO 2005/070332), US 5,688,801, US 6,803,055, US 5,770,231, US 7,118,763, US 4,389,330 to Dunn, US 4,530,840, US 6,673,767 to Brodebeck, US 6,143,314 to Chandrashekar, WO 2004/081196, WO 2001/035929, WO 2008/153611 A2 to QLT USA, WO 2000/024374, WO 2002/038185, WO 2008/100576, WO 2011/151355 A1 to Laboratorios Farmaceuticos ROVI, S.A., WO 2011/42453, US 10085936 to Gutierrez Aduriz, US 10463607 to Gutierrez Aduriz, US 10182982 to Gutierrez Aduriz, US 2020/0085728 A1 to Gutierrez Aduriz, EP 2394664 A1 to Laboratorios Farmaceuticos ROVI, S.A., WO 2011/151355 A1 to Laboratorios Farmaceuticos ROVI, S.A., US 10058504 Gutierrez Aduriz, US 10881605 Gutierrez Aduriz, US 10195138 Gutierrez Aduriz, US 2021/0077380 A1 to Laboratorios Farmaceuticos ROVI, S.A., EP 2394663 A1 to Laboratorios Farmaceuticos ROVI, S.A., WO 2011/151356 A2 to Laboratorios Farmaceuticos ROVI, S.A., US 10350159 to Gutierrez Aduriz, US 2019/0328654 A1 to Laboratorios Farmaceuticos ROVI, S.A., EP 2529757 A1 to Laboratorios Farmaceuticos ROVI, S.A., WO 2013/178811 A1 to Laboratorios Farmaceuticos ROVI, S.A., US 10335366 to Gutierrez Aduriz, US 2019/0254960 A1 to Laboratorios Farmaceuticos ROVI, S.A., US 11007139 to Gutierrez Aduriz, EP 2529756 A2 to Laboratorios Farmaceuticos ROVI, S.A., WO 2013/178812 A1 to Laboratorios Farmaceuticos ROVI, S.A., US 2008/0287464 A1 to Wright, US 2009/0264491 A1 to McKay, US 2004/0010224 A1 to Bodmeier, US 2007/0077304 A1 to Luk, US 2010/0015195 A1 to Jain, US 2010/0266655 A1 to Dadey, WO 95/29664 to Alkermes, WO 2004/011054 A2 to Alza, WO 2007/041410 A2 to Luk, WO 2008/059058 A1 to Bourges, WO 2010/018159 A1 to Schoenhammer.

**[004]** Two such LAI products containing risperidone have been approved by the U.S.F.D.A.

**[005]** RISPERDAL CONSTA® (NDA N021346; dosage strengths- 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial; US 6596316, US 6379703, US 6194006, WO 2000/40221) is an intramuscular risperidone-containing PLGA microparticle formulation, and it is intended to deliver therapeutic levels of risperidone suitable for bi-weekly administration. However, due to the inherent lag phase of most microparticle-based products, the patient is required to supplement the first weeks with daily doses of oral risperidone after first administration, i.e. oral supplementation. Approximately three weeks after a single intramuscular injection of RISPERDAL CONSTA® and concurrent daily doses of oral risperidone, the microspheres release sufficient risperidone in the systemic circulation that the patient can discontinue supplementation with daily doses of the oral therapy. However, this period of oral supplementation could be a risk factor of non-compliance. Also, the presence in the body of two doses at the same time could present a potential risk of adverse events, such as irregular formulation behavior and toxicity.

**[006]** PERSERIS® (NDA N210655; dosage strengths- 90 mg and 120 mg per dose; US 9180197, US 9186413, US 9597402, US 10010612, US 10058554, US 10376590, US 10406160) is a risperidone-containing extended-release formulation intended for subcutaneous administration in adipose (fatty) tissue.

**[007]** Another LAI product containing risperidone is still undergoing clinical evaluation for the treatment of schizophrenia: Correll et al. (NPJ Schizophrenia (Nov. 25, 2020), 6:37), Edison Investment Research Limited ("Doria Phase III Trial hits primary endpoint, Laboratorios Farmaceuticos ROVI, S.A. March 19, 2019, [www.edisongroup.com/publication/doria-phase-iii-trial-hits-primary-endpoint/23705/](http://www.edisongroup.com/publication/doria-phase-iii-trial-hits-primary-endpoint/23705/)), NCT02086786, NCT03160521, NCT01788774, NCT01320410, NCT03870880, NCT03160521, NCT01788774, and Anta et al. (Newer formulations of risperidone: remarks about Risperidone ISM" in CNS Drugs (Sep. 5, 2020; [doi.org/10.1007/s40263-020-00762-0](https://doi.org/10.1007/s40263-020-00762-0)). The composition of the product is not disclosed in those publications.

**[008]** U.S. 6,331,311 issued to Brodbeck also discloses injectable depot compositions comprising a biocompatible polymer such as PLGA, a solvent such as N-methyl-2-pyrrolidone and a beneficial agent such as a drug, further comprising an emulsifying agent such as polyols. However, the compositions disclosed do not perform satisfactorily when the beneficial agent is risperidone.

**[009]** U.S. 4,938,763, issued to Dunn et al., discloses a method for an injectable *in situ* forming implant. A biodegradable polymer or copolymer dissolved in a water-miscible solvent with a biologically active agent either is dissolved or dispersed within the polymeric solution. Once the polymeric solution is exposed to body fluids, the solvent diffuses, and the polymer solidifies thereby entrapping the drug within the polymer matrix. Even though Dunn et al. discloses the use of water miscible solvents for obtaining *in situ* forming polymeric implants, it discloses a number of polymers and solvents and even proportions between the different ingredients that do not produce a satisfactory implant with the appropriate release characteristics, particularly when the implant contains risperidone as active principle.

[010] The particle size of the PLGA copolymer used in injectable extended-release compositions has not been recognized as being associated with preparation of a LAI extended-release composition by reconstitution of the powder, i.e. by mixing of the solvent with the powdered drug and powdered PLGA copolymer.

[011] During reconstitution and clinical evaluation of comparator LAI depot compositions containing DMSO, PLGA and risperidone, the instant inventors identified, in unpublished work, an important pharmaceutical potential limitation. It was found that when the powder was reconstituted by mixing the DMSO with the powdered mixture of PLGA and risperidone, agglomeration of the powder occurred, thereby causing potential setbacks in the clinical environment of use, e.g. delays in administration, and/or incomplete dissolution of the PLGA polymer prior to administration, etc. Incomplete dissolution of the PLGA during the target mixing time in the clinic prior to administration is particularly problematic, because it may ultimately negatively impact the performance of (drug release from) the respective solid implant, thereby potentially changing the plasma profile of active moiety and affecting efficacy.

[012] It would be desirable to provide a kit for forming the injectable extended-release composition (or long-acting injectable depot composition) wherein the agglomeration of powdered PLGA and risperidone during mixing with DMSO is reduced or eliminated and wherein the rate (speed) of dissolution of powdered PLGA is maximized. In other words, the time required to dissolve the PLGA completely is reduced or minimized. Such a kit and corresponding powdered materials would help minimize or reduce related setbacks in the clinical environment.

#### SUMMARY OF THE INVENTION

[013] The present invention seeks to overcome the disadvantages of and/or to provide improvements over other injectable extended-release compositions comprising risperidone and/or paliperidone. The present invention includes injectable extended-release or depot composition(s), implant(s) formed from said injectable extended-release composition(s), method(s) of forming (preparing) said implant(s), kit(s) comprising components used to form said injectable extended-release composition(s), method(s) of preparing said injectable extended-release compositions, therapeutic uses of said compositions, implants or kits, method(s) of administering risperidone and/or paliperidone by administering said injectable extended-release composition(s), and method(s) of treating disease(s), condition(s), or disorder(s) that is(are) therapeutically responsive to risperidone and/or paliperidone by administering said injectable extended-release composition(s).

[014] The present invention provides an improved long-acting injectable (LAI) depot composition for delivery of risperidone or another antipsychotic drug. The composition comprises an improved grade of PLGA polymer possessing a particle size distribution that is advantageous (exhibits improved performance) when compared to grades of PLGA used in other injectable extended-release compositions.

[015] The present invention relates to a risperidone-containing or paliperidone-containing composition suitable for forming one or more *in situ* intramuscular implants which can continuously maintain the required plasma levels of active moiety (which is risperidone and/or paliperidone) for at about 28 days or or 28+/-5 days or 28+/-4 days or 28+/-3 days 28+/-2 days or 28+/-1 day or about 26-33 days or about 28-33 days. Moreover, the composition exhibits improved pharmaceutical performance. The term "implant" as used herein refers to compositions based on the formation of a solid and stable polymeric matrix system entrapping drug particles. This term is used to avoid confusion with the term microparticles which is commonly referred to performed polymeric microparticles obtained by solvent evaporation or spray-drying techniques. The compositions of the invention contain drug particles, suspended in a polymer solution, that are entrapped in a solid polymer matrix *in situ* at the moment of the injection as the solvent diffuses and the polymer precipitates forming a matrix that contains drug particles. The term "implant" as used herein, refers to a depot or extended-release composition, since the composition of the present invention is an injectable depot composition, particularly an extended-release injectable composition that forms an extended-release depot when injected. The LAI depot composition is also considered an injectable suspension (or an extended-release injectable composition) comprising particles of risperidone suspended within a polymeric solution of DMSO and PLGA, wherein the LAI depot composition forms an extended-release composition or a depot (implant) after administration. The terms "depot", "extended-release", "prolonged release" or "sustained release" indistinctively as used herein, refer to a composition that contains drug particles, suspended in a polymer solution, that are entrapped in a solid polymer matrix *in situ* at the moment of the injection as the solvent diffuses and the polymer precipitates forming a matrix that contains drug particles and/or refer to a composition that forms a deposit from which the drug is release in a sustained or extended manner. Thus, for the object of this invention, the terms "depot", "extended-release", "prolonged release" or "sustained release" are used herein interchangeably with the same meaning.

[016] After administration, the injectable depot or extended-release composition provides therapeutic plasma levels of active moiety from the start and continuously over a period of at least about 28 days. It does not require oral supplementation with risperidone or paliperidone nor does it require loading doses of oral risperidone or oral paliperidone to achieve target steady state plasma concentration of active moiety. Unlike the use of other LAI (long-acting injectable) depot compositions containing risperidone, the composition of the invention also provides the advantage that therapeutic plasma concentrations of active moiety can be maintained following termination of an oral dosing regimen of risperidone by administering the LAI depot composition as defined herein. Also, unlike the use of other LAI depot compositions containing risperidone, the composition of the invention also provides the advantage that therapeutic plasma concentrations of active moiety can be maintained following termination of a LAI depot composition dosing regimen by orally

administering once-daily doses of risperidone. Therapeutic levels of active moiety are provided from the first day to the last day of a dosing period.

