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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 3

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear
		2002-0082245		Yelle, William E.	06/27/2002	
		2003-0157180		Francois et al.	08/21/2003	
		2011-0105536		Lewyn-Briscoe et al.	05/05/2011	
		2012-0263795-		Francois et al.	10/18/2012	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Foreign Patent Document Office[3]	Number[4]	KindCode[5]	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear	T[6]
		WO	2004/010981		ALZA Corporation	02/05/2004		
		WO	2008/021342		Teva Pharmaceutical Industries, LTD.	02/21/2008		
		WO	2009/025859		Teva Pharmaceutical Industries, LTD.	02/26/2009		
		WO	2009/047499		CIPLA Limited	04/16/2009		
		WO	2011/053829		Janssen Pharmaceutica NV	05/05/2011		

Examiner Signature		Date Considered	

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1 Unique citation designation number. 2 See attached Kinds of U.S. Patent Documents. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

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Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
		New Drug Application (NDA) dated October 25, 2007 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invega Sustenna (paliperidone palmitate) 39mg, 78mg, 117mg, 156mg, and 234 mg extended-release injectable suspension	
		Supplemental New Drug Application (sNDA) dated March 14, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invega Sustenna (paliperidone palmitate) extended-release injectable suspension, 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg	
		Alphs et al. Annals of General Psychiatry 2011, 10:12	
		Altamura et al., Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. Drugs. 2003; 63(5): 493-512	
		Berwaerts et al., Journal of Affective Disorders 138 (2012) 247–258	
		Canuso et al. 2010, Expert Opinion Pharmacother., Volume 11 (15), pages 2557-2567.	
		Cleton et al., ASSESSMENT OF THE DOSE PROPORTIONALITY OF PALIPERIDONE PALMITATE 25, 50, 100 AND 150 MG EQ., A NEW LONG-ACTING INJECTABLE ANTIPSYCHOTIC FOLLOWING ADMINISTRATION IN THE DELTOID OR GLUTEAL MUSCLES, PI-74, Clinical Pharmacology & Therapeutics, Volume 83, Supplement 1, MARCH 2008, S31	
		Ereshefsky L., Pharmacokinetics and drug interactions: update for new antipsychotics. J Clin Psychiatry. 1996;57 Suppl 11:12-25	
		Gefvert et al. Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Consta) in patients with schizophrenia. Int J Neuropsychopharmacol. 2005; 8(1): 27-36	
		Kane et al., Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. Eur Neuropsychopharmacol. 1998; 8(1): 55-66	
		Levron et al., Clinical pharmacokinetics of haloperidol decanoate. Comparison with other prolonged-action neuroleptics. Encephale. 1987; 13(2): 83-7 [see English Summary as provided]	
		Markowitz et al., "Benefit-Risk Assessment of Maintenance Therapy in Schizophrenia Comparing Long-Acting Injectable (LAI) Paliperidone Palmitate with Paliperidone ER", Presented at the 164th Annual Meeting of the American Psychiatric Association, May 14-18, 2011, Honolulu, HI, USA	

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Examiner Name	Claytor, Deirdre
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OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
		Mauri et al., Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet. 2007;46(5):359-88	
		Pandina et al., Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 218–226	
		Sheehan et al., Comparison of the Peak-to-trough Fluctuation in Plasma Concentration of Long-acting Injectable Antipsychotics and Their Oral Equivalents, *Innov Clin Neurosci*. 2012;9(7–8):17–23	
		Vermeir et al., Absorption, metabolism, and excretion of paliperidone, a new monoaminergic antagonist, in humans. Drug Metab Dispos. 2008 Apr;36(4):769-79	

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SUBMISSION UNDER MPEP 609.06 Page 1 of 1	*Application Number*	12/337,144
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U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Name of Patentee or Applicant of Cited Document	U.S. Patent Document Number	Kind Code[2] (if known)	Pages, Columns, Lines, where relevant passages or relevant figures appear
		Lewyn-Briscoe et al.	13/903,638 (PRD3131USDIV1)		

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Name of Patentee or Applicant of Cited Document	Foreign Patent Document Office[3]	Number[4]	KindCode[5]	Pages, Columns, Lines, where relevant passages or relevant figures appear	T[6]

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITOL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
		International Search Report Re: International Application No.: PCT/US2010/054807 dated January 11, 2011 (PRD3131WOPCT).	
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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

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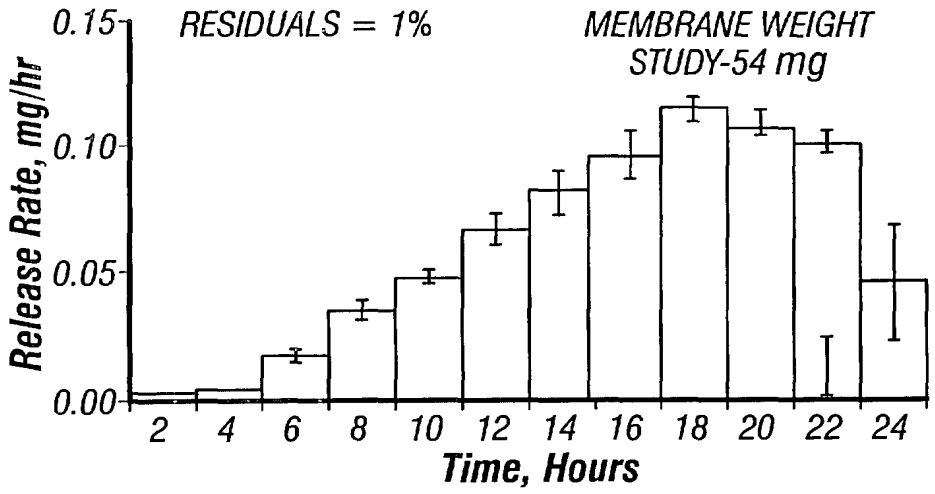
(54) Title: METHODS AND DOSAGE FORMS FOR CONTROLLED DELIVERY OF PALIPERIDONE



(57) Abstract: Dosage forms and methods for providing a substantially ascending rate of release of paliperidone are provided. The sustained release dosage forms provide therapeutically effective average steady-state plasma paliperidone concentrations when administered once per day. This once-a-day dosing regimen results in only one peak plasma paliperidone concentration occurrence in each 24 hour period. In addition, the peak plasma paliperidone concentration occurs at a later time following dose administration and exhibits a lesser magnitude than the peak plasma paliperidone concentration that occurs following administration of paliperidone in an immediate-release dosage form.

WO 2004/010981 A1

METHODS AND DOSAGE FORMS FOR CONTROLLED DELIVERY OF PALIPERIDONE

FIELD OF THE INVENTION

[0001] This invention pertains to the controlled delivery of pharmaceutical agents and methods, dosage forms and devices. In particular, the invention is directed to methods, dosage forms and devices for the controlled delivery of paliperidone, with reduced degradation of the active agent.

BACKGROUND OF THE INVENTION

[0002] The art is replete with descriptions of oral dosage forms for the controlled release of pharmaceutical agents. While a variety of sustained release dosage forms for delivering certain drugs exhibiting short half-life may be known, not every drug may be suitably delivered from those dosage forms because of solubility, metabolic processes, absorption and other physical, chemical and physiological parameters that may be unique to the drug and the mode of delivery. Examples of such drugs that are not likely candidates for controlled release dosage forms are those exhibiting a long half-life such as paliperidone. It has also been found that paliperidone degrades into notable amounts of impurities. The major degradation products include C-9 ketone, N-oxides, and various dimmers of its degradants.

[0003] Paliperidone is more fully described in US Pat. No. 4,804,663. The paliperidone compound differs from risperidone and related prior art compounds described in US Pat. Nos. 4,352,811 and 4,458,076 by its substitution on the 1-position of the piperidine moiety.

[0004] Paliperidone is practically insoluble in water, freely soluble in methylene chloride and soluble in methanol and 0.1 N hydrochloric acid. Additionally, since paliperidone has a long half-life of about one day, it is not a typical candidate for extended delivery. However, side effects such as anxiety, somnolence, dizziness, constipation, extrapyramidal symptoms, may be related

to high blood plasma concentration levels restricting the ability to administer a single daily immediate release dose.

[0005] Traditional stability improvements for pharmaceutical agents were explored including use of antioxidants (increased levels of BHT), and incorporation of chelating agents. These traditional methods for reducing degradation proved insufficient.

[0006] It is expected that the side effects are likely a result of either rate of rise and/or actual drug blood plasma concentrations exceeding a threshold maximum tolerable concentration (MTC). However, in order to obtain a therapeutic effect, concentrations need to be sustained above a minimum pharmacodynamic concentration (MPC).

[0007] Another aspect of delivery of paliperidone is that administration may require low drug loading in the dosage form. Dosage forms may need to contain drug in the range of 5% to 20% of the overall weight of the dosage form. The low drug loading requirement presents problems in formulating compositions and fabricating dosage forms that are suitable for oral administration that deliver at the desired rate of release for an extended period of time.

[0008] Prior art osmotic dosage forms mention delivery of risperidone from a liquid gelatin capsule without mention of delivery of paliperidone or of a preferred rate of delivery or identification of a solid capsule dosage form. Published patent application by ALZA Corporation, WO 00/35419.

[0009] Other art discloses delivery of risperidone through transdermal methods with patches without claiming any rate of release or desired plasma concentration profile. Published patent application by Janssen, WO 96/31201. Furthermore, this art does not identify delivery of paliperidone much less delivery of paliperidone through oral controlled release delivery.

[00010] There is also art disclosing delivery of risperidone and/or paliperidone through injectable implants for long term, multi-day, delivery. This art includes the published patent application by Alkermes WO 01/34120, and US Pat. Nos. 5,654,008; 5650,173; 5,770,231; 6,077,843; 6,368,632; 6,110,923; 5,965,168; and 5,692,477 by Alkermes. US patents claiming injectable dosage forms to provide almost zero order delivery include US Pat.

Nos. 5,871,778 and 5,656,299 by Yoishitomi Pharmaceutical Industries. This art does not disclose preferred release rates and does not teach or motivate toward an ascending rate of release, much less such release through an oral delivery system.

[00011] Prior art for oral delivery does not address delivery of extended, controlled release paliperidone.

[00012] Oral controlled release dosage forms include, US Pat. No. 5,536,507 which describes a three component pharmaceutical formulation that utilizes, *inter alia*, a pH sensitive polymer and optionally an osmotic agent that will swell in the higher pH regions of the lower portion of the small intestine and the large intestine to release drug in those environments. Additional components of the dosage form include a delayed release coating and an enteric coating to provide a dosage form that releases very little, if any, of the drug in the stomach, a relatively minimal amount in the small intestine and reportedly about 85% or more in the large intestine. Such a dosage form provides for a widely varying time-release of drug after administration that may not begin for 1-3 hours until the dosage form has passed from the stomach and an additional 3 hours or more for the dosage form to pass into the large intestine.

[00013] Exemplary sustained release paliperidone dosage forms, methods of preparing such dosage forms and methods of using such dosage forms described herein are directed to osmotic dosage forms for oral administration.

[00014] In addition to osmotic systems as described herein, however, there are many other approaches to achieving sustained release of drugs from oral dosage forms known in the art. These different approaches include, for example, diffusion systems such as reservoir devices and matrix devices, dissolution systems such as encapsulated dissolution systems (including, for example, "tiny time pills") and matrix dissolution systems, combination diffusion/dissolution systems and ion-exchange resin systems as described in *Remington's Pharmaceutical Sciences*, 1990 ed., pp. 1682-1685.

Paliperidone dosage forms that operate in accord with these other approaches are encompassed by the scope of the disclosure herein to the extent that the drug release characteristics and/or the blood plasma paliperidone

concentration characteristics as recited herein and in the claims describe those dosage forms either literally or equivalently.

[00015] Osmotic dosage forms in general utilize osmotic pressure to generate a driving force for imbibing fluid into a compartment formed, at least in part, by a semipermeable membrane that permits free diffusion of fluid but not drug or osmotic agent(s), if present. A significant advantage to osmotic systems is that operation is pH-independent and thus continues at the osmotically determined rate throughout an extended time period even as the dosage form transits the gastrointestinal tract and encounters differing microenvironments having significantly different pH values. A review of such dosage forms is found in Santus and Baker, "Osmotic drug delivery: a review of the patent literature," Journal of Controlled Release 35 (1995) 1-21, incorporated in its entirety by reference herein. In particular, the following U.S. Patents, owned by the assignee of the present application, ALZA Corporation, directed to osmotic dosage forms, are each incorporated in their entirety herein: Nos. 3,845,770; 3,916,899; 3,995,631; 4,008,719; 4,111,202; 4,160,020; 4,327,725; 4,519,801; 4,578,075; 4,681,583; 5,019,397; and 5,156,850.

[00016] Devices in which a drug composition is delivered as a slurry, suspension or solution from a small exit orifice by the action of an expandable layer are described in U. S. Patents Nos. 5,633,011; 5,190,765; 5,252,338; 5,620,705; 4,931,285; 5,006,346; 5,024,842; and 5,160,743, which are incorporated herein by reference. Typical devices include an expandable push layer and a drug layer surrounded by a semipermeable membrane. In certain instances, the drug layer is provided with a subcoat to delay release of the drug composition to the environment of use or to form an annealed coating in conjunction with the semipermeable membrane.

[00017] Devices in which a drug composition is delivered in a dry state from a large exit orifice by the action of an expandable layer are described in US Patent Nos. 4,892,778, 4,915,949 and 4,940,465. Those references describe a dispenser for delivering a beneficial agent to an environment of use that includes a semipermeable wall containing a layer of expandable material that pushes a dry drug layer out of the compartment formed by the wall. The

exit orifice in the device is substantially the same diameter as the inner diameter of the compartment formed by the wall.

[00018] While dosage forms delivering the drug composition to the environment of use in the dry state may provide suitable release of drug at various drug loadings over a prolonged period of time, the exposure of the drug layer to the environment of use may result in agitation-dependent release of drug that in some circumstances is difficult to control. Accordingly, it may be advantageous to release the drug as a slurry or suspension that may be metered by control of rate of expansion of the push layer and the size of the exit orifice in the dosage form as in accordance with this invention.

[00019] US Patent 5,169,638 describes a buoyant controlled release pharmaceutical powder formulation to be filled into capsules that uses a pH dependent polymer formed from alginic acid and hydroxypropylmethyl cellulose to release pharmaceuticals at a controlled rate. It appears that this capsule formulation was intended to mimic the characteristics of a tableted formulation.

[00020] No description is provided of a formulation that provides the uniform release characteristics of the dosage forms containing paliperidone and related compounds of the present invention.

[00021] US Patent Nos. 4,892,778 and 4,940,465, describe a dispenser for delivering a beneficial agent to an environment of use that includes a semipermeable wall containing a layer of expandable material that pushes a drug layer out of the compartment formed by the wall. The exit orifice in the device is substantially the same diameter as the inner diameter of the compartment formed by the wall.

[00022] US Patent No. 4,915,949, describes a dispenser for delivering a beneficial agent to an environment of use that includes a semipermeable wall containing a layer of expandable material that pushes a drug layer out of the compartment formed by the wall. The drug layer contains discrete tiny pills dispersed in a carrier. The exit orifice in the device is substantially the same diameter as the inner diameter of the compartment formed by the wall.

[00023] US Patent No. 5,126,142, describes a device for delivering an ionophore to livestock that includes a semipermeable housing in which a composition containing the ionophore and a carrier and an expandable

hydrophilic layer is located, along with an additional element that imparts sufficient density to the device to retain it in the rumen-reticular sac of a ruminant animal. The ionophore and carrier are present in a dry state during storage and the composition changes to a dispensable, fluid-like state when it is in contact with the fluid environment of use. A number of different exit arrangements are described, including a plurality of holes in the end of the device and a single exit of varying diameter to control the amount of drug released per unit time due to diffusion and osmotic pumping.

[00024] Prior to this invention, paliperidone's related compound, risperidone, was administered in conventional forms, such as a nonrate-controlling, dose-dumping immediate release tablet, or by a dose-dumping capsule, and usually at multiple, repetitive dosing intervals throughout the day. The product is marketed as Risperdal® by Janssen Pharmaceutica Products, L.P. Physicians' Desk Reference, Thompson Healthcare, 56th Ed., pp. 1796-1800 (2002).

[00025] The Risperdal® mode of therapy, however, continues to lead to an initial high dose of risperidone in the blood plasma after administration, followed by a decreased level of risperidone in the blood plasma. Moreover, this peak and trough occurs twice to three times during a 24-hour period due to the multiple dosing regimen. The concentration differences in dosing patterns are related to the presence and absence of administered drug, which is a major disadvantage, associated with this prior dosage form and mode of administration.

[00026] Conventional dosage forms and their mode of operation, including dose peaks and valleys, are discussed in Pharmaceutical Sciences, Remington, 18th Ed., pp. 1676-1686 (1990), Mack Publishing Co.; The Pharmaceutical and Clinical Pharmacokinetics, 3rd Ed., pp. 1-28 (1984), Lea and Febreger, Philadelphia; and in U.S. Patents Nos. 3,598,122 and 3,598,123, both issued to Zaffaroni.

[00027] A dosage form exhibiting substantially ascending release rate profile is Concerta® marketed by McNeil Consumer Healthcare and ALZA Pharmaceuticals. Physicians' Desk Reference, Thompson Healthcare, 56th Ed., pp. 1998-2001 (2002). The Concerta® product, however indicated for

once-a-day administration, only delivers at a substantially ascending rate of release for up to about 8 hours.

[00028] Patent applications relating to Concerta® include published PCT Pat. Application No. WO99/62496A1. This patent application discloses the substantially ascending release rate profile related to Concerta® for delivery over about 8 hours for once-a-day dosing.

[00029] Related patent applications include published PCT Pat. Application No. WO98/14168; WO98/23263; WO 98/06380A2 and US 2001/0012847A1.

[00030] Still other applications relating to providing increasing rate of release delivery profile include US 2002/0035357A1; WO 01/52819A1 and WO 01/37813A2 & A3.

[00031] There remains a need for effective dosing methods, dosage forms and devices that will permit the controlled release of paliperidone and related compounds over a prolonged period of time at a substantially ascending rate of release to reduce the amount of the active agent that the patient is exposed to at any particular time and to increase the time between dosing, preferably to obtain a once-a-day dosing regimen while reducing associated side effects.

SUMMARY OF THE INVENTION

[00032] The present invention is designed for once-a-day administration of an oral dosage form to deliver paliperidone for more than about 22 hours utilizing a capsule-shaped tablet. This approximately 22 hours of release is at a substantially ascending rate of release from the core with 90% delivery occurring at about 20 hours. This novel profile provides therapeutic delivery above the MPC while keeping the plasma levels below the MTC and low enough such that side effects will be reduced and the development of tolerance is increased. This delivery profile provides 24 hours of efficacy without high plasma levels.

[00033] The present invention provides for a substantially ascending release rate. It has been surprisingly discovered that the instant profile best provides efficacious therapy over 24 hours while potentially reducing negative side effects associated with administration of the drug.

[00034] The present invention utilizes a slow, but substantially ascending, rate of release when the dosage form is likely to be in the colonic region of the gastrointestinal (GI) tract. The profile is not previously used to deliver any drug, but is designed to increase the therapeutic index of paliperidone.

[00035] It has been surprisingly found that the described ascending release rate can provide for a substantially ascending blood plasma concentration of drug with peak concentration occurring later than about 16 hours after administration. This ascending blood plasma concentration reduces the intraday tolerance effect developed.

[00036] It has been further surprisingly discovered that the addition of an osmagent, salt, into the first drug layer, but not in the second drug layer, impacts the delivery profile such that a substantially ascending release rate results.

[00037] It has been further surprisingly discovered that maintaining the ratio of the concentration of drug in the first drug layer and the concentration of drug in the second drug layer impacts the delivery profile such that the desired substantially ascending rate of release results.

[00038] The dosage form utilizes a semipermeable membrane surrounding a three-layer core: the first layer is referred to as a first drug layer and contains low amounts of drug and an osmotic agent such as salt; the middle layer referred to as the second drug layer contains higher amounts of drug, excipients and no salt; and the third layer referred to as the push layer contains osmotic agents and no drug. At least one orifice is drilled through the membrane on the first drug layer end of the capsule-shaped tablet.

[00039] In the aqueous environment of the GI tract, water is imbibed through the semipermeable membrane at a controlled rate determined by the properties of the membrane and the osmolality of the core consitituents. This causes the push layer to swell and the drug layers to hydrate and form viscous, but deformable, masses. The push layer expands against the second drug layer, which in turn pushes against the hydrated first drug layer. The first drug layer, followed by the second drug layer, exits the system through the orifice(s) in the membrane at the same rate that water is imbibed into the core. The

biologically inert components of the tablet remain intact during the GI transit and are eliminated as a shell along with insoluble core components.

[00040] The dosage form incorporating the present invention is designed to be a once-a-day dosage form that is therapeutically effective while providing increased stability.

[00041] In still another aspect, the invention comprises a dosage form comprising a membrane defining a compartment, the membrane surrounding an inner protective subcoat, at least one exit orifice formed or formable therein and at least a portion of the membrane being semipermeable; an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semipermeable portion of the membrane; a first drug layer located adjacent the exit orifice; and a second drug layer located within the compartment between the first drug layer and the expandable layer, the drug layers comprising the compound paliperidone or a pharmaceutically acceptable acid addition salt thereof.

[00042] As the drug is relatively insoluble, the first drug layer has a tendency not to mix into the second drug layer. Depending upon the relative viscosity of the first drug layer and second drug layer, different release profiles are obtained. It is imperative to identify the optimum viscosity for each layer. In the present invention, viscosity is modulated by addition of salt, sodium chloride.

[00043] The delivery profile from the core is dependent on the weight, formulation and thickness of each of the drug layers.

[00044] The ratio of core diameter to core length is also an important factor. The shape of the system as a capsule shaped tablet is an important feature contributing to the substantially ascending profile from the core.

[00045] The delivery system is designed to achieve maximum blood plasma concentrations between 14 and 22 hours and preferably between 18 and 21 hours after dosing. Peak concentrations most preferably occur between approximately hour 18 and hour 20.

[00046] The present invention is designed to be a once-a-day dosage form that is therapeutically effective while producing fewer side effects than an immediate release dosage form administered multiple times per day. The

present invention provides two key features: a substantially ascending delivery that affects the pharmacodynamics and development of tolerance, and the substantially ascending delivery provides adequate plasma concentrations for pharmacological effect. Development of tolerance is related to the sedation effects (using a representative measure such as digit vigilance).

[00047] In one aspect, the invention comprises a sustained release dosage form adapted to release over a prolonged period of time at a substantially ascending rate of release, the compound paliperidone.

[00048] In another aspect, the invention comprises a method of treating a condition in a subject responsive to administration paliperidone or a pharmaceutically acceptable acid addition salt thereof, which comprises orally administering to the subject a dosage form adapted to release the compound at a substantially ascending rate of release over a prolonged period of time. Most preferably, the dosage form is administered orally, once a day.

[00049] In still another aspect, the invention comprises a dosage form comprising a membrane defining a compartment, the membrane having at least one exit orifice formed or formable therein and at least a portion of the membrane being semipermeable; an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semipermeable portion of the membrane; a first drug layer located adjacent the exit orifice; and a second drug layer located within the compartment between the first drug layer and the expandable layer, the drug layers comprising the compound paliperidone or a pharmaceutically acceptable acid addition salt thereof.

[00050] In still another aspect, the invention comprises a dosage form comprising a membrane defining a compartment, the membrane having at least one exit orifice formed or formable therein and at least a portion of the membrane being semipermeable; an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semipermeable portion of the membrane; a first drug layer located adjacent the exit orifice; and a second drug layer located within the compartment between the first drug layer and the expandable layer, the drug layers comprising the compound paliperidone or a pharmaceutically acceptable acid addition salt

thereof, and the first drug layer comprising salt and the second drug layer containing no salt.

[00051] In still another aspect, the invention comprises a dosage form comprising a membrane defining a compartment, the membrane having at least one exit orifice formed or formable therein and at least a portion of the membrane being semipermeable; an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semipermeable portion of the membrane; a first drug layer located adjacent the exit orifice; and a second drug layer located within the compartment between the first drug layer and the expandable layer, the drug layers comprising the compound paliperidone or a pharmaceutically acceptable acid addition salt thereof second drug layer.

[00052] The dosage form may optionally comprise a flow-promoting layer between the membrane and the drug layers.

[00053] In another aspect, the invention comprises a method of treating a condition responsive to administration of paliperidone or a pharmaceutically acceptable acid addition salt thereof, which comprises administering the compound to provide a substantially ascending plasma concentration of the compound. The C_{max} occurs at a time greater than about 16 hours and preferably at about 20 hours.

BRIEF DESCRIPTION OF THE FIGURES

[00054] Figure 1 illustrates a two-orifice embodiment of the present invention, prior to administration to a subject;

[00055] Figure 2 illustrates the model delivery profile providing a substantially ascending rate of release of paliperidone demonstrating the effect of different types of lubricating subcoats;

[00056] Figure 3 illustrates an embodiment of the present invention prior to administration to a subject, with an optional lubricating subcoat and barrier layer;

[00057] Figure 4 illustrates the model delivery profile providing a substantially ascending rate of release of paliperidone demonstrating the effect of different amounts of sodium chloride in the first drug layer;

[00058] Figure 5 illustrates the effect of drug concentration ratio between the first drug layer and the second drug layer on rate of release of paliperidone;

[00059] Figures 6A, 6B, 6C and 6D illustrate the effect of membrane weight on rate of release of paliperidone;

[00060] Figure 7 illustrates potential degradation pathways for paliperidone under stress conditions;

[00061] Figure 8 illustrates tabular comparison of dosage form stability with and without use of the protective subcoat of the present invention;

[00062] Figures 9A and 9B illustrate graphical comparison of dosage form stability with and without use of the protective subcoat of the present invention;

DETAILED DESCRIPTION OF THE INVENTION

[00063] The present invention is best understood by reference to the following definitions, the drawings and exemplary disclosure provided herein.

Definitions

[00064] By "dosage form" is meant a pharmaceutical composition or device comprising a pharmaceutically active agent, such as paliperidone or a pharmaceutically acceptable acid addition salt thereof, the composition or device optionally containing inactive ingredients, i.e., pharmaceutically acceptable excipients such as suspending agents, surfactants, disintegrants, binders, diluents, lubricants, stabilizers, antioxidants, osmotic agents, colorants, plasticizers, coatings and the like, that are used to manufacture and deliver active pharmaceutical agents.

[00065] By "active agent", "drug", or "compound" is meant an agent, drug, or compound having the characteristics of paliperidone or risperidone or a pharmaceutically acceptable acid addition salt thereof.

[00066] By "pharmaceutically-acceptable acid addition salt" or "pharmaceutically acceptable salt", which are used interchangeably herein, are meant those salts in which the anion does not contribute significantly to the toxicity or pharmacological activity of the salt, and, as such, they are the pharmacological equivalents of the bases of the paliperidone compound. Examples of pharmaceutically acceptable acids that are useful for the purposes of salt formation include but are not limited to hydrochloric, hydrobromic, hydroiodic, citric, acetic, benzoic, mandelic, phosphoric, nitric, mucic, isethionic, palmitic, and others.

[00067] The expressions "exit," "exit orifice," "delivery orifice" or "drug delivery orifice," and other similar expressions, as may be used herein include a member selected from the group consisting of a passageway; an aperture; an orifice; and a bore. The expression also includes an orifice that is formed or formable from a substance or polymer that erodes, dissolves or is leached from the outer wall to thereby form an exit orifice. The expression includes one or multiple passageways, apertures, orifices, bores or pores.

[00068] A drug "release rate" refers to the quantity of drug released from a dosage form per unit time, e.g., milligrams of drug released per hour (mg/hr). Drug release rates for drug dosage forms are typically measured as an *in vitro* rate of dissolution, i.e., a quantity of drug released from the dosage form per unit time measured under appropriate conditions and in a suitable fluid. The dissolution tests described herein were performed on dosage forms placed in metal coil sample holders attached to a USP Type VII bath indexer in a constant temperature water bath at 37°C. Aliquots of the release rate solutions were injected into a chromatographic system to quantify the amounts of drug released during the testing intervals.

[00069] By "release rate assay" is meant a standardized assay for the determination of the release rate of a compound from the dosage form tested using a USP Type VII interval release apparatus. It is understood that reagents of equivalent grade may be substituted in the assay in accordance with generally accepted procedures.

[00070] For clarity and convenience herein, the convention is utilized of designating the time of drug administration as zero hours (t = 0 hours) and

times following administration in appropriate time units, e.g., t = 30 minutes or t = 2 hours, etc.

[00071] As used herein, unless otherwise specified, a drug release rate obtained at a specified time "following administration" refers to the *in vitro* drug release rate obtained at the specified time following implementation of an appropriate dissolution test. The time at which a specified percentage of the drug within a dosage form has been released may be referenced as the "T_x" value, where "x" is the percent of drug that has been released. For example, a commonly used reference measurement for evaluating drug release from dosage forms is the time at which 70% or 90% of drug within the dosage form has been released. This measurement is referred to as the "T_{70}" or "T_{90}" for the dosage form.

[00072] By "immediate-release dosage form" is meant a dosage form that releases drug substantially completely within a short time period following administration, i.e., generally within a few minutes to about 1 hour.

[00073] By "extended release dosage form" or "controlled release dosage form" is meant a dosage form that releases drug in a substantially consistent predetermined rate for many hours. Controlled release dosage forms in accord with the present invention exhibit T_{90} values of at least about 18 hours or more and preferably about 20 hours or more. The dosage forms release drug over periods of time of at least about 16 hours, preferably 18 hours or more and, more preferably, 20 hours or more.

[00074] By "sustained release dosage form" is meant a dosage form that releases drug substantially continuously for many hours. Sustained release dosage forms of the present invention release drug over periods of time of at least about 16 hours, preferably about 20 hours or more and, more preferably, about 20 hours or more.

[00075] Dosage forms in accord with the present invention exhibit controlled release rates of paliperidone for a prolonged period of time.

[00076] By "sustained release " is meant a predetermined continuous release of active agent to an environment over a prolonged period of time.

[00077] By "uniform release rate" is meant an average hourly release rate from the core that varies positively or negatively by no more than about 30%

and preferably no more than about 25%, most preferably no more than about 10%, from either the preceding or the subsequent average hourly release rate as determined in a USP Type VII Interval Release Apparatus where the cumulative release is between 25% and 75%.

[00078] By "prolonged period of time" is meant a continuous period of time of at least about 8 hours, preferably 10-14 hours or more and, more preferably, 16 hours or more. For example, the exemplary osmotic dosage forms described herein generally begin releasing paliperidone at about one hour following administration and the uniform rate of release, as defined above, continues for a prolonged period of time from about 25% to until at least about 75% and preferably at least about 85% of the drug is released from the dosage form. Release of paliperidone continues thereafter for several more hours although the rate of release is generally slowed somewhat from the uniform release rate.

[00079] By "C" is meant the concentration of drug in the blood plasma of a subject, generally expressed as mass per unit volume, typically nanograms per milliliter. For convenience, this concentration may be referred to as "plasma drug concentration" or "plasma concentration" herein which is intended to be inclusive of drug concentration measured in any appropriate body fluid or tissue. The plasma drug concentration at any time following drug administration is referenced as C_{time}, as in C_{9h} or C_{24h}, etc.

[00080] By "steady state" is meant the condition in which the amount of drug present in the blood plasma of a subject does not vary significantly over a prolonged period of time. A pattern of drug accumulation following continuous administration of a constant dose and dosage form at constant dosing intervals eventually achieves a "steady-state" where the plasma concentration peaks and plasma concentration troughs are essentially identical within each dosing interval. As used herein, the steady-state maximal (peak) plasma drug concentration is referenced as C_{max} and the minimal (trough) plasma drug concentration is referenced as C_{min}. The times following drug administration at which the steady-state peak plasma and trough drug concentrations occur are referenced as the T_{max} and the T_{min}, respectively.

[00081] Persons of skill in the art appreciate that plasma drug concentrations obtained in individual subjects will vary due to intrapatient variability in the many parameters affecting drug absorption, distribution, metabolism and excretion. For this reason, unless otherwise indicated, mean values obtained from groups of subjects are used herein for purposes of comparing plasma drug concentration data and for analyzing relationships between *in vitro* dosage form dissolution rates and *in vivo* plasma drug concentrations.

[00082] A relationship between an administered dose of paliperidone and the magnitude of the peak plasma paliperidone concentration obtained following dose administration is used herein to illustrate significant differences between the dosage forms and methods of the present invention and prior art dosage forms. For example, as described below in more detail, a unitless numerical value is derived by calculating the ratio of the numerical value of the mean C_{max} (ng/ml) to the numerical value of the dose (mg), i.e., C_{max}/dose. The difference in the values of the derived ratios characterize the reduction in the magnitude of peak plasma paliperidone concentrations following administration of the sustained release paliperidone dosage forms of the present invention compared to peak plasma paliperidone concentrations following administration of conventional immediate-release paliperidone dosage forms. Administration of dosage forms in accord with the present invention preferably provides steady-state C_{max}/dose ratios of less than about 30 and more preferably less than about 25.

[00083] It has been surprisingly discovered that sustained release paliperidone dosage forms exhibiting T_{90} values of about 16 hours or more and more preferably about 20 hours or more and which release paliperidone at a controlled release rate for a prolonged period of time can be prepared. Administration of such dosage forms once daily provides therapeutically effective average steady-state plasma paliperidone concentrations.

[00084] The exemplary sustained release paliperidone dosage forms, methods of preparing such dosage forms and methods of using such dosage forms described herein are directed to osmotic dosage forms for oral administration. In addition to osmotic systems as described herein, however, there are many other approaches to achieving sustained release of drugs from

oral dosage forms known in the art. These different approaches may include, for example, diffusion systems such as reservoir devices and matrix devices, dissolution systems such as encapsulated dissolution systems (including, for example, "tiny time pills") and matrix dissolution systems, combination diffusion/dissolution systems and ion-exchange resin systems as described in *Remington's Pharmaceutical Sciences*, 1990 ed., pp. 1682-1685. Paliperidone dosage forms that operate in accord with these other approaches are encompassed by the scope of the claims below to the extent that the drug release characteristics and/or the plasma paliperidone concentration characteristics as recited in the claims describe those dosage forms either literally or equivalently.

[00085] Osmotic dosage forms, in general, utilize osmotic pressure to generate a driving force for imbibing fluid into a compartment formed, at least in part, by a semipermeable wall that permits free diffusion of fluid but not drug or osmotic agent(s), if present. A significant advantage to osmotic systems is that operation is pH-independent and thus continues at the osmotically determined rate throughout an extended time period even as the dosage form transits the gastrointestinal tract and encounters differing microenvironments having significantly different pH values. A review of such dosage forms is found in Santus and Baker, "Osmotic drug delivery: a review of the patent literature," Journal of Controlled Release 35 (1995) 1-21. In particular, the following U.S. Patents, owned by the assignee of the present application, ALZA Corporation, directed to osmotic dosage forms, are each incorporated in their entirety herein: Nos. 3,845,770; 3,916,899; 3,995,631; 4,008,719; 4,111,202; 4,160,020; 4,327,725; 4,519,801; 4,578,075; 4,681,583; 5,019,397; and 5,156,850.

[00086] Figure 1 is a cutaway view of one embodiment of dosage form 10 in accord with the present invention. In this embodiment, the internal compartment defined by membrane 20 contains a multilayer-compressed core having a first component drug layer 30, a second component drug layer 40 and a third component push layer 50.

[00087] While the preferred embodiment in Figure 1 illustrates a capsule-shaped tablet, the tablet geometry may be other shapes including a standard

biconvex shape. Such a preferred shape as well as other alternate shapes will impact and alter release rates.

[00088] In operation, following oral ingestion of dosage form 10, the osmotic activity gradient across wall 20 causes gastric fluid to be imbibed through wall 20 thereby converting first drug layer 30 and second drug layer 40 into deliverable compositions, i.e. solutions or suspensions, and concurrently swelling the osmopolymer(s) in push layer 50. The deliverable first drug layer 30 and second drug layer 40 are released through exits 60 as fluid continues to enter the internal compartment and push layer 50 continues to swell. As release of first drug layer 30 and second drug layer 40 occurs, fluid continues to be imbibed and push layer 50 continues to swell thereby driving continued release. In this manner, drug is released in a continuous manner over an extended time period.

[00089] As described in more detail below, third component push layer 50 comprises osmotically active component(s), but does not contain active drug. The osmotically active component(s) in push layer 50 typically comprises an osmagent and one or more osmopolymer(s) having relatively large molecular weights which exhibit swelling as fluid is imbibed such that significant release of these osmopolymers through exits 60 does not occur. Additional excipients such as binders, lubricants, antioxidants and colorants may also be included in push layer 50. The third component layer is referred to herein as an expandable or a push layer since, as fluid is imbibed, the osmopolymer(s) swell and push against the deliverable drug formulation of the second component drug layer to thereby facilitate release of the drug formulation from the dosage form.