**[017]** The invention employs a dosing regimen of intramuscular administration of 75-100 mg or 25-150 mg of risperidone (in a LAI depot composition as described herein) once every about 28 days. It does not require oral supplementation with risperidone as does RISPERDAL CONSTA. It provides a therapeutically effective plasma concentration of risperidone from the first day of administration (within 2 to 24 hours or within 8 to 24 hours after administration) throughout a period of about 27-31 days or about 27-29 days, unlike RISPERDAL CONSTA and PERSERIS.

**[018]** Improved performance of the kit, the injectable extended-release composition, and the respective implant was achieved by controlling the particle size distribution of the PLGA polymer. The particle size distribution was *a priori* predicted to be irrelevant to performance of the kit, the LAI depot composition, or the implant formed therefrom, because the polymer is presumably completely dissolved in the solvent when the injectable composition is prepared before administration. However, the inventors discovered that the particle size of the polymer, in fact, has an impact upon dissolution of the PLGA/drug mix and upon the clinical suitability of the LAI depot composition, and may have an impact upon the release of the drug from the respective implant formed after administration of the LAI depot composition. It is important to note that these types of compositions need to be reconstituted rapidly and completely prior to administration.

**[019]** The PLGA (poly(lactic-co-glycolic acid)) copolymer used in the invention has a particle size distribution as follows: a) particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786>; b) particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis; c) a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, and where not more than 70% of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>; d) a particle size mass distribution where not more than 70% of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>; e) a particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis and with a D80 not below 135 microns when measured by laser diffraction analysis; f) a particle size volume distribution with a D80 not below 135 microns when measured by laser diffraction analysis; g) a D50 of about 50-150 microns; h) a D10 of about 10-50 microns; i) a D90 of about 170-300 microns; and/or j) a D50 of about 50-150 microns, a D10 of about 10-50 microns, and a D90 of about 170-300 microns. The invention contemplates grades of PLGA possessing a combination of two or more of these particle size distributions.

**[020]** Preferred embodiments of the invention include those wherein the PLGA has a particle size mass distribution as follows: D10 ranging from about 10 microns to about 50 microns, D50 ranging from about 50 microns to about 150 microns, and D90 ranging from about 170 microns to about 300 microns.

**[021]** In some embodiments, the PLGA copolymer has been sized, i.e. sieved and/or comminuted, to achieve the required particle size distribution. Suitable methods of comminution include, for example micronizing, milling, hammering, crushing, grinding, triturating, and/or pulverizing the PLGA.

**[022]** The invention also provides a powder mixture of drug and PLGA copolymer, wherein the drug is risperidone, paliperidone, or a mixture thereof, and the PLGA copolymer has a particle size mass distribution and/or particle size volume distribution as defined herein. The powder mixture can be included in a sealed container, which is optionally further included in a pharmaceutical kit. The mixture can be sterile, such as sterilization with beta or gamma radiation.

**[023]** The mixture of drug and PLGA may comprise about 25 mg to about 150 mg, about 25 mg to about 125 mg, about 25 mg to about 100 mg, about 50 mg to about 150 mg, about 50 mg to about 125 mg, about 50 mg to about 100 mg, about 75 mg to about 150 mg, about 75 mg to about 125 mg, about 75 mg to about 100 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, or about 150 mg of drug, which can be risperidone, paliperidone or a combination thereof.

**[024]** The PLGA can be a sterile biodegradable thermoplastic copolymer having a monomer ratio of lactic to glycolic acid (i.e. lactide to glycolide) of about 50:50 to about 75:25, about 45:55 to about 75:25, about 45:55 to about 80:20, about 65:35 to about 80:20, about 70:30 to about 80:20; about 50:50 to about 65:35, or about 65:35 to about 75:25, about 45:55 to about 55:45, or about 48:52 to about 52:48, or about 50:50, i.e. 50:50  $\pm$ 10%, or 75:25  $\pm$ 10%. The PLGA comprise an acid end group or it may be end-capped. The end cap can be an ester group. Sterilization of the PLGA can be with beta or gamma irradiation, or if the PLGA is sterilized in solution form, it may be sterilized by filtration.

**[025]** The PLGA of the composition can have an inherent viscosity in the range of 0.20-0.60 dl/g, about 0.3-0.58 dl/g, about 0.30-0.55 dl/g, about 0.36-0.52 dl/g, about 0.40-0.58 dl/g, about 0.36-0.43 dL/g, or about 0.46-0.51 dl/g measured in chloroform at 25°C or 30°C at a concentration of 0.1% wt/v or 0.5% wt/v with a Ubbelohde size 0c or 0b glass capillary viscometer or in chloroform at 30°C and at a concentration of 0.5% wt/v with a size 25 Cannon-Fenske glass capillary viscometer (USP<911> viscosity - capillary methods or Eur.Ph 2.2.9. capillary viscometer method). In some embodiments, the PLGA has been sterilized.

**[026]** The mass ratio of risperidone to (PLGA + risperidone), expressed as the percentage of the risperidone weight with respect to total weight of the risperidone plus PLGA, is typically about 15-40% weight, about 25-35% wt, about 30-35%, about 31-35%, about 32-34% or about 33% wt.

**[027]** The invention also provides a pharmaceutical kit comprising a first container and a second container, wherein a) said first container comprises DMSO; and b) said second container comprises drug and PLGA;

wherein said drug is risperidone, paliperidone or a combination thereof, and said PLGA has a particle size distribution and monomer ratio as defined herein. A LAI depot composition is formed by mixing the contents of the containers.

**[028]** Another embodiment of the pharmaceutical kit comprises a first container, a second container, and a third container, wherein a) said first container comprises DMSO; b) said second container comprises drug selected from risperidone, paliperidone or a combination thereof; and c) said third container comprises powdered PLGA having a particle size distribution and monomer ratio as defined herein. A LAI depot composition is formed by mixing the contents of the containers.

**[029]** In some embodiments, a pharmaceutical kit comprises about 75 mg of drug (which is risperidone, paliperidone, or a mixture thereof), about 350 mg of DMSO, and about 150 mg of PLGA having a L:G monomer molar ratio of about 45:55 to about 55:45 (or about 50:50) and particle size distribution as defined herein.

**[030]** In some embodiments, a pharmaceutical kit comprises about 100 mg of drug (which is risperidone, paliperidone, or a mixture thereof), about 467 mg of DMSO, and about 200 mg of PLGA having a L:G monomer molar ratio of about 45:55 to about 55:45 (or about 50:50) and particle size distribution as defined herein.

**[031]** In some embodiments, the pharmaceutical kit comprises an excess of the components used to form the LAI depot composition.

**[032]** For a 100 mg drug dosage strength, an exemplary pharmaceutical kit may comprise about 115 mg (or about 100-130 mg or about 105-125 mg or about 110-120 mg) of drug (which is risperidone, paliperidone, or a mixture thereof), about 537 mg (or about 515-560 mg or about 520-550 mg or about 530-545 mg) of DMSO, and about 230 mg (or about 215-245 mg or about 220 to about 235 mg) of PLGA having a L:G monomer molar ratio of about 45:55 to about 55:45 (or about 50:50) and particle size distribution as defined herein.

**[033]** For a 75 mg drug dosage strength, an exemplary pharmaceutical kit may comprise about 90 mg (or about 75-105 mg or about 80-100 mg or about 85-105 mg) of drug (which is risperidone, paliperidone, or a mixture thereof), about 420 mg (or about 405-435 mg or about 415-425 mg) of DMSO, and about 180 mg (or about 165-200 mg or about 170-190 mg or about 175-185 mg) of PLGA having a L:G monomer molar ratio of about 45:55 to about 55:45 (or about 50:50) and particle size distribution as defined herein.

**[034]** The invention also provides a method of preparing a LAI depot composition comprising mixing the components DMSO, drug, and PLGA copolymer, thereby forming said composition, wherein the PLGA has a L:G monomer (lactide monomer : glycolide monomer) molar ratio of about 45:55 to about 55:45 (or about 50:50) and a particle size distribution as defined herein. The components may be included in plural containers and may be included in a pharmaceutical kit.

**[035]** In some embodiments, the DMSO and PLGA are mixed to form a polymeric solution, which is then mixed with the drug to form the LAI depot composition. The polymeric solution, excluding the drug, may be

sterilized by sterile filtration through a filtration medium having a nominal pore size of 0.22 microns or less, or by irradiation, or by a combination thereof.

**[036]** In some embodiments, the method of preparing the LAI sustained release composition comprises a) mixing DMSO with a powdered mixture of PLGA and drug for a period of 10 min or less, 5 min or less, 4 min or less, 3 min or less, 2 min or less, 1 min or less, or 30 sec or less, thereby forming said LAI depot composition, wherein at least 80% wt of the drug is suspended therein and wherein the PLGA is completely dissolved therein. When using syringes as the containers, mixing of the components is accomplished by engaging the syringes with each other and pushing-pulling their respective plungers repeatedly as needed. In some embodiments, the plungers are pushed through 200 pushes (passes) or less, 150 pushes or less, 100 pushes or less, 75 pushes or less, or 50 pushes. A push refers to passage of the liquid from one syringe to another.

**[037]** When grades of PLGA possessing the particle size distribution characteristics described herein are used, agglomeration of the powdered mixture during mixing with DMSO does not occur or is substantially reduced as compared to use of a powdered mixture comprising PLGA with particle size distribution characteristics that fall outside those specified herein. Accordingly, use of the PLGA as described herein permits much faster and complete dissolution of the PLGA than achieved with other grades of PLGA.

**[038]** Before administration, the LAI depot composition typically has a viscosity (apparent viscosity) in the range of about 1.0-7.0 Pa.s, about 1.5-7.0 Pa.s, or about 1.8-6.5 Pa.s. measured at 25°C by rotational rheometry using cone-plate geometry and applying a share stress ramp of 0.1 to 300 Pa.S (USP<912> viscosity - rotational methods or Eur.Ph: 2.2.10. viscosity - rotating viscometer method). If not otherwise specified, the apparent viscosity values of the extended-release (depot) composition or suspension throughout the present specification are to be understood as measured at 25°C by rotational rheometry using cone-plate geometry and applying a share stress ramp of 0.1 to 300 Pa.S.

**[039]** In some embodiments, the mass ratio of DMSO to drug can be about 5:1 to about 4:1, about 4.6:1 to about 4.8:1, about 4.6:1 to about 4.7:1, about 4.67:1, about 4.66:1 or about 4.68:1, or about 4.66:1.