[00090] As described in more detail below, first component drug layer 30 comprises osmotically active components, and a lower amount of active drug than in second component drug layer 40. The osmotically active component(s) in the first component drug layer comprises an osmagent such as salt and one or more osmopolymer(s) having relatively small molecular weights which exhibit swelling as fluid is imbibed such that release of these osmopolymers through exit 60 occurs similar to that of drug layer 40. Additional excipients such as binders, lubricants, antioxidants and colorants may also be included in

first drug layer 30.

[00091] Second drug layer 40 comprises paliperidone in an admixture with selected excipients adapted to provide an osmotic activity gradient for driving fluid from an external environment through membrane 20 and for forming a deliverable drug formulation upon imbibition of fluid. The excipients may include a suitable suspending agent, also referred to herein as a drug carrier, but no osmotically active agent, "osmagent," such as salt, sodium chloride. It has been surprisingly discovered that the omission of salt from this second drug layer, which contains a higher proportion of the overall drug in the dosage form, in combination with the salt in the first drug layer component, provides an improved ascending rate of release creating a longer duration of ascending rate.

[00092] Drug layer 40 has a higher concentration of the drug than does drug layer 30. The ratio of the concentration of drug in the first drug layer 30 to the concentration of drug in the second drug layer 40 is maintained at less than 1 and preferably less than 0.33 to provide the desired substantially ascending rate of release.

[00093] Drug layer 40 may also comprise other excipients such as lubricants, binders, etc.

[00094] Drug layer 40, as with drug layer 30, further comprises a hydrophilic polymer carrier. The hydrophilic polymer provides a particle in the drug composition that contributes to the controlled delivery of the active drug. Representative examples of these polymers are poly(alkylene oxide) of 100,000 to 750,000 number-average molecular weight, including poly(ethylene oxide), poly(methylene oxide), poly(butylene oxide) and poly(hexylene oxide); and a poly(carboxymethylcellulose) of 40,000 to 400,000 number-average molecular weight, represented by poly(alkali carboxymethylcellulose), poly(sodium carboxymethylcellulose), poly(potassium carboxymethylcellulose) and poly(lithium carboxymethylcellulose). Drug layer 40 can further comprise a hydroxypropylalkylcellulose of 9,200 to 125,000 number-average molecular weight for enhancing the delivery properties of the dosage form as represented by hydroxypropylethylcellulose, hydroxypropylmethylcellulose, hydroxypropylbutylcellulose and hydroxypropylpentylcellulose; and a

poly(vinylpyrrolidone) of 7,000 to 75,000 number-average molecular weight for enhancing the flow properties of the dosage form. Preferred among these polymers are the poly(ethylene oxide) of 100,000 - 300,000 number average molecular weight. Carriers that erode in the gastric environment, i.e., bioerodible carriers, are especially preferred.

[00095] Other carriers that may be incorporated into drug layer 40, and/or drug layer 30, include carbohydrates that exhibit sufficient osmotic activity to be used alone or with other osmagents. Such carbohydrates comprise monosaccharides, disaccharides and polysaccharides. Representative examples include maltodextrins (i.e., glucose polymers produced by the hydrolysis of corn starch) and the sugars comprising lactose, glucose, raffinose, sucrose, mannitol, sorbitol, and the like. Preferred maltodextrins are those having a dextrose equivalence (DE) of 20 or less, preferably with a DE ranging from about 4 to about 20, and often 9-20. Maltodextrin having a DE of 9-12 has been found to be useful.

[00096] Drug layer 40 and drug layer 30 typically will be a substantially dry, <1% water by weight, composition formed by compression of the carrier, the drug, and other excipients as one layer.

[00097] Drug layer 40 may be formed from particles by comminution that produces the size of the drug and the size of the accompanying polymer used in the fabrication of the drug layer, typically as a core containing the compound, according to the mode and the manner of the invention. The means for producing particles include granulation, spray drying, sieving, lyophilization, crushing, grinding, jet milling, micronizing and chopping to produce the intended micron particle size. The process can be performed by size reduction equipment, such as a micropulverizer mill, a fluid energy grinding mill, a grinding mill, a roller mill, a hammer mill, an attrition mill, a chaser mill, a ball mill, a vibrating ball mill, an impact pulverizer mill, a centrifugal pulverizer, a coarse crusher and a fine crusher. The size of the particle can be ascertained by screening, including a grizzly screen, a flat screen, a vibrating screen, a revolving screen, a shaking screen, an oscillating screen and a reciprocating screen. The processes and equipment for preparing drug and carrier particles are disclosed in Pharmaceutical Sciences, Remington, 17th Ed., pp. 1585-

1594 (1985); Chemical Engineers Handbook, Perry, 6th Ed., pp. 21-13 to 21-19 (1984); Journal of Pharmaceutical Sciences, Parrot, Vol. 61, No. 6, pp. 813-829 (1974); and Chemical Engineer, Hixon, pp. 94-103 (1990).

[00098] First drug layer 30 comprises paliperidone in an admixture with selected excipients adapted to provide an osmotic activity gradient for driving fluid from an external environment through membrane 20 and for forming a deliverable drug formulation upon imbibition of fluid. The excipients may include a suitable suspending agent, also referred to herein as a drug carrier, and an osmotically active agent, i.e., an "osmagent," such as salt. Other excipients such as lubricants, binders, etc. may also be included. It has been surprisingly found that when first component drug layer 30 comprises an osmotically active component, and a lower amount of active drug than in second component drug layer 40, an improved ascending rate of release can be created that provides a longer duration of ascending rate. Additionally, with the low doses of paliperidone delivered from a dosage form, and the low amount of that total in the first drug layer 30, the addition of salt has been found to provide a consistent predetermined release rate providing a substantially ascending rate of release over 20 hours.

[00099] The osmotically active component in the first drug layer typically comprises an osmagent and one or more osmopolymer(s) having relatively small molecular weights which exhibit swelling as fluid is imbibed such that release of these osmopolymers through exit 60 occurs similar to that of drug layer 40.

[000100] First drug layer 30 may also comprise additional excipients such as binders, lubricants, antioxidants and colorants.

[000101] It has been surprisingly discovered that the ratio of drug concentration between the first drug layer and the second drug layer alters the release rate profile. Release rate profile is calculated as the difference between the maximum release rate and the release rate achieved at the first time point after start-up (for example, at 6 hours), divided by the average release rate between the two data points.

[000102] For instance, in Example 1, the drug concentration in first drug layer 30 is 0.8% and the drug concentration in the second drug layer 40 is 2.5%

resulting in a 0.33 ratio between the two layers that provides a 60% release rate profile. It has been found that lower drug concentration ratio provide improved release rate curve slope. High drug concentration ratio produces less ascending release rates as shown in Figure 5. The drug concentration ratio to produce greater than 50% ascending release rate curve slope is less than 0.44.

[000103] Similarly, it has been found that reduced salt in the first drug layer 30 also reduces the release rate curve slope. For example when no salt is added the release rate curve slope is about 57. When 20% salt is added, the release rate curve slope increases to 80%. See Figure 4. The amount of salt required to provide the preferred ascending release rate profile is at least 20%.

[000104] It has been surprisingly discovered that the ascending rate of release of paliperidone provides superior bioavailability, absorption and efficacy over multiple dosings of immediate release dosage forms as well as substantially zero order rates of release over prolonged periods of time.

[000105] Drug layer 30 and drug layer 40 may optionally contain surfactants and disintegrants in both drug layers. Exemplary of the surfactants are those having an HLB value of between about 10 - 25, such as polyethylene glycol 400 monostearate, polyoxyethylene-4-sorbitan monolaurate, polyoxyethylene-20-sorbitan monooleate, polyoxyethylene-20-sorbitan monopalmitate, polyoxyethylene-20-monolaurate, polyoxyethylene-40 -stearate, sodium oleate and the like. Disintegrants may be selected from starches, clays, celluloses, algins and gums and crosslinked starches, celluloses and polymers. Representative disintegrants include corn starch, potato starch, croscarmelose, crospovidone, sodium starch glycolate, Veegum HV, methylcellulose, agar, bentonite, carboxymethylcellulose, alginic acid, guar gum and the like.

[000106] A representative compound of paliperidone having antipsychotic activity is immediate release risperidone, Risperdal®.

[000107] Blood plasma concentrations in a subject may be determined by clinical assay to determine a correlation between tolerability and clinical effect and blood plasma concentrations of drug. The present invention provides for a period of delivery utilizing a substantially ascending blood plasma concentration profile.

[000108] Dosage forms of the present invention have core drug release T_{90} values of greater than 12 hours, preferably greater than 16 hours and most preferably greater than 20 hours, and release paliperidone for a continuous period of time of about 22 hours. After about one hour following administration, the dosage form begins releasing paliperidone from the core at a substantially ascending rate of release that continues for a prolonged period of time of about 16 hours or more.

[000109] Wall 20 is formed to be permeable to the passage of an external fluid, such as water and biological fluids, and is substantially impermeable to the passage of paliperidone, osmagent, osmopolymer and the like. As such, it is semipermeable. The selectively semipermeable compositions used for forming wall 20 are essentially nonerodible and substantially insoluble in biological fluids during the life of the dosage form.

[000110] Representative polymers for forming wall 20 comprise semipermeable homopolymers, semipermeable copolymers, and the like. Such materials comprise cellulose esters, cellulose ethers and cellulose ester-ethers. The cellulosic polymers have a degree of substitution (DS) of their anhydroglucose unit of from greater than 0 up to 3, inclusive. Degree of substitution (DS) means the average number of hydroxyl groups originally present on the anhydroglucose unit that are replaced by a substituting group or converted into another group. The anhydroglucose unit can be partially or completely substituted with groups such as acyl, alkanoyl, alkenoyl, aroyl, alkyl, alkoxy, halogen, carboalkyl, alkylcarbamate, alkylcarbonate, alkylsulfonate, alkysulfamate, semipermeable polymer forming groups, and the like, wherein the organic moieties contain from one to twelve carbon atoms, and preferably from one to eight carbon atoms.

[000111] The semipermeable compositions typically include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tri-cellulose alkanylates, mono-, di-, and tri-alkenylates, mono-, di-, and tri-aroylates, and the like. Exemplary polymers include cellulose acetate having a DS of 1.8 to 2.3 and an acetyl content of 32 to 39.9%; cellulose diacetate having a DS of 1 to 2 and an acetyl content of 21 to 35%;

cellulose triacetate having a DS of 2 to 3 and an acetyl content of 34 to 44.8%; and the like. More specific cellulosic polymers include cellulose propionate having a DS of 1.8 and a propionyl content of 38.5%; cellulose acetate propionate having an acetyl content of 1.5 to 7% and an acetyl content of 39 to 42%; cellulose acetate propionate having an acetyl content of 2.5 to 3%, an average propionyl content of 39.2 to 45%, and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a DS of 1.8, an acetyl content of 13 to 15%, and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53%, and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a DS of 2.6 to 3, such as cellulose trivalerate, cellulose trilamate, cellulose tripalmitate, cellulose trioctanoate and cellulose tripropionate; cellulose diesters having a DS of 2.2 to 2.6, such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dicaprylate, and the like; and mixed cellulose esters, such as cellulose acetate valerate, cellulose acetate succinate, cellulose propionate succinate, cellulose acetate octanoate, cellulose valerate palmitate, cellulose acetate heptanoate, and the like. Semipermeable polymers are known in U.S. Patent No. 4,077,407, and they can be synthesized by procedures described in Encyclopedia of Polymer Science and Technology, Vol. 3, pp. 325-354 (1964), Interscience Publishers Inc., New York, NY.

[000112] Additional semipermeable polymers for forming wall 20 comprise cellulose acetaldehyde dimethyl acetate; cellulose acetate ethylcarbamate; cellulose acetate methyl carbamate; cellulose dimethylaminoacetate; semipermeable polyamide; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; cross-linked selectively semipermeable polymers formed by the coprecipitation of an anion and a cation, as disclosed in U.S. Patents Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,142; semipermeable polymers, as disclosed by Loeb, et al. in U.S. Patent No. 3,133,132; semipermeable polystyrene derivatives; semipermeable poly(sodium styrenesulfonate); semipermeable poly(vinylbenzyltrimethylammonium chloride); and semipermeable polymers exhibiting a fluid permeability of 10^{-5} to 10^{-2} (cc. mil/cm hr.atm), expressed as per atmosphere of hydrostatic or osmotic pressure differences across a

semipermeable wall. The polymers are known to the art in U.S. Patents Nos. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers, Scott and Roff (1971) CRC Press, Cleveland, OH.

[000113] Wall 20 may also comprise a flux-regulating agent. The flux regulating agent is a compound added to assist in regulating the fluid permeability or flux through wall 20. The flux-regulating agent can be a flux-enhancing agent or a flux-decreasing agent. The agent can be preselected to increase or decrease the liquid flux. Agents that produce a marked increase in permeability to fluid such as water are often essentially hydrophilic, while those that produce a marked decrease to fluids such as water are essentially hydrophobic. The amount of regulator in the wall when incorporated therein generally is from about 0.01% to 20% by weight or more. The flux regulator agents may include polyhydric alcohols, polyalkylene glycols, polyalkylenediols, polyesters of alkylene glycols, and the like. Typical flux enhancers include polyethylene glycol 300, 400, 600, 1500, 4000, 6000 and the like; low molecular weight glycols such as polypropylene glycol, polybutylene glycol and polyamylene glycol: the polyalkylenediols such as poly(1,3-propanediol), poly(1,4-butanediol), poly(1,6-hexanediol), and the like; aliphatic diols such as 1,3-butylene glycol, 1,4-pentamethylene glycol, 1,4-hexamethylene glycol, and the like; alkylene triols such as glycerine, 1,2,3-butanetriol, 1,2,4-hexanetriol, 1,3,6-hexanetriol and the like; esters such as ethylene glycol dipropionate, ethylene glycol butyrate, butylene glycol dipropionate, glycerol acetate esters, and the like. Presently preferred flux enhancers include the group of difunctional block-copolymer polyoxyalkylene derivatives of propylene glycol known as pluronics (BASF). Representative flux-decreasing agents include phthalates substituted with an alkyl or alkoxy or with both an alkyl and alkoxy group such as diethyl phthalate, dimethoxyethyl phthalate, dimethyl phthalate, and [di(2-ethylhexyl) phthalate], aryl phthalates such as triphenyl phthalate, and butyl benzyl phthalate; insoluble salts such as calcium sulfate, barium sulfate, calcium phosphate, and the like; insoluble oxides such as titanium oxide; polymers in powder, granule and like form such as polystyrene, polymethylmethacrylate, polycarbonate, and polysulfone; esters such as citric acid esters esterified with long chain alkyl groups; inert and substantially water

impermeable fillers; resins compatible with cellulose based wall forming materials, and the like.

[000114] Other materials may be included in the semipermeable wall composition for imparting flexibility and elongation properties, for making wall less brittle and to render tear strength. Suitable materials include phthalate plasticizers such as dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, straight chain phthalates of six to eleven carbons, di-isononyl phthalte, di-isodecyl phthalate, and the like. The plasticizers include nonphthalates such as triacetin, dioctyl azelate, epoxidized tallate, tri-isoctyl trimellitate, tri-isononyl trimellitate, sucrose acetate isobutyrate, epoxidized soybean oil, and the like. The amount of plasticizer in a wall when incorporated therein is about 0.01% to 20% weight, or higher.

[000115] Push layer 50, the third component, comprises an expandable composition in contacting layered arrangement with the second component drug layer 40 as illustrated in Figure 1 or in contacting layered arrangement with barrier layer 55 as illustrated in Figure 3. Push layer 50 comprises a polymer that imbibes an aqueous or biological fluid and swells to push the drug composition through the exit of the device. A polymer having suitable imbibition properties may be referred to herein as an osmopolymer. The osmopolymers are swellable, hydrophilic polymers that interact with water and aqueous biological fluids and swell or expand to a high degree, typically exhibiting a 2-50 fold volume increase. The osmopolymer can be non-crosslinked or crosslinked, but in a preferred embodiment are at least lightly crosslinked to create a polymer network that is too large and entangled to exit the dosage form. Thus, in a preferred embodiment, the expandable composition is retained within the dosage form during its operative lifetime.

[000116] Representatives of fluid-imbibing displacement polymers comprise members selected from poly(alkylene oxide) of 1 million to 15 million number-average molecular weight, as represented by poly(ethylene oxide), and poly(alkali carboxymethylcellulose) of 500,000 to 3,500,000 number-average molecular weight, wherein the alkali is sodium, potassium or lithium. Examples of additional polymers for the formulation of the push layer composition comprise osmopolymers that form hydrogels, such as Carbopol® acidic

carboxypolymer, a polymer of acrylic cross-linked with a polyallyl sucrose, also known as carboxypolymethylene, and carboxyvinyl polymer having a molecular weight of 250,000 to 4,000,000; Cyanamer® polyacrylamides; cross-linked water swellable indenemaleic anhydride polymers; Good-rite® polyacrylic acid having a molecular weight of 80,000 to 200,000; Aqua-Keeps® acrylate polymer polysaccharides composed of condensed glucose units, such as diester cross-linked polygluran; and the like. Representative polymers that form hydrogels are known to the prior art in U.S. Patent No. 3,865,108, issued to Hartop; U.S. Patent No. 4,002,173, issued to Manning; U.S. Patent No. 4,207,893, issued to Michaels; and in Handbook of Common Polymers, Scott and Roff, Chemical Rubber Co., Cleveland, OH.

[000117] Suitable osmagents, also known as osmotic solutes and osmotically effective agents, that may be found in the first drug layer and the push layer in the dosage form are those which exhibit an osmotic activity gradient across the wall 20. Suitable osmagents comprise a member selected from the group consisting of sodium chloride, potassium chloride, lithium chloride, magnesium sulfate, magnesium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, mannitol, urea, inositol, magnesium succinate, tartaric acid, raffinose, sucrose, glucose, lactose, sorbitol, inorganic salts, organic salts and carbohydrates.

[000118] Exemplary solvents suitable for manufacturing the dosage form components comprise aqueous or inert organic solvents that do not adversely harm the materials used in the system. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride nitroethane, nitropropane tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme,

water, aqueous solvents containing inorganic salts such as sodium chloride, calcium chloride, and the like, and mixtures thereof such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

[000119] Figure 3 illustrates an alternate embodiment including an optional third component barrier layer 55 separating second component drug layer 40 from push layer 50. Figure 3 also illustrates dosage form 10 including an inner wall 90.

[000120] Figure 3 illustrates the preferred embodiment of dosage form 10 including the protective inner wall or subcoat 90 and an optional third component barrier layer 55 separating second component drug layer 40 from push layer 50.

[000121] The composition of barrier layer 55 is inert with the respect to the composition of second component drug layer 40 and substantially impermeable; such that drug from drug layer 40 and the components of push layer 50 are prevented from mixing. Suitable materials include water-insoluble polymers, fats, fatty acids and fatty acid esters that are solids at ambient and body temperatures, and waxes. Representative water-insoluble polymers include ethyl cellulose, cellulose acetate, polyvinylchloride, copolymers of polyethylene and vinyl acetate, poly(methylmethacrylate), acrylic polymers such as Eudragit® L or Eudragit® R, polycaprolactone, poly(lactic-co-glycolic) acid polymers (PLGA), high density polyethylene, rubber, styrene butadiene, polysilicone, nylon, , polystyrene, polytetrafluoroethylene, and halogenated polymers. Representative waxes include paraffin wax and beeswax. Representative fats, fatty acids and fatty acid esters include C_{16} - C_{24} long chain fatty acids, esters of such long chain fatty acids such as stearic acid and oleic acid, and mixtures of the foregoing. Mixtures of the above-described materials may be utilized, e.g., a mixture of ethyl cellulose and stearic acid, which is presently preferred.

[000122] Protective subcoat 90 is permeable to the passage of gastric fluid entering the compartment defined by wall 20 and provides a protective function that reduces the degradation of paliperidone under stress conditions.

[000123] Inner wall 90 further provides a lubricating function that facilitates the movement of first drug layer 30, second drug layer 40 and push layer 50 toward exit 60. Inner wall 90 may be formed from hydrophilic materials and excipients. Outer wall 20 is semipermeable, allowing gastric fluid to enter the compartment, but preventing the passage of the materials comprising the core in the compartment. The deliverable drug formulation is released from exit 60 as described above with respect to the embodiment of Figure 3.

[000124] Figure 7 illustrates potential degradation pathways for paliperidone under stress conditions. Subcoat 90 provides a means for reducing this potential degradation.

[000125] Inner wall 90 may be formed from hydrophilic materials and excipients. Wall 20 is semipermeable, allowing gastric fluid to enter the compartment, but substantially impermeable to the passage of materials comprising the core in the compartment. The deliverable drug formulation is released from exit 60 as described above with respect to the embodiment of Figure 3.

[000126] Inner wall 90, is located between at least drug layers 30 and 40, and wall 20 to reduce degradation of the active agent of drug layer 30 and drug layer 40. Inner wall90 promotes stability of the drug composition.

[000127] Inner wall 90 also reduces friction between the external surface of drug layer 30 and drug layer 40, and the inner surface of wall 20. Inner wall 90 promotes release of the drug composition from the compartment and reduces the amount of residual drug composition remaining in the compartment at the end of the delivery period, particularly when the slurry, suspension or solution of the drug composition that is being dispensed is highly viscous during the period of time in which it is being dispensed. In dosage forms in which there is high drug loading, i.e., 40% or greater active agent in the drug layer based on the overall weight of the drug layer, and no inner wall, it has been observed that significant residual amounts of drug may remain in the device after the period of delivery has been completed. In some instances, amounts of 20% or greater may remain in the dosage form at the end of a twenty-four hour period when tested in a release rate assay.

[000128] Inner wall 90 is formed as an inner coat of a flow-promoting agent, i.e., an agent that lowers the frictional force between the outer wall 20 and the external surface of drug layer 40. Inner wall 90 appears to reduce the frictional forces between outer wall 20 and the outer surface of drug layer 30 and drug layer 40, thus allowing for more complete delivery of drug from the device. Particularly in the case of active compounds having a high cost, such an improvement presents substantial economic advantages since it is not necessary to load the drug layer with an excess of drug to insure that the minimum amount of drug required will be delivered. Inner wall 90 may be formed as a coating applied over the compressed core.

[000129] Inner wall 90 is further characterized by a protective agent, i.e., an agent that reduces the degradation of paliperidone in drug layer 30 and drug layer 40. Particularly in the case of active compounds having a high cost, such an improvement presents substantial economic advantages. Inner wall 90 may be formed as a coating applied over the compressed core.

[000130] Inner wall 90 typically may be 0.01 to 5 mm thick, more typically 0.5 to 5mm thick, and it comprises a member selected from hydrogels, gelatin, low molecular weight polyethylene oxides, e.g., less than 100,000 MW, hydroxyalkylcelluloses, e.g., hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcelluose, hydroxybutylcellulose and hydroxyphenylcellulose, and hydroxyalkyl alkylcelluloses, e.g., hydroxypropyl methylcellulose, and mixtures thereof. The hydroxyalkylcelluloses comprise polymers having a 9,500 to 1,250,000 number-average molecular weight. For example, hydroxypropyl celluloses having number average molecular weights of between 80,000 to 850,000 are useful. The inner wall may be prepared from conventional solutions or suspensions of the aforementioned materials in aqueous solvents or inert organic solvents.

[000131] Prefered materials for the inner wall include hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, povidone [poly(vinylpyrrolidone)], polyethylene glycol, and mixtures thereof.

[000132] Most prefered are mixtures of hydroxypropyl cellulose and povidone, prepared in organic solvents, particularly organic polar solvents such as lower alkanols having 1-8 carbon atoms, preferably ethanol, mixtures of hydroxyethyl

cellolose and hydroxypropyl methyl cellulose prepared in aqueous solution, and mixtures of hydroxyethyl cellulose and polyethylene glycol prepared in aqueous solution. Most preferably, the inner wall comprises a mixture of hydroxypropyl cellulose and providone prepared in ethanol.

[000133] It is preferred that inner wall 90 comprises between about 50% and about 90% hydroxypropylcellulose identified as EF having an average molecular weight of about 80,000 and between about 10% and about 50% polyvinylpyrrolidone identified as K29-32.

[000134] Conveniently, the weight of the inner wall applied to the compressed core may be correlated with the thickness of the inner wall and residual drug remaining in a dosage form in a release rate assay such as described herein. As such, during manufacturing operations, the thickness of the inner wall may be controlled by controlling the weight of the inner wall taken up in the coating operation.

[000135] When inner wall 90 is formed as a subcoat, i.e., by coating onto the tabletted composite including one or all of the first drug layer, second drug layer and push layer, the inner wall can fill in surface irregularities formed on the core by the tabletting process. The resulting smooth external surface facilitates slippage between the coated composite core and the semipermeable wall during dispensing of the drug, resulting in a lower amount of residual drug composition remaining in the device at the end of the dosing period. When inner wall 90 is fabricated of a gel-forming material, contact with water in the environment of use facilitates formation of the gel or gel-like inner coat having a viscosity that may promote and enhance slippage between outer wall 20 and drug layer 30 and drug layer 40.

[000136] Subcoat 90 has also been shown to reduce degradation of the paliperidone during stability testing and could improve and extend shelf life of the resulting formulation.

[000137] Figures 8, 9A and 9B illustrate the increased stability of paliperidone in the dosage forms incorporating the protective subcoat compared to dosage forms not incorporating the protective subcoat.

[000138] Pan coating may be conveniently used to provide the completed dosage form, except for the exit orifice. In the pan coating system, the wall-

forming composition for the inner wall or the outer wall, as the case may be, is deposited by successive spraying of the appropriate wall composition onto the compressed trilayered or multilayered core comprising the drug layers, optional barrier layer and push layer, accompanied by tumbling in a rotating pan. A pan coater is used because of its availability at commercial scale. Other techniques can be used for coating the compressed core. Once coated, the wall is dried in a forced-air oven or in a temperature and humidity controlled oven to free the dosage form of solvent(s) used in the manufacturing. Drying conditions will be conventionally chosen on the basis of available equipment, ambient conditions, solvents, coatings, coating thickness, and the like.

[000139] Other coating techniques can also be employed. For example, the wall or walls of the dosage form may be formed in one technique using the air-suspension procedure. This procedure consists of suspending and tumbling the compressed core in a current of air and the semipermeable wall forming composition, until the wall is applied to the core. The air-suspension procedure is well suited for independently forming the wall of the dosage form. The air-suspension procedure is described in U.S. Patent No. 2,799,241; in J. Am. Pharm. Assoc., Vol. 48, pp. 451-459 (1959); and, ibid., Vol. 49, pp. 82-84 (1960). The dosage form also can be coated with a Wurster® air-suspension coater using, for example, methylene dichloride methanol as a cosolvent for the wall forming material. An Aeromatic® air-suspension coater can be used employing a cosolvent.

[000140] Dosage forms in accord with the present invention are manufactured by standard techniques. For example, the dosage form may be manufactured by the wet granulation technique. In the wet granulation technique, the drug and carrier are blended using an organic solvent, such as denatured anhydrous ethanol, as the granulation fluid. The remaining ingredients can be dissolved in a portion of the granulation fluid, such as the solvent described above, and this latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass blend is then forced through a predetermined screen onto oven trays. The blend is dried for 18 to 24 hours at 24°C to 35°C in a forced-air oven. The dried granules are then sized. Next, magnesium

stearate, or another suitable lubricant, is added to the drug granulation, and the granulation is put into milling jars and mixed on a jar mill for 10 minutes. The composition is pressed into a layer, for example, in a Manesty® press or a Korsch LCT press. For a trilayered core, granules or powders of the drug layer compositions and push layer composition are sequentially placed in an appropriately-sized die with intermediate compression steps being applied to each of the first two layers, followed by a final compression step after the last layer is added to the die to form the trilayered core. The intermediate compression typically takes place under a force of about 50-100 newtons. Final stage compression typically takes place at a force of 3500 newtons or greater, often 3500-5000 newtons. The compressed cores are fed to a dry coater press, e.g., Kilian® Dry Coater press, and subsequently coated with the wall materials as described above.

[000141] One or more exit orifices are drilled in the drug layer end of the dosage form, and optional water soluble overcoats, which may be colored (e.g., Opadry colored coatings) or clear (e.g., Opadry Clear), may be coated on the dosage form to provide the finished dosage form.

[000142] In another manufacture the drug and other ingredients comprising the drug layer are blended and pressed into a solid layer. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form, and it also possesses dimensions corresponding to the push layer, if included, for forming a contacting arrangement therewith. The drug and other ingredients can also be blended with a solvent and mixed into a solid or semisolid form by conventional methods, such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected shape. Next, if included, a layer of osmopolymer composition is placed in contact with the layer of drug in a like manner. The layering of the drug formulation and the osmopolymer layer can be fabricated by conventional two-layer press techniques. An analogous procedure may be followed for the preparation of the trilayered core. The compressed cores then may be coated with the inner wall material and the semipermeable wall material as described above.

[000143] Another manufacturing process that can be used comprises blending the powdered ingredients for each layer in a fluid bed granulator. After the

powdered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinylpyrrolidone) in water, is sprayed onto the powders. The coated powders are then dried in the granulator. This process granulates all the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant, such as stearic acid or magnesium stearate, is mixed into the granulation using a blender e.g., V-blender or tote blender. The granules are then pressed in the manner described above.

[000144] The dosage form of the invention is provided with at least one exit 60. Exit 60 cooperates with the compressed core for the uniform release of drug from the dosage form. The exit can be provided during the manufacture of the dosage form or during drug delivery by the dosage form in a fluid environment of use.

[000145] Exit 60 may include an orifice that is formed or formable from a substance or polymer that erodes, dissolves or is leached from the outer wall to thereby form an exit orifice. The substance or polymer may include, for example, an erodible poly(glycolic) acid or poly(lactic) acid in the semipermeable wall; a gelatinous filament; a water-removable poly(vinyl alcohol); a leachable compound, such as a fluid removable pore-former selected from the group consisting of inorganic and organic salt, oxide and carbohydrate.

[000146] An exit, or a plurality of exits, can be formed by leaching a member selected from the group consisting of sorbitol, lactose, fructose, glucose, mannose, galactose, talose, sodium chloride, potassium chloride, sodium citrate and mannitol to provide a uniform-release dimensioned pore-exit orifice.

[000147] The exit can have any shape, such as round, triangular, square, elliptical and the like for the uniform metered dose release of a drug from the dosage form.

[000148] The dosage form can be constructed with one or more exits in spaced-apart relation or one or more surfaces of the dosage form.

[000149] Drilling, including mechanical and laser drilling, through the semipermeable wall can be used to form the exit orifice. Such exits and equipment for forming such exits are disclosed in U.S. Patents Nos. 3,916,899,

by Theeuwes and Higuchi and in U.S. Patent No. 4,088,864, by Theeuwes, et al. It is presently preferred to utilize two exits of equal diameter.

[000150] Dosage forms of this invention exhibit sustained release of drug over a continuous time period that includes a prolonged time when drug is released at an ascending release rate as determined in a standard release rate assay such as that described herein. When administered to a subject, the dosage forms of the invention provide substantially ascending blood plasma drug concentrations in the subject that are less variable over a prolonged period of time than those obtained with immediate release dosage forms. When the dosage forms of this invention are administered on a continuous once-a-day basis, the dosage forms of the invention provide therapeutically effective ascending plasma drug concentrations while providing steady-state peak plasma drug concentrations that occur at a later time following dose administration and that exhibit a lesser magnitude than the steady-state peak plasma drug concentrations that occur following twice or three times a day administration of an immediate-release dosage form.

[000151] The practice of the foregoing methods of orally administering a dosage form to a subject once a day is preferred. Other disease states and conditions, which may be manifested or diagnosed as requiring an antipsychotic, may be treated with the paliperidone dosage forms and methods of the invention. In addition, other disease states and conditions which may or may not manifest in association with depression or anxiety, but which may be responsive to treatment with paliperidone may also be treated with the dosage forms and methods of the invention.

[000152] Preferred methods of manufacturing dosage forms of the present invention are generally described below. All percentages are weight percent unless otherwise noted.

EXAMPLE 1

Paliperidone Capsule Shaped Tablet, Trilayer 1.9 mg System

[000153] A dosage form adapted, designed and shaped as an osmotic drug delivery device is manufactured as follows: 100 g of paliperidone, 7345 g of polyethylene oxide with average molecular weight of 200,000, and 200 g of sodium chloride, USP are added to a fluid bed granulator bowl. Next a binder solution is prepared by dissolving 800 g of hydroxypropylmethyl cellulose identified as 2910 having an average viscosity of 5 cps in 9,200 g of water. The dry materials are fluid bed granulated by spraying with 6750 g of binder solution. Next, the wet granulation is dried in the granulator to an acceptable moisture content, and sized using by passing through a 7-mesh screen. Next, the granulation is transferred to a blender and mixed with 5 g of butylated hydroxytoluene as an antioxidant and lubricated with 50 g of stearic acid.

[000154] Next, a second drug compartment composition is prepared as follows: 280 g of paliperidone and 9165 g of polyethylene oxide with average molecular weight of 200,000 are added to a fluid bed granulator bowl. Next a binder solution is prepared by dissolving 800 g of hydroxypropylmethyl cellulose identified as 2910 having an average viscosity of 5 cps in 9,200 g of water. The dry materials are fluid bed granulated by spraying with 6750 g of binder solution. Next, the wet granulation is dried in the granulator to an acceptable moisture content, and sized using by passing through a 7-mesh screen. Next, the granulation is transferred to a blender and mixed with 5 g of butylated hydroxytoluene as an antioxidant and lubricated with 50 g of stearic acid.

[000155] Next, a push composition is prepared as follows: first, a binder solution is prepared. 15.6 kg of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 is dissolved in 104.4 kg of water. Then, 24 kg of sodium chloride and 1.2 kg of ferric oxide are sized using a Quadro Comil with a 21-mesh screen. Then, the screened materials and 88.44 kg of Polyethylene oxide (approximately 7,000,000 molecular weight) are added to a fluid bed granulator bowl. The dry materials are fluidized and mixed while 46.2 kg of binder solution is sprayed from 3 nozzles onto the powder.

The granulation is dried in the fluid-bed chamber to an acceptable moisture level. The coated granules are sized using a Fluid Air mill with a 7-mesh screen. The granulation is transferred to a tote tumbler, mixed with 15 g of butylated hydroxytoluene and lubricated with 294 g magnesium stearate.

[000156] Next, the paliperidone drug compositions for the first and the second compartments and the push composition are compressed into trilayer tablets. First, 50 mg of the paliperidone compartment one composition is added to the die cavity and pre-compressed, then 50 mg of the paliperidone compartment two composition is added to the die cavity and pre-compressed, then 110 mg of the push composition is added and the layers are pressed into a 3/16" diameter longitudinal, deep concave, trilayer arrangement.

[000157] The trilayered arrangements are coated with a subcoat laminate. The wall forming composition comprises 70% hydroxypropyl cellulose identified as EF, having an average molecular weight of 80,000 and 30% of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000. The wall-forming composition is dissolved in anhydrous ethyl alcohol, to make an 8% solids solution. The wall-forming composition is sprayed onto and around the bilayered arrangements in a pan coater until approximately 20 mg of laminate is applied to each tablet.

[000158] The trilayered arrangements are coated with a semi-permeable wall. The wall forming composition comprises 99% cellulose acetate having a 39.8% acetyl content and 1% polyethylene glycol comprising a 3.350 viscosity-average molecular weight. The wall-forming composition is dissolved in an acetone:water (95:5 wt:wt) co solvent to make a 5% solids solution. The wall-forming composition is sprayed onto and around the bilayered arrangements in a pan coater until approximately 45 mg of membrane is applied to each tablet.

[000159] Next, two 25 mil (0.6 mm) exit passageways are laser drilled through the semi-permeable wall to connect the drug layer with the exterior of the dosage system. The residual solvent is removed by drying for 144 hours as 45 C. and 45% humidity. After drilling, the osmotic systems are dried for 4 hours at 45 C. to remove excess moisture.

[000160] The dosage form produced by this manufacture is designed to deliver 1.9 mg of paliperidone in an ascending delivery pattern from two drug-

containing cores. First core contains 1% paliperidone, 73.45% polyethylene oxide possessing a 200,000 molecular weight, 20% sodium chloride, USP, 5% hydroxypropylmethyl cellulose having an average viscosity of 5 cps, 0.05% butylated hydroxytoluene, and 0.5% stearic acid. Second drug core contains 2.8% paliperidone, 91.65% polyethylene oxide possessing a 200,000 molecular weight, 5% hydroxypropylmethyl cellulose having an average viscosity of 5 cps, 0.05% butylated hydroxytoluene, and 0.5% stearic acid. The push composition is comprised 73.7% polyethylene oxide comprising a 7,000,000 molecular weight, 20% sodium chloride, 5% polyvinylpyrrolidone possessing an average molecular weight of 40,000, 1% ferric oxide, 0.05% butylated hydroxytoluene, and 0.25% magnesium stearate. The semi permeable wall is comprised of 99% cellulose acetate of 39.8% acetyl content and 1% polyethylene glycol. The dosage form comprises two passageways, 25 mils (0.6 mm) on the center of the drug side.

Example 2

Paliperidone Capsule Shaped Tablet, Trilayer 0.5 mg System

[000161] A dosage form adapted, designed and shaped as an osmotic drug delivery device is manufactured as follows: 25 g of paliperidone, 7420 g of polyethylene oxide with average molecular weight of 200,000, and 200 g of sodium chloride, USP are added to a fluid bed granulator bowl. Next a binder solution is prepared by dissolving 800 g of hydroxypropylmethyl cellulose identified as 2910 having an average viscosity of 5 cps in 9,200 g of water. The dry materials are fluid bed granulated by spraying with 6750 g of binder solution. Next, the wet granulation is dried in the granulator to an acceptable moisture content, and sized using by passing through a 7-mesh screen. Next, the granulation is transferred to a blender and mixed with 5 g of butylated hydroxytoluene as an antioxidant and lubricated with 50 g of stearic acid.

[000162] Next, a second drug compartment composition is prepared as follows: 70 g of paliperidone and 9375 g of polyethylene oxide with average molecular weight of 200,000 are added to a fluid bed granulator bowl. Next a binder solution is prepared by dissolving 800 g of hydroxypropylmethyl cellulose identified as 2910 having an average viscosity of 5 cps in 9,200 g of water. The dry materials are fluid bed granulated by spraying with 6750 g of binder solution. Next, the wet granulation is dried in the granulator to an acceptable moisture content, and sized using by passing through a 7-mesh screen. Next, the granulation is transferred to a blender and mixed with 5 g of butylated hydroxytoluene as an antioxidant and lubricated with 50 g of stearic acid.

[000163] Next, a push composition is prepared as follows: first, a binder solution is prepared. 15.6 kg of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 is dissolved in 104.4 kg of water. Then, 24 kg of sodium chloride and 1.2 kg of ferric oxide are sized using a Quadro Comil with a 21-mesh screen. Then, the screened materials and 88.44 kg of Polyethylene oxide (approximately 7,000,000 molecular weight) are added to a fluid bed granulator bowl. The dry materials are fluidized and mixed while 46.2 kg of binder solution is sprayed from 3 nozzles onto the powder.

The granulation is dried in the fluid-bed chamber to an acceptable moisture level. The coated granules are sized using a Fluid Air mill with a 7-mesh screen. The granulation is transferred to a tote tumbler, mixed with 15 g of butylated hydroxytoluene and lubricated with 294 g magnesium stearate.

[000164] Next, the paliperidone drug compositions for the first and the second compartments and the push composition are compressed into trilayer tablets. First, 50 mg of the paliperidone compartment one composition is added to the die cavity and pre-compressed, then 50 mg of the paliperidone compartment two composition is added to the die cavity and pre-compressed, then 110 mg of the push composition is added and the layers are pressed into a 3/16" diameter longitudinal, deep concave, trilayer arrangement.

[000165] The trilayered arrangements are coated with a subcoat laminate. The wall forming composition comprises 70% hydroxypropyl cellulose identified as EF, having an average molecular weight of 80,000 and 30% of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000. The wall-forming composition is dissolved in anhydrous ethyl alcohol, to make an 8% solids solution. The wall-forming composition is sprayed onto and around the bilayered arrangements in a pan coater until approximately 20 mg of laminate is applied to each tablet.

[000166] The trilayered arrangements are coated with a semi-permeable wall. The wall forming composition comprises 99% cellulose acetate having a 39.8% acetyl content and 1% polyethylene glycol comprising a 3.350 viscosity-average molecular weight. The wall-forming composition is dissolved in an acetone:water (95:5 wt:wt) co solvent to make a 5% solids solution. The wall-forming composition is sprayed onto and around the bilayered arrangements in a pan coater until approximately 39 mg of membrane is applied to each tablet.

[000167] Next, two 25 mil (0.6 mm) exit passageways are laser drilled through the semi-permeable wall to connect the drug layer with the exterior of the dosage system. The residual solvent is removed by drying for 144 hours as 45 C. and 45% humidity. After drilling, the osmotic systems are dried for 4 hours at 45 C to remove excess moisture.

[000168] The dosage form produced by this manufacture is designed to deliver 0.25 mg of paliperidone in an ascending delivery pattern from two drug-

containing cores. First core contains 0.25% paliperidone, 74.20% polyethylene oxide possessing a 200,000 molecular weight, 20% sodium chloride, USP, 5% hydroxypropylmethyl cellulose having an average viscosity of 5 cps, 0.05% butylated hydroxytoluene, and 0.5% stearic acid. Second drug core contains 0.7% paliperidone, 93.75% polyethylene oxide possessing a 200,000 molecular weight, 5% hydroxypropylmethyl cellulose having an average viscosity of 5 cps, 0.05% butylated hydroxytoluene, and 0.5% stearic acid. The push composition is comprised 73.7% polyethylene oxide comprising a 7,000,000 molecular weight, 20% sodium chloride, 5% polyvinylpyrrolidone possessing an average molecular weight of 40,000, 1% ferric oxide, 0.05% butylated hydroxytoluene, and 0.25% magnesium stearate. The semi permeable wall is comprised of 99% cellulose acetate of 39.8% acetyl content and 1% polyethylene glycol. The dosage form comprises two passageways, 25 mils (0.6 mm) on the center of the drug side.

CLAIMS

WE CLAIM:

1. A method for treating a condition responsive to paliperidone comprising orally administering a capsule shaped tablet core dosage form containing paliperidone wherein the dosage form releases the paliperidone at a substantially ascending release rate for a prolonged period of time.

2. A method for administering an active agent to a subject comprising:

Administering a dosage from to the subject wherein the dosage form comprises:

(a) a capsule shaped tablet core comprising a plurality of layers wherein a drug composition contains an active agent in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane surrounding the capsule shaped tablet core to form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the semipermeable membrane into the compartment; and

(c) an orifice formed through the semipermeable membrane and into the capsule shaped tablet core to permit the active agent to be released from within the compartment into the external fluid environment;

wherein the dosage form releases the active agent at a substantially ascending release rate for a prolonged period of time.

3. A method for administering an active agent to a subject comprising:

Administering a dosage from to the subject wherein the dosage form comprises:

(a) a capsule shaped tablet core comprising a plurality of layers wherein a composition containing about 50-60% of an active agent, about 5-15% of a structural polymer carrier and about 15-40% of a solubilizing

surfactant is contained in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane surrounding the capsule shaped tablet core to form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the semipermeable membrane into the compartment; and

(c) an orifice formed through the semipermeable membrane and into the capsule shaped tablet core to permit the active agent to be released from within the compartment into the external fluid environment;

wherein the dosage form releases the active agent at a substantially ascending release rate for a prolonged period of time.

4. The method according to Claim 2 wherein the active agent is paliperidone.

5. The method according to Claim 2 wherein the active agent is risperidone.

6. The method according to Claim 2 wherein at least a first drug composition layer comprises an osmagent and a second drug composition layer does not comprise an osmagent.

7. The method according to Claim 6 wherein the osmagent is sodium chloride salt.

8. The method according to Claim 7 wherein the osmagent is at least 20% of the first layer drug composition.

9. The method according to Claim 6 wherein the first drug composition layer is proximal to the exit orifice.

10. The method according to Claim 4, wherein the capsule shaped tablet core comprises two layers and the paliperidone is contained within a first

layer and the fluid-expandable polymer is contained within a second layer and the orifice is formed through the semipermeable membrane adjacent the first layer.

11. The method according to Claim 4, wherein the capsule shaped tablet core comprises three layers and a portion of the paliperidone is contained within a first drug composition layer and the remaining portion of the paliperidone is contained within a second drug composition layer, wherein the portion of paliperidone contained within the first layer is less than the portion of paliperidone contained within the second layer, and wherein the fluid-expandable polymer is contained within a third layer and the orifice is formed through the semipermeable membrane adjacent the first layer.

12. The method according to Claim 11 characterized by producing a substantially ascending blood plasma concentration of paliperidone.

13. The method according to Claim 12 wherein a C_{max} occurs after about 14 hours after administration to the subject.

14. The method according to Claim 12 wherein a C_{max} occurs between about 16 hours and about 22 hours after administration to the subject.

15. The method according to Claim 12 wherein a C_{max} occurs between about 18 hours and about 21 hours after administration to the subject.

16. The method according to Claim 10, wherein the proportion of paliperidone contained within the first layer to the paliperidone contained within the second layer is less than 1.0.

17. The method according to Claim 10, wherein the proportion of paliperidone contained within the first layer to the paliperidone contained within the second layer is less than about .33.

18. The method according to Claim 10 wherein the concentration of paliperidone in the first drug layer to the concentration of paliperidone in the second drug layer is less than .44.

19. The method according to Claim 10 wherein the concentration of paliperidone in the first drug layer to the concentration of paliperidone in the second drug layer is less than .33.

20. The method according to Claim 11, wherein the first layer comprises an osmagent and the second layer comprises no osmagent.

21. The method of Claim 20 wherein the osmagent is at least 20% of the first layer.

22. A method for delivering an active agent, the method comprising orally administering to a subject a capsule shaped tablet dosage form containing an active agent wherein the dosage form releases the active agent from the dosage form at a substantially ascending release rate for a prolonged period of time.

23. The method of Claim 22 wherein the active agent is paliperidone.

24. The method according to Claim 23, wherein the dosage form comprises:

(a) a capsule shaped tablet core containing a plurality of layers wherein paliperidone is contained in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane surrounding the capsule shaped tablet core to form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the semipermeable membrane into the compartment; and

(c) an orifice formed through the semipermeable membrane and into the capsule shaped tablet core to permit paliperidone to be released from the compartment into the external fluid environment.

25. The method according to Claim 24, wherein the capsule shaped tablet core comprises two layers and the paliperidone is contained within a first layer and the fluid-expandable polymer is contained within a second layer and the orifice is formed through the semipermeable membrane adjacent to the first layer.

26. The method according to Claim 24, wherein the capsule shaped tablet core comprises three layers and a portion of the paliperidone is contained within a first layer and the remaining portion of the paliperidone is contained within a second layer, wherein the portion of paliperidone contained within the first layer is less than the portion of paliperidone contained within the second layer, and wherein the fluid-expandable polymer is contained within a third layer and the orifice is formed through the semipermeable membrane adjacent the first layer.

27. The method according to Claim 26, wherein the proportion of paliperidone contained within the first layer to the paliperidone contained within the second layer is less than 1.0.

28. The method according to Claim 26, wherein the proportion of paliperidone contained within the first layer to the paliperidone contained within the second layer is less than about .33.

29. The method according to Claim 26 wherein the concentration of paliperidone in the first drug layer to the concentration of paliperidone in the second drug layer is less than .44.

30. The method according to Claim 26 wherein the concentration of paliperidone in the first drug layer to the concentration of paliperidone in the second drug layer is less than .33.

31. The method according to Claim 26, wherein the first layer comprises an osmagent and the second layer comprises no osmagent.

32. The method of Claim 31 wherein the osmagent is at least 20% of the first layer.

33. A capsule shaped tablet dosage form comprising a drug layer composition having an active agent wherein the dosage form, following oral administration to a subject, releases the active agent from the dosage form at a substantially ascending release rate for a prolonged period of time.

34. The dosage form of Claim 33 wherein the active agent is paliperidone.

35. The dosage form according to Claim 34 comprising:

(a) a capsule shaped tablet core containing a plurality of layers wherein the paliperidone is contained in at least one layer and at least one other layer comprises a suitable fluid-expandable polymer;

(b) a semipermeable membrane surrounding the capsule shaped tablet core to form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the semipermeable membrane into the compartment; and

(c) an orifice formed through the semipermeable membrane and into the capsule shaped tablet core to permit paliperidone to be released from within the compartment into the external fluid environment.

36. The dosage form according to Claim 35, wherein the capsule shaped tablet core comprises two layers and the paliperidone is contained within a first layer and the fluid-expandable polymer is contained within a

second layer and the orifice is formed through the semipermeable membrane adjacent the first layer.

37. The dosage form according to Claim 35, wherein the capsule shaped tablet core comprises three layers and a portion of the paliperidone is contained within a first layer and the remaining portion of the paliperidone is contained within a second layer, wherein the portion of paliperidone contained within first layer is less than the portion of paliperidone contained within the second layer, and wherein the fluid-expandable polymer is contained within a third layer and the orifice is formed through the semipermeable membrane adjacent the first layer.

38. The dosage form according to Claim 37, wherein the proportion of paliperidone contained within the first layer to the paliperidone contained within the second layer is less than 1.0.

39. The dosage form according to Claim 37, wherein the proportion of paliperidone contained within the first layer to the paliperidone contained within the second layer is less than about .33.

40. The dosage form according to Claim 37 wherein the concentration of paliperidone in the first drug layer to the concentration of paliperidone in the second drug layer is less than .44.

41. The dosage form according to Claim 37 wherein the concentration of paliperidone in the first layer to the concentration of paliperidone in the second drug layer is less than .33.

42. The dosage form according to Claim 37, wherein the first layer comprises an osmagent and the second layer comprises no osmagent.

43. The dosage form of Claim 37 wherein the osmagent is at least 20% of the first layer.

44. The dosage form of Claim 37 characterized by releasing the paliperidone from the dosage form at a substantially ascending rate of release for about 10 hours to about 14 hours.

45. The dosage form of Claim 37 characterized by releasing the paliperidone from the dosage form at a substantially ascending rate of release for about 14 hours to about 18 hours.

46. The dosage form of Claim 37 characterized by releasing the paliperidone from the dosage form at a substantially ascending rate of release for about 18 hours to about 20 hours.

47. The dosage form of Claim 37 characterized by having a T_{90} from the core occurring at about 20 hours.

48. The dosage form according to Claim 35 further comprising a subcoat for reducing the rate of degradation of paliperidone, which subcoat comprises a hydroxyalkylcellulose polymer possessing a 8,500 to 4,000,000 molecular weight that at least partially surrounds the core and is positioned between an inside surface of the semipermeable membrane and the core.

49. The dosage form according to Claim 35 further comprising a subcoat for reducing the rate of degradation of paliperidone which subcoat comprises a mixture of hydroxypropyl cellulose and providone prepared in ethanol that at least partially surrounds the core and is positioned between an inside surface of the semipermeable membrane and the core.

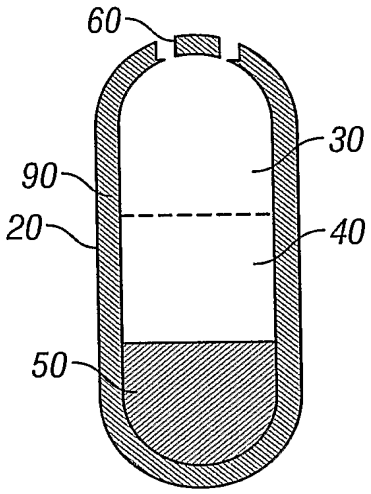

60
30
90
20
40
50

FIG. 1

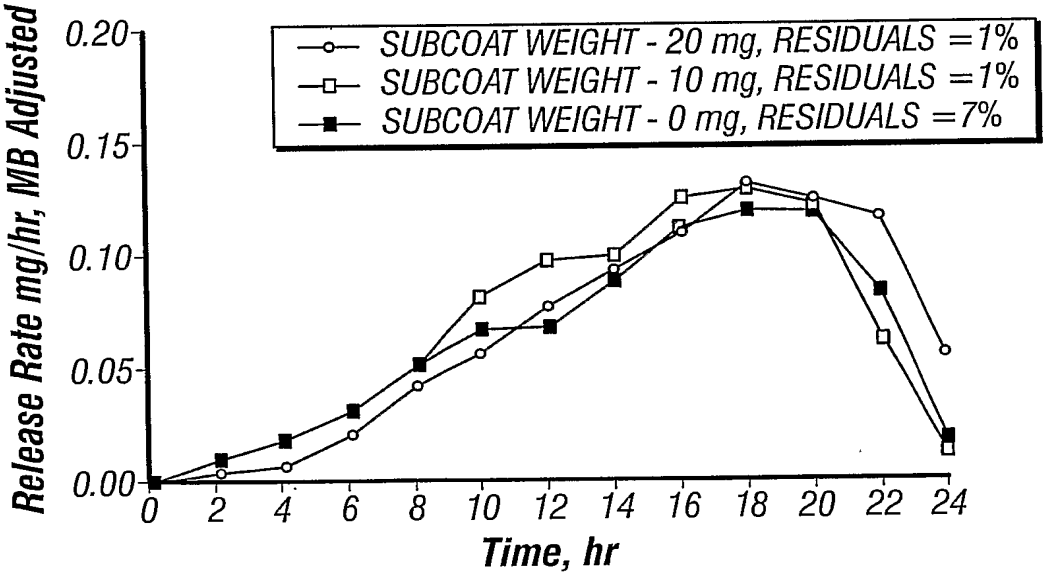

SUBCOAT WEIGHT - 20 mg, RESIDUALS =1%
SUBCOAT WEIGHT - 10 mg, RESIDUALS =1%
SUBCOAT WEIGHT - 0 mg, RESIDUALS =7%
Release Rate mg/hr, MB Adjusted
0.20
0.15
0.10
0.05
0.00
0
2
4
6
8
10
12
14
16
18
20
22
24
Time, hr

FIG. 2

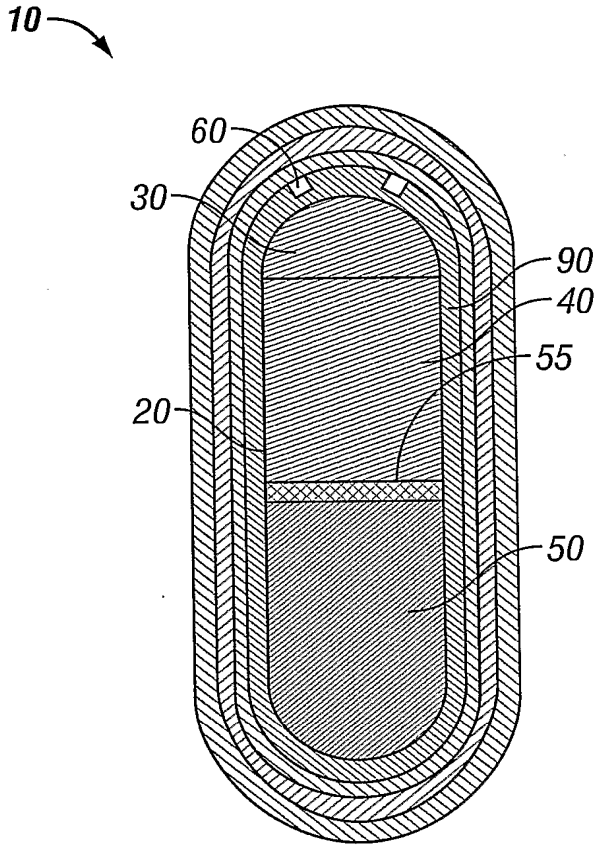

10
60
30
90
40
55
20
50

FIG. 3

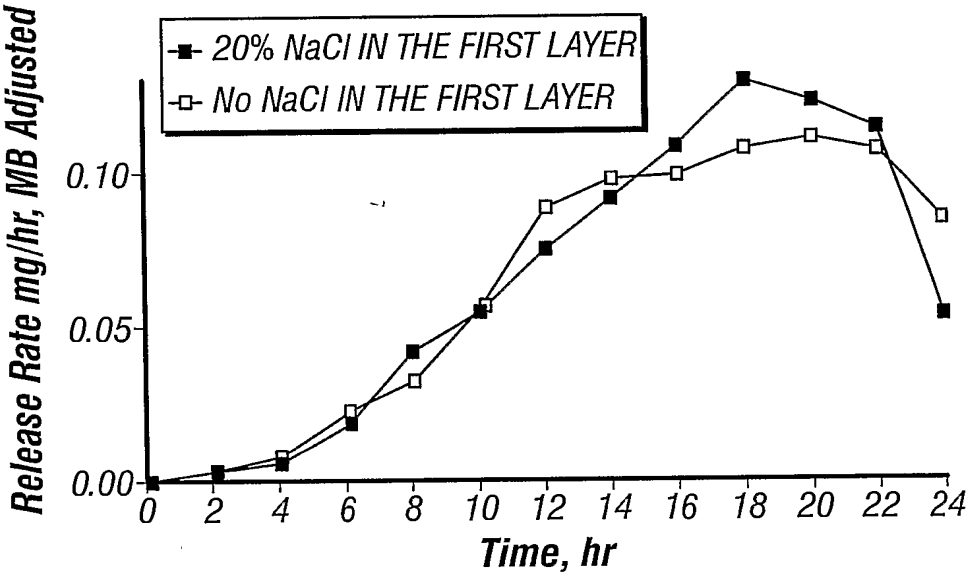

20% NaCl IN THE FIRST LAYER
No NaCl IN THE FIRST LAYER
Release Rate mg/hr, MB Adjusted
0.10
0.05
0.00
0
2
4
6
8
10
12
14
16
18
20
22
24
Time, hr

FIG. 4

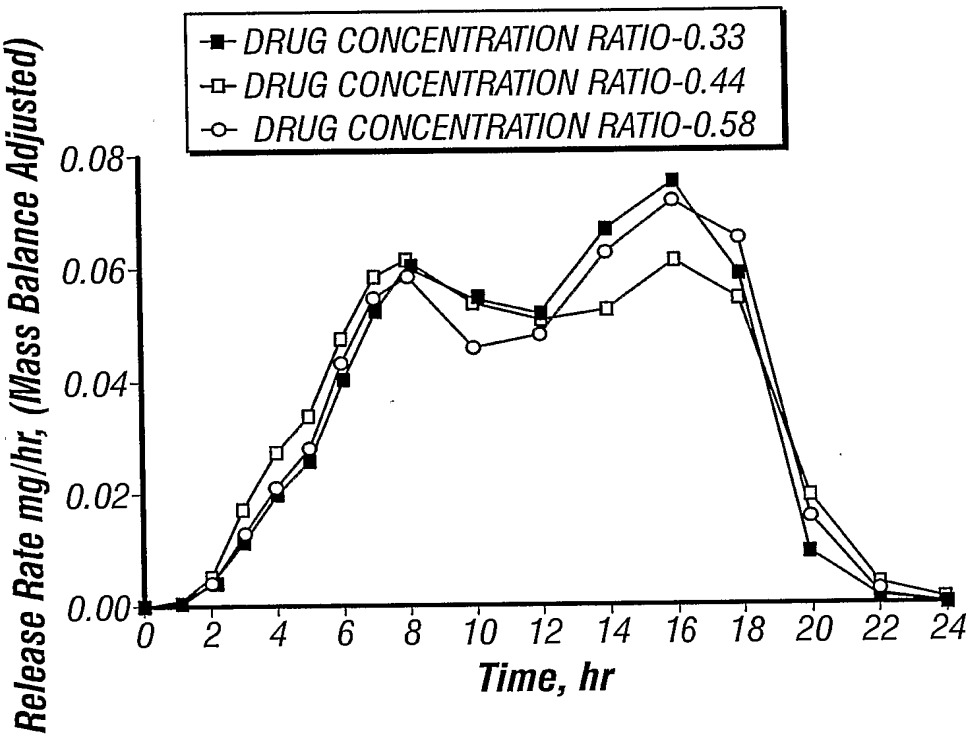

DRUG CONCENTRATION RATIO-0.33
DRUG CONCENTRATION RATIO-0.44
DRUG CONCENTRATION RATIO-0.58
Release Rate mg/hr, (Mass Balance Adjusted)
0.08
0.06
0.04
0.02
0.00
0
2
4
6
8
10
12
14
16
18
20
22
24
Time, hr

FIG. 5

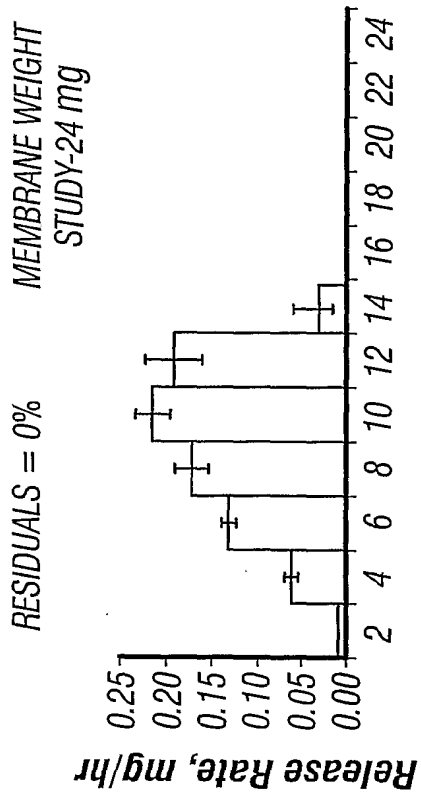


FIG. 6A

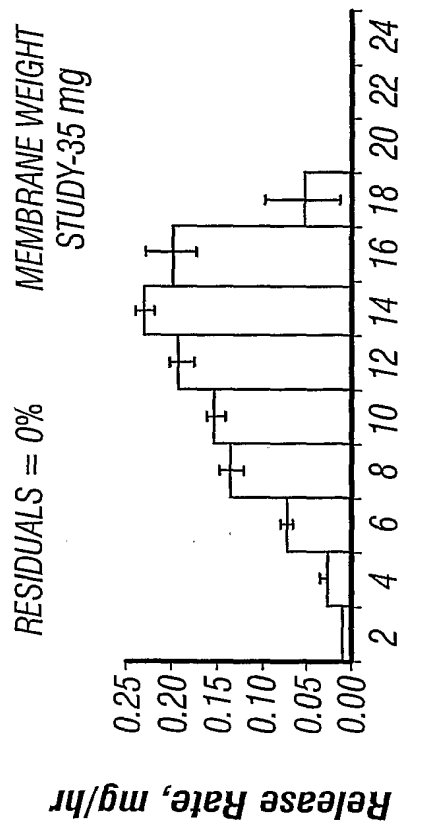


FIG. 6B

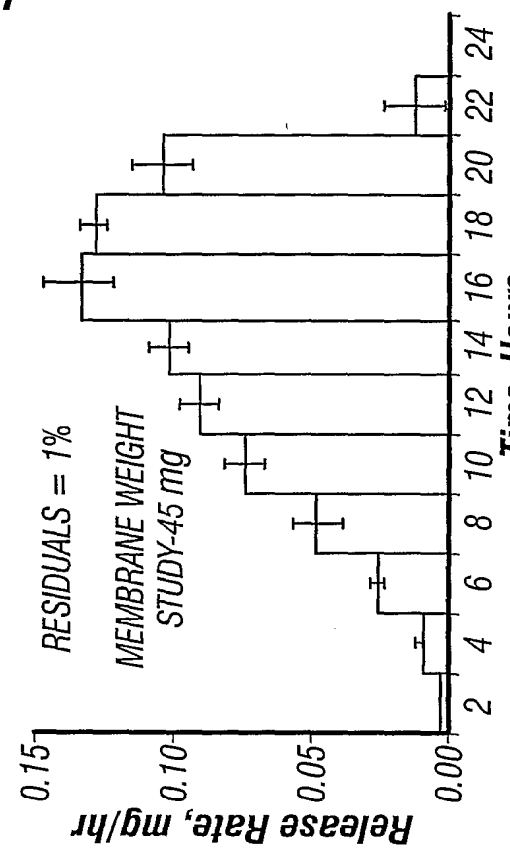


FIG. 6C

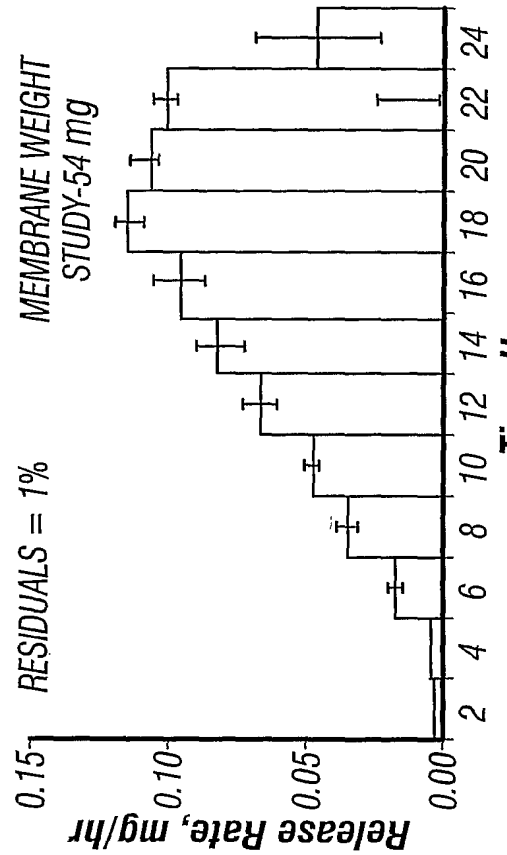


FIG. 6D

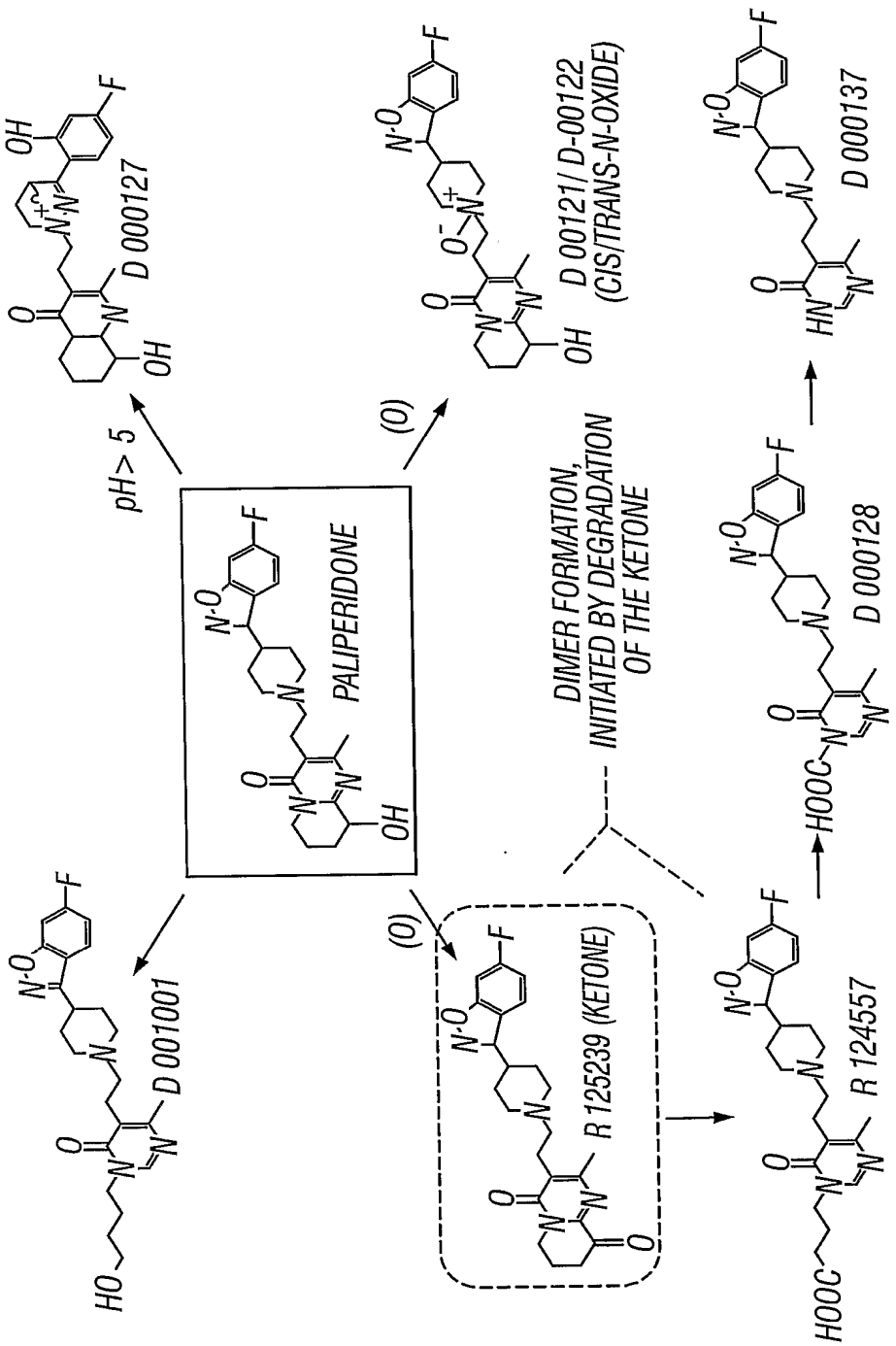

pH> 5
(O)
PALIPERIDONE
D 000127
D 00121/ D-00122
(CIS/TRANS-N-OXIDE)
D 000137
DIMER FORMATION,
INITIATED BY DEGRADATION
OF THE KETONE
D 000128
D 001001
R 125239 (KETONE)
R 124557

FIG. 7

		ACCELERATED STABILITY CONDITIONS	
NON-SUBCOATED SYSTEM	STABILITY TIME POINT	40°C/75%RH	50°C/75%RH
	T= 0	0.66	0.66
	2 WEEKS	0.82	0.92
	1 MONTH	0.83	1.19
	2 MONTHS	1.12	1.65
	3 MONTHS	1.02	2.07
	4 MONTHS	1.10	
SUBCOATED SYSTEM	T=0	0.68	0.68
	2 WEEKS	0.77	0.79
	1 MONTH	0.76	0.98
	2 MONTHS	0.96	1.50
	3 MONTHS	0.88	1.54
	4 MONTHS	0.96	

FIG. 8

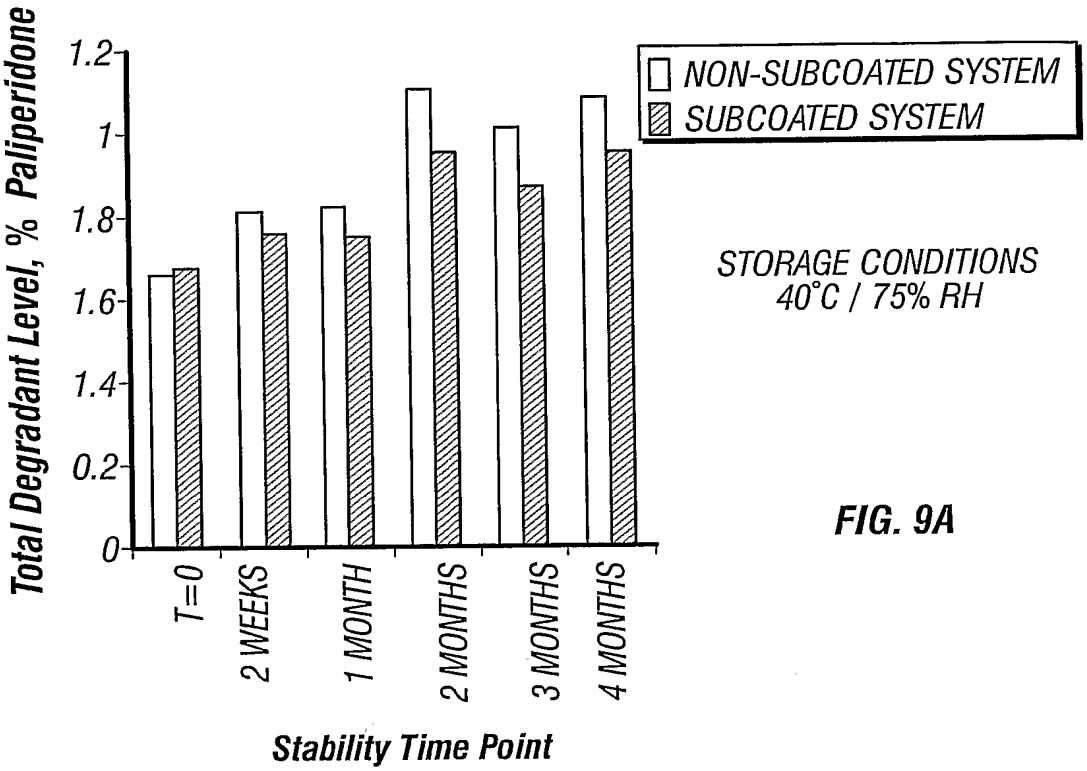

Total Degradant Level, % Paliperidone
1.2
1
1.8
1.6
1.4
0.2
0
T=0
2 WEEKS
1 MONTH
2 MONTHS
3 MONTHS
4 MONTHS
Stability Time Point
NON-SUBCOATED SYSTEM
SUBCOATED SYSTEM
STORAGE CONDITIONS
40°C / 75% RH

FIG. 9A

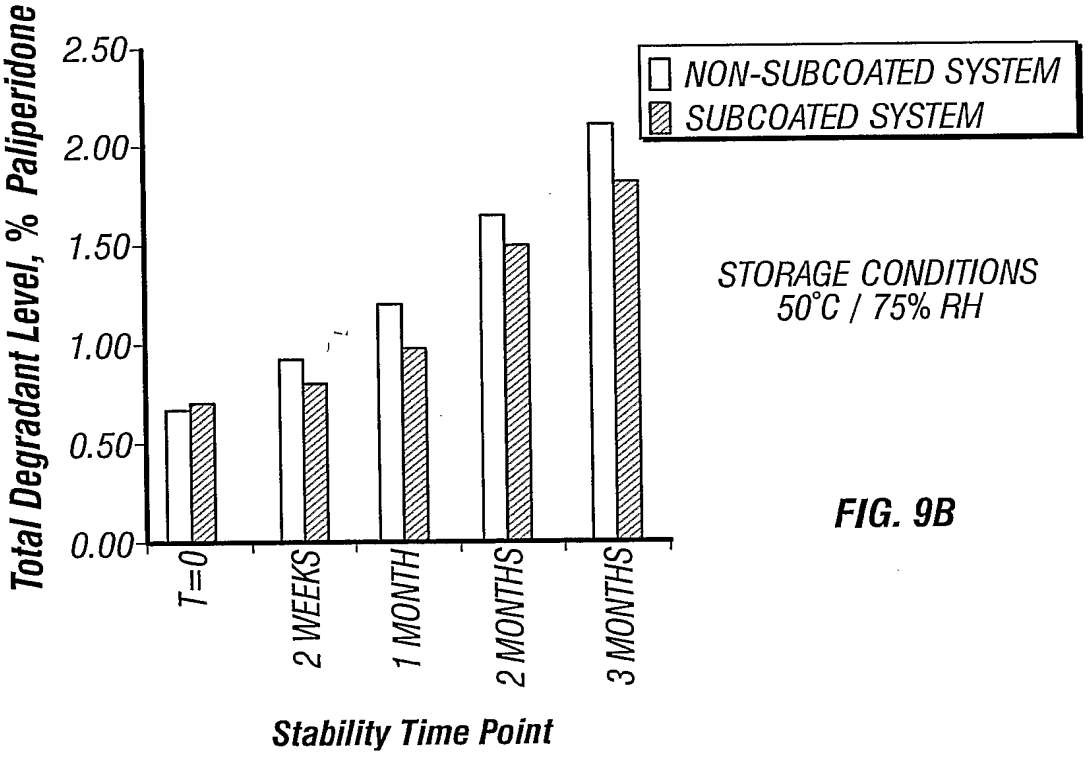

Total Degradant Level, % Paliperidone
2.50
2.00
1.50
1.00
0.50
0.00
T=0
2 WEEKS
1 MONTH
2 MONTHS
3 MONTHS
Stability Time Point
NON-SUBCOATED SYSTEM
SUBCOATED SYSTEM
STORAGE CONDITIONS
50°C / 75% RH

FIG. 9B

INTERNATIONAL SEARCH REPORT

Internati · · pplication No
PCT/U· ·3/23433

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/24 A61K31/506 A61P25/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 35419 A (ALZA CORP) 22 June 2000 (2000-06-22) cited in the application claims; figures 1-18; examples	2,3,6, 22,33
X	WO 99 62496 A (ALZA CORP) 9 December 1999 (1999-12-09) cited in the application the whole document	2,3,5,6, 22,33
A	US 2002/035357 A1 (COPPARI MARCELO A ET AL) 21 March 2002 (2002-03-21) the whole document	1-49
A	US 2002/051807 A1 (VERGEZ JUAN A ET AL) 2 May 2002 (2002-05-02) the whole document	1-49

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 2003	17/12/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Villa Riva, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/ 03/23433

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 44039 A (BORGHIJS HERMAN KAREL ;FRANCOIS MARC KAREL JOZEF (BE); MONBALIU JO) 27 November 1997 (1997-11-27) the whole document	1-49

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int nal application No.
. .T/US 03/23433

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 1-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ation on patent family members

International Application No
PCT/US 03/23433

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2354472 A1	22-06-2000
		CN 1331580 T	16-01-2002
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		HU 0104721 A2	29-06-2002
		JP 2002532406 T	02-10-2002
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		WO 9962496 A1	09-12-1999
		ZA 200007111 A	05-06-2001
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		BG 62684 B1	31-05-2000
		BG 102443 A	30-06-1999
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		DE 69708284 T2	25-07-2002
		DK 904081 T3	25-02-2002
		EA 536 B1	28-10-1999
		EE 9800136 A	15-10-1998
		WO 9744039 A1	27-11-1997
		EP 0904081 A1	31-03-1999
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		HK 1017852 A1	08-03-2002
		HR 970276 A1	30-04-1998
		HU 9901319 A2	30-08-1999
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(54) Title: CRYSTAL FORMS OF 9-HYDROXY-RISPERIDONE (PALIPERIDONE)

(57) Abstract: The present invention provides amorphous and crystalline forms of Paliperidone, and processes for preparing thereof.