**[040]** In some embodiments, the content of DMSO in the LAI depot composition can be about 55-65% wt, about 57-63% wt, about 60-62% wt, or about 61% wt based upon the total weight of the composition.

**[041]** In some embodiments, the concentration of PLGA in the LAI depot composition can be about 24%-50% wt, about 24%-40% wt, about 25-27% wt or about 26% wt, (expressed as the percentage of polymer weight based on total composition weight).

**[042]** In some embodiments, the content of drug, in particular risperidone, in the LAI depot composition can be about 10-15% wt, about 11-14% wt, about 12-14% wt, or about 13% wt based upon the total weight of the composition.

**[043]** The sum total of all components of the LAI depot composition is 100%.

[044] In some embodiments, prior to administration, the LAI depot composition comprises about 75 mg (or about 65-85 mg or about 70-80 mg) of drug, DMSO, and PLGA, wherein the content of drug is about 10-15% wt, the content of DMSO is about 55-65% wt, the content of PLGA is about 24%-30% wt, and the PLGA has a L:G monomer ratio of about 45:55 to 55:45.

5 [045] In some embodiments, prior to administration, the LAI depot composition comprises about 75 mg (or about 65-85 mg or about 70-80 mg) of drug, DMSO, and PLGA, wherein the content of drug is about 12-14% wt, the content of DMSO is about 57-63% wt, the content of PLGA is about 25-27% wt, and the PLGA has a L:G monomer ratio of about 45:55 to 55:45.

[046] In some embodiments, prior to administration, the LAI depot composition comprises about 100 mg (or  
10 about 85-115 mg or about 90-110 mg or about 95-105 mg) of drug, DMSO, and PLGA, wherein the content of drug is about 10-15% wt, the content of DMSO is about 55-65% wt, the content of PLGA is about 24%-30% wt, and the PLGA has a L:G monomer ratio of about 45:55 to 55:45.

[047] In some embodiments, prior to administration, the LAI depot composition comprises about 100 mg (or  
15 about 85-115 mg or about 90-110 mg or about 95-105 mg) of drug, DMSO, and PLGA, wherein the content of drug is about 12-14% wt, the content of DMSO is about 57-63% wt, the content of PLGA is about 25-27% wt, and the PLGA has a L:G monomer ratio of about 45:55 to 55:45.

[048] Prior to administration and after mixing of the DMSO, drug, and PLGA, the drug may be partially dissolved or substantially completely undissolved in the LAI depot composition. In some embodiments, a)  $\leq 2.5\%$ ,  $\leq 5\%$ ,  $\leq 7.5\%$ ,  $\leq 10\%$ ,  $\leq 20\%$  of the drug is dissolved in said composition before administration; and/or  
20 b)  $> 0\%$ ,  $\geq 0.5\%$ ,  $\geq 1\%$ ,  $\geq 5\%$ ,  $\geq 10\%$ ,  $\geq 15\%$ , or up to about 20% wt of the drug is dissolved in said composition before administration. All combinations of these embodiments are contemplated.

[049] The invention also provides a method of administering drug, the method comprising administering to a subject a LAI sustained release composition as defined herein. The method can further comprise the step of forming said LAI sustained release composition by mixing the respective components thereof. The method  
25 can further comprise providing a pharmaceutical kit as defined herein. The drug is as defined herein. The invention also provides the LAI depot composition as defined herein for use in the treatment of a subject in need thereof. Also, the invention provides for the use of the LAI depot composition as defined herein in the manufacture of a medicament.

[050] The LAI sustained release composition may be administered intramuscularly or subcutaneously. It  
30 may also be administered into adipose tissue. Intramuscular administration into the gluteal or deltoid muscle is preferred.

[051] The invention also provides a stable LAI sustained release composition suitable for forming an *in situ* solid implant following administration to a subject, said implant comprising from about 75 mg to about 100 mg of risperidone, PLGA, and DMSO, wherein the risperidone and PLGA are contained in a first container, and

the DMSO is contained in a second container, wherein the concentration of PLGA is between 20 and 50 % by weight, with respect to the weight of the biocompatible copolymer and the solvent, wherein the risperidone has a particle size volume distribution with a D10 equal or above 10 microns, a D50 between 60 and 130 microns, and a D90 below or equal 225 microns, when measured by laser diffraction analysis, characterized in that the

5 PLGA has been sized and has a particle size as defined herein.

**[052]** The invention also provides a method of treating a disease, condition, or disorder that is therapeutically responsive to risperidone and/or paliperidone, the method comprising administering to a subject in need thereof a LAI depot composition as defined herein. The method of treating may comprise the method of preparing the LAI depot composition and may also comprise the method of administering the LAI depot composition. The  
10 invention also provides for the LAI depot composition as defined herein for use in the treatment of a disease, condition, or disorder that is therapeutically responsive to risperidone and/or paliperidone. The invention also provides for the use of the LAI depot composition as defined herein for the manufacture of a medicament for the treatment of a disease, condition, or disorder that is therapeutically responsive to risperidone and/or paliperidone.

15 **[053]** The invention provides a method of treating a disease, condition, or disorder that is therapeutically responsive to risperidone and/or paliperidone, the method comprising preparing the LAI sustained release composition and administering the LAI depot composition to a subject in need thereof, thereby treating said disease, disorder, or condition. The method may further comprise the step of providing a pharmaceutical kit as described herein. The invention provides the LAI depot composition as defined herein for use in treating a  
20 disease, condition, or disorder that is therapeutically responsive to risperidone and/or paliperidone, comprising preparing the LAI depot composition, and administering the LAI depot composition to a subject in need thereof, thereby treating said disease, disorder, or condition.

**[054]** In some embodiments, the method of administering comprises a) providing a pharmaceutical kit comprising a container with DMSO and a container with drug and PLGA, wherein the PLGA has a particle size  
25 distribution as described herein; b) preparing a LAI depot composition as described herein by mixing the components of the containers, thereby forming the LAI depot composition; and c) administering the LAI depot composition to a subject.

**[055]** In some embodiments, the method of treating (or the therapeutic use of the composition) comprises a) providing a pharmaceutical kit comprising a container with DMSO and a container with drug and PLGA,  
30 wherein the PLGA has a particle size distribution as described herein; b) preparing a LAI depot composition as described herein by mixing the components of the containers, thereby forming the LAI depot composition; and c) administering the LAI sustained release composition to a subject in need thereof.

**[056]** In the methods, therapeutic uses and kits described herein, the DMSO, PLGA, and drug may be divided among two, three, or more containers in the pharmaceutical kit.

[057] Exemplary diseases, conditions or disorders include, for example, psychosis, delusional psychosis, psychotic depression, obsessive-compulsion disorder, schizophrenia, bipolar disorder, schizoaffective disorders, non-schizophrenic psychoses, Asperger's syndrome, Tourette's syndrome, obsessive-compulsion disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, personality disorders, aggression, depression, dementia, intellectual disabilities and behavioral disturbances in mental retardation and autism, autistic spectrum disorders, anxiety, eating disorders, nervous anxiety, insomnia, idiopathic dystonia, substance abuse, and any combination thereof. Treatment of episodes of acute exacerbation of the above diseases, conditions, and disorders is within the scope of the invention. Schizophrenia, schizoaffective disorder, bipolar disorder, and bipolar mania are preferred. Schizophrenia is preferred, particularly schizophrenia in adults for whom tolerability and effectiveness has been established with oral risperidone.

[058] The invention includes all combinations of the aspects, embodiments and sub-embodiments set forth herein.

#### BRIEF DESCRIPTION OF THE FIGURES

[059] The following figures are provided to help with the interpretation of the object of the present invention, but do not imply any limitation.

[060] Figure 1. Cumulative percentage of released risperidone over time (days) in an *in vitro* dissolution test from a comparative composition comprising a PLGA with a particle size mass distribution where more than 10% of the particles have a particle size of 300 microns or more, when measured by analytical sieving according to USP<786>.

[061] Figure 2. Cumulative percentage of released risperidone over time (days) from a composition of the invention in an *in vitro* dissolution test.

[062] Figure 3. Cumulative percentage of released risperidone over time (days) in an *in vitro* dissolution test from a composition comprising a PLGA with a particle size mass distribution where at least 70 % of the particles have a particle size less than 150 microns, when measured by analytical sieving according to USP<786>.

[063] Figure 4. Particle size distribution of the PLGA of the composition of the invention measured by laser diffraction analysis. Horizontal axis: particle size in microns. Vertical axis: volume (%), indicating the percentage in volume of particles with the corresponding particle size, measured by laser diffraction by wet dispersion method in water and dispersing by stirring at 3,000 rpm.

[064] Figures 5A-5C depict graphs of the cumulative percentage of risperidone released *in vivo* in New Zealand White rabbits over time (days) from implants formed from injectable compositions. a) FIG. 5A- cumulative percentage of released risperidone an *in vivo* dissolution test from a comparative composition comprising a PLGA with a particle size mass distribution where not more than 10% of the particles have a particle size of 300 microns or more, when measured by analytical sieving according to USP<786>;

composition comprising PLGA (50:50 L:G ratio); DMSO; risperidone; polymer solution apparent viscosity of 1.30 (Pa.s); injection of an amount of injectable composition equivalent to 15 mg of risperidone; b) FIG. 5B- cumulative percentage of released risperidone in an *in vivo* dissolution test from a composition comprising a PLGA with a particle size mass distribution where not more than 70 % of the particles have a particle size less  
5 than 150 microns, when measured by analytical sieving according to USP<786>; composition comprising composition comprising PLGA (50:50 L:G ratio); DMSO; risperidone; polymer solution apparent viscosity of 1.30 (Pa.s); injection of an amount of injectable composition equivalent to 15 mg of risperidone; and c) FIG. 5C- cumulative percentage of released risperidone an *in vivo* dissolution test from a comparative composition comprising a PLGA with a particle size mass distribution where at least 70% of the particles have a particle  
10 size of 300 microns or more, when measured by analytical sieving according to USP<786>; composition comprising PLGA (50:50 L:G ratio); DMSO; risperidone; polymer solution apparent viscosity of 1.30 (Pa.s); injection of an amount of injectable composition equivalent to 15 mg of risperidone.

#### DETAILED DESCRIPTION OF THE INVENTION

[065] The invention employs particular grades of PLGA to improve pharmaceutical performance of a  
15 pharmaceutical kit used to prepare a respective LAI depot composition, to improve preparation of the respective LAI extended-release composition, and to improve performance of a respective implant formed in situ after administration of the LAI depot composition. It was found that the particle size of the PLGA improves its dissolution behavior when a mixture of drug and PLGA is mixed with DMSO.