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CRYSTAL FORMS OF 9-HYDROXY-RISPERIDONE (PALIPERIDONE)

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This patent application claims the benefits of U.S. Provisional Application No. 60/928,747 filed May 10, 2007, No. 60/930,392 filed May 15, 2007, No. 60/929,126 filed June 14, 2007, No. 60/958,571 filed July 5, 2007, No. 60/929,703 filed July 10, 2007, No. 60/935,094 filed July 26, 2007, No. 60/837,804 filed August 14, 2006, No. 60/928,745 filed May 10, 2007, No. 60/935,093 filed July 26, 2007 and No. XX/XXXXXX (Attorney Docket No. 1662/A454P1) filed on August 7, 2007 with a title: "Pure Paliperidone and Processes for Preparing Thereof", the disclosures of which are hereby incorporated by reference.

FIELD OF INVENTION

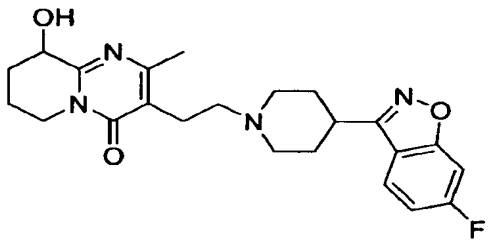
[0002] The present invention is related to crystalline forms of 9-hydroxy-risperidone (paliperidone) and methods of preparation thereof.

BACKGROUND OF THE INVENTION

[0003] RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

[0004] Risperidone is a selective monoaminergic antagonist which has affinity for serotonin-5-HT2, dopamine-D2, H1-histamine, alpha1- and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. It is a potent D2-antagonist. This active pharmaceutical ingredient is metabolized by cytochrome P-450 IID6 to produce 9-hydroxy-risperidone, also known as Paliperidone, which has a similar pharmacological activity to risperidone.

[0005] Paliperidone, 3-[2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidyl]ethyl]-7-hydroxy-4-methyl-1,5-diazabicyclo[4.4.0]deca-3,5-dien-2-one, is a 5-HT antagonist belonging to the chemical class of benzisoxazole derivatives and a racemic mixture having the following structural formula:



Paliperidone

[0006] Paliperidone is a metabolite of Risperidone. Marketed under the name, Invega®, Paliperidone is a psychotropic agent approved in the United States for the treatment of schizophrenia.

[0007] Paliperidone is described in U.S. Patent No. 5,158,952. U.S. Patent No. 5,254,556 describes a process for Paliperidone synthesis.

[0008] Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like 9-hydroxy-risperidone, may give rise to a variety of crystalline forms having distinct crystal structures and physical properties.

[0009] The difference in the physical properties of different crystalline forms results from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula yet having distinct advantageous physical properties compared to other crystalline forms of the same compound or complex.

[00010] The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for dèsigning, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

[00011] There is a need in the art for polymorphic forms of 9-hydroxy-risperidone, Paliperidone.

SUMMARY OF THE INVENTION

[00012] In one of the embodiments, the present invention provides amorphous solid paliperidone.

[00013] The present invention also provides crystalline Form I of paliperidone, characterized by data selected from the group consisting of:

(i) X-ray powder diffraction (PXRD) spectrum with peaks at about: 10.1, 12.4, 14.3, 17.0 and 17.2 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 163.1, 161.2 and 156.8 ± 0.2 ppm; and

(iii) a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.8, 43.9 and 39.5 ± 0.1 ppm.

[00014] In an embodiment, the present invention provides a mixture of crystalline Form I and Form V of paliperidone.

[00015] In an embodiment, the present invention provides crystalline Form II of paliperidone, characterized by data selected from the group consisting of

(i) X-ray powder diffraction spectrum with peaks at about: 10.3, 14.6, 22.0, 24.6 and 25.0 degrees two theta ± 0.2 degrees two theta;

(ii) X-ray powder diffraction spectrum with peaks at about: 10.3, 13.3, 13.9, 14.6 and 15.1 degrees two theta ± 0.2 degrees two theta;

(iii)a solid-state ^{13}C NMR spectrum with signals at about 163.4, 121.8 and 116.7 ± 0.2 ppm; and

(iv) a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 95 to 180 ppm of about 65.7, 24.1 and 19.0 ± 0.1 ppm.

[00016] In an embodiment, the present invention provides crystalline Paliperidone Form III, characterized by data selected from the group consisting of

(i) X-ray powder diffraction spectrum with peaks at about: 10.8, 14.1, 15.8 and 16.8 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 164.1, 161.3 and 157.9 ± 0.2 ppm; and

(iii) a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 46.7, 43.9 and 40.5 ± .0.1 ppm.

[00017] In an embodiment, the present invention provides crystalline Paliperidone Form IV, characterized by data selected from the group consisting of

(i) X-ray powder diffraction spectrum with peaks at about: 10.2, 12.2 and 15.5 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 162.6, 160.5 and 157.6 ± 0.2 ppm; and

(iii)a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.9, 43.8 and 40.9 ± 0.1.

[00018] An embodiment of the present invention provides crystalline Paliperidone Form V, characterized by data selected from the group consisting of

(i) X-ray powder diffraction spectrum with four or more peaks from the list of: about 9.8, 10.9, 15.8, 21.2 and 21.6 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 163.4, 161.4 and 157.9 ± 0.2 ppm; and

(iii)a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of about 51.1, 49.1 and 45.6 ± 0.1 ppm.

[00019] An embodiment of the present invention provides crystalline Paliperidone Form VI, characterized by data selected from the group consisting of

(i) an X-ray powder diffraction spectrum with four or more peaks from the list of: about 8.5, 8.8, 9.7, 11.2 and 11.6 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 163.4, 161.4 and 157.9 ± 0.2 ppm;

(iii)a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of about 51.1, 49.1 and 45.6 ± 0.1 ppm.

[00020] The present invention also provides pure or substantially pure amorphous solid Paliperidone, and crystalline Form I, II, III, IV, V or VI of Paliperidone.

[00021] The present invention also provides processes for preparing the amorphous solid Paliperidone, or crystalline Form I, II, III, IV, V or VI of Paliperidone.

BRIEF DESCRIPTION OF THE DRAWINGS

[00022] Figure 1 illustrates the PXRD pattern for amorphous and Form II mixture 9-hydroxy-risperidone of the present invention, wherein the unit for the vertical axis is cps and the unit for the horizontal axis is degree two theta.

[00023] Figure 2 illustrates the PXRD pattern for pure amorphous 9-hydroxy-risperidone of the present invention, wherein the unit for the vertical axis is cps and the unit for the horizontal axis is degree two theta.

[00024] Figure 3 illustrates the PXRD pattern for substantially pure crystalline 9-hydroxy-risperidone Form I of the present invention, wherein the unit for the vertical axis is cps and the unit for the horizontal axis is degree two theta.

[00025] Figures 4 and 5 illustrate solid-state ^{13}C NMR spectrum of Paliperidone Form I in the 115-180 ppm range and in the 0-180 range.

[00026] Figure 6 illustrates the PXRD pattern for crystalline 9-hydroxy-risperidone Form II of the present invention, wherein the unit for the vertical axis is cps and the unit for the horizontal axis is degree two theta.

[00027] Figures 7 and 8 illustrate solid-state ^{13}C NMR spectrum of Paliperidone Form II in the 95 -180 ppm range and in the 0-180 range.

[00028] Figure 9 illustrates the PXRD pattern for crystalline 9-hydroxy-risperidone Form III of the present invention, wherein the unit for the vertical axis is cps and the unit for the horizontal axis is degree two theta.

[00029] Figures 10 and 11 illustrate solid-state ^{13}C NMR spectrum of Paliperidone Form III in the 115-180 ppm range and in the 0-180 range.

[00030] Figure 12 illustrates the PXRD pattern for 9-hydroxy-risperidone Form IV of the present invention, wherein the unit for the vertical axis is cps and the unit for the horizontal axis is degree two theta.

[00031] Figures 13 and 14 illustrate solid-state ^{13}C NMR spectrum of Paliperidone Form IV in the 115-180 ppm range and in the 0-180 range.

[00032] Figure 15 illustrates the PXRD pattern for crystalline 9-hydroxy-risperidone Form V of the present invention, wherein the unit for the vertical axis is cps and the unit for the horizontal axis is degree two theta.

[00033] Figures 16 and 17 illustrate solid-state ^{13}C NMR spectrum of Paliperidone Form V in the 110-180 ppm range and in the 0-180 range.

[00034] Figure 18 illustrates the PXRD pattern for pure crystalline 9-hydroxy-risperidone Form VI of the present invention, wherein the unit for the vertical axis is cps and the unit for the horizontal axis is degree two theta.

[00035] Figure 19 illustrates the PXRD pattern for crystalline 9-hydroxy-risperidone Form VI of the present invention, wherein the unit for the vertical axis is cps and the unit for the horizontal axis is degree two theta.

[00036] Figure 20 is a table of PXRD peaks for Paliperidone crystalline forms which may be used in determining the percent contamination of a certain Paliperidone crystalline form by other Paliperidone crystalline forms.

DETAILED DESCRIPTION OF THE INVENTION

[00037] As used herein, 9-hydroxy-risperidone is interchangeable with Paliperidone.

[00038] As used herein, "room temperature" means a temperature of about 18°C to about 26°C. Preferably, "room temperature" means about 20°C to about 25°C.

[00039] As used in this patent application, "overnight" preferably means a duration of about 12 hours to about 18 hours.

[00040] As used herein, the percent of crystalline form in amorphous material is quantified by methods known in the art using a "crystallinity index" available in most XRD software. This index is used to measure the percent of crystalline contamination within the amorphous material.

[00041] With regard to determining percent of one or more crystalline forms present in another, a person skilled in the art can select a characterizing peak or a number of peaks from the known crystalline form (see Figure 20 for reference) and quantify it following the known art. The XRD analysis for quantitation purposes can be performed according, for instance, to the European Pharmacopoeia version 5.6, "Characterization of crystalline solids by XRPD", pg 4432-4437.

[00042] As used herein, the term chemical shift difference refers to the difference in chemical shifts between a reference signal and another signal in the same NMR spectrum. In the present patent application the chemical shift differences were calculated by subtracting the chemical shift value of the signal exhibiting the lowest chemical shift (reference signal) in the solid state ^{13}CNMR spectrum in a specific range (for example 100 to 180 ppm) from chemical shifts values of another (observed) signal in the same NMR spectrum in the range. These chemical shift differences are to provide a measurement for a substance, compensating for a phenomenon in NMR spectroscopy wherein, depending on the instrumentation, temperature, and calibration method used, a shift in the solid-state NMR "fingerprint" is observed. This shift in the solid-state NMR "fingerprint", having chemical shift resonances at a certain positions, is such that although the individual chemical shifts of signals have altered, the difference between chemical shifts of each signal and another is retained.

[00043] In another embodiment, the present invention provides amorphous Paliperidone.

[00044] In another embodiment, the amorphous paliperidone can contain less than 60%, preferably less than 50% and more preferably less than about 40% of crystalline Paliperidone forms such as Form I, II and V. In one example, the powder X-ray diffraction (PXRD) pattern of the amorphous paliperidone can be depicted substantially as Figure 1. The amorphous Paliperidone may be prepared by exposing Form II to n-decane for a sufficient period to obtain the amorphous Paliperidone.

The period necessary will depend on the quantities used, temperature and can be periodically checked by PXRD until the amorphous Paliperidone is obtained to the desired extent.

[00045] In another embodiment, the present invention provides substantially pure amorphous Paliperidone, preferably having less than 20%, more preferably less than 10%, even more preferably less than about 5%, and most preferably less than 1%, of any one crystalline Paliperidone. Specifically, substantially pure amorphous Paliperidone may have less than 20%, more preferably less than 10%, even more preferably less than about 5%, and most preferably less than 1%, of any one of crystalline Forms I, II and V of Paliperidone. The substantially pure amorphous Paliperidone can have less than 20% of crystalline forms of Paliperidone combined. In one example, the PXRD pattern of the substantially pure amorphous paliperidone can be depicted substantially as Figure 2.

[00046] The present invention further provides a process for the preparation of substantially pure amorphous paliperidone comprising: providing a solution of paliperidone and dichloromethane, and removal of the solvent to obtain amorphous paliperidone. The solution of paliperidone and dichloromethane may be prepared by combining Paliperidone and dichloromethane and heating for a period to allow complete dissolution. The solvent may be removed through evaporation for example by maintaining at a temperature from about 35°C, preferably under reduced pressure or alternatively by spray drying. When using the spray drying technique, the paliperidone solution can be sprayed in a chamber with ambient nitrogen at a co-current flow. The spray rate of the solution is preferably at about 5.6 ml/min. Further, the co-current flow of nitrogen may vary between about 70°C and about 120°C at 30 m^3/h. To obtain the amorphous paliperidone in such process, the temperature for the outlet solids from such chamber may be from about 45°C to about 80°C.

[00047] In another embodiment, the present invention provides crystalline 9-hydroxy-risperidone (paliperidone), characterized by X-ray powder diffraction reflections at about: 10.1, 12.4, 14.3, 17.0 and 17.2 ± 0.2 degrees two theta, designated as a Form I. The crystalline paliperidone can be further characterized by one or more X-ray powder diffraction peaks at about 12.9, 18.9, 21.9, 24.8 and 26.2 ± 0.2 degrees two-theta. A typical powder x-ray diffractogram pattern for a mixture

of crystalline paliperidone containing Form I is shown in Figure 3B. The crystalline form may have a melting point of about 166 to 167°C.

[00048] The crystalline Form I can have solid-state ^{13}C NMR spectrum with signals at about 163.1, 161.2 and 156.8 ± 0.2 ppm or a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.8, 43.9 and 39.5 ± 0.1 ppm. In addition, the solid-state ^{13}C NMR spectrum of Form I may have one or more signals at about 121.2 and 117.3 ± 0.2 ppm. In addition, the solid-state ^{13}C NMR spectrum of Form I may have chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.8, 43.9, 39.5 and 3.9 ± 0.1 ppm. A typical ^{13}C NMR spectrum of Form I is depicted in Figures 4 and 5. The signal exhibiting the lowest chemical shift in the chemical shift range of 115 to 180 ppm is, typically, at about 117.3 ± 1ppm. Form I is preferably anhydrous, showing weight loss of about 0.6% (between 25-168°C), as measured by TGA. The water content of Form I is about 0.5%, as measured by KF titration.

[00049] In one embodiment of the present invention, the crystalline paliperidone Form I is substantially pure. The Form I has high crystalline purity, wherein the crystalline paliperidone form I contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of other crystalline forms of paliperidone. For instance, the Form I has high crystalline purity, wherein the crystalline paliperidone Form I contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of Paliperidone Forms I and V. The pure Form I can have less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of other crystalline forms of Paliperidone combined. For instance, the pure Form I can have less than 20% preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of Paliperidone Forms II and V combined.

[00050] Form I may be prepared by recrystallization from acetonitrile or methanol. The present invention provides a process for preparing Form I, comprising dissolving Paliperidone in at least one solvent selected from acetonitrile and methanol to form a solution; and precipitation of Paliperidone from the solution to obtain Paliperidone Form I. Preferably, the dissolving step is performed by

heating Paliperidone in the at least one solvent to reflux. Preferably, the precipitation is conducted by removing the solvent via evaporation (such as under reduced pressure) or cooling.

[00051] The present invention also provides a process for preparing Form I, comprising slurrying solid Paliperidone in at least one solvents selected from the group consisting of ethanol/water (volume ratio about 1:1), acetone/water (volume ratio of about 1:1), dichlorobenzene, isopropanol, water and acetone for a duration of at least about 30 minutes, preferably ranging from about 12 hours to about 48 hours, at a temperature of about room temperature to about 60°C to obtain Form I. As used in this patent application, "about 1:1" refers to a ratio X:Y, wherein X ranges from 0.8 to 1.2 and Y ranges from 0.8 to 1.2.

[00052] The present invention also provides a process for preparing Form I, comprising dissolving Paliperidone in dichloromethane by heating to form a heated solution via complete dissolution; adding the heated solution dropwise into hexane maintained at a temperature of room temperature or less, e.g., cooled at a temperature of about 0°C to about 5°C, to precipitate Paliperidone as Form I. Preferably, one volume of the heated solution is added dropwise into about 3 volumes of the cooled hexane. The hexane is cooled preferably in an ice bath.

[00053] In another embodiment, paliperidone Form I is prepared as a mixture of Form I and V, for instance, a mixture of Form I having about 8% by weight of paliperidone Form V with the PXRD pattern as substantially shown in Figure 3B. In another embodiment, the present invention presents substantially pure crystalline 9-hydroxy-risperidone Form I. The substantially pure crystalline 9-hydroxy-risperidone Form I contains less than 8% and preferably less than 5% of other crystalline forms of paliperidone. An example of the PXRD pattern for the substantially pure Form I is as substantially depicted in Figure 3A.

[00054] In one embodiment, the present invention provides a crystalline form of 9-hydroxy-risperidone (paliperidone), characterized by X-ray powder diffraction (PXRD) reflections at about: 10.3, 14.6, 22.0, 24.6 and 25.0 degrees two theta ± 0.2 degrees two theta or alternatively characterized by X-ray powder diffraction (PXRD) reflections at about: 10.3, 13.3, 13.9, 14.6 and 15.1 degrees two theta ± 0.2 degrees two theta designated as Form II. This form can be further characterized by any one or more of the X-ray powder diffraction reflections selected from the list of: 13.1, 13.8, 14.1, 18.7 and 28.0 degrees two-theta, ± 0.2 degrees two-theta. An

example of the powder x-ray diffraction pattern for the crystalline Form II is shown in Figure 6. Preferably, the above Form II is preferably anhydrous, showing weight loss of about 0.4% (between 25-145°C), as measured by TGA. The water content of this Form II is about 0.5%, as measured by KF titration.

[00055] The crystalline Form II can alternatively be characterized by a solid-state ^{13}C NMR spectrum with signals at about 163.4, 121.8 and 116.7 ± 0.2 ppm ± 0.2 ppm or a solid-state ^{13}C NMR spectrum having chemical shifts differences in the 95 to 180 ppm range between the signal exhibiting the lowest chemical shift in this range and another in the chemical shift range of about 65.7, 24.1 and 19.0 ± 0.1 ppm. In addition, the solid-state ^{13}C NMR spectrum of Form II may have one or more signals at about 163.4, 156.2, 121.8, 116.7 and 97.7 ± 0.2 ppm. In addition, the solid-state ^{13}C NMR spectrum of Form II may have chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 95 to 180 ppm of about 65.7, 58.5, 24.1 and 19.0 ± 0.1 ppm ± 0.1 ppm. A typical ^{13}C NMR spectrum of Form II is depicted in Figures 7 and 8. The signal exhibiting the lowest chemical shift in the chemical shift range between 95 to 180 ppm is typically, at about 97.7 ± 1ppm.

[00056] In one embodiment of the present invention, the crystalline paliperidone Form II is substantially pure. The Form II has high crystalline purity, wherein the crystalline paliperidone form II contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1% of any one of other crystalline forms of paliperidone. Specifically, the Form II has high crystalline purity, wherein the crystalline paliperidone form II contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of Paliperidone Forms I and V. The pure Form II can have less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of other crystalline forms of Paliperidone combined. For instance, the pure Form II can have less than 20% preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of Paliperidone Forms I and V combined.

[00057] The present invention further provides a process for the preparation of crystalline Form II of paliperidone comprising crystallization from a solution of paliperidone and a solvent selected from a group consisting of: ethanol, methanol, n-propanol, isopropanol, n-butanol, 2-butanol, isobutanol, 2-pentanol, n-pentanol,

ethanol/water (volume ratio ranging from about 1:1 to about 3:1), isopropanol/water (volume ratio ranging from about 1:1 to about 3:1), acetonitrile, toluene, chlorobenzene, dichlorobenzene, 1,2-dichloroethane, isobutyl acetate, n-butyl acetate, ethyl acetate/water (volumn ratio ranging from about 1:1 to about 3:1), diethyl carbonate, acetone, acetone/water (volume ratio ranging from about 1:1 to about 3:1), methyl ethyl ketone (MEK), methyl isopropyl ketone (MIPK), methyl isobutyl ketone (MIBK), dibutyl ether, polyglycol methyl ether (PGME), dioxane, propylene glycol, Cellosolve, tetrahydrofuran (THF), dimethyl formamide (DFM), dimethyl acetamide (DMA), dimethyl sulfoxide (DMSO) and DMC.

[00058] The present invention further provides a process for the preparation of crystalline Form II of paliperidone, comprising providing a solution of Paliperidone in dichloromethane; adding at least one anti-solvent selected from the group consisting of methyl t-butyl ether (MTBE), methyl ethyl ketone (MEK), ethyl acetate, acetonitrile, cyclohexane, heptane, toluene and butanol to precipitate Paliperidone as Form II. The solution of Paliperidone is preferably prepared by heating Paliperidone in dichloromethane to reflux. In an embodiment of the process, the Paliperidone solution is cooled before the addition of the at least one anti-solvent. Preferably, the at least one anti-solvent is added gradually, e.g., dropwise. Alternatively, the at least one anti-solvent is added at once, especially when the at least one anti-solvent is cooled to below room temperature before addition to the dichloromethane solution of Paliperidone. Preferably, during and/or after the addition of the at least one anti-solvent, the mixture is stirred, more preferably, at about room temperature. The stirring is preferably for about 1 hour to 3 hours, more preferably about 1.5 hour.

[00059] In the above processes for preparing Form II, the ingredients may be heated in order to achieve dissolution. Stirring may also be employed to promote dissolution. Preferably, the ingredients are heated to reflux. Whether the ingredients are heated, the process may further comprise cooling, to induce crystallization.

[00060] Crystallization is often by cooling. Cooling may be to a temperature of about -10°C to about 25°C. The paliperidone crystalline form may be recovered by any method known to the skilled artisan. Preferably, the paliperidone crystalline form is recovered from the mixture by filtration, and then dried under reduced pressure (< 1 atmosphere).

[00061] In another embodiment, the present invention provides a crystalline form of 9-hydroxy-risperidone, characterized by X-ray powder diffraction reflections at about: 10.8, 14.1, 15.8 and 16.8 degrees two theta ± 0.2 degrees two theta, designated as Form III. In another embodiment, the crystalline Form III is further characterized by X-ray powder diffraction reflections at about 25.8. In yet another embodiment, this crystalline form is further characterized by one or more X-ray powder diffraction reflections selected from the list of about 9.9, 11.0, 12.0, 17.3 and 32.5 degrees two theta ± 0.2 degrees two theta. A typical powder x-ray diffraction diagram for the crystalline Form III is shown in Figure 9.

[00062] The crystalline Form III can alternatively be characterized by a solid-state ^{13}C NMR spectrum with signals at about 164.1, 161.3 and 157.9 ± 0.2 ppm or a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift within the range and another in the chemical shift range of 115 to 180 ppm of about 46.7, 43.9 and 40.5 ± 0.1 ppm. In addition, the solid-state ^{13}C NMR spectrum may have one or more signals at about 164.1, 161.3, 157.9, 123.9 and 117.4 ± 0.2 ppm. In addition, the solid-state ^{13}C NMR spectrum of Form III may have chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 46.7, 43.9, 40.5 and 6.5 ± 0.1 ppm. A typical ^{13}C NMR spectrum for Form III is depicted in Figures 10 and 11. The signal exhibiting the lowest chemical shift in the chemical shift range between 115 to 180 ppm is typically at about 117.4 ± 1 ppm.

[00063] Preferably, the above Form III is an NMP solvate, showing weight loss of about 19.2% (between 25-168°C), as measured by TGA. Preferably, the Form III is a monosolvate of NMP. The water content of this Form III is about 0.2%, as measured by KF titration.

[00064] In one embodiment of the present invention, the crystalline Paliperidone Form III is pure. The Form III has high crystalline purity, wherein the crystalline Paliperidone form III contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1% of any one of other crystalline forms of paliperidone. Specifically, the Form III has high crystalline purity, wherein the crystalline paliperidone form III contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of Paliperidone Forms I , II and V. The pure Form III can have

less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of other crystalline forms of Paliperidone combined. For instance, the pure Form III can have less than 20% preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of Paliperidone Forms I, II and V combined.

[00065] The present invention further provides a process for the preparation of crystalline Form III of Paliperidone comprising providing a solution of paliperidone and 1-methyl-2-pyrrolidone (NMP) and crystallizing for example by cooling to obtain the Paliperidone Form III .

[00066] In the process for preparing Form III, the ingredients may be heated in order to achieve dissolution. Stirring may also be employed to promote dissolution. Preferably, the ingredients are heated to reflux. Whether the ingredients are heated, the process may further comprise cooling, to induce crystallization.

[00067] The present invention further provides a process for the preparation of crystalline Form III of Paliperidone, comprising stirring Paliperidone Form II solid in about 10 volumes of N-methyl 2-pyrrolidone (NMP) at about 50°C to about 65°C for about 12 hours to about 30 hours, preferably about 24 hours to convert Form II to Form III.

[00068] The paliperidone crystalline Form III may be recovered by any method known to the skilled artisan. Preferably, the paliperidone crystalline form is recovered from the mixture by filtration, and then dried under reduced pressure (< 1 atmosphere).

[00069] In another embodiment, the present invention provides a crystalline form of 9-hydroxy-risperidone, characterized by X-ray powder diffraction reflections at about: 10.2, 12.2 and 15.5 degrees two theta ± 0.2 degrees two theta, designated as Form IV. Form IV can be further characterized by an additional X-ray powder diffraction reflections at about 13.6 degrees two theta ± 0.2 degrees two theta. Optionally, this crystalline form can be further characterized by X-ray powder diffraction reflections at about 23.9 and 33.2 degrees two theta ± 0.2 degrees two theta. A typical powder x-ray diffraction diagram for the crystalline Form IV is shown in Figure 12.

[00070] The crystalline Form IV can alternatively be characterized by a solid-state ^{13}C NMR spectrum with signals at about 162.6, 160.5 and 157.6 ± 0.2 ppm or a solid-state ^{13}C NMR spectrum having chemical shifts differences between the

signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.9, 43.8 and 40.9 ± 0.1 ppm. In addition, the solid-state ^{13}C NMR spectrum may have one or more signals at about 162.6, 160.5, 157.6, 118.6 and 116.7 ± 0.2 ppm. In addition, the solid-state ^{13}C NMR spectrum for Form IV may have chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.9, 43.8, 40.9 and 1.9 ± 0.1 ppm ± 0.1 ppm. A typical ^{13}C NMR spectrum for Form IV is depicted in Figures 13 and 14. The signal exhibiting the lowest chemical shift in the chemical shift range between 115 to 180ppm is typically at about 116.7 ± 1ppm.

[00071] In one embodiment of the present invention, the crystalline paliperidone Form IV is pure. The Form IV has high crystalline purity, wherein the crystalline paliperidone form IV contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of other crystalline forms of paliperidone. Specifically, the Form IV has high crystalline purity, wherein the crystalline paliperidone form IV contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of Paliperidone Forms I , II and V. The pure Form IV can have less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of other crystalline forms of Paliperidone combined. For instance, the pure Form IV can have less than 20% preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of Paliperidone Forms I, II and V combined.

[00072] The present invention further provides a process for the preparation of crystalline Form IV of paliperidone comprising crystallization from a solution of paliperidone and a solvent selected from the group consisting of dioxane, a mixture of acetone/water (volume ratio ranging from about 3:1 to about 5:1), and methanol/water (volume ratio ranging from about 3:1 to about 5:1).

[00073] In the processes for preparing Form IV, the ingredients may be heated in order to achieve dissolution. Stirring may also be employed to promote dissolution. Preferably, the ingredients are heated to reflux. Where the ingredients are heated, the process may further comprise cooling, to induce crystallization. The crystalline Form IV of paliperidone is recovered from the mixture by filtration.

[00074] The present invention further provides a process for the preparation of crystalline Form IV of Paliperidone, comprising providing a solution of Paliperidone in n-propanol or dioxane; and adding water as an anti-solvent to the solution to induce precipitation of Paliperidone as Form IV.

[00075] The present invention further provides a process for the preparation of crystalline Form IV of Paliperidone, comprising providing a solution of Paliperidone in about 30 to about 50 volumes, i.e., about one gram/30 ml to about one gram/50 ml), preferably about 40 volumes, of acetone/water (volume ratio ranging from about 1;1 to about 3:1) by heating to reflux; after Paliperidone is completely dissolved the hot solution is filtrated through hi-flow; and the temperature of the solution is reduced, e.g., by cooling the solution, preferably to a temperature of about 0°C to about 5°C, induce precipitation of Form IV.

[00076] In yet another embodiment, a process is presented for preparing Form IV comprising exposing Paliperidone Form III to moist environment such as at least 60% to 80% relative humidity for a sufficient period to allow for conversion. The period of time necessary can be determined by periodic analyses of PXRDs.

[00077] In another embodiment, the present invention provides a crystalline form of 9-hydroxy-risperidone, characterized by 4 or more X-ray powder diffraction reflections from the following list, about: 9.8, 10.9, 15.8, 21.2 and 21.6 degrees two theta ± 0.2 degrees two theta, designated as Form V. Form V can be further characterized by additional X-ray powder diffraction reflections at about: 14.1, 18.0 and/or 26.0 degrees two theta ± 0.2 degrees two theta.

[00078] The crystalline Form V can alternatively be characterized by a solid-state ^{13}C NMR spectrum with signals at about 163.4, 161.4 and 157.9 ± 0.2 ppm or a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of about 51.1, 49.1 and 45.6 ± 0.1 ppm. In addition, the solid-state ^{13}C NMR spectrum of Form V may have one or more signals at about 163.4, 161.4, 157.9, 119.5 and 112.3 ± 0.2 ppm. In addition, the solid-state ^{13}C NMR spectrum of Form V may have chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of about 51.1, 49.1, 45.6 and 7.2 ± 0.1 ppm. A typical ^{13}C NMR spectrum for Form V is depicted in Figures 16 and 17. The signal exhibiting the lowest chemical shift in

the chemical shift range between 100 to 180 ppm is typically at about 112.3 ± 1ppm.

[00079] A typical powder x-ray diffraction diagram for the crystalline Form V is shown in Figure 6. Preferably, the above Form V is anhydrous, showing weight loss of about 0.1% (between 25-155°C), as measured by TGA. The water content of this Form V is about 0.3%, as measured by KF titration.

[00080] Form V may be prepared by crystallization from acetonitrile.

[00081] In one embodiment of the present invention, the crystalline paliperidone Form V is pure. The Form V has high crystalline purity, wherein the crystalline paliperidone form V contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of ther crystalline forms of paliperidone. Specifically, the Form V has high crystalline purity, wherein the crystalline paliperidone Form V contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of Paliperidone Forms I and II. The pure Form V can have less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of other crystalline forms of Paliperidone combined. For instance, the pure Form V can have less than 20% preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of Paliperidone Forms I and II combined .

[00082] The present invention further provides a process for the preparation of crystalline Form V of paliperidone comprising crystallization from a solution of paliperidone and a solvent selected from the group consisting of a mixture of acetone/water (3:1, volume ratio), n-propanol, and dioxane, and drying the obtained material under reduced pressure. Drying under reduced pressure preferably is at about 50°C to about 55°C for a sufficient period to obtain crystalline paliperidone form V, preferably overnight.

[00083] In the process for preparing Form V, the ingredients may be heated in order to achieve dissolution. Stirring may also be employed to promote dissolution. Preferably, the ingredients are heated to reflux. Where the ingredients are heated, the process may further comprise cooling, to induce crystallization. The obtained solid material may be washed, preferably with acetone. Further, these crystallization steps of dissolving paliperidone by heating in a solvent and cooling the heated solution followed by a washing step may be repeated prior to recovering

the above crystalline paliperidone, preferably these crystallization steps are repeated three times. The crystalline form of paliperidone is recovered from the mixture by filtration. Where the solvent is n-propanol or dioxane and the mixture of paliperidone and solvent is heated to obtain a solution, the hot solution may be added dropwise into cold water, wherein the cold water preferably has a temperature of about 0°C to about 5°C.

[00084] The paliperidone crystalline Form V may be recovered by any method known to the skilled artisan. Preferably, the paliperidone crystalline Form V is recovered from the mixture by filtration, and then dried under reduced pressure (< 1 atmosphere).

[00085] The present invention also provides a process for preparing crystalline Form V of paliperidone, comprising drying crystalline Form IV of paliperidone to obtain Form V. Preferably, the drying is conducted under reduced pressure. More preferably, the drying is conducted under reduced pressure in an vacuum oven at about 50°C to about 60°C, e.g., at about 55°C, preferably overnight, followed by cooling to yield the crystalline Form V. Preferably, the cooling is to about room temperature.

[00086] The present invention also provides a process for preparing a mixture of crystalline Forms II and V of paliperidone, comprising heating crystalline Form III of paliperidone to about 110°C to about 130°C, preferably at about 120°C, followed by cooling to obtain the mixture. Preferably, the heating is conducted for about 15 minutes to about 1 hour, more preferably about 30 minutes. The heating can be conducted in ambient conditions. The cooling, preferably, is to room temperature.

[00087] The present invention also provides a process for preparing a mixture of crystalline Forms II and V of Paliperidone, comprising drying crystalline Form VI (to be described below) of Paliperidone to obtain the mixture. Preferably, the drying is conducted under reduced pressure. More preferably, the drying is conducted under reduced pressure in an vacuum oven at about 50°C to about 60°C, e.g., at about 55°C, preferably overnight, followed by cooling to yield the mixture of crystalline Forms II and V. Preferably, the cooling is to about room temperature.

[00088] The present invention also provides a process for preparing a mixture of crystalline Forms II and V of Paliperidone, comprising recrystallization of

Paliperidone from acetone/water (volume ratio of about 1:5); and drying the solid product to obtain the mixture of Forms II and V.

[00089] The present invention also provides a process for preparing a mixture of solid Paliperidone comprising crystalline Form II, comprising recrystallization of Paliperidone from acetone/water (volume ratio about 1:1).

[00090] The present invention also provides a process for preparing a mixture of solid Paliperidone comprising crystalline Form II and amorphous Paliperidone solid, comprising recrystallization of Paliperidone from dichlorobenzene or propylene glycol.

[00091] In another embodiment, the present invention provides a crystalline form of 9-hydroxy-risperidone (paliperidone), characterized by X-ray powder diffraction reflections at about: 5.8, 8.4, 9.5 and 11.6 degrees two theta ± 0.2 degrees two theta, designated Form VI. This crystalline form can be further characterized by one or more X-ray powder diffraction peaks at about 15.2, 24.8 and 31.7 degrees two-theta ± 0.2 degrees two-theta. Examples of powder x-ray diffraction patterns for the crystalline Form VI are shown in Figure 18 and 19.

[00092] In one embodiment of the present invention, the crystalline paliperidone Form VI is pure. The Form VI has high crystalline purity, wherein the crystalline paliperidone form VI contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of other crystalline forms of paliperidone. Specifically, the Form VI has high crystalline purity, wherein the crystalline paliperidone form VI contains less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of any one of Paliperidone Forms I , II and V. The pure Form VI can have less than 20%, preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of other crystalline forms of Paliperidone combined. For instance, the pure Form VI can have less than 20% preferably less than 10%, more preferably less than 5%, and most preferably less than 1%, of Paliperidone Forms I, II and V combined.

[00093] The present invention further provides a process for the preparation of crystalline Form VI of paliperidone comprising crystallization from a solution of paliperidone and an ethanol/water mixture in a volume ratio of about 2:1 to about 4:1, preferably 3:1.

[00094] The present invention also provides a process for preparing a mixture of crystalline Form VI of Paliperidone, comprising recrystallization of Paliperidone from methanol/water (volume ratio of about 3:1) to yield Form VI.

[00095] In the processes for preparing Form VI, the ingredients may be heated in order to achieve dissolution. Stirring may also be employed to promote dissolution. Preferably, the ingredients are heated to reflux. Where the ingredients are heated, the process may further comprise cooling, to induce crystallization.

[00096] The powder X-ray diffraction patterns disclosed in this patent application were collected using an X-ray diffractometer with Cu radiation at λ = 1.5418 Å.

[00097] In yet another embodiment, the present invention provides pharmaceutical compositions comprising at least one of the above-described crystalline or amorphous forms of paliperidone and a pharmaceutically acceptable excipient.

[00098] Pharmaceutical compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, buccally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups, and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration, suitable forms for administration include suppositories with hydrophilic or hydrophobic vehicle. For topical administration, the invention provides suitable transdermal delivery systems known in the art, and for nasal delivery, there are provided suitable aerosol delivery systems known in the art.

[00099] In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients or adjuvants. Selection of excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

[000100] Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose,

starch, pregelitinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol, and talc.

[000101] Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate, and starch.

[000102] The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®), and starch.

[000103] Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, and tribasic calcium phosphate.

[000104] When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and die. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and die, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the die. Lubricants include

magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

[000105] Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

[000106] Solid and liquid compositions may also be dried using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

[000107] In liquid pharmaceutical compositions of the present invention, the active ingredient and any other solid excipients are suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

[000108] Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol, and cetyl alcohol.

[000109] Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth, and xanthan gum.

[000110] Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol, and invert sugar may be added to improve the taste.

[000111] Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole, and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

[000112] According to the present invention, a liquid composition may also contain a buffer such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate, or sodium acetate.

[000113] Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

[000114] The solid compositions of the present invention include powders, granulates, aggregates, and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant, and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well known in the pharmaceutical arts.

[000115] Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches, and losenges, as well as liquid syrups, suspensions, and elixirs.

[000116] The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin, and, optionally, contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

[000117] The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

[000118] A composition for tableting or capsule filling can be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended, and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried, and then screened and/or milled to the desired particle

size. The granulate may then be tableted or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

[000119] A tableting composition can be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet, and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

[000120] As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

[000121] A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

[000122] In another embodiment, the present invention provides a method of treating a patient comprising administering to a patient in need thereof a therapeutically effective amount of the above crystalline form of paliperidone. Preferably, the patient suffers from a condition which may be treated with a norepinephrine or a serotonin re-uptake inhibitor. Such patient may be suffering from depression.

[000123] While it is apparent that the invention disclosed herein is well calculated to fulfill the objects stated above, it will be appreciated that numerous modifications and embodiments may be devised by those skilled in the art. Therefore, it is intended that the appended claims cover all such modifications and embodiments as falling within the true spirit and scope of the present invention. In the tables presented below in the Examples,"Wet" or "w" indicates analyzed after isolation, and "dry" or "d" means dried in a vacuum oven at 55°C overnight

EXAMPLES

Preparation of Paliperidone Form I

Example 1:

A mixture of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrrido[1,2-a]- pyrimidin-4-one (CMHTP, 4.393 g, 0.0168 mol), 6-fluoro-3-piperidino-1,2-benisoxazol (FPBI, 4.695 g, 0.0203 mol), sodium carbonate (4.968 g, 0.0422 mol) and potassium iodide (0.288 g, 0.0017 mol) in N,N-dimethylformamide (DMF, 50 ml) was heated for 8 h at 85°C. The mixture was poured into water (500 ml) and extracted with dichloromethane (4 x 100 ml). The extracts were combined, washed with water (4 x 100 ml), dried with anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to afford the crude product. Crystallization from acetonitrile (100 ml) afforded 4.63 g of the product, 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl}-9-hydroxy- 2-methyl-4H-pyrrido[1,2-a]pyrimidin-4-one, in a chemical purity of more than 90%; Yield 58%. PXRD depicted 90% Form I and 10% Form V.

Preparation of Paliperidone Form II

Example 2:

A slurry of Paliperidone (2 g) in ethanol (52 ml.) was heated to reflux and the insoluble solid filtrated out. After filtration, the solution was cooled to room temperature and stirred for 5 hours. The mixture was cooled to 0-4 °C (ice bath) and stirred for an additional half hour. A solid was obtained by filtration and dried in a vacuum oven at 55°C for overnight to give 1.75 g of Paliperidone, characterized by X-ray powder diffraction reflections at about: 10.3, 14.6, 22.0, 24.6 and 25.0 degrees two theta ± 0.2 degrees two theta.

Example 3:

A slurry of Paliperidone (2 g) in acetonitrile (36 ml.) was heated to reflux and the insoluble solid filtrated out. After filtration, the solution was cooled to room temperature and stirred for 5 hours. The mixture was cooled to 0-4 °C (ice bath) and filtered, washed with 40 ml. of acetonitrile and dried in a vacuum oven at 55°C for overnight to give 1.86 g of Paliperidone, characterized by X-ray powder diffraction reflections at about: 10.3, 14.6, 22.0, 24.6 and 25.0 degrees two theta ± 0.2 degrees two theta.

Example 4:

A slurry of Paliperidone (2 g) in isopropanol (80 ml.) was heated to reflux and the insoluble solid filtrated out. After filtration, the solution was cooled to room temperature. The mixture was cooled to 0-4 °C (ice bath) and stirred for an additional hour. A solid was obtained by filtration and dried in a vacuum oven at 55°C for overnight to give 1.75 g of Paliperidone, characterized by X-ray powder diffraction reflections at about: 10.3, 14.6, 22.0, 24.6 and 25.0 degrees two theta ± 0.2 degrees two theta.

Example 5:

A slurry of Paliperidone (1 g) in methanol (20 ml.) was heated to reflux and 0.05 g of activated carbon (SX-1) were added and stirred for 20 minutes at the same temperature. The mixture was filtered and the solution was cooled to room temperature and stirred for 2 hours. The mixture was cooled to 0-4 °C (ice bath) and stirred for an additional half hour. A solid was obtained by filtration and dried in a vacuum oven at 55°C for overnight to give 0.73 g of Paliperidone, characterized by X-ray powder diffraction reflections at about: 10.3, 14.6, 22.0, 24.6 and 25.0 degrees two theta ± 0.2 degrees two theta.

Preparation of Paliperidone Form III

Example 6:

A slurry of Paliperidone (1 g) in 1-methyl-2-pyrrolidone (5 ml.) was heated to 140 °C and the resulting solution was cooled to room temperature. The solid was filtrated and dried in a vacuum oven at 55 °C for overnight to give 0.53 g of Paliperidone, characterized by X-ray powder diffraction reflections at about: 10.8, 14.1, 15.8 and 16.8 degrees two theta ± 0.2 degrees two theta.

Preparation of Paliperidone Form IV

Example 7:

A slurry of Paliperidone (1 g) in 7 mL dioxane was heated to reflux temperature. Into the resulting solution was added at once 15 ml of water that were previously cooled in an ice bath. The solid was filtrated and analyzed by XRD to give Form IV.

Example 8:

A slurry of Paliperidone (5 g) in a mixture of acetone/water 3:1 (200 ml) was heated to reflux and the resulting solution was cooled to 0°C. The slurry was vacuum filtrated and the resulting solid was crystallized again from 175 ml of the solvent mixture, and a third time from 100 ml. The solid was filtrated and analyzed by XRD to give Form IV.

Example 9:

200mg of Paliperidone Form III was placed for 7 days in 100% relative humidity cell. The solid material was analyzed by XRD to give Form IV.

Preparation of Paliperidone form V

Example 10:

a. Preparation of Paliperidone crude

A 250ml reactor equipped with a mechanical stirrer, a reflux condenser was charged under nitrogen with CMHTP, i.e., 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrrido[1,2-a]-pyrimidin-4-one, (20 gr), F-BIP, i.e., : 6-fluoro-3-piperidino-1,2-benisoxazole, (19.2 gr), Sodium carbonate (16 gr) and acetonitrile (200 ml). The suspension was heated to 65°C and stirred for 26.5 hours. The reaction mixture was cooled to -10°C, filtered under reduced pressure, and washed 3 times with acetonitrile (3 x 40ml each). The resulting solid was slurried in 200 ml water at room temperature, filtered under reduced pressure, washed 3 times with water (3 x 80 ml each), and with 40 ml acetone. The crude was dried in a vacuum oven at 50°C under reduced pressure for overnight to give 29 gr of Paliperidone crude.

b. Crystallization of Paliperidone

A slurry of Paliperidone crude obtained in example 8a (28 gr) in a 1120 ml of a mixture of acetone/water (3:1) was heated to reflux till complete dissolution. After one hour, the solution was cooled to 0-4°C, filtrated, and washed with 60 ml of acetone. The procedure was repeated three times and finally the material was dried in a vacuum oven at 50°C under reduced pressure for overnight to give 15.2 gr of Paliperidone Form V.

Example 11:

Hot solution of Paliperidone (1 gr) in n-Propanol (30 ml) was dropped wise added into ice bath cooled water (50 ml). The solid was filtrated and dried overnight in a vacuum oven at 55°C to give 0.57 gr of Paliperidone Form V.

Example 12:

Hot solution of Paliperidone (1 gr) in dioxane (10 ml) was dropped wise added into ice bath cooled water (50 ml). The solid was filtrated and dried overnight in a vacuum oven at 55°C to give 0.52 gr of Paliperidone Form V.

Example 13:

0.83 gr of Paliperidone Form IV was dried overnight at 55°C in a vacuum oven under reduced pressure. The solid material was cooled to room temperature and analyzed by XRD to give 0.45 gr of Paliperidone Form V.

Example 14:

A mixture of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrrido[1,2-a]- pyrimidin-4-one (CMHTP, 4.393 g, 0.0168 mol), 6-fluoro-3-piperidino-1,2-benisoxazol (FPBI, 4.695 g, 0.0203 mol), sodium carbonate (4.968 g, 0.0422 mol) and potassium iodide (0.288 g, 0.0017 mol) in N,N-dimethylformamide (DMF, 50 ml) was heated for 8 h at 85°C. The mixture was poured into water (500 ml) and extracted with dichloromethane (4 x 100 ml). The extracts were combined, washed with water (4 x 100 ml), dried with anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to afford the crude product. Crystallization from acetonitrile (100 ml) afforded 4.63 g of the product, 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl}-9-hydroxy- 2-methyl-4H-pyrrido[1,2-a]pyrimidin-4-one, in a chemical purity of more than 90%; Yield 58%. PXRD depicted 90% Form I and 10% Form V.

Preparation of Amorphous Paliperidone

Example 15:

A slurry of Paliperidone Form II was slurried in n-Decane (1 mL) at 60°C for 24 hours. The solid was filtered and analyzed by XRD, to obtain amorphous Paliperidone

mixed with Form II. The level of amorphous Paliperidone was about 40% [see Figure 1]

Example 16:
5 g Paliperidon was dissolved in 85 ml of Dichloromethane at 40°C.
The solution was sprayed (5.6 ml/min) to the chamber with ambient nitrogen (30m³/h, 120°C) at co-current flow. The Atomizing flow (660 l/h) of nitrogen gave the Droplets affect which lead to the high evaporation rate. The temperature of the outlet solids were fixed to 80° C. The obtained sample was analyzed by XRD and found to be amorphous.

Example 17:
5 g Paliperidon was dissolved in 85 ml of Dichloromethane at 40°C.
The solution was sprayed (5.6 ml/min) to the chamber with ambient nitrogen (30m³/h, 70°C) at co-current flow. The Atomizing flow (660 l/h) of nitrogen gave the Droplets affect which lead to the high evaporation rate. The temperature of the outlet solids were fixed to 45° C. The obtained sample was analyzed by XRD and found to be amorphous.

Example 18:

A slurry of Paliperidone (1 g) in dichloromethane (17 ml) was heated to reflux until complete dissolution. The solvent was evaporated at 35°C under reduced pressure in a rotary evaporator. The solid was analyzed by PXRD to give pure amorphous Paliperidone. [see Figure 2]

Preparation of Pure Paliperidone Form I
Example 19:
A 100 ml flask equipped with a mechanical stirrer, a reflux condenser was charged under nitrogen with CMHTP (2 g), F-BIP (1.92 g), sodium carbonate (1.6 g), potassium iodide (0.03 g) and isopropyl alcohol (20 ml). The suspension was heated to 65oC and stirred for 24 hours to obtain yellowish slurry. The reaction mixture was cooled to -10oC in 2 hours, then filtered under reduced pressure and rinsed with 3 portions of isopropyl alcohol (10 ml each). The resulting solid was reslurried 3 times with water (20 ml each time) and 3 times with acetone (10 ml each), filtered and dried

at room temperature for 1 hour and at 60oC under reduced pressure for 1 hour to obtain Paliperidone (1.84 g, 57.7%). The solid was analyzed by XRD to be form 1.

Preparation of Paliperidone Form VI

Example 20:

A slurry of Paliperidone (1 gr) in a mixture of methanol/water 3:1 (37 ml) was heated to reflux temperature until complete dissolution was achieved. The resulting solution was cooled to 0°C. The solid was vacuum filtrated and analyzed by XRD to give Form VI.

Preparation of Paliperidone Mixtures

Example 21: A mixture of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrrido[1,2-a]- pyrimidin-4-one (CMHTP, 4.393 g, 0.0168 mol), 6-fluoro-3-piperidino-1,2-benisoxazol (FPBI, 4.695 g, 0.0203 mol), sodium carbonate (4.968 g, 0.0422 mol) and potassium iodide (0.288 g, 0.0017 mol) in N,N-dimethylformamide (DMF, 50 ml) was heated for 8 h at 85°C. The mixture was poured into water (500 ml) and extracted with dichloromethane (4 x 100 ml). The extracts were combined, washed with water (4 x 100 ml), dried with anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to afford the crude product. Crystallization from acetonitrile (100 ml) afforded 4.63 g of the product, 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl}-9-hydroxy- 2-methyl-4H-pyrrido[1,2-a]pyrimidin-4-one, in a chemical purity of more than 90%; Yield 58%. PXRD depicted 90% Form I and 10% Form V.

Example 22:

200mg of Paliperidone Form III was heated to 120^{0}C for 30 min in ambient conditions. The solid material was cooled to RT and analyzed by XRD to give a mixture of Forms V and II.

Example 23:

1.44 gr of Paliperidone Form VI was dried overnight at 55^{0}C in a vacuum oven under reduced pressure. The solid material was cooled to RT and analyzed by XRD to give a mixture of 0.66gr Paliperidone Forms V and II.

Example 24: Preparation of Paliperidone Form I by slurry in different solvents. Slurry of Paliperidone in the indicated volumes of the indicated solvents was stirred at the indicated temperatures and the indicated times. The solid was collected by vacuum filtration, dried where is indicated (in a vacuum oven at 55°C for overnight) and analyzed. The results are displayed in the next table.

Starting form	solvent	Solvent volume (ml/g)	Stirring temp.	Stirring time	Wet / dry
II	Ethanol / water 1:1	10	60°C	26h	w
II	dichlorobenzen	10	60°C	26h	w
II	Acetone / water 1:1	10	60°C	26h	w
I	IPA	10	60°C	17h	w + d
I	water	10	60°C	24h	w + d
I	acetone	10	25°C	47h	w + d
I	IPA	10	25°C	47h	w + d
I	water	10	25°C	47h	w + d

Example 25: Preparation of Paliperidone Form I by addition of a different hot solvent.

Slurry of Paliperidone in 17 volumes of dichloromethane was heated to reflux until complete dissolution. The hot solution was added dropwise into 50 volumes of hexane that was previously cooled in an ice bath. The resulting solid was collected by vacuum filtration, dried in a vacuum oven at 55 °C, and analyzed to give Form I.

Example 26: Preparation of Paliperidone Form I.

a. Preparation of Paliperidone crude

A 250 ml reactor equipped with a mechanical stirrer, a reflux condenser was charged under nitrogen with CMHTP (50 g), F-BIP (48 g), Sodium carbonate (40 g) and isopropanol (500 ml). The suspension was heated to 65oC and stirred for 25. The reaction mixture was cooled to -5 °C, filtered under reduced pressure, and washed 2 times with 200 ml water, followed by 200 ml IPA. The crude was dried in a vacuum oven at 50°C under reduced pressure for overnight to give Paliperidone crude.

b. Crystallization of Paliperidone in methanol

A slurry of 2 g of Paliperidone (obtained in section a) in 20 ml methanol was heated to reflux and an additional 20 ml of methanol were added (foreign bodies were removed from the mixture). After cooling to room temperature the mixture was stirred for overnight. The material was filtrated and dried in a vacuum oven at 50 oC under reduced pressure for overnight to give Paliperidone Form I.

c. Crystallization of Paliperidone in acetonitrile

A slurry of 2 g of Paliperidone (obtained in section a) in 36 ml acetonitrile was heated to reflux. After cooling to room temperature the mixture was cooled to 0 °C. The material was filtrated, washed with acetonitrile and dried in a vacuum oven at 50 oC under reduced pressure for overnight to give Paliperidone Form I.

Example 27: Preparation of Paliperidone Form II by crystallization.

A slurry of Paliperidone, in the indicated solvent, at the indicated volumes was heated to the indicated temperatures until complete dissolution, wherein each of the ratios presented in the table below represents volume ratio of the two solvents named immediately preceding the ratio. After the compound was dissolved, the oil bath was removed and the solution was cooled to room temperature (excepted were is indicated). The solid was filtrated, dried in a vacuum oven at 55°C for overnight, and analyzed as shown in the next table.

solvent	Solvent vol. (ml/g)	Heating temp.	Cooling temp.	Wet / dry
ethanol	28	reflux	r.t.	w + d
n-propanol	20	reflux	r.t.	w + d

IPA	42	reflux	r.t.	w + d
methanol	48	reflux	r.t.	w + d
toluene	15	reflux	r.t.	w + d
Iso-butyl acetate	55	reflux	r.t.	w + d
n-butanol	20	reflux	r.t.	w + d
MIBK	39	reflux	r.t.	w + d
2-pentanol	22	reflux	r.t.	w + d
PGME	8	reflux	r.t.	w + d
n-butyl acetate	31	reflux	r.t.	w + d
Diethyl carbonate	28	reflux	r.t.	w + d
chlorobenzen	6	reflux	r.t.	w + d
Cellosolve	8	reflux	r.t.	w + d
n-pentanol	15	reflux	r.t.	w + d
THF	24	reflux	r.t.	w + d
1,2-dichloroethane	12	reflux	r.t.	w + d
DMF	5	reflux	r.t.	w + d
Dimethyl acetamide	5	reflux	r.t.	d
Dichlorobenzen	5	reflux	r.t.	w + d
Propylene glycole	5	reflux	r.t.	w + d
DMSO	5	reflux	r.t.	w + d
DMC	33	reflux	r.t.	w + d
2-butanol	20	reflux	r.t.	w + d
MIPK	54	reflux	r.t.	w + d
Iso-butanol	26	reflux	r.t.	w + d

Ethanol/water 3:1	12	reflux	r.t.	w + d
Ethanol/water 1:1	36	reflux	r.t.	w + d
MEK	69	reflux	r.t.	w + d
acetonitrile	100	reflux	r.t.	w + d
EtOAc/water 3:1	50	reflux	r.t.	w + d
EtOAc/water 1:1	55	reflux	r.t.	w + d
dioxane	6	reflux	r.t.	w + d
Dibutyl ether	165	reflux	r.t.	w + d
acetone	155	reflux	r.t.	w + d
Acetone/water 3:1	25	reflux	r.t.	w + d
Acetonitril/water 1:1	40	reflux	r.t.	w + d
n-butanol	23	135°C	r.t.	w + d
cellosolve	8	115°C	r.t.	w + d
chlorobenzen	7	115°C	r.t.	w + d
DMSO	5	110°C	r.t.	w + d
Dibutyl ether	140	130°C	r.t.	w + d
PGME	7	130°C	r.t.	w + d
Iso-butyl acetate	35	reflux	r.t.	w + d
n-propanol	30	90°C	r.t.	w + d
ethanol	80	70°C	r.t.	w
IPA/water 1:1	19	reflux	0°C	w + d
IPA/water 3:1	10	reflux	0°C	w + d

Example 28: Preparation of Paliperidone Form II by addition of a different solvent

Slurry of Paliperidone in 20 volumes (ml/g) of dichloromethane was heated to reflux until complete dissolution. The solution was cooled to room temperature and the indicated anti-solvent was gradually added until precipitation. The mixture was stirred at room temperature for 1.5 h and the solid was collected by vacuum filtration (dried in a vacuum oven at 55 °C for overnight where is indicated) and analyzed as shown in the next table.

Anti-solvent	Anti-Solvent volume (ml/g)	Wet / dry
MTBE	15	w + d
MEK	20	w + d
EtOAc	20	w + d
Acetonitril	25	w + d
Cyclohexane	30	w + d
heptane	15	w + d
toluene	15	w + d

Example 29: Preparation of Paliperidone Form II by addition of a different solvent at a different temperature.

Slurry of Paliperidone in the indicated volumes of the indicated solvent was heated to reflux until complete dissolution. The cooled anti-solvent was added at once. The resulting solid was collected by vacuum filtration (dried in a vacuum oven at 55 °C for overnight where is indicated), and analyzed as shown in the next table, wherein "Wet" indicates analyzed after isolation, and "dry" means dried in a vacuum oven at 55°C overnight.

solvent	Total solvent vol. (ml/g)	Anti-solvent	Anti-solvent vol. (ml/g)	Wet / dry
toluene	15	hexane	35	w
butanol	7	water	70	d

Example 30: Preparation of Paliperidone Form III by slurry in NMP.

Slurry of Paliperidone Form II in 10 volumes of NMP the indicated volumes was stirred for 24 h at 60 °C. The solid was collected by vacuum filtration, and analyzed to give Form III..

Example 31: Preparation of Paliperidone Form IV by addition of a different solvent at a different temperature.

A slurry of Paliperidone (1g) in 7 ml n-butanol was heated to reflux temperature. Into the resulting solution was added at once 70 ml. of water that were previously cooled in an ice bath. The solid was filtrated and analyzed by XRD to give Form IV.

Example 32: Preparation of Paliperidone Form IV by crystallization.

A slurry of Paliperidone, in the indicated solvent, at the indicated volumes was heated to the indicated temperatures until complete dissolution, wherein each of the ratios presented in the table below represents volume ratio of the two solvents named immediately preceding the ratio. After the compound was dissolved, the oil bath was removed and the solution was cooled to room temperature (excepted were is indicated). The solid was filtrated and analyzed as shown in the next table.

solvent	**Solvent vol. (ml/g)**	**Heating temp.**	**Cooling temp.**
Acetone / water 5:1	40	reflux	r.t.
Acetone / water 3:1	40	reflux	0°C
methanol / water 3:1	34	reflux	0°C

Example 33: Preparation of Paliperidone Form IV by addition of a different solvent at a different temperature.

Slurry of Paliperidone in the indicated solvent was heated to reflux until complete dissolution. The hot solution was added dropwise into an anti-solvent that was previously cooled in an ice bath. The resulting solid was collected by vacuum filtration, and analyzed as shown in the next table.

solvent	Solvent vol. (ml/g)	Anti-solvent	Anti-solvent vol. (ml/g)
n-propanol	30	water	50
dioxane	10	water	50

Example 34: Preparation of Paliperidone Form IV by filtration through activated carbon

A slurry of Paliperidone in 40 volumes (i.e., g/40 ml) of acetone/water (3:1, volume ratio) was heated to reflux until complete dissolution. After the compound was

dissolved, the hot solution was filtrated through hi-flow and cooled in an ice bath. The solid was filtrated and analyzed as shown in the next table.

Type of active carbon	Time of reflux	Time of cooling
HB ultra	40 min	60 min
CGP super	60 min	50 min
GBG	65 min	50 min
SX plus	55 min	60 min
ROX 0.8	55 min	2 h
A super eur	60 min	2 h

Example 35: Preparation of mixture of Paliperidone by crystallization.

A slurry of Paliperidone, in the indicated solvent, at the indicated volumes was heated to the indicated temperatures until complete dissolution, wherein each of the ratios presented in the table below represents volume ratio of the two solvents named immediately preceding the ratio. After the compound was dissolved, the oil bath was removed and the solution was cooled to room temperature (excepted were is indicated). The solid was filtrated and analyzed as shown in the next table.

solvent	Solvent vol. (ml/g)	Heating temp.	Cooling temp.	Wet	dry
Acetone / water 1:1	98	reflux	0°C	II + 9.7, 10.9, 15.8, 21.2, 26.0	II ???
dichlorobenzen	5	120°C	r.t.	Am. + II	
Propylene glycole	7	120°C	r.t.	II + Am.	
Acetone / water 1:5	40	reflux	0°C		II + V
methanol / water 3:1	34	reflux	0°C	VI	V + II

CLAIMS

What Is Claimed Is:

1. Amorphous Paliperidone.

2. The amorphous Paliperidone of claim 1, having less than 60% by weight of crystalline Paliperidone.

3. The amorphous Paliperidone of claim 2, having less than 50% by weight of crystalline Paliperidone.

4. The amorphous Paliperidone of claim 3, having about 40% by weight of crystalline Paliperidone.

5. The amorphous Paliperidone of claim 1, wherein the amorphous Paliperdione displays a PXRD spectrum substantially as in Figure 1.

6. A process for preparing the amorphous Paliperidone of claim 1 comprising: exposing a Paliperidone crystalline form characterized with X-ray powder diffraction spectrum with peaks at about: 10.3, 14.6, 22.0, 24.6 and 25.0 degrees two theta ± 0.2 degrees two theta to n-decane to obtain the amorphous Paliperidone.

7. The amorphous Paliperidone of claim 4, wherein the amorphous Paliperidone is substantially pure.

8. The amorphous Paliperidone of claim 4, wherein the amorphous Paliperidone is free of Forms I, II, III, IV, V or VI.

9. The substantially pure amorphous Paliperidone of claim 7, having less than 20% of crystalline forms of paliperidone.

10. The substantially pure amorphous Paliperidone of claim 8, having less than 10% of crystalline forms of paliperidone

11. The substantially pure amorphous Paliperidone of claim 9, having less than 5% of crystalline forms of paliperidone.

12. The substantially pure amorphous Paliperidone of claim 9, having less than 1% of crystalline forms of paliperidone.

13. The substantially pure amorphous Paliperidone of claim 7 displaying a PXRD spectrum substantially as depicted in Figure 2

14. A process for preparing the substantially pure amorphous Paliperidone of claim 7 comprising: providing a solution of paliperidone and dichloromethane; and removing the solvent to obtain the substantially pure amorphous paliperidone.

15. The process of claim 14 wherein the solvent removal is by spray drying.

16. Crystalline Paliperidone, designated as Form I, characterized by data selected from the group consisting of:

(i) X-ray powder diffraction spectrum with peaks at about: 5.8, 8.4, 9.5 and 11.6 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 163.1, 161.2 and 156.8 ± 0.2 ppm; and

(iii) a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.8, 43.9 and 39.5 ± 0.1 ppm.

17. The crystalline Paliperidone of claim 16, wherein the X-ray powder diffraction spectrum includes one or more additional peaks at about 15.2, 24.8 and 31.7 ± 0.2 degrees two-theta.

18. The crystalline Paliperidone of claim 16 wherein the X-ray powder diffraction spectrum is substantially as in Figure 3.

19. The crystalline Paliperidone of claim 16 wherein the solid-state ^{13}C NMR spectrum has one or more signals at about 121.2 and 117.3 ± 0.2 ppm.

20. The crystalline Paliperidone of claim 16, wherein the solid-state ^{13}C NMR spectrum has chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.8, 43.9, 39.5 and 3.9 ± 0.1 ppm.

21. The crystalline Paliperidone of claim 16, wherein the ^{13}C NMR spectrum is substantially as depicted in Figure 4 or 5.

22. The crystalline Paliperidone of claim 16, having a melting point of about 166 to about 167°C.

23. The crystalline Paliperidone of claim 16, which is anhydrous.

24. The crystalline Paliperidone of claim 23, having a water content of about 0.5%.

25. The crystalline Paliperidone of claim 16, having less than 20% of any one of other crystalline forms of paliperidone.

26. The crystalline form of Paliperidone of claim 25 having less than 20% of any one of Forms II and V of paliperidone.

27. The crystalline Paliperidone of claim 26, having less than 10% of any one of Forms II and V of paliperidone.

28. The crystalline Paliperidone of claim 27, having less than 5% of any one of Forms II and V of paliperidone.

29. The substantially pure amorphous Paliperidone of claim 9, having less than 1% of Form II , V, or mixtures thereof, of paliperidone.

30. Crystalline Paliperidone, characterized by an X-ray powder diffraction spectrum with peaks at about: 10.1, 12.4, 14.3, 17.0 and 17.2 ± 0.2 degrees two theta.

31. The crystalline Paliperidone of claim 26, further characterized by one or more X-ray powder diffraction peaks at about 12.9, 18.9, 21.9, 24.8 and 26.2 ± 0.2 degrees two-theta.

32. The crystalline Paliperidone of claim 30, having a powder x-ray diffraction diagram substantially as depicted in Figure 3A.

33. A crystalline form of Paliperidone, designated as Form II, characterized by data selected from the group consisting of:

(i) X-ray powder diffraction spectrum with peaks at about: 10.3, 14.6, 22.0, 24.6 and 25.0 degrees two theta ± 0.2 degrees two theta;

(ii) X-ray powder diffraction spectrum with peaks at about: 10.3, 13.3, 13.9, 14.6 and 15.1 degrees two theta ± 0.2 degrees two theta;

(iii)a solid-state ^{13}C NMR spectrum with signals at about 163.4, 121.8 and 116.7 ± 0.2 ppm; and

(iv)a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 95 to 180 ppm of about 65.7, 24.1 and 19.0 ± 0.1 ppm.

34. The crystalline form of Paliperidone of claim 33, wherein the X-ray powder diffraction spectrum in (i) includes one or more additional peaks at about: 13.1, 13.8, 14.1, 18.7 and 28.0 ± 0.2 degrees two-theta.

35. The crystalline form of Paliperidone of claim 34, wherein the X-ray powder diffraction spectrum is substantially as depicted in Figure 6.

36. The crystalline form of Paliperidone of claim 33 wherein the solid-state ^{13}C NMR spectrum has one or more additional signals at about 163.4, 156.2, 121.8, 116.7 and 97.7 ± 0.2 ppm or chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 95 to 180 ppm of about 65.7, 58.5, 24.1 and 19.0 ± 0.1 ppm ± 0.1 ppm.

37. The crystalline form of Paliperidone of claim 33 having less than 20% of any one of other crystalline forms of paliperidone.

38. The crystalline form of Paliperidone of claim 37 having less than 20% of any one of Forms I and V of paliperidone.

39. The crystalline form of Paliperidone of claim 38 having less than 10% of any one of Forms I and V of paliperidone.

40. The crystalline form of Paliperidone of claim 39 having less than 5% of any one of Forms I and V of paliperidone..

41. The crystalline form of Paliperidone of claim 40 having less than 1% of any one of Forms I and V of paliperidone.

42. The crystalline form of Paliperidone of claim 33, wherein the ^{13}C NMR spectrum is substantially as depicted in Figures 7 or 8.

43. The crystalline form of Paliperidone of claim 33, which is anhydrous.

44. The crystalline form of Paliperidone of claim 43, having a water content of about 0.5%.

45. A process for the preparation of the crystalline form of Paliperidone of claim 33, comprising crystallization from a solution of paliperidone and a solvent selected from a group consisting of: ethanol and isopropanol.

46. A crystalline form of Paliperidone, designated as Form III, characterized by data selected from the group consisting of:

(i) X-ray powder diffraction spectrum with peaks at about: 10.8, 14.1, 15.8 and 16.8 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 164.1, 161.3 and 157.9 ± 0.2 ppm; and

(iii)a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 46.7, 43.9 and 40.5 ± 0.1 ppm.

47. The crystalline form of claim 46, wherein the X-ray powder diffraction spectrum has an additional peak at about 25.8 ± 0.2 degrees two theta.

48. The crystalline form of claim 47, wherein the X-ray powder diffraction spectrum has one or more peaks selected from the list of about: 9.9, 11.0, 12.0, 17.3 and 32.5 ± 0.2 degrees two theta.