[066] The term "stable" as used herein refers to a pharmaceutical composition or kit wherein the total content  
20 of drug-related impurities does not increase above a target level during storage of the composition or kit 6 months at 40 °C and 75 % relative humidity (RH). The term "stable" also refers to a pharmaceutical composition or kit wherein the inherent viscosity of the PLGA copolymer does not decrease below a target level during said storage conditions. The target total content of impurities originating from the decomposition of risperidone does not exceed 5 % area, preferably 3 % area, more preferably 2 % area, and most preferably 1 % area  
25 determined by liquid chromatography (HPLC) at 260 nm if such a composition is stored for 6 months at 40 °C and 75 % relative humidity (RH). The target minimum inherent viscosity of the PLGA is 0.20 dL/g after storage for 6 months under said storage conditions.

[067] As used herein, the term "loading dose" or "loading doses" refers to a) oral administration of a dose of  
30 drug to a subject on a daily basis for a period of plural days, wherein said loading doses are sufficient to establish in the subject a steady state plasma concentration of active moiety that is within a therapeutic range; and/or b) administration of one or more higher doses of LAI depot composition comprising drug prior to administration of a maintenance dose of LAI depot composition comprising said drug, wherein said one or

more higher doses are sufficient to establish in the subject a steady state plasma concentration of active moiety that is within a therapeutic range prior to administration of said maintenance dose.

**[068]** As used herein, the term “maintenance dose” refers to an amount of LAI depot composition comprising a specified amount of drug, wherein said amount is administered to a subject from the first (initial) administration of said LAI depot composition through subsequent administrations (about once every 28 days or about once monthly) of said LAI depot composition. Said maintenance dose is sufficient to establish in the subject a steady state plasma concentration of active moiety that is within a therapeutic range without requiring administration of loading dose(s) of LAI depot composition comprising risperidone and without requiring oral supplementation with risperidone.

**[069]** As used herein, the term “oral supplementation” refers to oral administration of a dose of drug to a subject on a daily basis after the subject has been administered a LAI depot composition of the invention comprising said drug.

**[070]** As used herein and unless otherwise specified, the drug or active ingredient included in the injectable composition can be present in free base, salt, amorphous, crystalline, anhydrous, hydrate, optically pure, optically enriched or racemic forms thereof. Combinations of these various forms are also within the scope of the invention. A prodrug, metabolite (paliperidone) or derivative of the drug can also be included.

**[071]** In some embodiments, the salt forms of risperidone can be made according to U.S. Publication No. 20040266791, the relevant disclosure of which is hereby incorporated by reference; however, other known salts can be used.

**[072]** As used herein, the term “prodrug” is taken to mean a compound that is administered in an inactive (or less than fully active) form and is subsequently converted to an active pharmacological agent through normal metabolic processes. A prodrug serves as a type of ‘precursor’ to the intended drug, e.g. risperidone, paliperidone or other drug.

**[073]** As used herein, the term “derivative” is taken to mean a compound that is obtained by chemical modification of a parent compound such that the “derivative” includes within it almost all or all of the chemical structure of the parent (or base) compound. A derivative is a compound that is formed from a similar compound or a compound that can be imagined to arise from another compound, if one atom is replaced with another atom or group of atoms. A derivative is a compound derived or obtained from another and containing essential elements of the parent substance. A derivative is a chemical compound that may be produced from another compound of similar structure in one or more steps.

**[074]** As used herein, the term “dosing period” refers to the period of days or weeks as measured from the initial day after administration of a dose to at least about 28 days after administration or to administration of a subsequent dose. During the dosing period, the implant will provide therapeutic plasma levels of drug for about

4 weeks or more. A dosing period can end after expiration of a predetermined number of days or after the plasma level of drug drops below therapeutic levels.

**[075]** As used herein, a "treatment period" refers to the weeks, months or years during which LAI sustained release compositions of the invention are administered to a subject. A treatment period generally comprises plural dosing periods. Dosing periods can occur sequentially or in an overlapping manner during a treatment period. For example, a first dose of injectable composition is administered, and a second dose of injectable composition can be administered at a time following administration of the first dose, such that each dose will have its own corresponding dosing period, and the dosing periods would overlap. Dosing periods will typically be sequential or overlap by no more than one or seven days.

**[076]** The intramuscular dose can be administered to any muscle or muscle group typically recognized by the pharmaceutical industry as a suitable site for an injectable composition. In some embodiments, the composition is administered to the gluteal and/or deltoid muscles. The composition can also be administered to the quadriceps muscle group. A dose can be administered to a single muscular site or can be divided into two or more portions and administered to two or more muscular sites of a subject. For example, a first portion of a dose can be administered to a first section of gluteal muscle and a second portion of the dose can be administered to a second section of gluteal muscle of a subject. The injectable composition can be administered to a subject in one or more injection sites on the same day and still be considered as being part of the same dosing period. For example, part of a dose can be administered to a first injection site and another part of the same dose can be administered to another injection site. A single-body implant will form at each injection site. Such a mode of administration within a same day is considered to be administration of a single dose with a single dosing period. Alternatively, administration can be modified such that there is one point of needle entry into the subject but more than one injection site below the skin, which can be achieved by making a first penetration into the skin and muscle and administering a portion of a dose, then partially withdrawing and redirecting the needle into another section of muscle, while maintaining the tip of the needle beneath the skin, and then injecting another portion of the dose into this other section of muscle. Such a mode of administration is still considered to be administration of a single dose within a single dosing period.

**[077]** A therapeutically effective amount of injectable composition refers to an amount of injectable composition comprising a specified dose of drug. Accordingly, a therapeutically effective amount of 25-150 mg of injectable composition comprises a dose of 25-150 mg of risperidone; therefore, the actual amount of LAI depot composition administered would be greater than 25-150 mg, the actual amount of injectable composition being determined according to the content drug in the LAI depot composition. For example, a 75 mg dose of risperidone in a therapeutically effective amount of LAI depot composition comprising about 13 wt % of risperidone would be equivalent to therapeutically effective amount of about 575 mg, said composition comprising DMSO, risperidone, and PLGA. Similarly, a 100 mg dose of risperidone in a therapeutically effective

amount of LAI depot composition comprising about 13 wt % of risperidone would be equivalent to therapeutically effective amount of about 767 mg, said composition comprising DMSO, risperidone, and PLGA.

**[078]** Although not required, the present injectable composition can further comprise an alkaline agent. An alkaline agent with low water solubility such as lower than 0.02 mg/ml can be included. The alkaline agent can be present in a molar ratio  $>2/5$  (drug/alkaline agent), meaning that the alkaline agent is present in molar excess over the drug. Preferred alkaline agents are alkaline or alkaline-earth hydroxides, such as magnesium hydroxide or aluminum hydroxide. Due to the limited water solubility of the alkaline agent, the d 0,5 of the particle size distribution, e.g. of the magnesium hydroxide, is preferably below 10 microns.

**[079]** The composition of the invention can be in the form of a pharmaceutical kit suitable for *in situ* formation of a biodegradable solid implant in a subject in need thereof. In some embodiments, the kit comprises: a first container comprising risperidone; a second container comprising a biocompatible PLGA copolymer; and a third container comprising DMSO. By mixing the contents of the third container with the contents of the second container, a polymeric solution is formed, which solution is then mixed with the contents of the first container to form the injectable composition as described herein. In some embodiments, the copolymer and drug (and/or a metabolite and/or a prodrug thereof) are included in a first container, and DMSO is included in a second container. In some embodiments, the containers are syringes, and the mixing of their contents may be performed by direct or indirect connection followed by moving the plungers of the syringes forwards and backwards. Embodiments of the invention include those wherein a) drug and/or copolymer is present in solid form in a container prior to mixing with the solvent; or b) drug and/or copolymer is present in particulate form or as a lyophilizate in a container prior to mixing with the solvent (DMSO).

**[080]** The invention also provides a process for preparing a stable LAI depot composition, the process comprising mixing the components of the composition for about 30 sec or less, about 1 minute or less, about 2 minutes or less, or up to about 3 minutes prior to administration, preferably up to about 2 minutes prior to administration, more preferably up to about 1 minute prior to administration, thereby forming the composition. In a preferred embodiment, the composition is prepared by mixing the solvent (DMSO) with a previous powder mixture of risperidone and biocompatible polymer (PLGA). In a preferred embodiment, the components are mixed by passing the contents between two devices, preferable syringes, for 200 pushes (passes) or less, 150 pushes or less, 100 pushes or less, 75 pushes or less or 50 pushes.

**[081]** As used herein, the term "polymeric solution" is taken to mean the fluid composition comprising a combination of DMSO and the PLGA dissolved therein. If not otherwise specified, the apparent viscosity value of the polymeric solution or the injectable composition is given in Pa.s units

**[082]** The polymeric solution has an apparent viscosity in the range of about 0.5 to about 3.0 Pa.s, about 0.7 to about 3.0 Pa.s, about 0.7 to about 2.0 Pa.s, about 1.5 to about 2.5 Pa.s, about 1.5 to about 2.3 Pa.s, about 1.5 to about 2.1 Pa.s,  $1.5-2.1 \pm 10\%$  Pa.s,  $1.6-1.9 \pm 10\%$  Pa.s, or  $1.7-1.8 \pm 10\%$  Pa.s, measured at 25°C

by rotational rheometry using cone-plate geometry and applying a share stress ramp of 0.1 to 300 Pa.S (USP<912> viscosity - rotational methods or Eur.Ph: 2.2.10. viscosity - rotating viscometer method). Before administration, the LAI depot composition has an apparent viscosity in the range of about 1.0-7.0 Pa.s, about 1.5-7.0 Pa.s, or about 1.8-6.5 Pa.s. In some embodiments, the values may vary about  $\pm 10\%$  from the specified limits. The apparent viscosity can be controlled primarily according to the molecular weight (the inherent viscosity) of the polymer and the concentration of polymer in the injectable composition.

**[083]** In some embodiments, the mass ratio of polymeric solution to drug, expressed as the mass of (polymer + solvent) to the mass drug, ranges from about 15:1 to about 5:1, about 12:1 to about 5:1, from about 7:1 to about 6.5:1, about 6.5:1 to about 6.8:1, about 6.67:1, about 6.66:1, or about 6.68:1.

10 **[084]** In some embodiments, the mass ratio of polymer to polymeric solution, expressed as the weight percentage of polymer with respect to the weight of polymer + solvent, is about 25-50%, about 25-35%, about 30-40%, about 28-32%, or about 30%.