49. The crystalline form of claim 48, wherein the powder x-ray diffraction spectrum is susbtantially as depicted in Figure 9.

50. The crystalline form of claim 46, wherein the solid-state ^{13}C NMR spectrum has one or more additional signals at about 164.1, 161.3, 157.9, 123.9 and 117.4 ± 0.2 ppm or chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 46.7, 43.9, 40.5 and 6.5 ± 0.1 ppm.

51. The crystalline form of claim 46, wherein the solid-state ^{13}C NMR spectrum is substantially as depicted in Figures 10 and 11.

52. The crystalline form of claim 46, which is an NMP solvate.

53. The crystalline form of claim 46, having a water content of about 0.2%.

54. The crystalline form of claim 46, having less than 20% of any one of other crystalline forms of paliperidone.

55. The crystalline form of Paliperidone of claim 54 having less than 20% of any one of Form I , II and V of paliperidone.

56. The crystalline form of claim 55, having less than 10% of any one of Forms I , II and V of paliperidone.

57. The crystalline form of claim 56, having less than 5% of any one of Forms I , II and V of paliperidone.

58. The crystalline form of claim 57, having less than 1% of any one of Forms I , II and V of paliperidone.

59. A process for preparing the crystalline form of claim 46, comprising

providing a solution of paliperidone in 1-methyl-2-pyrrolidone; and

crystallizing paliperidone from the solution to obtain the crystalline form of claim 40.

60. A crystalline form of Paliperidone, designated as Form IV, characterized by data selected from the group consisting of:

(i) X-ray powder diffraction spectrum with peaks at about: 10.2, 12.2 and 15.5 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 162.6, 160.5 and 157.6 ± 0.2 ppm; and

(iii)a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.9, 43.8 and 40.9 ± 0.1.

61. The crystalline form of claim 60, wherein the X-ray powder diffraction spectrum further has a peak at about 13.6 ± 0.2 degrees two theta.

62. The crystalline form of claim 61, wherein the X-ray powder diffraction spectrum further has peaks at about 23.9 and 33.2 ± 0.2 degrees two theta.

63. The crystalline form of claim 62, wherein the powder x-ray diffraction spectrum is substantially as depicted in Figure 12.

64. The crystalline form of claim 60, wherein the solid-state ^{13}C NMR spectrum has one or more signals at about 162.6, 160.5, 157.6, 118.6 and 116.7 ± 0.2 ppm or having chemical shift differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 115 to 180 ppm of about 45.9, 43.8, 40.9 and 1.9 ± 0.1 ppm ± 0.1 ppm.

65. The crystalline form of claim 64, wherein the solid-state ^{13}C NMR spectrum is substantially as depicted in Figures 13 and 14.

66. The crystalline form of claim 60, wherein the crystalline paliperidone Form IV is substantially pure.

67. The crystalline form of claim 66, wherein the Form IV has less than 20% of any one of other crystalline forms of paliperidone.

68. The crystalline form of Paliperidone of claim 67 having less than 20% of any one of Form I , II and V or mixtures thereof known crystalline forms of paliperidone.

69. The crystalline form of claim 68, wherein the Form IV has less than 10% by weight of Form I , II, V or mixtures thereof known crystalline forms of paliperidone.

70. The crystalline form of claim 69, wherein the Form IV has less than 5% by weight of Forms I , II and V of paliperidone.

71. The crystalline form of claim 70, having less than 1% of any one of Forms I , II and V of paliperidone.

72. A process for preparing the crystalline form of claim 60, comprising

providing a solution of paliperidone in a solvent selected from the group consisting of dioxane and a mixture of acetone/water in a volume ratio of 3:1; and

crystallizing paliperidone from the solution to obtain the crystalline form of claim 60.

73. A crystalline form of Paliperidone, designated as Form V, characterized by data selected from the group consisting of:

(i) X-ray powder diffraction spectrum with four or more peaks from the list of: about 9.8, 10.9, 15.8, 21.2 and 21.6 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 163.4, 161.4 and 157.9 ± 0.2 ppm; and

(iii)a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of about 51.1, 49.1 and 45.6 ± 0.1 ppm.

74. The crystalline form of claim 73, wherein the X-ray powder diffraction spectrum further has one or more peaks from the following: about 14.1, 18.0 and 26.0 ± 0.2 degrees two theta.

75. The crystalline form of claim 73, wherein the solid state ^{13}C NMR spectrum further has one or more signals at 119.5 and 112.3 ± 0.2 ppm.

76. The crystalline form of claim 75 wherein the solid state ^{13}C NMR spectrum is substantially as depicted in Figures 16 and 17.

77. The crystalline form of claim 73 wherein the X-ray powder diffraction spectrum is substantially as depicted in Figures 15.

78. The crystalline form of claim 73 wherein the form is anhydrous.

79. The crystalline form of claim 78 wherein the water content is about 0.3%, as measured by KF titration.

80. The crystalline form of claim 73, having less than 20% of any one of other crystalline forms of paliperidone.

81. The crystalline form of Paliperidone of claim 80 having less than 20% of any one of Forms I and II of paliperidone.

82. The crystalline form of claim 81, having less than 10% of any one of Forms I and II of paliperidone.

83. The crystalline form of claim 82, having less than 5% of any one of Forms I and II of paliperidone.

84. The crystalline form of claim 83, having less than 1% of any one of Forms I and II of paliperidone.

85. A crystalline form of Paliperidone, designated as Form VI, characterized by data selected from the group consisting of

(i) an X-ray powder diffraction spectrum with four or more peaks from the list of: about 8.5, 8.8, 9.7, 11.2 and 11.6 degrees two theta ± 0.2 degrees two theta;

(ii) a solid-state ^{13}C NMR spectrum with signals at about 163.4, 161.4 and 157.9 ± 0.2 ppm;

(iii)a solid-state ^{13}C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift and another in the chemical shift range of 100 to 180 ppm of about 51.1, 49.1 and 45.6 ± 0.1 ppm.

86. The crystalline form of claim 85 wherein the X-ray powder diffraction spectrum further has peaks at about: 5.7, 15.3, 23.8 and 24.8 ± 0.2 degrees two theta.

87. The crystalline form of claim 86 wherein the X-ray powder diffraction spectrum is substantially as depicted in Figure 18.

88. The crystalline form of claim 85, having less than 20% of any one of other crystalline forms of paliperidone.

89. The crystalline form of Paliperidone of claim 88 having less than 20% of any one of Forms I , II and V of paliperidone.

90. The crystalline form of claim 89, having less than 10% of any one of Forms I , II and V of paliperidone.

91. The crystalline form of claim 90, having less than 5% of any one of Forms I , II and V of paliperidone.

92. The crystalline form of claim 91, having less than 1% of any one of Forms I , II and V of paliperidone.

93. A process for preparing the crystalline form of claim 85, comprising crystallizing paliperidone from a solution of paliperidone in an ethanol/water mixture in a volume ratio of about 3:1.

Figure 1. Powder X-ray diffractogram of Amorphous Paliperidone

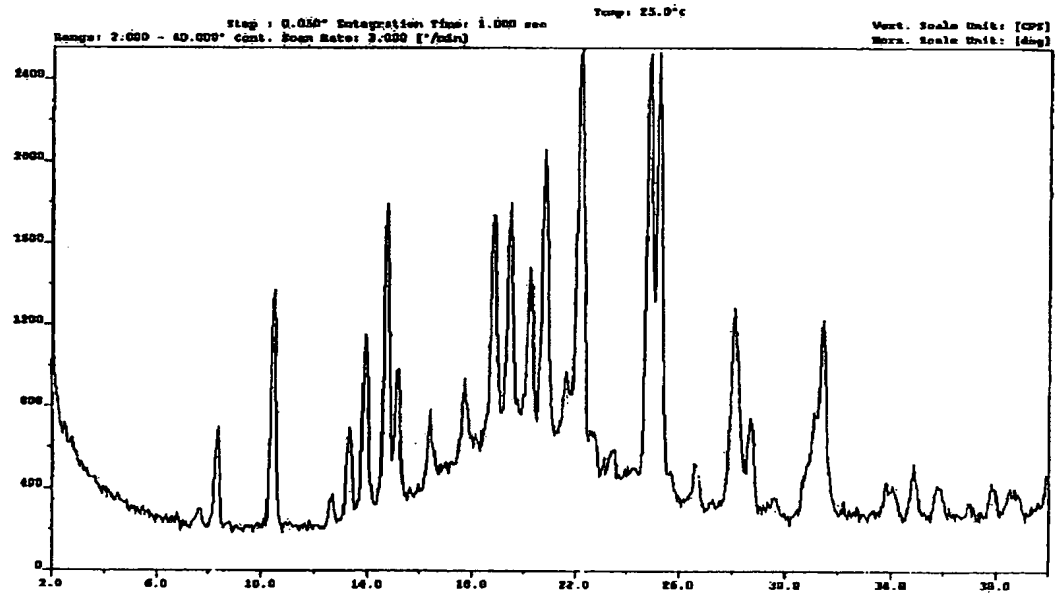


Figure 2. Powder X-ray diffractogram of Pure Amorphous Paliperidone

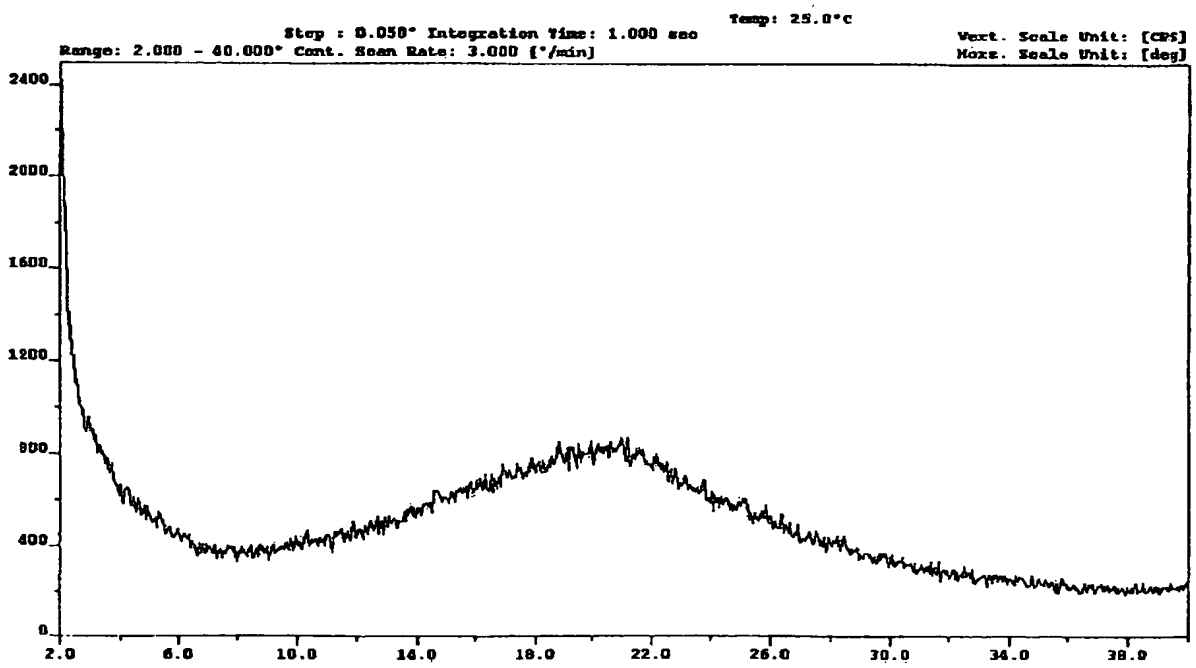


Figure 3.

A. Powder X-ray diffractogram of Pure Paliperidone Form I.

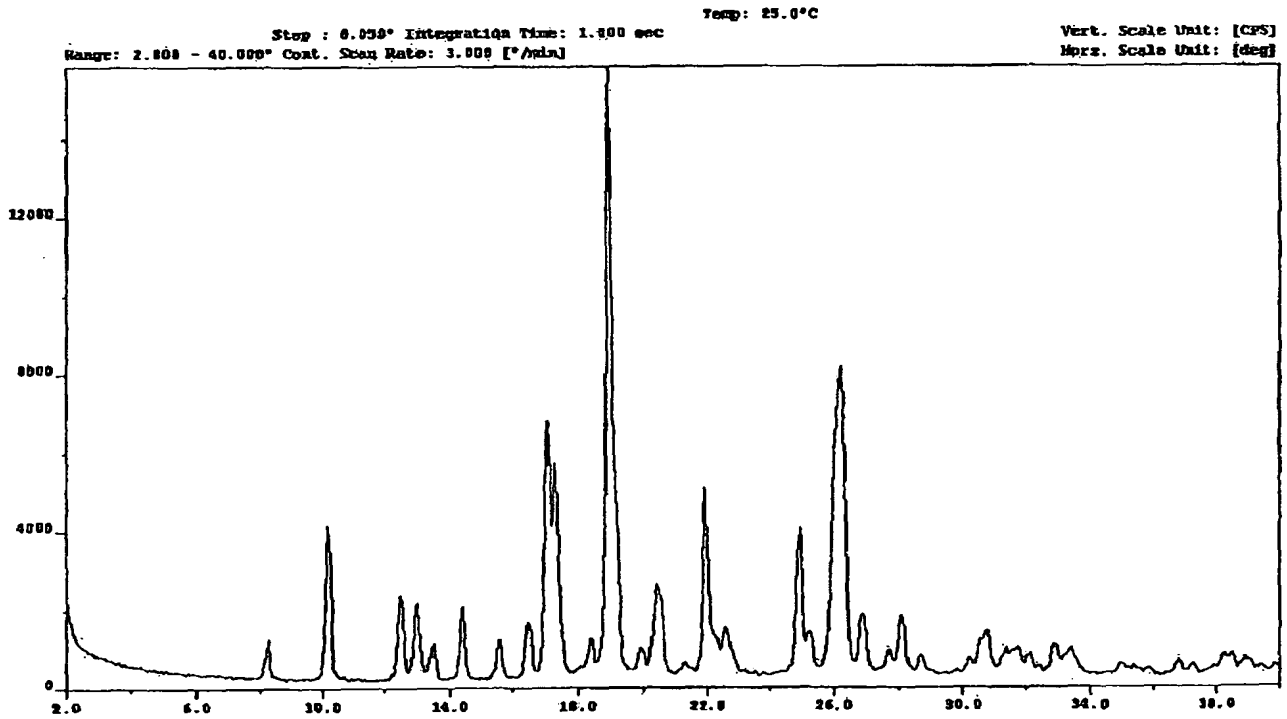


Figure 3.

B. Powder X-ray diffractogram of Paliperidone Form I and and about 8% Form V.

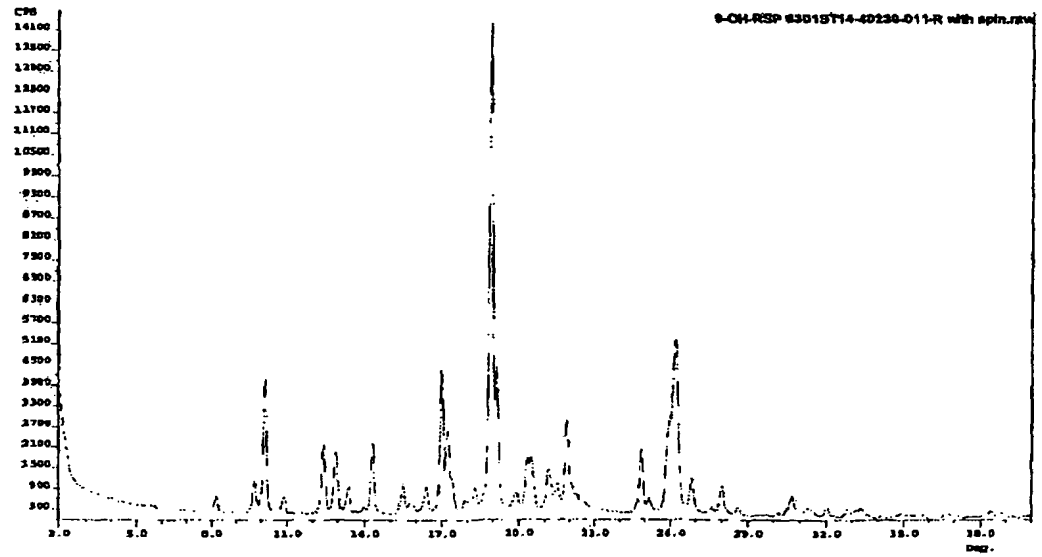


Figure 4. A solid-state ^{13}C NMR spectrum of Paliperidone Form I in the 115-180 ppm range.

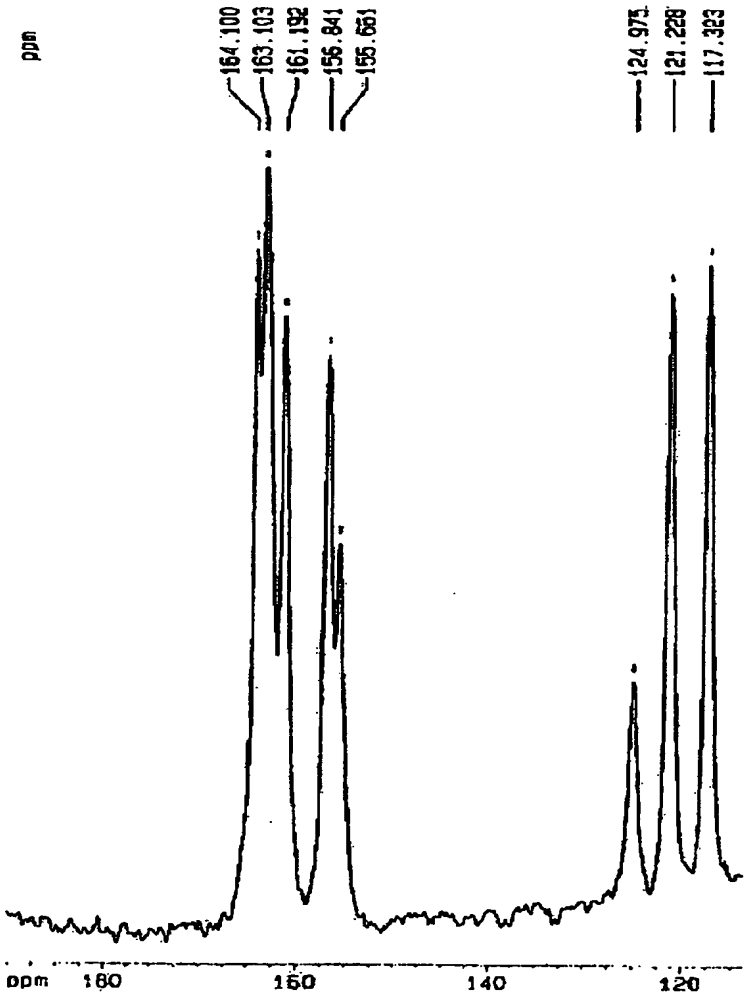


Figure 5. A solid-state ^{13}C NMR spectrum of Paliperidone Form I

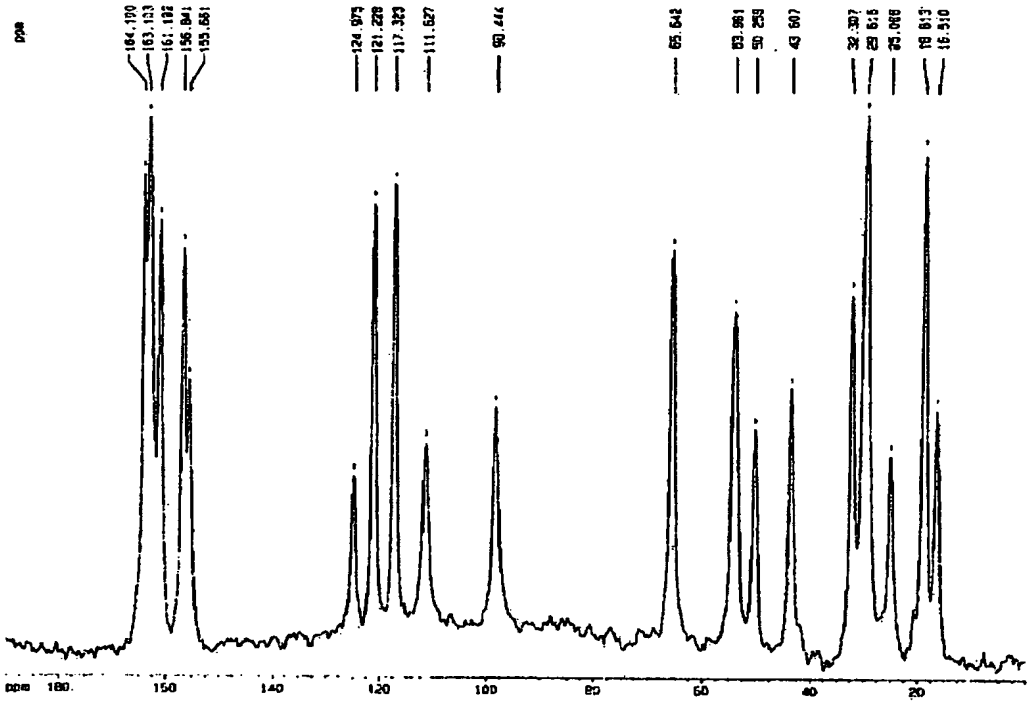


Figure 6. Powder X-ray diffractogram of Paliperidone Form II.

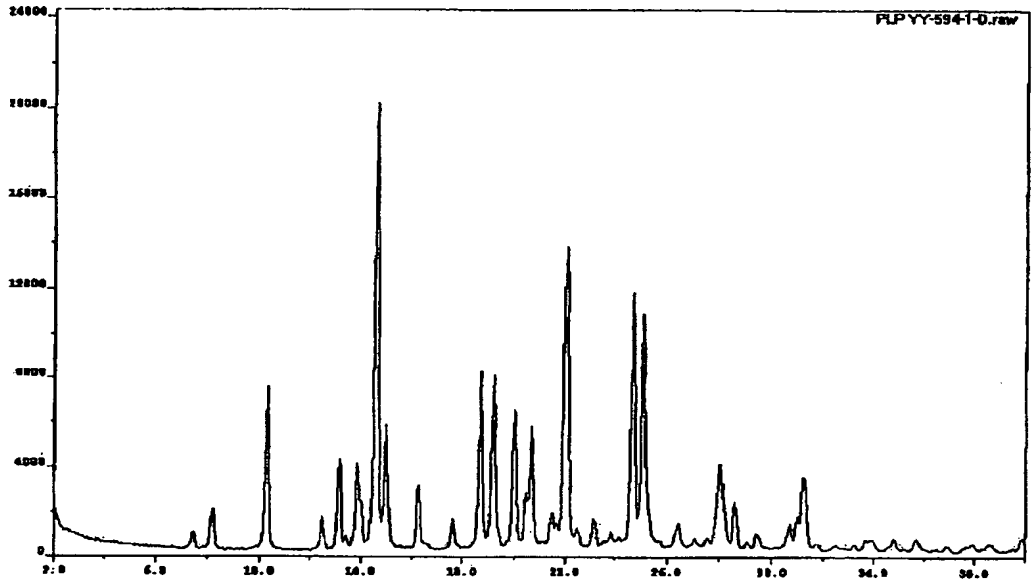


Figure 7. A solid-state ^{13}C NMR spectrum of Paliperidone Form II in the 95-180 ppm range.

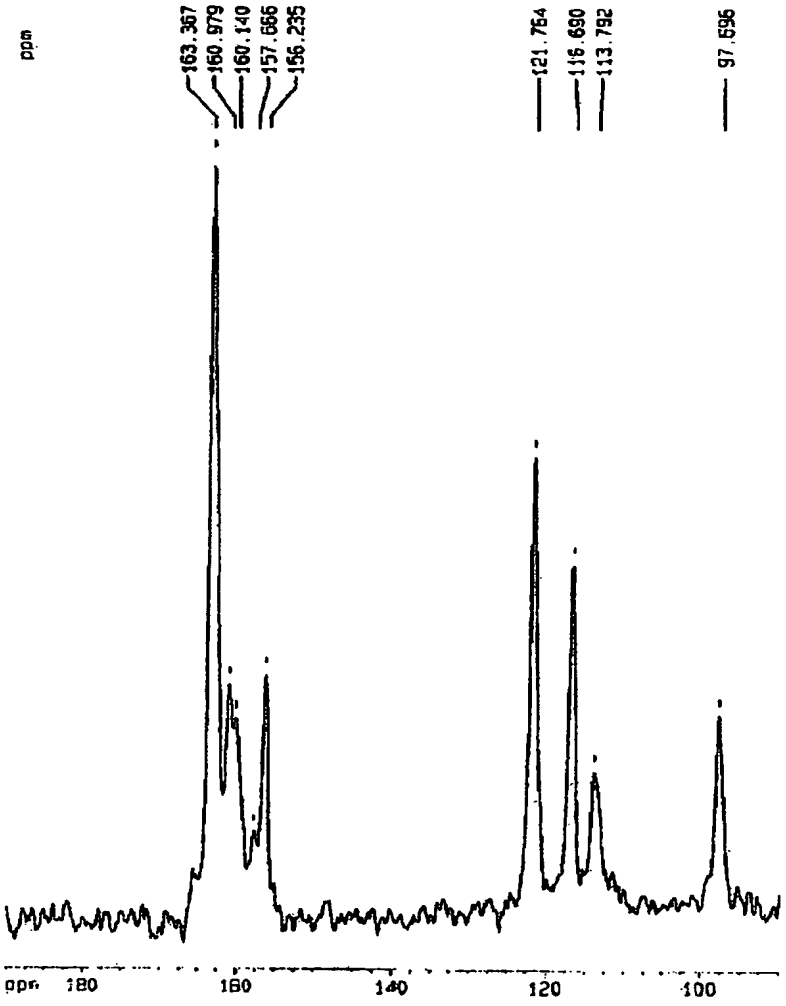


Figure 8: a solid-state ^{13}C NMR spectrum of Paliperidone Form II

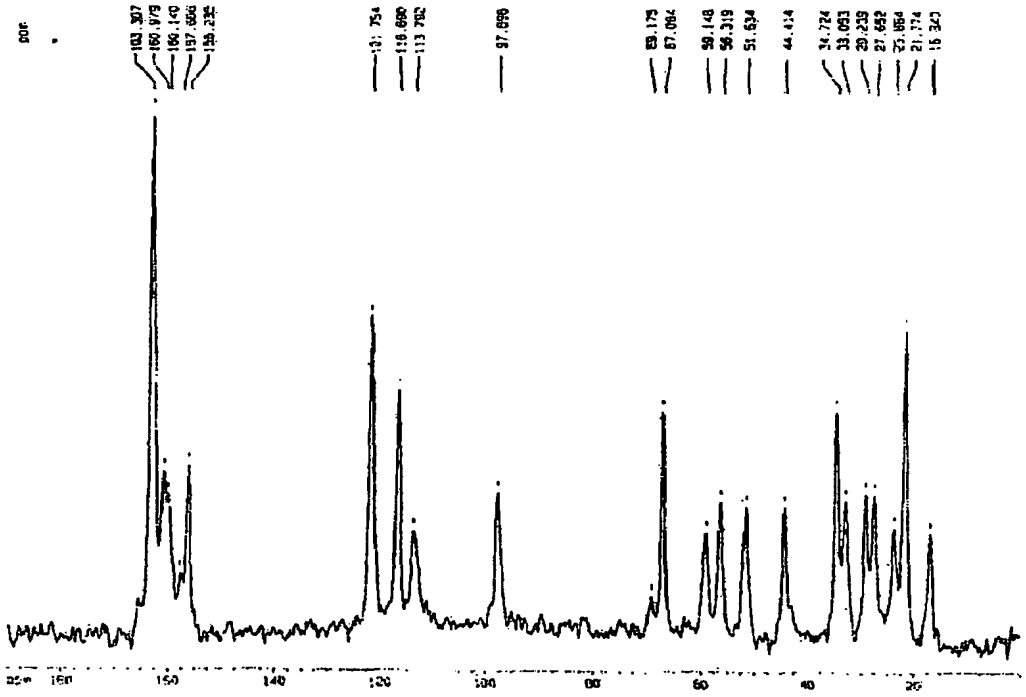


Figure 9. Powder X-ray diffractogram of Paliperidone Form III.

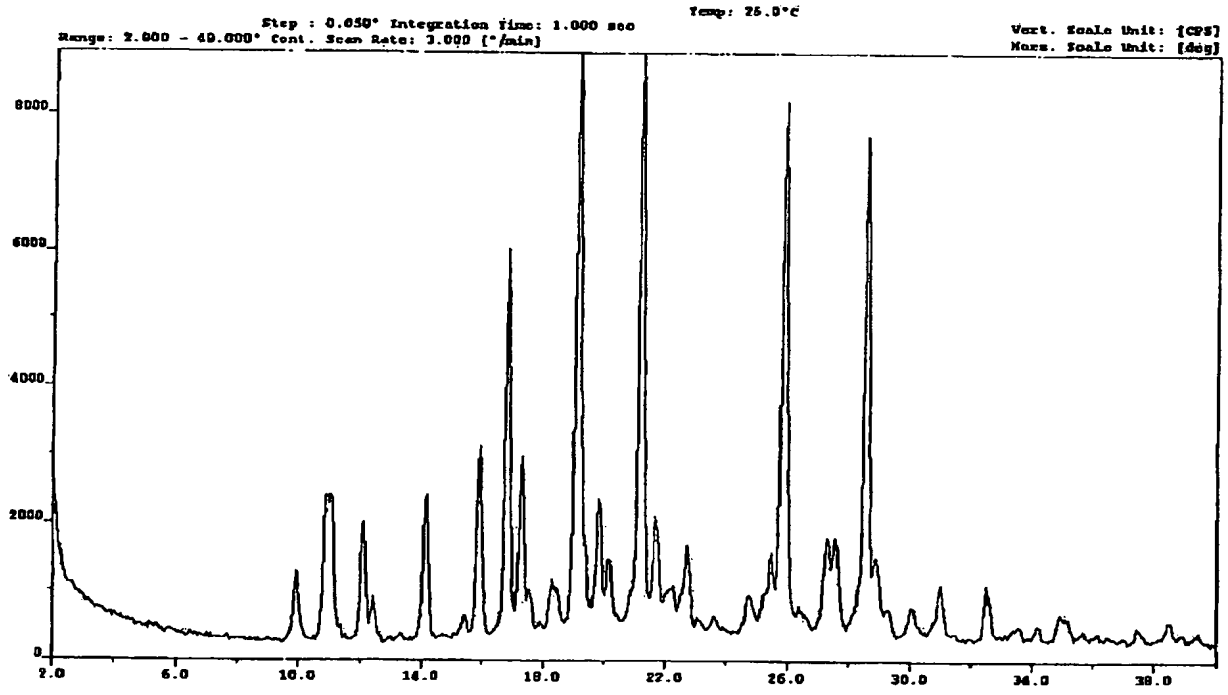


Figure 10. A solid-state ^{13}C NMR spectrum of Paliperidone Form III in the 115-180 ppm range.

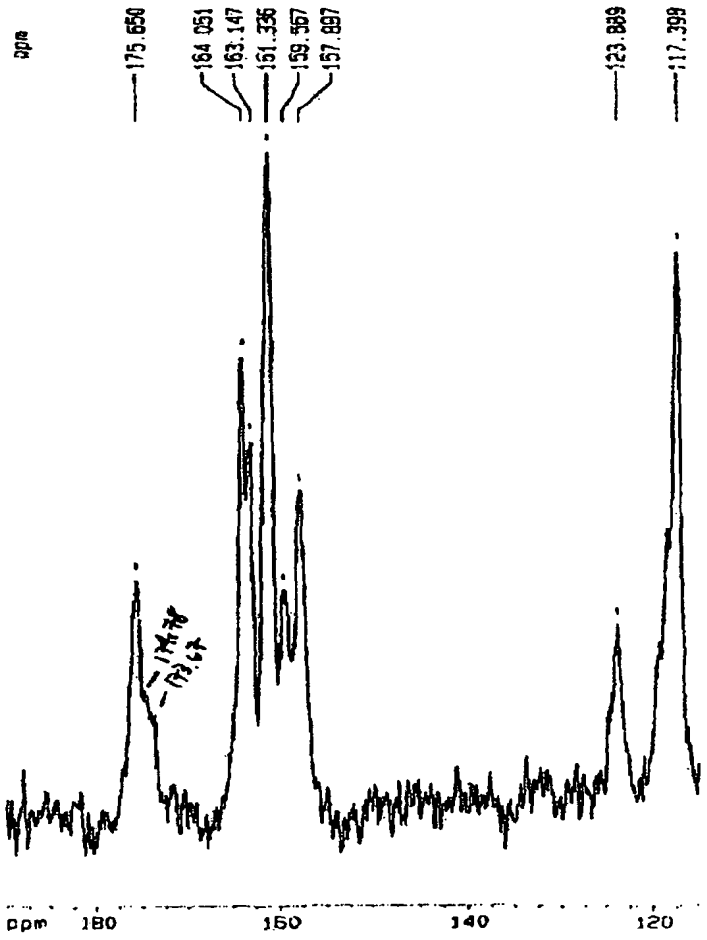


Figure 11. Solid-state ^{13}C NMR spectrum of Paliperidone Form III

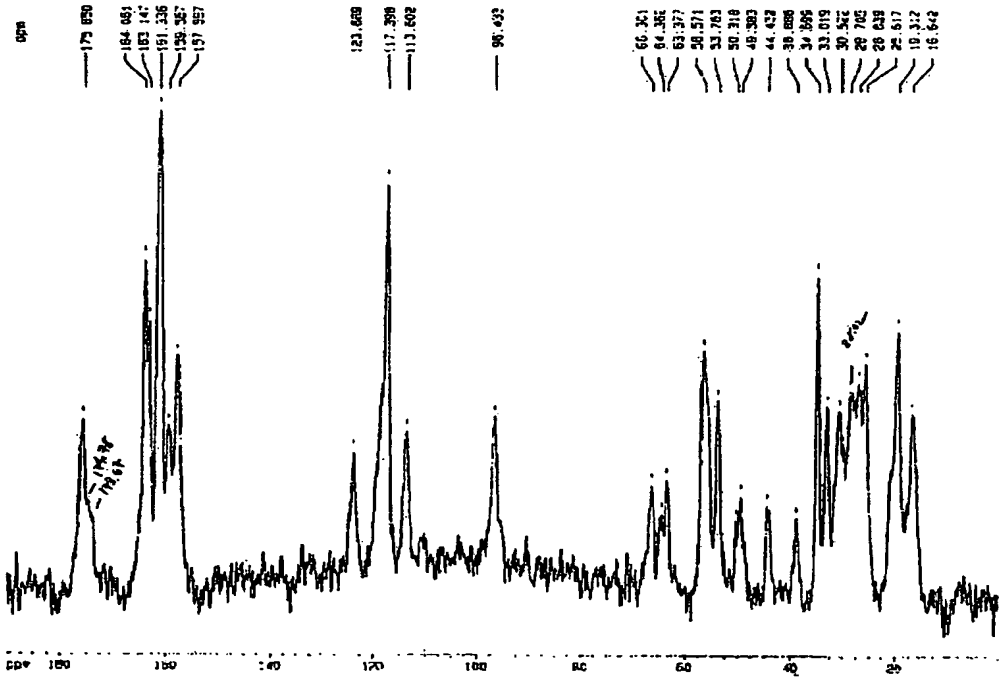


Figure 12. Powder X-Ray Diffraction of Paliperidone Form IV.

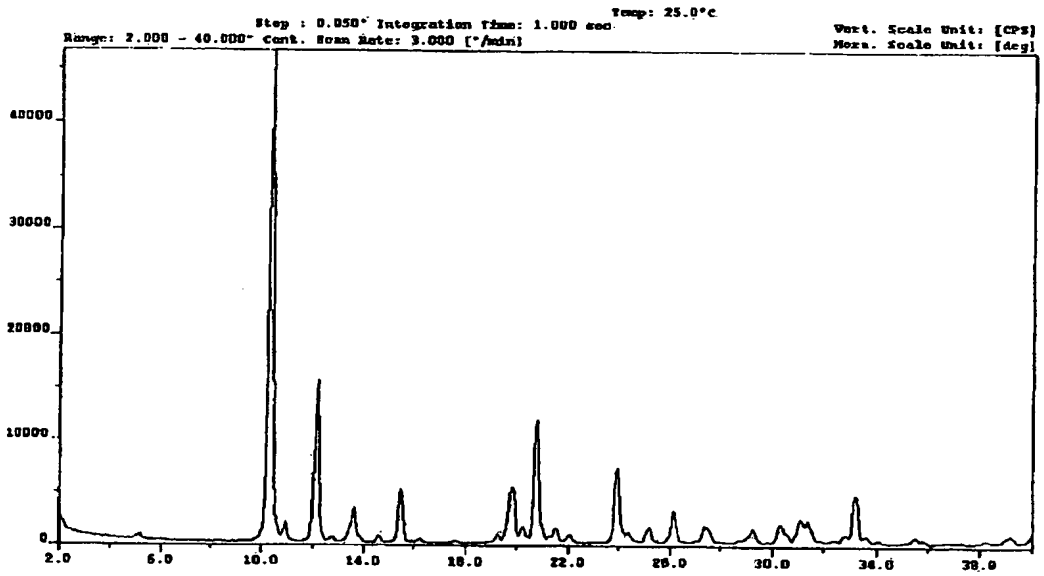


Figure 13. Solid-state ^{13}C NMR spectrum of Paliperidone Form IV in the 115-180 ppm range.

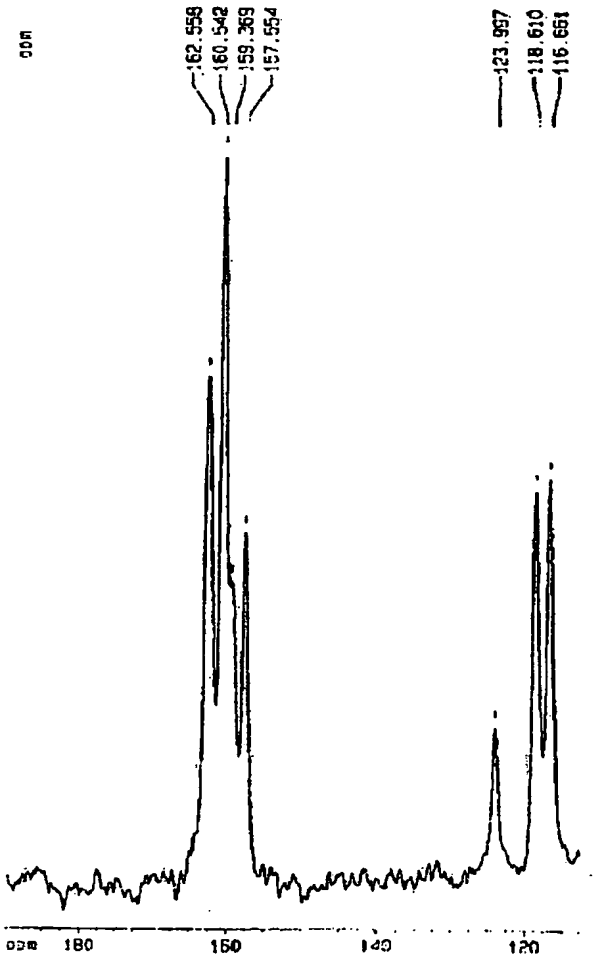


Figure 14. Solid-state ^{13}C NMR spectrum of Paliperidone Form IV

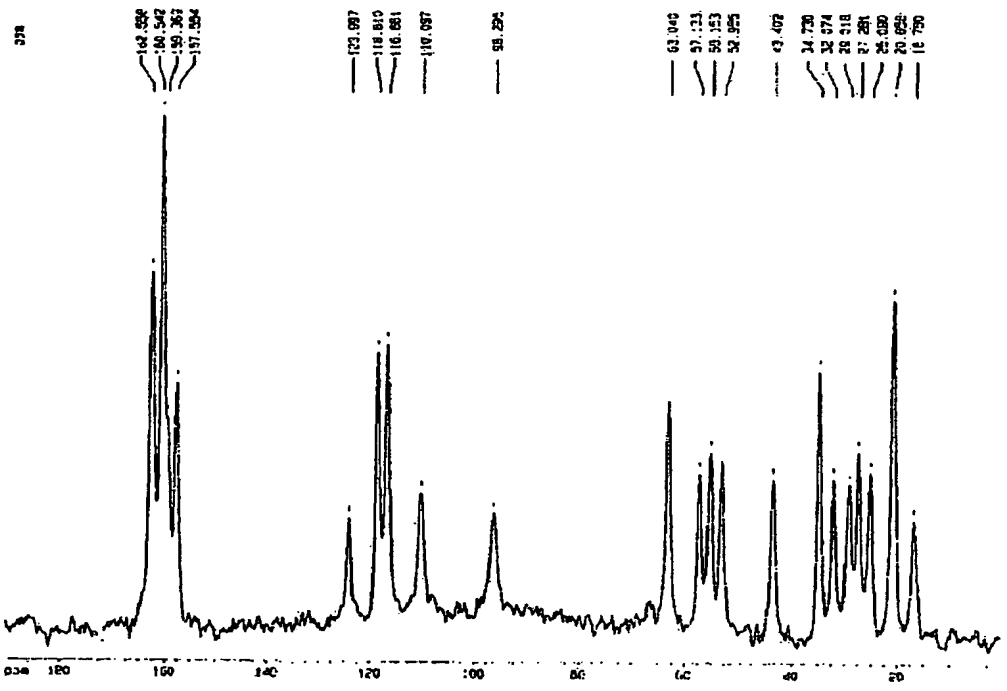


Figure 15. Powder X-Ray Diffraction of Paliperidone Form V.

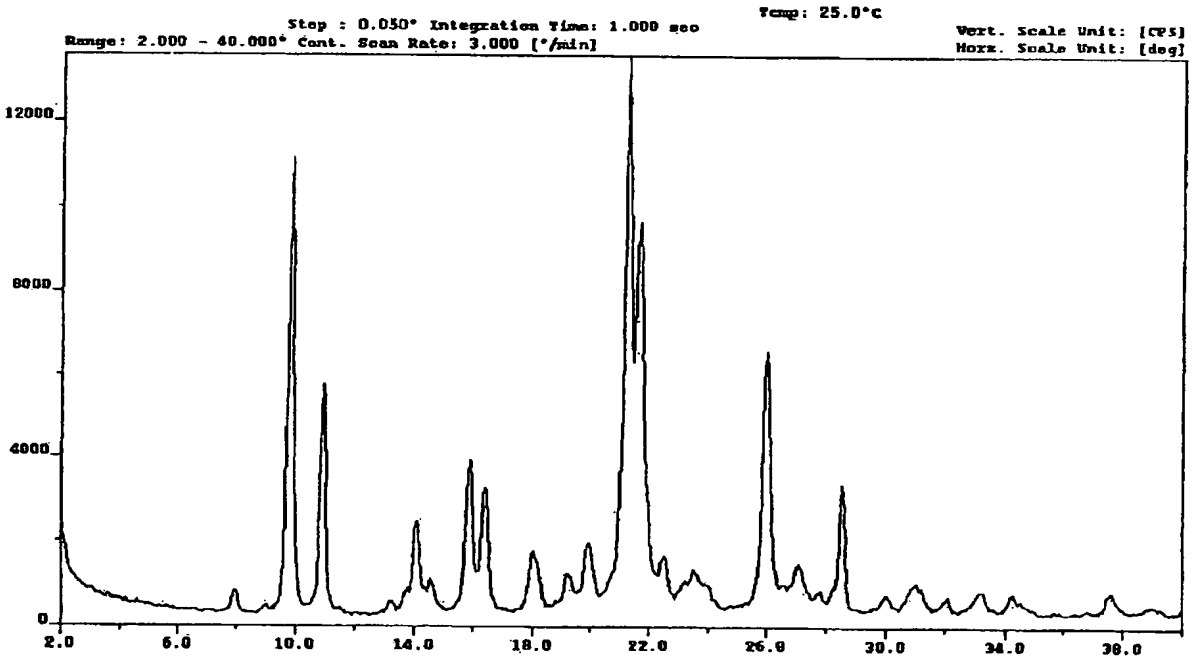


Figure 16. Solid-state ^{13}C NMR spectrum of Paliperidone Form V in the 100-180 ppm range.

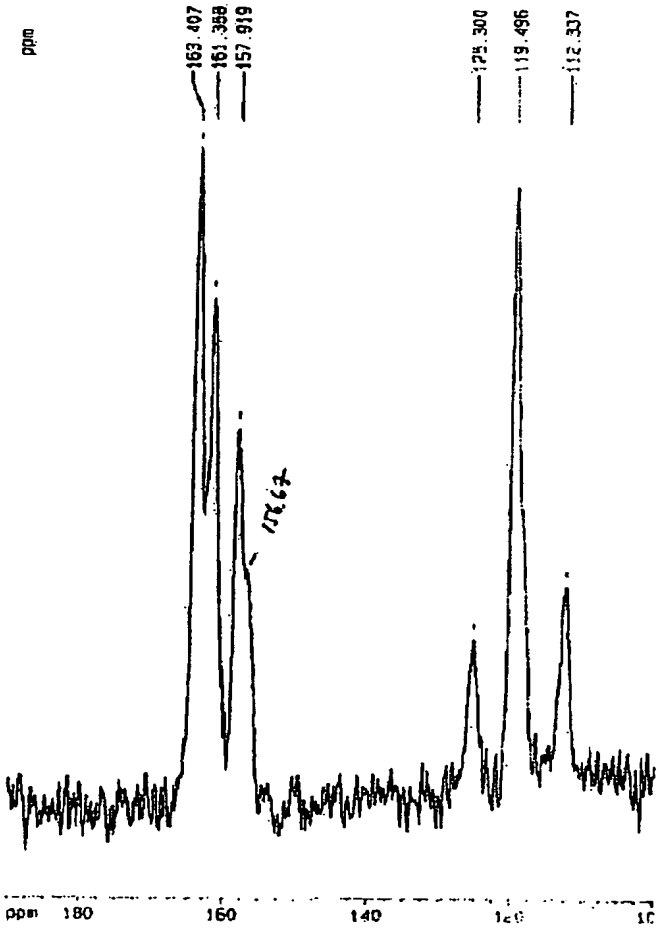


Figure 17. Solid-state ^{13}C NMR spectrum of Paliperidone Form V

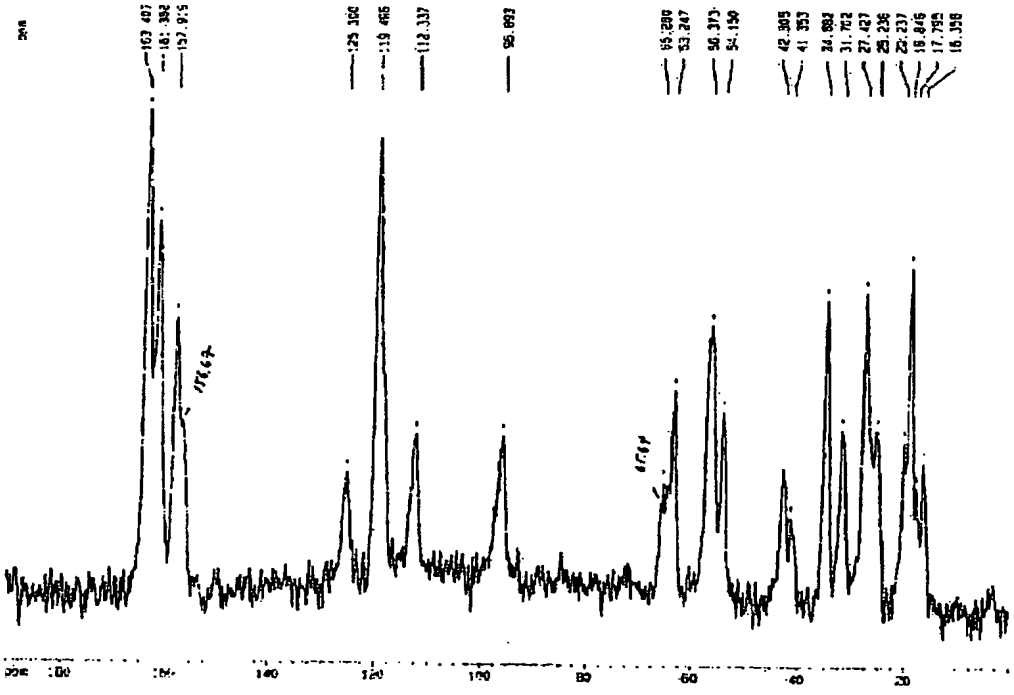


Figure 18. Powder X-Ray Diffraction of Pure Paliperidone Form VI.

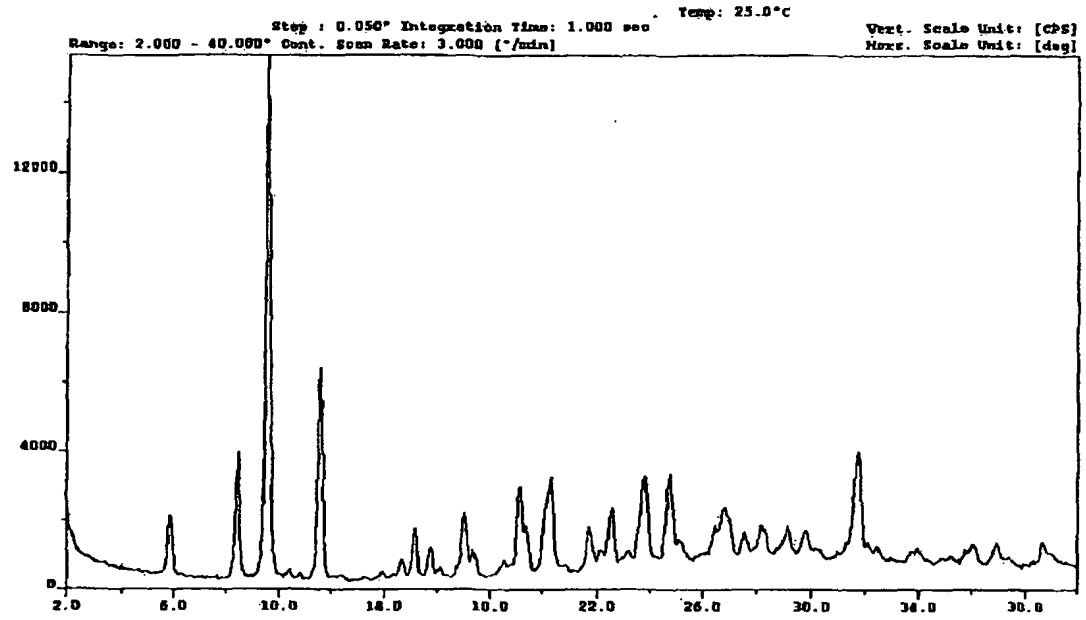


Figure 19. Powder X-Ray Diffraction of Paliperidone Form VI.

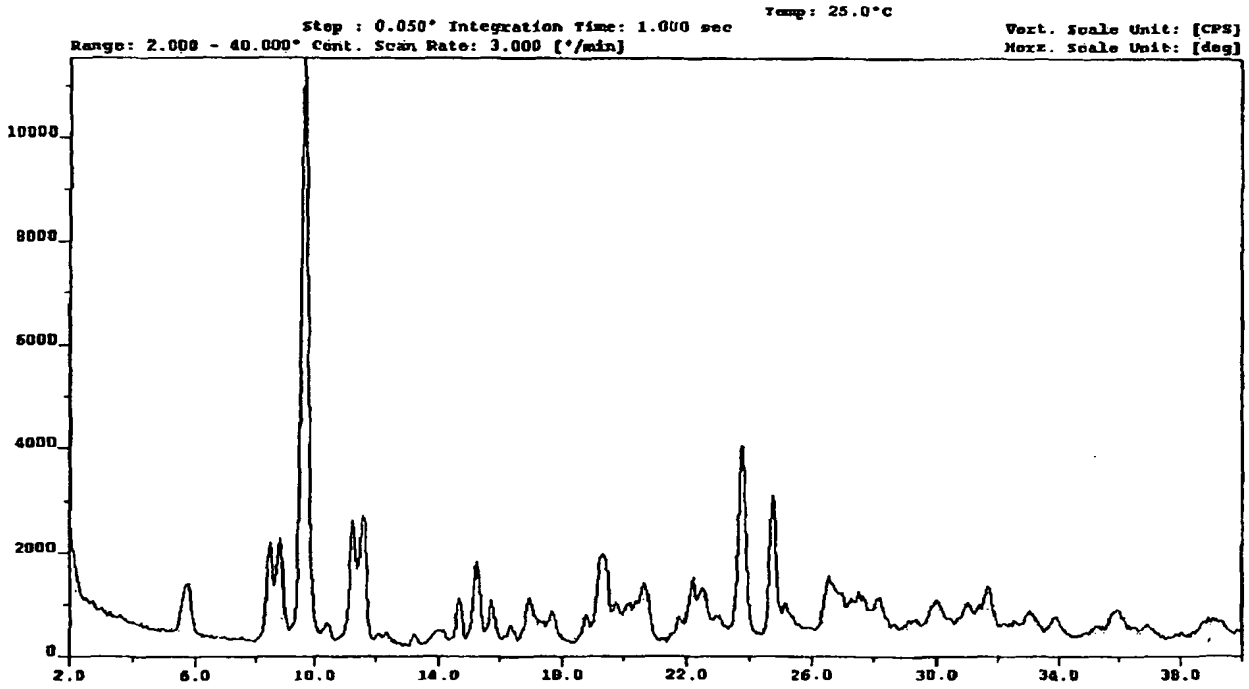


Figure 20. Peaks that can be used in determining percent presence in contaminating polymorphic form

I	II	III	IV	V	VI
10.1	8.1	10.8	10.3	9.7	5.8
12.4	10.3	14.1	12.1	10.9	8.4
14.3	13.1	15.9	15.4	14.0	9.5
17.0	13.7	16.8	19.8	15.8	11.6
17.2	14.6	17.2	20.7	16.3	19.1
18.9	14.9	19.1	23.9	21.1	20.3
21.9	16.2	21.1	33.1	21.5	23.7
24.8	18.6	21.7		26.0	24.7
26.2	19.2	25.8			31.7
	20.0				
	20.6				
	22.0				
	24.6				
	25.0				
	27.9				
	31.2				

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(54) Title: PALIPERIDONE SUSTAINED RELEASE FORMULATION

(57) Abstract: The present invention provides sustained release dosage forms comprising Paliperidone and processes for preparing the same.

WO 2009/025859 A1

PALIPERIDONE SUSTAINED RELEASE FORMULATION

CROSS REFERENCE TO RELATED APPLICATION

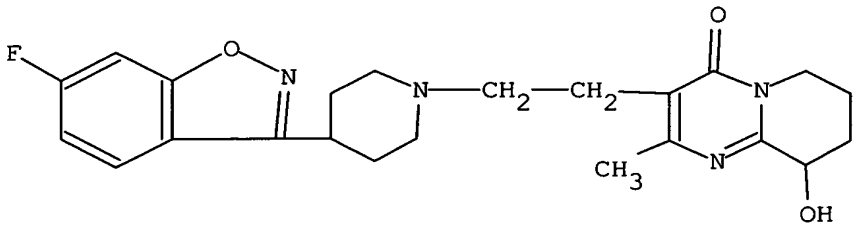
The present application claims the benefit of U.S. Provisional Application No. 60/935,597, filed August 21, 2007, the disclosure of which is incorporated by reference.

The present invention relates to sustained release pharmaceutical compositions comprising Paliperidone or a salt thereof, and a process for preparing the same.

BACKGROUND OF THE INVENTION

Paliperidone is described in U.S. Pat. No. 4,804,663. The paliperidone compound differs from risperidone and related prior art compounds described in U.S. Pat. Nos. 4,352,811 and 4,458,076 by its substitution on the 1-position of the piperidine moiety.

Paliperidone (CAS Registry No. 144598-75-4) has the chemical name 4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl. Paliperidone is represented by the structural formula:



Paliperidone is practically insoluble in water, freely soluble in methylene chloride and soluble in methanol and 0.1 N hydrochloric acid. Additionally, since paliperidone has a long half-life of about one day, it is not a typical candidate for extended delivery. However, side effects such as anxiety, somnolence, dizziness, constipation, extrapyramidal symptoms, may be related to high blood plasma

concentration levels restricting the ability to administer a single daily immediate release dose.

A published patent application, US 2004/0092534, discloses extended release formulations and methods for providing ascending rate of release of paliperidone utilizing a capsule-shaped tablet. The dosage form utilizes a semipermiable membrane surrounding a three layer core: the first layer contains low amounts of drug and an osmotic agent; the middle layer contains higher amounts of drug and without osmotic agent and the third layer is a push layer. In addition to the said structure of capsules shape tablet, there is at least one orifice which drilled through the membrane on the first drug layer end. All this capsule shaped tablet is designed to be a once-a day dosage form.

U.S. patent application publication No. US 2006/034927 relates also to a Paliperidone dosage form for sustained release of a drug comprising: a delay layer comprising (i) a polymeric matrix, and (ii) microencapsulated drug, wherein the delay layer is substantially free of non-microencapsulated drug; and a second layer comprising (iii) a polymeric matrix, and (iv) non-microencapsulated drug matrix; wherein the second layer is located adjacent to the delay layer.

The difficulties with the above mentioned dosage forms are being of low cost effectiveness, requiring very special and expensive equipment and resulting in relatively small production of final dosage form.

Accordingly, there remains a need to provide alternative means of controlling delivery in a variety of patterns.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a dosage form for sustained release of paliperidone. The dosage form comprises at least a first component and second component, wherein the first component comprises at least one delay layer comprising a polymer, and the second component comprises non-coated Paliperidone and optionally comprises also coated Paliperidone; wherein the second component is located adjacent to the first component.

The dosage form of the first aspect may be coated with one or more additional delayed release layers, in the presence of Paliperidone, or in its absence.

In one of the aspects, the present invention provides methods for the preparation of the dosage forms described above.

In another aspect, the invention provides an extended release tablet of Paliperidone in the form of an inlay tablet. The inlay tablet comprises at least an inlay core and outer layer: (a) the inlay core comprising non-coated Paliperidone and at least one polymer capable of delaying the release of Paliperidone from the inlay core and capable of swelling upon hydration, wherein the inlay core optionally further comprises coated Paliperidone; and (b) the outer layer comprising a pharmaceutical excipient which is substantially water insoluble, wherein the outer layer partially surrounds the inlay core.

The invention provides a dosage form for the sustained release of Paliperidone, wherein the dosage form exhibits relative bioavailability, based on the area under the plasma concentration curve (AUC) for the same duration after oral administration in human subjects, of between about 1.5 and about 3.0, preferably between about 1.7 and about 3.0, and more preferably between about 1.9 and about 3.0, compared with commercially available INVEGA® extended release tablets containing the same amount of Paliperidone administered at the same dose in the human subjects.

The invention also provides a dosage form for the sustained release of Paliperidone, wherein the dosage form exhibits a relative Cmax, based on the plasma concentrations at various time after oral administration in human subjects, of between about 1.6 and about 3.0, preferably between about 1.7 and about 3.0, and more preferably between about 2.0 and about 3.0, compared with commercially available INVEGA® extended release tablets containing the same amount of Paliperidone, administered at the same dose in the human subjects.

In another aspect, the invention provides a process of making the inlay tablet of the invention, wherein the process comprises

(1) mixing Paliperidone and at least one polymer capable of delaying the release of Paliperidone and capable of swelling upon hydration, wherein at least part of the Paliperidone remains non-coated; and

(2) partially covering the mixture of step (1) with an outer layer comprising a pharmaceutical excipient which is substantially water insoluble to obtain the inlay tablet.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic diagram showing an embodiment of the inlay tablet of the present invention, comprising an inlay core containing non-coated Paliperidone partially surrounded or incompletely covered by an inert insoluble outer layer.

Figure 2 shows the dissolution profiles of the Paliperidone extended release tablets in the form of inlay tablets prepared according to Example 8.

Figure 3 shows the least-square mean plasma concentrations versus time after the oral administration of the 6 mg inlay tablets of the present invention in the Test Group and the oral administration of the INVEGA 6 mg commercially available Paliperidone tablets in the Reference Group.

Figure 4 shows the natural logarithm of the least-square mean plasma concentrations versus time after the oral administration of the 6 mg inlay tablets of the present invention in the Test Group and the oral administration of the INVEGA 6 mg commercially available Paliperidone tablets in the Reference Group.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, the term "coated Paliperidone" means one or more Paliperidone particles which have been microencapsulated with at least one microencapsulation material. Such materials include, but are not limited to, proteins, polysaccharides, starches, waxes, fats, natural and synthetic polymers, and resins and/or combinations thereof. In this invention, "non-coated Paliperidone" means one or more Paliperidone particles which have not been microencapsulated with any microencapsulation material.

The term "microencapsulated with at least one microencapsulating material" means that the Paliperidone particles are surrounded by a layer of the at least one microencapsulating material without any pharmaceutical excipients existing between the Paliperidone particles and the layer of the at least one microencapsulating material.

In the present invention, the term "polymer" comprises natural and/or synthetic polymers and can also mean a combination of polymers of various types. The "polymer having an effect of delaying Paliperidone release" or "polymer capable of delaying the release of Paliperidone" includes polymers that form a viscous and gelatinous surface barrier or gel layer upon hydration, which barrier or gel layer controls Paliperidone release from and the penetration of liquids into the center of

Paliperidone particles. The physicochemical characteristics of this barrier or gel layer control water uptake and the mechanism of Paliperidone release from the Paliperidone particles. The release of Paliperidone can occur via diffusion of Paliperidone through the barrier or gel layer, and preferably via gradual erosion of the barrier or gel layer. Suitable examples of the "polymer having an effect of delaying Paliperidone release" or "polymer capable of delaying the release of Paliperidone" include polyvinylpyrrolidone, polyethylene oxide such as POLYOX WSR-301, polysaccharides and hydrophilic cellulose derivatives such as methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl methylcellulose, carboxy methylcellulose and sodium carboxy methylcellulose. Preferred examples of the "polymer having an effect of delaying Paliperidone release" or "polymer capable of delaying the release of Paliperidone" include POLYOX WSR-301 and hydroxypropyl methylcellulose such as METHOCEL K15MP, K15M, K100M, K100LV, F4M, E4M, E3, E5, E10M, E15LV, E15LN, E15CLV, E50 and K3. Preferred examples of the polymer include METHOCEL K15MP and POLYOX WSR-301.

The term "delay layer" means a layer that functions, at least in part, to retard the release of the drug from the dosage form, including halting the release for a certain period of time.

In the invention, when two components (or two layers) are "adjacent", that means the two components (or two layers) are in physical proximity with each other. Preferably, the two components (or two layers) are in direct contact at at least one point.

In the invention, the term "core" refers to a component that is at least partially surrounded or covered by another component.

As used herein, the term "ascending release kinetics" means that the amount of Paliperidone released as a function of time increases over a period of time. Preferably, the amount of Paliperidone released as a function of time increases continuously, gradually and/or steadily, instead of in a step-wise fashion.

The first aspect of the present invention provides a dosage form for sustained release of paliperidone. The dosage form comprises at least two components, wherein the first component comprises at least one delay layer comprising a polymer, and the second component comprises non-coated Paliperidone; wherein the second component is located adjacent to the first component.

In an embodiment of the dosage form of the first aspect of the invention, the at least one delay layer of the first component may further comprise Paliperidone, but at least part of the Paliperidone is non-coated Paliperidone, so that the at least one delay layer does not further comprise only Paliperidone which is coated.

In one of the embodiments of the first aspect of the present invention, the sustained release Paliperidone dosage form comprises a plurality of particulates, wherein each of the particulates comprises at least two components: the first component comprising at least one delay layer comprising a polymer, and the second component comprising non-coated Paliperidone, wherein the second component is located adjacent to the first component.

Optionally, the second component further comprises coated Paliperidone.

According to an alternative embodiment of the preferred embodiment of the first aspect of the present invention, a layer of the first component contacts a layer of the second component along one face. Optionally, a layer of the second component is partially or completely surrounded by a layer of the first component. Optionally, the dosage form is partially or completely surrounded by a coating layer.

According to another alternative embodiment of the preferred embodiment of the first aspect of the present invention, the dosage form comprises three layers, so that two layers of the first component surround a layer of the second component. Optionally, at least one of the two layers of the first component also comprises non-coated Paliperidone. Optionally, the dosage form is partially or completely surrounded by a coating layer. The coating layer may also include non-coated Paliperidone.

According to an embodiment of the first aspect of the invention, the dosage form further comprises a sub-layer between a layer of the first component and a layer of the second component.

Each layer can contain other pharmaceutical excipients, so as to give suitable properties for compression, lubrication and/or binding as is well known to one skilled in the art.

In a second aspect, the present invention also discloses a multi-particulate dosage form, comprising a plurality of the particulates wherein each particulate comprises at least two components, wherein the first component comprises at least one extended release layer comprising a polymer and the second component comprises non-coated Paliperidone and optionally comprises also coated

Paliperidone, wherein the second component is located adjacent to the first component.

Further said particulate may be covered by a delayed release layer.

According to a preferred embodiment of the second aspect of the present invention, said dosage form comprises at least a first population of particulates and at least a second population of the particulates, wherein said first population differs from said second population in at least one of 1) weight ratio between said first component and said second component; 2) weight ratio between coated and non-coated paliperidone, 3) weight ratio between paliperidone and other components in the particulate; 4) nature and thickness of coating layer;5) existence and relative weight of core and/or sub layer; 6)existence of a second delay layer and the weight ratio between the layers.

In the aspects of the present invention described herein, the extended release layer preferably comprises at least one polymer such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, ethyl cellulose or polymethacrylates and at least one plasticizer. Preferred examples of the polymer in the extended release layer are METHOCEL K15MP AND ETHOCEL 7 CPS. The plasticizer can be hydrophilic such as triethyl citrate and polyethylene glycol and/or hydrophobic such as diethyl phthalate, dibutyl phthalate, dibutyl sebacate and acetyl tributyl citrate.

The cores employed in the second aspect of the invention described herein may be commercially available inert cores, such as microcrystalline cellulose spheres (e.g. CELLETS®), sugar spheres, or glass spheres. The cores employed in the second aspect of the invention described herein are covered by a layer comprising Paliperidone or a salt thereof. This layer preferably comprises Paliperidone or a salt thereof and at least one pharmaceutically acceptable excipient that acts as a binder.

The particulates in said dosage form may differ in the onset time of paliperidone release and in the rate of release after said onset time. According to a preferred embodiment of the present invention, an ascending release is achieved via controlling the parameters of composition and of relative location of the dosage-form layers.

According to an embodiment of the invention, those parameters are selected so that the onset time for liberation from the first population is earlier than that from the second population, etc.

In a third aspect, this invention also discloses a multi-particulate dosage form, comprising a plurality of the particulates wherein each particulates comprises at least three layers, wherein a first layer comprising non-coated Paliperidone or salt thereof and a polymer, a second layer is a delay release layer, which covers said the first Paliperidone layer and a third layer comprising non-coated Paliperidone together with a polymer.

According to a preferred embodiment of the third aspect of the invention, the second layer is a pH–sensitive layer, and the third layer is a delayed release layer that comprises said non-coated Paliperidone. This dosage form may comprise at least one additional delayed release layer that covers the first layer.

The core employed in the third aspect of the invention described herein may be one of the commercially available inert cores, such as microcrystalline cellulose spheres (e.g. CELLETS®), sugar spheres, or glass spheres. The core employed in the third aspect of the invention described herein is covered by a layer comprising Paliperidone or a salt thereof. This layer preferably comprises Paliperidone or a salt thereof and at least one pharmaceutically acceptable excipient that acts as a binder such as methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and povidone , copovidone, starch, Arabic gum, acasia gum, gelatin.

According to a preferred embodiment of the third aspect of the invention, a substantial fraction of the Paliperidone in the third layer is released before the release of a fraction of Paliperidone in the first layer. By adding an organic acid to the layer coating the pH sensitive layer, a micro pH acidic environment can be obtained, so that the pH sensitive delay layer cannot dissolve until the acid comprising layer is released from the dosage form completely. By this way the release of the inner Paliperidone layer can be controlled.

The term "sustained release dosage form" means a dosage form that releases the drug for 4-24 hours. The dosage forms in accord with the present invention exhibit t90 values of at least 4 hours or more and preferably up to about 24 hours or more, for once per daily dosing. The dosage forms continuously release drug for sustained periods of at least about 6 hours, preferably about 8 hours or more and, in particular embodiments, about 12 hours or more.

The fourth aspect of the invention is directed to Paliperidone extended release tablets in the form of inlay tablets. The inlay tablet comprises at least an inlay core and outer layer: (a) the inlay core comprising non-coated Paliperidone and at least one

polymer capable of delaying the release of Paliperidone from the inlay core and capable of swelling upon hydration, wherein the inlay core optionally can further comprise coated Paliperidone; and (b) the outer layer comprising a pharmaceutical excipient which is substantially water insoluble, wherein the outer layer partially surrounds the inlay core.

The at least one "polymer capable of delaying the release of Paliperidone from the inlay core and capable of swelling upon hydration" is at least one polymer that forms a viscous and gelatinous surface barrier or gel layer upon hydration, which barrier or gel layer controls Paliperidone release from and the penetration of liquids into Paliperidone particles. The release of Paliperidone can occur via diffusion of Paliperidone through the barrier or gel layer, and/or via gradual erosion of the barrier or gel layer. Suitable examples of the polymer include polyvinylpyrrolidone, poly(ethylene oxide) such as POLYOX WSR-301, polysaccharides and hydrophilic cellulose derivatives such as methyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl methylcellulose, carboxy methylcellulose and sodium carboxy methylcellulose. Preferred examples of the "polymer having an effect of delaying Paliperidone release from the particles" include POLYOX WSR-301 and hydroxypropyl methylcellulose such as METHOCEL K15MP, K15M, K100M, K100LV, F4M, E4M, E3, E5, E15M, E15LV, E15LN, E15CLV, E50 and K3. A preferred at least one "polymer capable of delaying the release of Paliperidone from the inlay core and capable of swelling upon hydration" is POLYOX WSR-301.

The "pharmaceutical excipient which is substantially water insoluble" of the outer layer renders the outer layer substantially water insoluble. Examples of "pharmaceutical excipient which is substantially water insoluble" in the outer layer include pharmaceutically acceptable polymers which are substantially water insoluble, such as pharmaceutically acceptable drug release modifying polymers which are substantially water insoluble. Suitable pharmaceutically acceptable polymers which are substantially water insoluble include cationic copolymers of ethylacrylate and methylacrylate with quarternary ammonium groups such as EUDRAGIT RS and EUDRAGIT RL, ethylacrylate methylmethacrylate copolymer with neutral ester groups, cellulose esters, cellulose ethers and cellulose esterethers, ethyl cellulose such as ETHYL CELLULOSE T10 PHARM, cellulose acetate, cellulose diacetate, cellulose triacetate and polyester polymers. Non-limiting

examples of the polyester polymers that can be used include poly(ε-caprolactone)s, poly(alkylene glycol adipate)s such as poly(ethylene glycol adipate), poly(propylene glycol adipate) and poly(butylene glycol adipate), polyvinyl acetate and blends and copolymers thereof. A preferred "pharmaceutical excipient which is substantially water insoluble" is ETHYLCELLULOSE T10 PHARM.

The inlay core preferably is in the form of a tablet or compressed slug.

The inlay core and the outer layer independently can further comprise at least one other pharmaceutical excipient such as pharmaceutically acceptable fillers, diluents, pH modifiers, glidants, lubricants, binders, dyes and flavoring agents.

In some of the embodiments of the inlay tablet of the invention, the inlay core comprises about 1-3% w/w Paliperidone, about 2-5% w/w filler such as STARLAC, about 5-15% w/w pH modifier such as magnesium carbonate, about 5-20% w/w release modifying polymer such as POLOYX WSR-301, about 0-1% w/w lubricant such as stearic acid and about 0-1% w/w glidant such as silicon dioxide.

In some of the embodiments of the inlay tablet of the invention, the outer layer comprises about 50-90% w/w release modifying polymer such as ETHYLCELLULOSE T10 PHARM, about 0-1% w/w dye such as FERRIC OXIDE YELLOW NF and about 0-1% w/w lubricant such as stearic acid.

Another aspect of the invention is directed to a dosage form for the sustained release of Paliperidone, wherein the dosage form exhibits relative bioavailability, based on the area under the plasma concentration curve (AUC) for the same duration, e.g., 0 to 96 hours, or 0 hour to infinity, after oral administration, of at least about 1.5, preferably at least about 1.7, and more preferably at least about 1.9, compared with commercially available INVEGA® extended release tablets containing the same amount of Paliperidone administered at the same dose. By a relative bioavailability, based on AUC, of at least about 1.5, it means that the AUC achieved in the human subjects orally administered the dosage form according to the first aspect of the invention is at least about 50% higher than the AUC, for the same duration, achieved in the human subjects orally administered the commercially available INVEGA® extended release tablets containing the same amount of Paliperidone, wherein the Paliperidone is administered at the same dose.