**[085]** In some embodiments, the mass ratio of solvent (DMSO) to polymeric solution, expressed as the weight percentage of solvent with respect to the weight of polymer + solvent, is about 50-75%, about 65-75%,  
15 about 60-70%, about 68-72%, or about 70%.

**[086]** The LAI extended-release compositions may further comprise one or more pharmaceutical excipients suitable for intramuscular administration.

**[087]** Following intramuscular administration, the LAI extended-release composition forms an in situ solid implant in the muscle tissue. In some embodiments, the implant begins release of risperidone within about 2  
20 hours after administration to provide a rapid (e.g. less than 1 day, less than 18 hours, less than 12 hours, less than 6 hours, less than 3 hours) onset of action and continuously for at least about 4 weeks. It provides therapeutically effective plasma levels of active moiety (risperidone + 9-OH-risperidone (paliperidone)) from the first day of administration for a period of at least about 4 weeks.

**[088]** The expression "about 50:50" as used in this description, refers to a monomer ratio of lactic acid to glycolic acid of biocompatible PLGA copolymer based on lactide and glycolide dimer of respective lactic acid  
25 and glycolic acid monomers. The L:G monomer molar ratio may have a standard technical error of  $\pm 10\%$ . The commercially available grades of PLGA copolymer are known to vary slightly in their actual ratio of monomers even though they may be listed as having a 50:50 monomer ratio. For example, a copolymer specified as having a monomer ratio of 50:50 may actually have a monomer ratio ranging from 45:55 to 55:45  
30 or 48:52 to 52:48. Accordingly, whenever the monomer ratio of "50:50" or "about 50:50" is specified herein, all ratios ranging from 45:55 to 55:45 are considered as being interchangeable therewith.

**[089]** Inherent viscosity can be measured in chloroform at 25°C or 30°C at a concentration of 0.1% wt/v or 0.5% wt/v with a Ubbelohde size 0c or 0b glass capillary viscometer or in chloroform at 30°C and at a concentration of 0.5% wt/v with a size 25 Cannon-Fenske glass capillary viscometer (USP<911> viscosity -

- capillary methods or Eur.Ph 2.2.9. capillary viscometer method). Suitable grades of PLGA copolymers as described herein (according to molecular weight, inherent viscosity and/or molar ratio of lactic acid monomer to glycolic acid monomer) are end-capped (such as with an ester group, e.g. lauryl ester, methyl ester) are available from EVONIK® (Essen, Germany), Boehringer Ingelheim (Ingelheim am Rhein, Germany),
- 5 ALKERMES (Dublin, Ireland) or SIGMA ALDRICH (ST. Louis, MO) and are marketed under the tradenames RESOMER®, LAKESHORE BIOMATERIALS™, or MEDISORB®. As the composition of some grades of end-capped PLGA is proprietary, the identity of the ester end-cap is not publicly available. Nonetheless, the performance properties of the grades of PLGA copolymer described herein are known and are used to characterize the material.
- 10 **[090]** The PLGA polymer in the LAI depot composition can have an inherent viscosity in the range of 0.20-0.60 dl/g, about 0.30-0.55 dl/g, about 0.36-0.52 dl/g, about 0.36-0.43 dl/g, about 0.40-0.58 dl/g, or about 0.46-0.51 dl/g measured in chloroform at 25°C or 30°C at a concentration of 0.1% wt/v or 0.5% wt/v with a Ubbelohde size 0c or 0b glass capillary viscometer or in chloroform at 30°C and at a concentration of 0.5% wt/v with a size 25 Cannon-Fenske glass capillary viscometer (USP<911> viscosity - capillary methods or Eur.Ph 2.2.9.
- 15 capillary viscometer method). If the PLGA polymer is completely dissolved in the formulation, the apparent viscosity of this polymer solution can be measured according to USP<912> viscosity - rotational methods or Eur.Ph: 2.2.10. viscosity - rotating viscometer method.
- [091]** The PLGA polymer can be irradiated with a beta or gamma radiation at a dose of about 10 to about 30 kGy at a temperature between -40°C and +35°C. Irradiation can serve to reduce the molecular weight of
- 20 and/or to sterilize the PLGA polymer. In some embodiments, the polymer is radiated at a temperature lower than 35 °C, more preferably lower than 25 °C and more preferably lower than 8°C. In a preferred embodiment of the invention, the biocompatible copolymer is gamma or beta irradiated in the dose range of 10-30 kGy ±10% measured at a temperature between -40°C to +35°C to adjust its molecular weight to range from about 27-47 kDa, about 31-43 kDa, about 31-40 kDa, about 30-46 kDa, or about 30-36 kDa. In a more preferred
- 25 embodiment, the polymer is radiated at 15-25 kGy ±10% measured at the temperature of 8 °C.
- [092]** After administration, the injectable composition forms an implant that provides a satisfactorily controlled release profile for the drug. By "satisfactorily controlled" release profile is meant that the implant will exhibit an initial release profile that is not too steep (fast), which would otherwise lead to plasma levels that are too high with concomitant toxic side effects, and an initial release profile that is not too flat (slow), which would
- 30 lead to plasma levels that are below therapeutic concentrations. An implant exhibiting a satisfactorily controlled initial release profile will release no more than 20% wt., no more than 15% wt, no more than 12% wt, no more than 10% wt, no more than 8% wt, no more than 6% wt, no more than 5% wt, no more than 4% wt, no more than 3% wt, no more than 2% wt or no more than 1% wt of its charge of drug within 24 hours after being placed in an aqueous environment. It will release at least 0.1% wt, at least 0.5% wt., at least 1% wt, at least 2% wt,

at least 3% wt, or at least 4% wt of its charge of drug within 24 hours after being placed in an aqueous environment. The invention includes all combinations of the embodiments herein.

**[093]** The plasma concentration profile during the dosing period can exhibit one, two, or more maxima and one, two or more minima. An initial maximum can be caused by dissolution of drug during the initial day(s) of the dosing period followed by a slowing of the release thereof and another maximum can be caused by increased rate of release during the remaining days of the dosing period. Embodiments of the invention include those wherein: a) the plasma profile exhibits a maximum during the initial one to six days or one to three days of the dosing period; b) the plasma profile exhibits a maximum during the latter 10 to 24 days of a 4-week dosing period; c) the plasma profile exhibits a maximum during the initial days of the dosing period and a maximum during the remaining days of the dosing period; d) the plasma profile is substantially level (a standard deviation within  $\pm 30\%$ ,  $\pm 25\%$ ,  $\pm 20\%$ ,  $\pm 15\%$ , or  $\pm 10\%$  of the average or mean) during the dosing period; e) the plasma profile exhibits a maximum during the initial two to six days or two to twelve days of the dosing period; and/or f) the plasma profile exhibits a maximum during the latter 10 to 28 days of a 4- to 5-week dosing period.

**[094]** In humans, the average plasma concentration of active moiety (risperidone + 9-OH-risperidone) can range from about 3-200, about 5-80, or about 10-60 ng/ml when an amount of injectable composition equivalent to a dose of about 20-80 mg, about 37.5-125 mg, or about 50-100 mg of risperidone is administered. The average C<sub>min</sub> during the dosing period is in the range of about 1-80, 5-50, or about 5-40 ng/ml when an amount of injectable composition equivalent to a dose of about 25-150, about 37.5-125, or about 50-100 mg, respectively, of risperidone is administered. The average C<sub>max</sub> during the dosing period is in the range of about 8-300, 10-150, or 10-120 ng/ml when an amount of injectable composition equivalent to a dose of 25-150, 37.5-125, or 50-100 mg, respectively, of risperidone is administered. Some individual subjects may, on an equivalent dose basis, exhibit plasma concentrations outside the ranges specified herein for reasons such as poor health, advanced age, compromised metabolism, renal failure, disease, etc. Even so, a majority of subjects in a patient population to which the injectable implant is administered will exhibit plasma concentrations with those specified herein.

**[095]** As used herein, whenever the plasma concentration of a drug is mentioned, such plasma concentration includes within it the sum total of the plasma concentration of active moiety, i.e. the drug and its active metabolite(s) together. For example, whenever the plasma concentration of risperidone is mentioned, such plasma concentration includes within it the sum total of the plasma concentrations of risperidone and its active metabolite(s), such as 9-OH-risperidone (paliperidone).

**[096]** In some embodiments, the particle size distribution of the drug is as follows: not more than 10% of the total volume of drug particles are less than 10 microns in size (equivalent diameter in volume as a function of applying Fraunhofer theory to irregularly shape particles; as measured by laser light scattering, such as with a

Malvern Mastersizer 2000) and not more than 10% of the total volume of drug particles are greater than 225 microns (or 235 microns) in size. In addition, the drug particles possess a d0.5 value preferably in the range of about 60-130 microns. Accordingly, in some embodiments, the risperidone comprises a broad particle size distribution, which can be monomodal, bimodal or trimodal.

- 5 **[097]** In other embodiments, the drug exhibits one of the following particle size distributions:

| Parameter      | I      | II     | III    | IV     | V            | VI     |
|----------------|--------|--------|--------|--------|--------------|--------|
| d0.1 (microns) | 27.49  | <30    | 17.41  | ≤20    | ≤10          | ≤10    |
| d0.5 (microns) | 79.90  | 40-130 | 51.61  | 40-130 | 40-130       | 40-130 |
| d0.9 (microns) | 176.66 | >170   | 175.32 | >170   | >225 or >235 | >200   |

**[098]** In another embodiment of the invention, the drug has the particle size distribution as follows:

- not more than 10% of the total volume of particles is less than 10 microns in size;
- not more than 10% of the total volume of particles is greater than 225 microns (or 235 microns) in
- 10 size or not more than 10% of the total volume of particles is greater than 200 microns in size, and
- the d0.5 of the size distribution is in the range of about 60-130 microns, about 40-90 microns, or about 40-130 microns.

**[099]** The particle size distribution was determined by light scattering technique using laser light diffraction in wet mode.

- 15 **[0100]** Embodiments of the invention include those wherein: a) the risperidone is present in solid form in the container prior to mixing with the solvent; b) the risperidone is present in particulate form or as a lyophilizate in the container prior to mixing with the solvent; c) the particle size distribution of the risperidone is as follows: not more than 10% of the total volume of drug particles are less than 10 microns in size and not more than 10% of the total volume of drug particles are greater than 225 microns (or 235 microns) in size; d) the d0.5 of the
- 20 particle size distribution is in the range of about 60-130 microns; e) the mass ratio of the amount of polymeric solution (polymer + solvent) and to the amount of risperidone in the injectable composition ranges from about 15:1 to 5:1; f) the mass ratio of the amount of solvent and the amount of risperidone (mg solvent/mg risperidone) in the injectable composition ranges from about 12:1 to 4:1; g) the kit further comprises an alkaline agent; h) the mole ratio of risperidone to alkaline agent ranges from 2/3 to 2/5; i) the solvent, polymeric solution,
- 25 risperidone and/or injectable composition is sterilized prior to administration; and/or j) the kit further comprises an alkaline agent in either or both containers.

- [0101]** According to another aspect, the invention provides a pharmaceutical kit suitable for the in-situ formation of a biodegradable implant in a body from the composition claimed, wherein the drug and the biocompatible polymer are contained in a first container, and the solvent is contained in a second, separate
- 30 container. Preferably, at least one of the first and second containers is a syringe, a vial, a device or a cartridge,

either disposable or not and more preferably both the first and the second containers are disposable syringes. This aspect of the invention is directed to a kit comprising a first container, preferably syringes, vials, devices or cartridges, all of them either being disposable or not, containing a polymer in solid form, such as PLGA and a drug in the appropriate amounts and a second container, likewise preferably syringes, vials, devices or cartridges, all of them being either disposable or not, containing the water-miscible solvent. When required, the contents of both containers are combined, for example through a connector or by using male-female syringes and mixed each other so that the compositions according to the invention are reconstituted, for example by moving forwards and backwards the plungers of the syringes.

**[0102]** According to another aspect, the invention provides a dosing regimen method for (or the LAI depot composition as described herein for use in) administering an injectable intramuscular extended-release composition according to the invention to a subject in need thereof, the method comprising:

- a) administering intramuscularly to the subject a first dose in the amount of 75 mg to 100 mg of risperidone on the LAI depot composition;
- b) administering intramuscularly to said patient 75 mg to 100 mg of risperidone in the LAI depot composition, at a point of time on the 28<sup>th</sup> day, or on the 26<sup>th</sup> day to the 33<sup>rd</sup> day or on the 26<sup>th</sup> day to the 31<sup>st</sup> day counting from the previous administration day; and
- c) repeating step b) whenever required.

**[0103]** Within a treatment period, administered doses of injectable composition are typically approximately the same.

**[0104]** Administration of a single dose is typically considered that amount of injectable composition administered to a subject within a period of up to 24 hours, up to 12 hours, up to 6 hours, up to 3 hours, up to one hour, up to 30 min, up to 15 min, or up to 5 min.

**[0105]** A dose can be administered to a single muscular site or can be divided into two or more portions and administered to two or more muscular sites of a subject. For example, a first portion of a dose can be administered to a first section of gluteal muscle and a second portion of the dose can be administered to a second section of gluteal muscle of a subject.

**[0106]** As used herein the term, "initial burst" or "initial release" refers to the sum of the plasma levels of drug plus those of active metabolite, which sum is also called "the active moiety" (risperidone and paliperidone together) throughout the present specification, from the moment of injection/administration of the injectable composition to a subject in need thereof until completion of the third day after the administration. For example, the drug can be risperidone and its metabolite can be paliperidone. In some embodiments, the initial period of release is within three days, within two days, within one day, within twelve hours, within 6 hours or within 2 hours after administration.

[0107] LAI sustained release compositions comprising various grades of PLGA, but being otherwise the same, were prepared to determine suitable grades of PLGA exhibiting improved performance. Their extent of agglomeration during initial mixing of the DMSO with drug and PLGA powder was determined by visual observation during a 3-min period of mixing. Formulations according to the invention did not agglomerate or  
5 took less time to deagglomerate and form a suitable LAI depot composition than did comparator formulations. Comparator formulations did not deagglomerate sufficiently or the PLGA did not dissolve completely within the target 3 min or less of mixing time or 200 pushes or less.

[0108] It was determined that too high a content of smaller particle sizes of PLGA caused excessive agglomeration of the powdered mix; whereas, too high a content of larger particle sizes of PLGA caused a  
10 substantial increase in the amount of time it took to dissolve the PLGA in the DMSO.

[0109] Accordingly, the grades of PLGA of the invention provide improved dissolution of the PLGA in the powdered mixture of PLGA and drug, provide reduced agglomeration of the powder during the mixing, and provide reduced dissolution time for the PLGA. As a result, a clinician preparing the LAI sustained release composition immediately before use does not have to spend excessive time mixing the components prior to  
15 administration and dosage form failures due to agglomeration are avoided.

[0110] Implants were then formed from their respective LAI injectable depot compositions. The drug release profile from the implants was then determined in vitro.

[0111] For implants made from PLGAs 1 and 2 (see the Examples) and mixed for no more than 3 min, the drug release was unsatisfactory (FIG. 1). The PLGA used in the composition of FIG. 1 had a particle size mass  
20 distribution where 16.8 % of the particles were bigger than 300 microns and 33.2 % of the particles were smaller than 150 microns, measured by analytical sieving according to USP<786>. Said PLGA had a particle size volume distribution with a D90 of 352 microns and a D80 of 273 microns when measured by laser diffraction analysis. The PLGA grades having too high a content of larger particle sizes exhibited incomplete dissolution of the PLGA during the reconstitution process of 3 min or less. As a result, the corresponding LAI depot  
25 compositions were not pharmaceutically suitable. However, for PLGAs 3 and 4 (see the Examples), the sustained release of drug from their respective implants was satisfactory (FIG. 2). The PLGA used in the composition of FIG. 2 had a particle size mass distribution where 1.2 % of the particles were bigger than 300 microns and 53.5 % of the particles were smaller than 150 microns, measured by analytical sieving according to USP<786>. Said PLGA had a particle size volume distribution with a D90 of 250 microns and a D80 of 193  
30 microns when measured by laser diffraction analysis (FIG. 4).

[0112] When PLGAs 5 and 6 were used (see the Examples), extensive particle agglomeration was observed, and a suitable LAI depot composition could not be prepared within the preferred time of no more than 3 minutes. The higher content of smaller particle sizes in the PLGA caused excessive agglomeration, and deagglomeration thereof was not possible within the target 3 min. Thus, those compositions were not

considered clinically suitable. In any case, although no injectable composition was obtained, because the agglomerates did not allow the composition to pass through the needle, the composition was assayed by preparing it first by mixing all the components in a vial and mixing them by vortex for 30 min. An equivalent amount of that composition was charged into a syringe and injected to form an implant. Even though the  
5 PLGAs 5 and 6 do not form an acceptable LAI depot composition for injection, they nonetheless provided a satisfactory sustained release of drug (FIG 3). The PLGA used in the composition of FIG. 3 had a particle size mass distribution where 0.3 % of the particles were bigger than 300 microns and 77.2 % of the particles were smaller than 150 microns, measured by analytical sieving according to USP<786>. Said PLGA had a particle size volume distribution with a D90 of 168 microns and a D80 of 114 microns when measured by laser  
10 diffraction analysis.

**[0113]** Accordingly, the PLGA having too high a content of large particle sizes provided inadequate drug release because the PLGA did not dissolve completely during the mixing period and the corresponding implant completed its drug release too quickly, i.e. three weeks rather than four weeks. Moreover, PLGA having too high a content of small particle sizes provided inadequate pharmaceutical performance, because the  
15 agglomeration of the powder during reconstitution was too extensive, whereby neither an acceptable LAI depot composition nor an acceptable implant could be formed.

**[0114]** The impact of PLGA particle size distribution upon drug release was evaluated in vivo in New Zealand White rabbits (FIGS. 5A-5C). Injectable compositions were made as described herein with PLGA copolymer (L:G ratio of 50:50, DMSO, and risperidone, wherein the apparent viscosity of the polymer solution (made from  
20 the DMSO and risperidone) was about 1.30 Pa.s. Three grades of PLGA copolymer differing in particle size distribution (measured by analytical sieving according to USP<786>) were evaluated: a) Grade 1 (FIG. 5A) where no more than 10% of the particles have a particle size of 300 microns; b) Grade 2 (FIG. 5B) where not more than 70 % of the particles have a particle size below 150 microns; and Grade C (FIG. 5C) where at least 70% of the particles have a particle size of 300 microns or more. It was unexpected that particle size distribution  
25 of the PLGA copolymer used to form the injectable depot composition would have an impact upon the in vivo drug release profile, because the PLGA copolymer is dissolved in the DMSO before administration to animals or humans, and because there was no difference in the apparent viscosity of the polymer solution used to form the composition.

**[0115]** Together, the in vitro and in vivo data demonstrate that grades of PLGA having a particle size  
30 distribution according to the invention were able to provide implants that released drug for the target 28-day period. The in vitro physicochemical data demonstrate that grades of PLGA having a particle size distribution according to the invention did not exhibit excessive agglomeration. Use of grades of PLGA of the invention allowed for a reduction in the time it took to completely dissolve the PLGA and for avoidance or substantial reduction of agglomeration of the powder during the target mixing time. In some embodiments, the powder

mixture of PLGA and drug of the invention exhibits reduced or no agglomeration with respect to an otherwise similar mixture but employing a grade of PLGA falling outside the claimed particle size distribution(s).

**[0116]** In some embodiments, the mixing time required to prepare a pharmaceutically acceptable LAI depot composition was 3 min or less, 2 min or less, or 1 min or less.

- 5 **[0117]** The present invention also relates to a stable injectable intramuscular extended-release composition suitable for forming an *in situ* solid implant comprising from 75 to 100 mg of risperidone, a biocompatible PLGA copolymer having a monomer ratio of lactide to glycolide of from 45:55 to 55:45 and DMSO as solvent, wherein the risperidone and the biocompatible polymer are contained in a first container, and the solvent is contained in a second container, wherein the concentration of the biocompatible copolymer is between 20 and 50 % by weight, with respect to the weight of the biocompatible copolymer and the solvent, wherein the risperidone has a particle size volume distribution with a D10 equal or above 10 microns, a D50 between 60 and 130 microns, and a D90 below or equal 225 microns, when measured by laser diffraction analysis, and wherein the PLGA has a particle size distribution as defined herein.

- 10 **[0118]** In a preferred embodiment, the composition releases less than 20 % of risperidone at 7 days, and less than 90 % at 21 days, with respect to the total amount of risperidone in the composition, when measured in an *in vitro* release test as described herein.

- [0119]** The invention provides a method of treating a disease, disorder or condition that is therapeutically responsive to risperidone and/or paliperidone. A preferred disease, disorder or condition is a psychosis. A subject in need thereof may be experiencing a first-time or recurrent psychosis and may or may not have been stabilized with an antipsychotic prior to administration of the LAI sustained release composition.

**[0120]** In some embodiments, the LAI depot composition is used in the treatment of schizophrenia, preferably in adults, and/or the composition is used in the treatment of schizophrenia, preferably in adults, both in acute exacerbation and maintenance of stable patients, and in particular in the acute exacerbation of schizophrenia for patients with moderate to severe symptoms, without prior stabilization with oral risperidone or paliperidone.

- 25 **[0121]** In a preferred embodiment, the LAI depot composition is used in the treatment of a schizophrenic subject experiencing an episode of acute exacerbation, wherein the subject has not undergone prior stabilization with oral antipsychotics. In a particular embodiment, the subject has not undergone dose titration with oral risperidone prior to administration of the composition. As used herein, the term "dose titration" refers to oral administration of risperidone to determine the appropriate dose for said subject.

- 30 **[0122]** In a preferred embodiment, the LAI depot composition is used in the treatment of a schizophrenic subject experiencing an episode of acute exacerbation with moderate to severe symptoms, wherein the subject has not undergone prior stabilization with oral antipsychotic medication. The patient can start the treatment immediately or right after a medical titration to be sure that risperidone is the chosen treatment and that the dose is the convenient one.

[0123] In a preferred embodiment, the LAI depot composition is used in the continuation (maintenance) treatment of a stable subject already being treated with another antipsychotic agent administered orally or via a long-acting injectable extended-release composition.

[0124] Other antipsychotic agents that can be administered to the subject include aripiprazole, olanzapine, blonanserin, quetiapine, haloperidol, flupenthixol, zuclopenthixol, brexpiprazole, cariprazine, iloperidone, lurasidone, ziprasidone, chlorpromazine, fluphenazine, perphenazine, and/or clozapine. These antipsychotics may be administered prior to or after administration of the LAI depot composition.

[0125] All values disclosed herein may have standard technical measure error (standard deviation) of  $\pm 10\%$ . The term "about" is intended to mean  $\pm 20\%$ ,  $\pm 15\%$ ,  $\pm 10\%$ ,  $\pm 5\%$ ,  $\pm 2.5\%$  or  $\pm 1\%$  relative to a specified value, i.e. "about" 20% means  $20 \pm 2\%$ ,  $20 \pm 1\%$ ,  $20 \pm 0.5\%$  or  $20 \pm 0.25\%$ .

## EXAMPLES

[0126] The following examples are illustrative of the invention and are not to be considered exhaustive of the full metes and bounds of the claimed invention.

### Example 1: Compositions and evaluation thereof

[0127] Amounts of the components used for preparing various LAI depot compositions are detailed in the tables below. Comparator formulations were prepared by using grades of PLGA having particle size distributions falling outside the claimed ranges. Formulations according to the invention were prepared by using grades of PLGA having particle size distributions within the claimed ranges. The PLGA and drug were included in a first container, and the DMSO was included in a second container.

Formulation 1:

| Ingredient                                                     | Amount (mg) |
|----------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (ester terminal group) 50:50 | 150         |
| Dimethyl sulfoxide                                             | 350         |
| Risperidone                                                    | 75          |

Formulation 2:

| Ingredient                                                     | Amount (mg) |
|----------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (ester terminal group) 50:50 | 200         |
| Dimethyl sulfoxide                                             | 467         |
| Risperidone                                                    | 100         |

**[0128]** The particle size volume distribution for risperidone was  $d(0.1) = 33 \mu\text{m}$ ,  $d(0.5) = 81 \mu\text{m}$  and  $d(0.9) = 160 \mu\text{m}$  as determined by laser ray diffraction (Malvern Mastersizer 2000, suspended in water until obscuration of 7.4%).

**[0129]** The components were placed into a pharmaceutical kit by placing the DMSO in a first container and placing the powdered risperidone and PLGA in a second container. The preferred container was a syringe.

**[0130]** The grades of PLGA evaluated were as follows.

- PLGA 1: PLGA milled to a particle size mass distribution where more than 10 % of the particles had a particle size above 300 microns when measured by analytical sieving according to USP<786>;
- 10 • PLGA 2: PLGA milled to a particle size volume distribution with D90 above 300 microns when measured by laser diffraction analysis;
- PLGA 3: PLGA milled to a particle size mass distribution where no more than 10 % of the particles had a particle size above 300 microns and no more than 70 % of the particles have a particle size below 150 microns when measured by analytical sieving according to USP<786>;
- 15 • PLGA 4: PLGA milled to a particle size volume distribution with D90 not above 300 microns and D80 not below 135 microns when measured by laser diffraction analysis;
- PLGA 5: PLGA milled to a particle size mass distribution where more than 70 % of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>;
- 20 • PLGA 6: PLGA milled to a particle size volume distribution with D80 below 135 microns when measured by laser diffraction analysis.

**[0131]** The LAI depot composition was prepared by connecting the syringes and mixing the components thereof by pushing and pulling the respective syringe plungers. Visual observation of the extent of agglomeration of the powder during mixing was made.

25 **[0132]** The mixing (reconstitution process) was carried out immediately prior to injection. The target maximum mixing time required for the assay was 3 minutes or less (or 200 pushes or less); however, preferred target maximum mixing times for formulations of the invention were 2 minutes or less, or 1 minute or less, or 30 sec or less (150 pushes or less, 100 pushes or less, or 50 pushes). The amount of time it took to deagglomerate the powder and to dissolve the PLGA was determined.

30 **[0133]** Implants were formed by injecting the sustained release composition into a phosphate buffered saline solution. The implants were subjected to in vitro drug dissolution (drug release) testing as follows: horizontal orbital motion at 50 rpm; medium: PBS pH 7.4.; temperature:  $37 \pm 0.5 \text{ }^{\circ}\text{C}$ . The concentration or amount of drug in the test solution was determined by HPLC with UV detection (wavelength 260 nm).

**Example 2: Particle size determination**

*Analytical sieving according to USP<786>*

**[0134]** The PLGA particle size mass distribution was determined by sieve stack technique using the following sizes: 355 > 300 > 250 > 150 > 125 > 106 > 75. The amplitude was 0.65 mm and the shaking time 5 minutes.

5 *Laser light diffraction*

**[0135]** The PLGA particle size distribution is expressed as volume distribution and was determined by laser diffraction technique by wet dispersion method. No sample pre-treatment was applied. The sample was directly added into the dispersion medium (water). Dispersion mechanism was stirring at 3,000 rpm and the sample was stabilized for 30 seconds before measuring.

10 **Example 3: Compositions**

**[0136]** The amounts of the components used for preparing various LAI depot compositions are detailed in the tables below. Formulations according to the invention are prepared by using grades of PLGA having particle size distributions within the claimed ranges. Respective LAI depot compositions are formed by mixing those components.

15 Formulation 3:

| Ingredient                                                     | Amount (mg) |
|----------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (ester terminal group) 75:25 | 150         |
| Dimethyl sulfoxide                                             | 350         |
| Risperidone                                                    | 75          |

Formulation 4:

| Ingredient                                                     | Amount (mg) |
|----------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (ester terminal group) 75:25 | 200         |
| Dimethyl sulfoxide                                             | 467         |
| Risperidone                                                    | 100         |

Formulation 5:

| Ingredient                                                     | Amount (mg) |
|----------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (ester terminal group) 50:50 | 50          |
| Dimethyl sulfoxide                                             | 117         |
| Risperidone                                                    | 25          |

Formulation 6:

| Ingredient                                                     | Amount (mg) |
|----------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (ester terminal group) 50:50 | 300         |
| Dimethyl sulfoxide                                             | 700         |
| Risperidone                                                    | 150         |

Formulation 7:

| Ingredient                                                   | Amount (mg) |
|--------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (carboxyl end group) 50:50 | 50          |
| Dimethyl sulfoxide                                           | 117         |
| Risperidone                                                  | 25          |

5 Formulation 8:

| Ingredient                                                   | Amount (mg) |
|--------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (carboxyl end group) 50:50 | 300         |
| Dimethyl sulfoxide                                           | 700         |
| Risperidone                                                  | 150         |

Formulation 9:

| Ingredient                                                     | Amount (mg) |
|----------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (ester terminal group) 50:50 | 150         |
| Dimethyl sulfoxide                                             | 350         |
| Paliperidone                                                   | 75          |

Formulation 10:

| Ingredient                                                     | Amount (mg) |
|----------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (ester terminal group) 50:50 | 200         |
| Dimethyl sulfoxide                                             | 467         |
| Paliperidone                                                   | 100         |

10

Formulation 11:

| Ingredient | Amount (mg) |
|------------|-------------|
|------------|-------------|

28

|                                                                |     |
|----------------------------------------------------------------|-----|
| Lactic-co-glycolic acid copolymer (ester terminal group) 50:50 | 120 |
| Dimethyl sulfoxide                                             | 228 |
| Risperidone                                                    | 56  |

Formulation 12:

| Ingredient                                                     | Amount (mg) |
|----------------------------------------------------------------|-------------|
| Lactic-co-glycolic acid copolymer (ester terminal group) 50:50 | 96          |
| Dimethyl sulfoxide                                             | 252         |
| Risperidone                                                    | 44          |

**[0137]** The PLGA has an inherent viscosity in the range of 0.20-0.60 dl/g, about 0.30-0.55 dl/g, about 0.36-0.52 dl/g, about 0.36-0.43, about 0.40-0.58 dl/g, or about 0.46-0.51 dl/g measured in chloroform at 25°C or 30°C at a concentration of 0.1% wt/v or 0.5% wt/v with a Ubbelohde size 0c or 0b glass capillary viscometer or in chloroform at 30°C and at a concentration of 0.5% wt/v with a size 25 Cannon-Fenske glass capillary viscometer (USP<911> viscosity - capillary methods or Eur.Ph 2.2.9. capillary viscometer method).

**[0138]** The PLGA has a particle size distribution as follows: a) particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786>; b) particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis; c) a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, and where not more than 70 % of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>; d) a particle size mass distribution where not more than 70 % of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>; e) a particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis and with a D80 not below 135 microns when measured by laser diffraction analysis; f) a particle size volume distribution with a D80 not below 135 microns when measured by laser diffraction analysis; g) a D50 of about 50-150 microns; h) a D10 of about 10-50 microns; i) a D90 of about 170-300 microns; and/or j) a D50 of about 50-150 microns, a D10 of about 10-50 microns, and a D90 of about 170-300 microns.

**[0139]** Before formation of respective implants, the respective LAI depot compositions formed from the above components have an apparent viscosity in the range of about 1.0-7.0 Pa.s, about 1.5-7.0 Pa.s, or about 1.8-6.5 Pa.s. (USP<912> viscosity - rotational methods or Eur.Ph: 2.2.10. viscosity - rotating viscometer method).

**[0140]**

#### Example 4: Method of treating psychosis

[0141] A subject presenting with schizophrenia was administered intramuscularly a 75 mg or 100 mg dose of risperidone in a LAI depot composition made according to the instant examples. The subject was evaluated and monitored to determine the therapeutic response of the subject to the risperidone. If the therapeutic response were determined to be inadequate, the higher dose of risperidone would be given.

- 5 [0142] The same procedure could be followed by administering the LAI depot composition subcutaneously, e.g. into the subject's adipose tissue.

[0143] The above method is used for treating bipolar disorder and other disorders disclosed herein that are therapeutically responsive to risperidone and/or paliperidone.

**Example 5: Method of Administering**

- 10 [0144] A subject was administered intramuscularly a 75 mg or 100 mg dose of risperidone in a LAI sustained release composition made according to the instant examples. The subject was evaluated and monitored to determine the clinical response of the subject to the risperidone.

[0145] The same procedure could be followed by administering the LAI depot composition subcutaneously, e.g. into the subject's adipose tissue.

15 **Example 6: In vivo evaluation**

[0146] Performance of implants formed from the respective injectable compositions described herein was evaluated as follows.

- [0147] The implantable formulations were prepared by direct reconstitution of two prefilled syringes, first one with polymer and risperidone mixture, and second with the solvent. Syringes were connected and the contents thereof mixed to form the extended-release injectable sustained release composition(s). The compositions were intramuscularly injected to New Zealand White rabbits weighing average of 3 Kg. The amount injected corresponded to a dose of 15 mg risperidone, and the composition was intramuscularly placed in the left hind leg using syringe with 20G needle. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d and periodically up to 28 days. The results are detailed in FIGS. 5A-5C.
- 20

**CLAIMS**

- 1) A powder mixture comprising powdered drug and powdered PLGA copolymer, wherein
  - a) the drug is selected from the group consisting of risperidone, paliperidone, or a mixture thereof; and
  - 5      b) the PLGA copolymer has a lactide (L) to glycolide (G) monomer ratio of 50:50  $\pm$ 10% to 75:25  $\pm$ 10%, 50:50  $\pm$ 10%, or 75:25  $\pm$ 10% and has a particle size distribution selected from the group consisting of:
    - i) particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786>;
    - 10      ii) particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis;
    - iii) a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, and where not more than 70% of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>;
    - 15      iv) a particle size mass distribution where not more than 70% of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>;
    - v) a particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis and with a D80 not below 135 microns when measured by laser diffraction analysis;
    - 20      vi) a particle size volume distribution with a D80 not below 135 microns when measured by laser diffraction analysis;
    - vii) a particle size volume distribution with a D50 of about 50-150 microns;
    - viii) a particle size volume distribution with a D10 of about 10-50 microns;
    - ix) a particle size volume distribution with a D90 of about 170-300 microns;
    - 25      x) a particle size volume distribution with a D50 of about 50-150 microns, a D10 of about 10-50 microns, and a D90 of about 170-300 microns, and
    - xi) a combination of any of the above.
- 2) A pharmaceutical kit comprising DMSO and the powder mixture of claim 1.
- 3) A method of preparing an extended-release injectable suspension, the method comprising
  - 30      a) mixing DMSO, PLGA copolymer, and drug to form said injectable suspension, wherein the drug particles are suspended within a polymeric solution formed from said DMSO and said PLGA copolymer, and wherein
  - b) the drug is selected from the group consisting of risperidone, paliperidone, or a mixture thereof; and

- c) the PLGA copolymer has a lactide (L) to glycolide (G) monomer ratio of 50:50  $\pm$ 10% to 75:25  $\pm$ 10%, 50:50  $\pm$ 10%, or 75:25  $\pm$ 10%, and has a particle size distribution selected from the group consisting of:
- i) particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786>;
  - ii) particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis;
  - iii) a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, and where not more than 70% of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>;
  - iv) a particle size mass distribution where not more than 70% of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>;
  - v) a particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis and with a D80 not below 135 microns when measured by laser diffraction analysis;
  - vi) a particle size volume distribution with a D80 not below 135 microns when measured by laser diffraction analysis;
  - vii) a particle size volume distribution with a D50 of about 50-150 microns;
  - viii) a particle size volume distribution with a D10 of about 10-50 microns;
  - ix) a particle size volume distribution with a D90 of about 170-300 microns;
  - x) a particle size volume distribution with a D50 of about 50-150 microns, a D10 of about 10-50 microns, and a D90 of about 170-300 microns, and
  - xi) a combination of any of the above.
- 4) An extended-release injectable suspension prepared according to the method of claim 3.
- 5) The extended-release injectable suspension of claim 4 having
- a) about 25 mg to about 150 mg of drug;
  - b) an apparent viscosity in the range of about 1.0-7.0 Pa.s;
  - c) a mass ratio of DMSO to drug of about 5:1 to about 4:1; and
  - d) a mass ratio of drug to (PLGA + drug), expressed as the percentage of the drug weight with respect to total weight of the drug plus PLGA, of about 15-40% weight.
- 6) The extended-release injectable suspension of claim 4 having
- a) a drug content of about 10-15% wt;
  - b) a DMSO content of about 55-65% wt; and
  - c) a PLGA content of about 24%-30% wt; said percentages being based on total composition weight.

- 7) The extended-release injectable suspension of any one of claims 4, 5, or 6 for use in the treatment of a subject in need thereof.
- 8) The extended-release injectable suspension for use of claim 7, for use in treating a disease, disorder, or condition that is therapeutically responsive to risperidone and/or paliperidone.
- 5 9) The extended-release injectable suspension for use of any one of claims 7 or 8, wherein after its administration, it forms an implant that provides a therapeutic plasma level of active moiety continuously from the first day and for at least about 28 days.
- 10) The extended-release injectable suspension for use of any one of claims 8 or 9, wherein the disease, condition, or disorder is selected from the group consisting of psychosis, delusional psychosis,  
10 psychotic depression, obsessive-compulsion disorder, schizophrenia, bipolar disorder, schizoaffective disorders, non-schizophrenic psychoses, Asperger's syndrome, Tourette's syndrome, obsessive-compulsion disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, personality disorders, aggression, depression, dementia, intellectual disabilities and behavioral disturbances in mental retardation and autism, autistic spectrum disorders, anxiety, eating disorders, nervous anxiety,  
15 insomnia, idiopathic dystonia, substance abuse, and any combination thereof.
- 11) The extended-release injectable suspension for use of any one of claims 10 or 11, wherein the disease, condition, or disorder is selected from the group consisting of schizophrenia, schizoaffective disorder, bipolar disorder, and bipolar mania.
- 12) The extended-release injectable suspension for use of any one of claims 10 or 11, for treating an  
20 episode of acute exacerbation of said disease, condition, or disorder.
- 13) The extended-release injectable suspension for use of any one of claims 7 to 12, wherein said extended-release injectable suspension is administered intramuscularly.
- 14) A pharmaceutical kit comprising a drug, DMSO, and a PLGA copolymer, wherein
- 25 a) the drug is selected from the group consisting of risperidone, paliperidone, or a mixture thereof; and
- b) the PLGA copolymer has a lactide (L) to glycolide (G) monomer ratio of 50:50  $\pm$ 10% to 75:25  $\pm$ 10%, 50:50  $\pm$ 10%, or 75:25  $\pm$ 10%, and has a particle size distribution selected from the group consisting of:
- 30 i) particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, when measured by analytical sieving according to USP<786>;
- ii) particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis;

- iii) a particle size mass distribution with not more than 10% above 300 microns, preferably not above 250 microns, and where not more than 70% of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>;
- iv) a particle size mass distribution where not more than 70% of the particles have a particle size below 150 microns, when measured by analytical sieving according to USP<786>;
- 5 v) a particle size volume distribution with a D90 not above 300 microns, preferably not above 280 microns when measured by laser diffraction analysis and with a D80 not below 135 microns when measured by laser diffraction analysis;
- vi) a particle size volume distribution with a D80 not below 135 microns when measured by laser diffraction analysis;
- 10 vii) a particle size volume distribution with a D50 of about 50-150 microns;
- viii) a particle size volume distribution with a D10 of about 10-50 microns;
- ix) a particle size volume distribution with a D90 of about 170-300 microns;
- x) a particle size volume distribution with a D50 of about 50-150 microns, a D10 of about 10-50 microns, and a D90 of about 170-300 microns, and
- 15 xi) a combination of any of the above.
- 15) The kit of claim 14 comprising two or more containers, wherein
- a) the DMSO is in a first container, and the PLGA and drug together are in a second container; or
- b) the DMSO is in a first container, the PLGA is in a second container, and the drug is in a third container.
- 20
- 16) The kit of claim 14 or 15, wherein
- a) the amount of drug is about 25 mg to about 150 mg;
- b) the mass ratio of drug to (PLGA + drug), expressed as the percentage of the drug weight with respect to total weight of the risperidone plus PLGA, is about 15-40%; and/or
- 25 c) the mass ratio of DMSO to drug is about 5:1 to about 4:1.
- 17) The kit of claim 14, 15, or 16, wherein
- a) the amount of drug is about 100 mg, the amount of DMSO is about 467 mg, and the amount of PLGA is about 200 mg;
- b) the amount of drug is about 75mg, the amount of DMSO is about 350 mg, and the amount of PLGA is about 150 mg;
- 30 c) the amount of drug is about 115 mg (or about 100-130 mg or about 105-125 mg or about 110-120 mg), the amount of DMSO is about 537 mg (or about 515-560 mg or about 520-550 mg or about 530-545 mg), and the amount of PLGA is about 230 mg (or about 215-245 mg or about 220 to about 235 mg); or

- d) the amount of drug is about 90 mg (or about 75-105 mg or about 80-100 mg or about 85-105 mg), the amount of DMSO is about 420 mg (or about 405-435 mg or about 415-425 mg), and the amount of PLGA is about 180 mg (or about 165-200 mg or about 170-190 mg or about 175-185 mg).
- 18) The invention according to any one of claims 1-17, wherein the PLGA has been sized.
- 5 19) The invention of claim 18, wherein the PLGA has been sieved and/or comminuted.
- 20) The invention of claim 19, wherein the PLGA has been micronized, milled, hammered, crushed, ground, triturated, and/or pulverized.
- 21) The invention of any one of claims 1-20, wherein the PLGA is end-capped with an ester group.
- 22) The invention of any one of claims 1-21, wherein the drug has a particle size volume distribution with
- 10 a D10 equal or above 10 microns, a D50 between 60 and 130 microns, and a D90 below or equal 225 microns, when measured by laser diffraction analysis.