In one of the embodiments, the invention provides a dosage form for the sustained release of Paliperidone, wherein the dosage form exhibits relative bioavailability, based on the area under the plasma concentration curve (AUC) for the

same duration after oral administration, of between about 1.5 and about 3.0, preferably between about 1.7 and about 3.0, and more preferably between about 1.9 and about 3.0, compared with commercially available INVEGA® extended release tablets containing the same amount of Paliperidone administered at the same dose.

Another aspect of the invention is directed to a dosage form for the sustained release of Paliperidone, wherein the dosage form exhibits a relative Cmax, based on the plasma concentrations at various time after oral administration in human subjects, of at least about 1.6, preferably at least about 1.7, and more preferably at least about 2.0, compared with commercially available INVEGA® extended release tablets containing the same amount of Paliperidone, administered at the same dose in the human subjects.

In one of the embodiments, the invention also provides a dosage form for the sustained release of Paliperidone, wherein the dosage form exhibits a relative Cmax, based on the plasma concentrations at various time after oral administration in human subjects, of between about 1.6 and about 3.0, preferably between about 1.7 and about 3.0, and more preferably between about 2.0 and about 3.0, compared with commercially available INVEGA® extended release tablets containing the same amount of Paliperidone, administered at the same dose in the human subjects.

Another aspect of the invention is directed to a dosage form for the sustained release of Paliperidone, wherein the dosage form exhibits an in vitro dissolution profile determined using a 50 RPM paddle method in a dissolution medium of 500 ml 0.05 M phosphate buffer, pH 6.8, 37oC, wherein the dissolution profile is less than about 10% dissolution in 4 hours, between about 10% to about 25% dissolution in 8 hours, between about 40% to about 60% dissolution in 16 hours and not less than about 70% in 24 hours after the start of the dissolution study, respectively.

In the fifth aspect, the invention provides a process of making the inlay tablet of the invention, wherein the process comprises

(1) mixing Paliperidone and at least one polymer capable of delaying the release of Paliperidone and capable of swelling upon hydration; and

(2) partially covering the mixture of step (1) with an outer layer comprising a pharmaceutical excipient which is substantially water insoluble to obtain the inlay tablet.

In a preferred embodiment of the process of preparing the inlay tablet, the mixture of step (1) is compressed into a slug or tablet before step (2).

In a further preferred embodiment of the process of preparing the inlay tablet, the mixture of step (1) is compressed into a slug or tablet before step (2); the slug or tablet is mixed with the at least one polymer capable of delaying the release of Paliperidone and capable of swelling upon hydration to form a mixture; and the mixture is compressed into a tablet before step (2). More preferably, a filler, pH modifier, glidant and/or lubricant is added in step (1). Optionally, the slug or tablet formed by compression is milled before being mixed with the at least one polymer capable of delaying the release of Paliperidone and capable of swelling upon hydration to form the mixture to be compressed into a tablet before step (2).

Preferably, in the process of preparing the inlay tablet, the product of step (2) is compressed to obtain the inlay tablet.

Some of the embodiments of the inlay tablets such as as exemplified in Example 8 can be prepared according to the ingredients listed in the table below.

Without being bound to any hypothesis, it is believed that the inlay tablet may function in the extended release of Paliperidone according to a theory schematically illustrated in Fig. 1, which shows an embodiment of the inlay tablet of the present invention. The tablet drawn in the far left of Fig. 1 depicts the inlay tablet before exposure to an aqueous medium, and the four tablets drawn in the right depict four stages of the inlay tablet exposed to an aqueous medium for increasing length of time demonstrating gel formation in the inlay core and the gradual swelling of the gel of the inlay core due to the absorption of water by the inlay core through the surface not covered by the inert insoluble outer layer, resulting in a gradual increase of the free surface of the inlay core leading to an ascending release of Paliperidone from the inlay core.

In all aspects of the invention described herein, the pharmaceutical composition preferably further comprises one or more pharmaceutical excipients.

The term "pharmaceutical excipients" means any pharmaceutically acceptable substances, other than the active drug substance or finished dosage form, that have been appropriately evaluated for safety and are included in drug delivery systems to (a) help in the processing of the drug delivery system during its manufacture; (b) support, protect or enhance the stability and/or bioavailability of the active drug substance; (c) make the active drug substance or the final dosage form more acceptable by the patients; (d) enhance the overall safety, effectiveness or delivery of the active drug substance during storage or use; or (e) help in product identification;.

The pharmaceutical excipients are added to aid the formulation and manufacture of the final dosage form for administration to the patients. The pharmaceutical excipients can be mixed with the active drug substance to make the final dosage form. Examples of "pharmaceutical excipients" include pharmaceutical grade fillers, diluents, pH modifiers, release modifying polymers, lubricants, glidants, disintegrants, carriers, bulking agents, binders, wetting agents, dyes (e.g., ferric oxide yellow and iron oxide red) and flavoring agents. Other excipients that may be incorporated into the final dosage form include preservatives, surfactants, antioxidants and any other excipient commonly used in the pharmaceutical industry.

Suitable fillers and diluents include, but are not limited to, cellulose-derived materials like powdered cellulose, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methylcellulose, carboxymethyl cellulose salts (such as carboxymethyl cellulose calcium) and other substituted and unsubstituted celluloses; starch such as maize starch; pregelatinized starch; lactose, preferably lactose monohydrate (e.g. Pharmatose®); talc; waxes; sugars; sugar alcohols like mannitol and sorbitol; acrylate polymers and copolymers; dextrates; dextrin; dextrose; maltodextrin; pectin; gelatin; inorganic diluents like calcium carbonate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, sodium chloride, combine materials like STARLAC and other diluents known to the pharmaceutical industry. More preferred fillers include talc, lactose monohydrate, pregelatinized starch, mannitol or sorbitol. An even more preferred filler is STARLAC.

Suitable pH modifiers are pharmaceutically acceptable buffering compounds such as alkaline earth metal carbonates, alkali metal carbonates, alkaline earth metal bicarbonates, alkali metal bicarbonates and magnesium oxide, e.g., magnesium carbonate, calcium carbonate, magnesium bicarbonate, calcium bicarbonate, sodium carbonate, potassium carbonate, sodium bicarbonate and potassium bicarbonate. A preferred pH modifier is magnesium carbonate.

Suitable disintegrants include croscarmellose sodium (e.g. Ac Di Sol®, Primellose®), crospovidone (e.g. Kollidon®, Polyplasdone®), microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium starch glycolate (e.g. Explotab®, Primoljel®) and starch. Preferred disintegrants include Copovidone and microcrystalline cellulose.

Glidants can be added to improve the flowability of a solid composition before compaction and to improve the accuracy of dosing especially during compaction and capsule filling. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, and talc. The preferred glidant is colloidal silicon dioxide.

A lubricant may be added to the pharmaceutical compositions of the present invention to reduce adhesion and/or ease the release of the product from e.g. the die. Suitable lubricants include, but are not limited to, stearic acid, magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate. Stearic acid and magnesium stearate are preferred.

Carriers include, but are not limited to, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, and silicic acid.

Binders include, but are not limited to, carboxymethyl cellulose, shelac, methyl cellulose, hydroxypropyl methylcellulose, HPMC, starch and polyvinylpyrrolidone. Other suitable binders include, but are not limited to, acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that can be included in the composition of the present invention include, but are not limited to, maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

According to the preferred embodiment, the total amount of Paliperidone in the dosage form ranges from about 1 mg to about 15 mg.

Some of the embodiments of the dosage forms of the invention do not contain coated Paliperidone.

Some of the embodiments of the dosage forms of the invention may contain coated Paliperidone.

In some of the embodiments of the dosage forms of the invention, the dosage forms may contain coated Paliperidone along with non-coated Paliperidone in one or more of the layers, or in one or more of the components.

In some of the embodiments of the dosage forms of the invention comprising a delayed release layer, the delayed release layer can further comprise Paliperidone. For instance, dosage forms having a delayed release layer further comprising Paliperidone are exemplified in Examples 1, 5 and 7 below.

Methods for making multilayered are described by W. C. Gunsel, Compression coated and layer tablets in Pharmaceutical Dosage Forms: Tablets, Vol 1, edited by H.H. Lieberman.

In a fourth aspect, the invention provides a process for preparing a pharmaceutical composition as described above in relation to the second aspect of the invention.

The process comprises preparing a sphere by coating a core with a layer comprising Paliperidone or a salt thereof and applying an extended release layer thereon.

The layer comprising Paliperidone or a salt thereof may be applied using any conventional method. Preferably, the core is coated with a Paliperidone containing layer using a solution/dispersion of Paliperidone or a salt thereof and a binder. The coating process is preferably performed using a fluidized bed coater, preferably equipped with a bottom or top spray device.

In another aspect of the invention described herein, the processes for preparing a final dosage composition of the invention preferably further comprises mixing a plurality of the spheres, which provide a sustained release of paliperidone or a salt thereof, with at least one pharmaceutically acceptable excipient such as a filler, binder, glidant, disintegrant or lubricant. The mixture can be filled into capsules or sachets or compressed into tablets.

The mixture may be compressed into tablets in the following way. The coated spheres are mixed with at least one pharmaceutically acceptable excipient and compressed into tablets. The excipients can be fillers such as microcrystalline cellulose, lactose monohydrate, maize starch, powdered cellulose, sorbitol and mannitol; binders such as povidone, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose; glidants such as talc, and silicon dioxide; disintegrants such as croscarmellose sodium, pregelatinized starch, crospovidone, hydroxypropyl cellulose, and sodium starch glycolate; and lubricants such as stearic acid, magnesium stearate, mineral oil, hydrogenated castor oil and sodium stearyl fumarate.

EXAMPLES

Examples of Paliperidone Extended Release Tablets

Example 1 (Paliperidone 9 mg tablets with ascending release kinetics)

Layer 1 (Inner Core)

Ingredient	mg / Tablet
Paliperidone	6.0
Lactose Monohydrate	73.5
Methocel K15MP	20.0
Magnesium Stearate	0.5
Total Weight	100.0

Layer 2 (pH Dependent Coating)

Ingredient	mg /Tablet
Eudragit FS 30D	3.3
Triethyl citrate	0.4
Talc	1.3
Water (process solvent)	
Total Weight	5.0

Layer 3 (Outer Coating)

Ingredient	mg /Tablet
Paliperidone	3.0
Lactose Monohydrate	141.0
Fumaric Acid	10.0
Methocel K15MP	40.0
Magnesium Stearate	1.0
Total Weight	195.0

Total Tablet Weight	300.0

Process

The inner tablet is prepared by mixing Paliperidone, Lactose Monohydrate, Methocel K15MP in a mixer, adding sieved Magnesium Stearate to the blend, mixing, and pressing the mixed blend to form tablets in a suitable tablet press.

1. The tablets from step 1 is coated with the coating dispersion to form Layer 2
2. Layer 3 is formed by mixing Paliperidone, Lactose Monohydrate, Methocel K15MP and Fumaric Acid in a mixer, adding sieved Magnesium Stearate to the blend and mixing.
3. The final tablets are prepared by press coating the tablets from step 2 with the blend from step 3.

Example 2 (Paliperidone 9 mg multi-particulate dosage form)

Pellets, Layer 1 (Active Core)

Ingredient	mg / product
Paliperidone	9.0
Microcrystalline Cellulose	91.0
Water (process solvent)	
Total Weight	100.0

Layer 2

Ingredient	mg /layer
Ethocel 7 CPS	20.0
PEG 3350	5.0
Alcohol 95% (process solvent)	
Isopropyl Alcohol (process solvent)	
Water (process solvent)	
Total Weight	25.0

Process

1. The core is prepared by mixing Paliperidone and Microcrystalline Cellulose in a mixer, adding water to the blend and mixing. Using extrusion and spheronization technique, pellets with diameter 200 – 1000 mm are produced and dried in a suitable dryer.
2. Ethocel 7 CPS and PEG 3350 are dissolved in a mixture of the process solvents.
3. The core is coated with the solution from step 2.

Example 3 (Paliperidone 9 mg multi-particulate dosage form)

Pellets, Layer 1 (Active Core))

Ingredient	mg / product
Paliperidone	9.0
Microcrystalline Cellulose	91
Water (process solvent)	
Total Weight	100.0

Layer 2

Ingredient	mg / product
Ethocel 7 CPS	20.0
PEG 3350	15.0
Alcohol 95% (process solvent)	
Isopropyl Alcohol (process solvent)	
Water (process solvent)	
Total Weight	35.0

Layer 3 (DR Coating)

Ingredient	mg / product
Methocel K15MP	30.0
PEG 3350	10.0
Talc	5.0
Ethanol (process solvent)	
Water (process solvent)	
Total Weight	45.0

{Inventors: What does "DR" stand for?}

Process

1. The core is made by mixing Paliperidone and Microcrystalline Cellulose in a mixer, adding water to the blend and mixing. Using extrusion & spheronization technique, pellets with diameter 200 – 1000 mm are produced and dried in a suitable dryer.
2. Ethocel 7 CPS and PEG 3350 are dissolved in a mixture of the process solvents.
3. The core is coated with the solution from step 2.
4. Methocel K15MP and PEG 3350 were dissolved in a mixture of the process solvents. Talc was added and mixed until dispersed.
5. The pellets were coated with the dispersion from step 4.

Example 4 (Paliperidone 9 mg multi-particulate dosage form)

A 1:1.33 (w/w) mixture of two types of pellets prepared as described in Examples 2 and 3 is prepared with ascending release kinetics

Example 5 (Paliperidone 9 mg multi-particulate dosage form)

Pellets, Layer 1 (First Drug Layer)

Ingredient	mg / product
sugar spheres	90.0
Paliperidone	6.0
Copovidone	4.0
Water (process solvent)	
Total Weight	100.0

Layer 2

Ingredient	mg / product
Ethocel 7 CPS	20.0
PEG 3350	15.0
Alcohol 95% (process solvent)	
Isopropyl Alcohol (process solvent)	
Water (process solvent)	
Total Weight	35.0

Layer 3 (Second Drug Layer)

Ingredient	mg / product
Paliperidone	3.0
Methocel K15MP	20.0
PEG 3350	7.0
Talc	6.0
Ethanol (process solvent)	
Water (process solvent)	
Total Weight	33.0

Process

1. The first drug layer is made by coating the sugar spheres with the dispersion of Paliperidone in a Copovidone aqueous solution.
2. Ethocel 7 CPS and PEG 3350 are dissolved in a mixture of the process solvents.
3. The pellets are coated with the solution from step 2
4. Methocel K15MP and PEG 3350 are dissolved in a mixture of the process solvents. Talc and Paliperidone are added and mixed until dispersed.
5. The second drug layer is made by coating the pellets with the dispersion from step 4.

Example 6 (Paliperidone 9 mg tablets with multi-particulate dosage form, with ascending release kinetics)

Process

1. The pellets from Example 5 are mixed with Lactose SD (2:1 w/w), 1% of magnesium stearate is added and mixed.
2. The tablets are compressed on a suitable tablet press.

Example 7 (Paliperidone 9 mg multi-particulate dosage form)

Pellets, Layer 1 (First Drug Layer)

Ingredient	mg / product
cellulose spheres	90.0
Paliperidone	6.0
Copovidone	4.0
Water (process solvent)	
Total Weight	100.0

Layer 2 (DR coating)

Ingredient	mg / product
Ethocel 7 CPS	20.0
PEG 3350	15.0
Alcohol 95% (process solvent)	
Isopropyl Alcohol (process solvent)	
Water (process solvent)	
Total Weight	35.0

Layer 3 (pH Dependent Coating)

Ingredient	mg / product
Eudragit FS 30D	8.0
Triethyl citrate	1.2
Talc	1.3
Water (process solvent)	
Total Weight	10.5

Layer 4 (Second Drug Layer)

Ingredient	mg / product
Paliperidone	3.0
Methocel K15MP	20.0
PEG 3350	7.0
Fumaric Acid	10.0
Talc	6.0
Ethanol (process solvent)	
Water (process solvent)	
Total Weight	46.0

Process

1. The first drug layer is made by coating the sugar spheres with the dispersion of Paliperidone in a Copovidone aqueous solution.
2. Ethocel 7 CPS and PEG 3350 are dissolved in a mixture of the process solvents.
3. The ER layer is prepared by coating the pellets with the solution from step 2.
4. The pH control layer is prepared by coating the pellets with the coating dispersion from Layer 3
5. Methocel K15MP and PEG 3350 are dissolved in a mixture of the process solvents. Talc and Paliperidone are added and mixed until dispersed.
6. The second drug ER layer is prepared by coating the pellets with the dispersion from step 5

Example 8 (Paliperidone extended release tablets in the form of inlay tablets)

Formulation of a Paliperidone Inlay Tablet

MATERIAL	% W/W range	mg per tablet	FUNCTION
Inlay Cores			
PALIPERIDONE	1-3	6.0	API
STARLAC	2-5	12.0	Filler
MAGNESIUM CARBONATE USP	5-15	26.0	pH modifier
POLYOX WSR-301	5-20	40.0	Release modifying polymer
STEARIC ACID NF/EP	0-1	1.5	Lubricant
Silicone Dioxide NF (Syloid 244 FP)	0-1	0.5	Glidant
Outer Layer			
ETHYLCELLULOSE T10 PHARM	50-90	216.5	Release modifying polymer
FERRIC OXIDE YELLOW NF	0-1	0.5	Dye
STEARIC ACID NF/EP	0-1	2.0	Lubricant
Final Inlay Tablet		305.0	

Paliperidone extended release tablets in the form of inlay tablets were prepared with the following process.

Process

1. 90 g Paliperidone, 180 g STARLAC, 390 g magnesium carbonate, 75 g POLYOX WSR-301 and 7.5 g silicone dioxide were sieved and mixed in a V-blender.
2. 15 g Stearic acid was sieved and added to the blend from step 1 and mixed.
3. The blend from step 2 was then compressed into slugs using a 20 mm flat punch.
4. The slugs were milled using a 0.8 mm screen.
5. 378.75 g of Milled slugs were then mixed with 272.5 g POLYOX WSR-301 and 3.75 g sieved stearic acid in a V-blender.
6. The blend from step 5 was then compressed into 86 mg tablets using a 5.5 mm normal concave punch, wherein the 86 mg tablets were used as the inlay cores in the rest of the process.
7. 3247.5 g of ETHYLCELLULOSE T10 PHARM and 7.5 g yellow ferric oxide were sieved and mixed in a V-blender.
8. 30 g Stearic acid was sieved and added to the blend from step 7 and mixed.
9. The tablets from step 6 were then recompressed with the blend from step 8 to create an incomplete outer layer on the tablets from step 6 in order to form inlay tablets, each weighing 305 mg, as the Paliperidone extended release tablets, wherein each of the tablets from step 6 acts as the inlay core for the Paliperidone extended release tablets.

Example 9 (Dissolution profile of the inlay tablets)

The dissolution of Paliperidone in the Paliperidone extended release tablets prepared as described in Example 8 were determined using a 50 RPM paddle method in a dissolution medium of 500 ml 0.05 M phosphate buffer, pH 6.8, wherein the dissolution was measured from 0 to 1440 minutes, i.e., 0 to 24 hours. The dissolution data are shown in Fig. 2.

Example 10 (Pharmacokinetics of the inlay tablets)

The pharmacokinetics of the Paliperidone extended release tablets, in the form of the inlay tablets containing 6 mg Paliperidone, of the present invention were determined in a group of 16 human subjects orally administered the inlay tablets. For comparison purposes, the pharmacokinetics of commercially available Paliperidone tablets, INVEGA 6 mg, were also determined in the 16 human subjects after oral administration. Plasma concentrations of Paliperidone in the 16 human subjects were

measured at 0 to 96 hours after oral administration of the Paliperidone extended release tablets of the present invention (i.e., the Test Group) or after oral administration of the commercially available INVEGA 6 mg Paliperidone tablets (i.e., the Reference Group).

The least-square mean plasma concentrations versus time after the oral administration of the Test Group and Reference Group are shown in Figure 3. The natural log of the least-square mean plasma concentrations versus time after the oral administration of the Test Group and Reference Group are shown in Figure 4. The mean values of the pharmacokinetic (PK) parameters of the Test Group and Reference Group are shown in the table below.

Mean PK Parameter Values

PK Parameters	Test Group	Reference Group
AUC_{96h} (h.ng/ml)	702.13	435.94
$AUC_{0-\infty}$ (h.ng/ml)	733.43	461.10
C_{max} (ng/ml)	22.33	12.82
$T_{1/2}$ (h)	20.17	19.96
k_e	0.04	0.04
LN AUC_{96h}	632.38	357.42
LN $AUC_{0-\infty}$	659.11	375.70
LN C_{max}	20.33	10.59

The ratio of the mean values of the pharmacokinetic (PK) parameters of the Test Group and Reference Group, as well as the 90% confidence intervals (CI) are shown in the table below.

Ratios of Mean PK Parameter Values (Test Group/Reference Group)

PK Parameters	Ratio	Lower CI	Higher CI	Treatment Effect (p)
AUC_{96h}	1.6106	1.2223	1.9990	0.0151
$AUC_{0-\infty}$	1.5906	1.2012	1.9800	0.0182
C_{max}	1.7416	1.3451	2.1381	0.0053
$T_{1/2}$	1.0109	0.9617	1.0600	
k_e	1.0041	0.9606	1.0477	

LN AUC_{96h}	1.7693	1.4459	2.1651	0.0002
LN $AUC_{0-\infty}$	1.7544	1.4356	2.1439	0.0002
LN C_{max}	1.9192	1.5686	2.3481	0.0001

Example 11 (Paliperidone 3 mg tablets with ascending release kinetics)

Layer 1 (external layer)

Ingredient	mg /Tablet
Polyethylene oxide (Polyox WSR-301)	95.00
Microcrystalline Cellulose (Avicel PH 101)	28.75
Magnesium Stearate	1.25
Total Weight	125.00

Layer 2 (internal layer)

Ingredient	mg / Tablet
Paliperidone	3.0
Polyethylene oxide (Polyox WSR-301)	60.0
Microcrystalline Cellulose (Avicel PH 101)	16.0
Sodium Chloride	20.0
Magnesium Stearate	1.0
Total Weight	100.0

Layer 3 (external layer)

Ingredient	mg /Tablet
Polyethylene oxide (Polyox WSR-301)	95.00
Microcrystalline Cellulose (Avicel PH 101)	28.75
Magnesium Stearate	1.25
Total Weight	125.00

Total Tablet Weight	350.0

Process

1. The composition of external layers is prepared by mixing polyethylene oxide (POLYOX WSR-301), microcrystalline cellulose (Avicel PH 101) in a mixer, adding sieved magnesium stearate to the blend and mixing.
2. The composition of internal layer is prepared by mixing Paliperidone, polyethylene oxide (POLYOX WSR-301), microcrystalline cellulose (Avicel PH 101) and sodium chloride in a mixer, adding sieved magnesium stearate to the blend and mixing.

3. The tablets are prepared by pressing the mixed blends to form three-layer tablets in a suitable tablet press, wherein two sides of the internal layer are in contact with the two external layers

Example 12 (Paliperidone 6 mg tablets with ascending release kinetics)

Layer 1 (external layer)

Ingredient	mg /Tablet
Hydroxypropyl methylcellulose (Methocel E10M)	65.0
Ethylcellulose T10	60.0
Povidone K-90	3.0
Stearic Acid	2.0
Water – process solvent	
Total Weight	130.00

Layer 2 (internal layer)

Ingredient	mg / Tablet
Paliperidone	6.0
Hydroxypropyl methylcellulose (Methocel E10M)	60.0
Ethylcellulose T10	50.0
Povidone K-90	2.0
Stearic Acid	2.0
Water – process solvent	
Total Weight	120.0

Layer 3 (external layer)

Ingredient	mg /Tablet
Hydroxypropyl methylcellulose (Methocel E10M)	65.0
Ethylcellulose T10	60.0
Povidone K-90	3.0
Stearic Acid	2.0
Water – process solvent	
Total Weight	130.00

Total Tablet Weight	380.0

Process

1. The composition of external layers is prepared by granulation of hydroxypropyl methylcellulose (Methocel E10M), ETHYLCELLULOSE T10 and Povidone K-90 in a high-shear mixer using water as a process solvent, drying and milling of the granulate, adding sieved Stearic Acid to the milled granulate and mixing.

2. The composition of internal layer is prepared by granulation OF Paliperidone, Hydroxypropyl methylcellulose (Methocel E10M), ETHYLCELLULOSE T10

and Povidone K-90 in a high-shear mixer using water as a process solvent, drying and milling of the granulate, adding sieved stearic acid to the milled granulate and mixing.

3. The tablets are prepared by pressing the mixed blends to form three-layer tablets in a suitable tablet press, when two sides of the internal layer are in contact with the two external layers.

We Claim:

1. A dosage form for sustained release of Paliperidone, comprising at least a first component and a second component located adjacent to the first component,

wherein

the first component comprises at least one delay layer comprising a polymer, and the second component comprises non-coated Paliperidone.

2. The dosage form of claim 1, wherein the second component further comprises coated Paliperidone.

3. The dosage form of any one of claims 1 to 2, further comprising a coating.

4. The dosage form of any one of claims 1 to 3, wherein the first component further comprises non-coated Paliperidone.

5. The dosage form of any one of claims 1 to 4, wherein (i) a layer of the first component contacts a layer of the second component along one face; (ii) the dosage form comprises three layers, so that two layers of the first component surround a layer of the second component; (iii) a layer of the second component is partially or completely surrounded by a layer of the first component; (iv) a layer of the second component is partially or completely surrounded by a sub-layer, which is partially or completely surrounded by a layer of the first component or (v) any one of (i) to (iv) further partially or completely surrounded by a coating layer.

6. The dosage form of claim 1, the first component being in a layer and the second component being in another layer, the dosage form further comprising a sub-layer between the layer of the first component and the layer of the second component.

7. The dosage form of any one of claims 1 to 6 exhibiting relative bioavailability, based on the AUC for the same duration after oral administration, of between about 1.5 and about 3.0 compared with INVEGA® extended release tablets containing the same amount of Paliperidone administered at the same dose.

8. The dosage form of claim 7, wherein the relative bioavailability is between about 1.7 and about 3.0.

9. The dosage form of claim 8, wherein the relative bioavailability is between about 1.9 and about 3.0.

10. The dosage form of any one of claims 1 to 9, wherein the dosage form exhibits a relative C_{max} after oral administration in human subjects of between about 1.6 and about 3.0 compared with INVEGA® extended release tablets containing the same amount of Paliperidone, administered at the same dose in the human subjects.

11. The dosage form of any one of claims 1 to 10, exhibiting an *in vitro* dissolution profile determined using a 50 RPM paddle method in a dissolution medium of 500 ml 0.05 M phosphate buffer, pH 6.8, wherein the dissolution profile is less than about 10% dissolution in 4 hours, between about 10% to about 25% dissolution in 8 hours, between about 40% to about 60% dissolution in 16 hours and not less than about 70% in 24 hours after the start of the dissolution study, respectively.

12. The dosage form of any one of claims 1 to 11, comprising a plurality of particulates, wherein each particulate comprises at least the first component and the second component.

13. The dosage form of claim 12, wherein the second component further comprises coated Paliperidone

14. The dosage form of claim 12, wherein at least some of the particulates are covered by a delayed release layer.

15. The dosage form of claim 12, wherein all of the particulates are covered by a delayed release layer.

16. The dosage form of claim 12, wherein the plurality of particulates comprises a first population of particulates and a second population of particulates, wherein

said first population differs from said second population in at least one of 1) weight ratio between said first component and said second component; 2) weight ratio between coated and non-coated paliperidone, 3) weight ratio between paliperidone and other components in the particulate; 4) nature and thickness of coating layer; 5) existence and relative weight of a core and/or sub layer; 6) existence of a second delay layer and the weight ratio between the layers.

17. The dosage form of claim 12, wherein the at least one polymer of the delay layer is selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methyl cellulose, ethyl cellulose and polymethacrylates.

18. The dosage form of claim 12, wherein the delay layer further comprises at least one plasticizer.

19. The dosage form of claim 18, wherein the plasticizer is hydrophilic.

20. The dosage form of claim 19, wherein the hydrophilic plasticizer is selected from triethyl citrate and polyethylene glycol; and the hydrophobic plasticizer is selected from diethyl phthalate, dibutyl phthalate, dibutyl sebacate and acetyl tributyl citrate.

21. The dosage form of claim 12, each particulate further comprises an inert core covered by a layer comprising Paliperidone or a salt thereof.

22. The dosage form of claim 21, wherein the inert core is selected from the group consisting of microcrystalline cellulose spheres, sugar spheres, and glass spheres.

23. The dosage form of claim 21, wherein the layer comprising Paliperidone or a salt thereof covering the core further comprises at least one pharmaceutically acceptable excipient that acts as a binder.

24. The dosage form of claim 12, wherein the particulates differ in the onset time of paliperidone release and in the rate of release after said onset time.

25. A process for preparing the dosage form of claim 12, comprising:
preparing a particulate by coating a core with a layer comprising non-coated Paliperidone or a salt thereof and applying an extended release layer thereon.

26. The process of claim 25, wherein the layer comprising non-coated Paliperidone or a salt thereof is applied by a process comprising coating the core with a non-coated Paliperidone containing layer using a solution or dispersion of Paliperidone or a salt thereof and a binder.

27. The process of claim 25, wherein the coating process is performed using a fluidized bed coater.

28. The process of claim 27, wherein the fluidize bed coater is equipped with a bottom or top spray device.

29. The dosage form of any one of claims 1 to 11, comprising a plurality of particulates wherein each of the particulates comprises at least three layers:
a first layer comprising Paliperidone or a salt thereof and a polymer;
a second layer being a delay release layer covering the first layer; and
a third layer comprising Paliperidone and a polymer.

30. The dosage form of claim 29, further comprising an acid comprising layer, wherein the second layer is a pH–sensitive layer.

31. The dosage form of claim 30, wherein the acid comprising layer comprises at least one organic acid.

32. The dosage form of claim 31, wherein the at least one organic acid is selected from ascorbic acid, tartaric acid and fumaric acid.

33. The dosage form of any one of claims 29 to 32, wherein the first layer comprises a core substantially enveloped by the second component, and wherein the core is covered by a layer comprising Paliperidone or a salt thereof.

34. The dosage form of claim 33, wherein the layer that covers the core comprises the Paliperidone or the salt thereof and at least one pharmaceutically acceptable excipient that acts as a binder.

35. The dosage form of claim 34, wherein the binder is selected from methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and povidone, copovidone, starch, Arabic gum, acasia gum and gelatin.

36. The dosage form of any one of claims 33 to 35, wherein the core is an inert core.

37. The dosage form of claim 36, wherein the inert core is selected from microcrystalline cellulose spheres, sugar spheres and glass spheres.

38. The dosage form of any one of claims 29 to 37, wherein more than half of the Paliperidone in the third layer is released before the release of a fraction of Paliperidone in the first layer.

39. The dosage form of claim 30, wherein the pH sensitive delay layer will not dissolve until the acid comprising layer is released from the dosage form completely, so that the release of the inner Paliperidone layer is controlled.

40. Paliperidone extended release tablet in the form of an inlay tablet comprising:
(a) an inlay core comprising non-coated Paliperidone and at least one polymer capable of delaying the release of Paliperidone from the inlay core and capable of swelling upon hydration; and
(b) an outer layer comprising a pharmaceutical excipient which is substantially water insoluble, wherein the outer layer partially surrounds the inlay core.

41. The extended release tablet of claim 40, wherein the at least one polymer of the inlay core is selected from the group consisting of polyvinylpyrrolidone, poly(ethylene oxide), POLYOX WSR-301, polysaccharides, hydrophilic cellulose derivatives, methyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl methylcellulose, carboxy methylcellulose and sodium carboxy methylcellulose.

42. The extended release tablet of claim 40, wherein the at least one polymer of the inlay core is selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl methylcellulose, carboxy methylcellulose and sodium carboxy methylcellulose.

43. The extended release tablet of claim 40, wherein the at least one polymer of the inlay core is selected from the group consisting of POLYOX WSR-301 and hydroxypropyl methylcellulose.

44. The extended release tablet of claim 40, wherein the at least one polymer of the inlay core is selected from the group consisting of POLYOX WSR-301 and METHOCEL K15MP.

45. The extended release tablet of any one of claims 40 to 44, wherein the pharmaceutical excipient which is substantially water insoluble of the outer layer is a pharmaceutically acceptable polymer which is substantially water insoluble.

46. The extended release tablet of claim 45, wherein the pharmaceutically acceptable polymer which is substantially water insoluble is selected from the group consisting of cationic copolymers of ethylacrylate and methylacrylate with quarternary ammonium groups, EUDRAGIT RS, EUDRAGIT RL, ethylacrylate methylmethacrylate copolymer with neutral ester groups, cellulose esters, cellulose ethers and cellulose esterethers, ethyl cellulose such as ETHYL CELLULOSE T10 PHARM, cellulose acetate, cellulose diacetate, cellulose triacetate and polyester polymers, poly(ε-caprolactone)s, poly(alkylene glycol adipate)s, poly(ethylene glycol adipate), poly(propylene glycol adipate) and poly(butylene glycol adipate), polyvinyl acetate and blends and copolymers thereof.

47. The extended release tablet of claim 46, wherein the pharmaceutically acceptable polymer which is substantially water insoluble is selected from the group consisting of POLYOX WSR-301 and ETHYLCELLULOSE T10 PHARM.

48. The extended release tablet of claim 46, wherein the pharmaceutically acceptable polymer which is substantially water insoluble is ethyl cellulose.

49. The extended release tablet of any one of claims 40 to 48, wherein the inlay core is in the form of a tablet or compressed slug.

50. The extended release tablet of any one of claims 40 to 48, wherein the inlay core and/or the outer layer independently further comprise at least one other pharmaceutical excipient.

51. The extended release tablet of claim 50, wherein the at least one other pharmaceutical excipient is selected from the group consisting of pharmaceutically acceptable fillers, diluents, pH modifiers, glidants, lubricants, binders, dyes and flavoring agents.

52. The extended release tablet of any one of claims 40 to 51, wherein

the inlay core comprises Paliperidone in about 1-3 % w/w, a filler in about 2-5% w/w, pH modifier in about 5-15% w/w, release modifying polymer in about 5-20% w/w, lubricant in about 0-1% w/w and glidant in about 0-1% w/w; and

the outer layer comprises a release modifying polymer in about 50-90% w/w, dye in about 0-1% w/w and lubricant in about 0-1% w/w.

53. The extended release tablet of claim 52, wherein

the inlay core comprises Paliperidone in about 1-3 % w/w, STARLAC in about 2-5% w/w, magnesium carbonate USP in about 5-15% w/w, POLYOX WSR-301 in about 5-20% w/w, stearic acid NF in about 0-1% w/w and silicone dioxide NF in about 0-1% w/w; and

the outer layer comprises ETHYLCELLULOSE T10 PHARM in about 50-90% w/w, Ferric Oxide Yellow NF in about 0-1% w/w and stearic acid NF in about 0-1% w/w.

54. A process of making the extended release tablet of claim 40, comprising

(1) mixing Paliperidone and at least one polymer capable of delaying the release of Paliperidone and capable of swelling upon hydration; and

(2) partially covering the mixture of step (1) with an outer layer comprising a pharmaceutical excipient which is substantially water insoluble to obtain the extended release tablet in the form of an inlay tablet.

55. The process of claim 54, wherein the mixture of step (1) is compressed into a slug or tablet before step (2).

56. The process of claim 54, wherein the mixture of step (1) is compressed into a slug or tablet before step (2); the slug or tablet is mixed with the at least one polymer capable of delaying the release of Paliperidone and capable of swelling upon hydration to form a mixture; and the mixture is compressed into a tablet before step (2).

57. The process of any one of claims 54 to 56, wherein a filler, pH modifier, glidant and/or lubricant is added in step (1).

58. The process of claim 55 or 56, wherein the slug or tablet formed by compression is milled before being mixed with the at least one polymer capable of delaying the release of Paliperidone and capable of swelling upon hydration to form the mixture to be compressed into a tablet before step (2).

59. The process of any one of claims 54 to 58, wherein the product of step (2) is compressed to obtain the inlay tablet.

Figure 1

Paliperidone Inlay Tablet Before and After Hydration

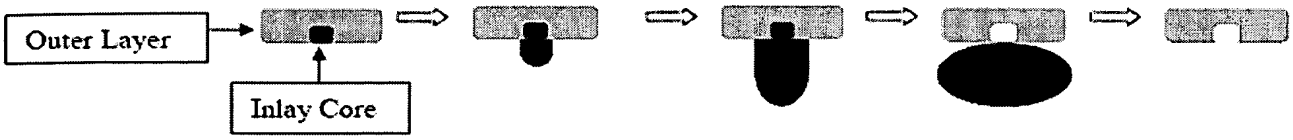


Figure 2

Dissolution Profile of Inlay Tablets

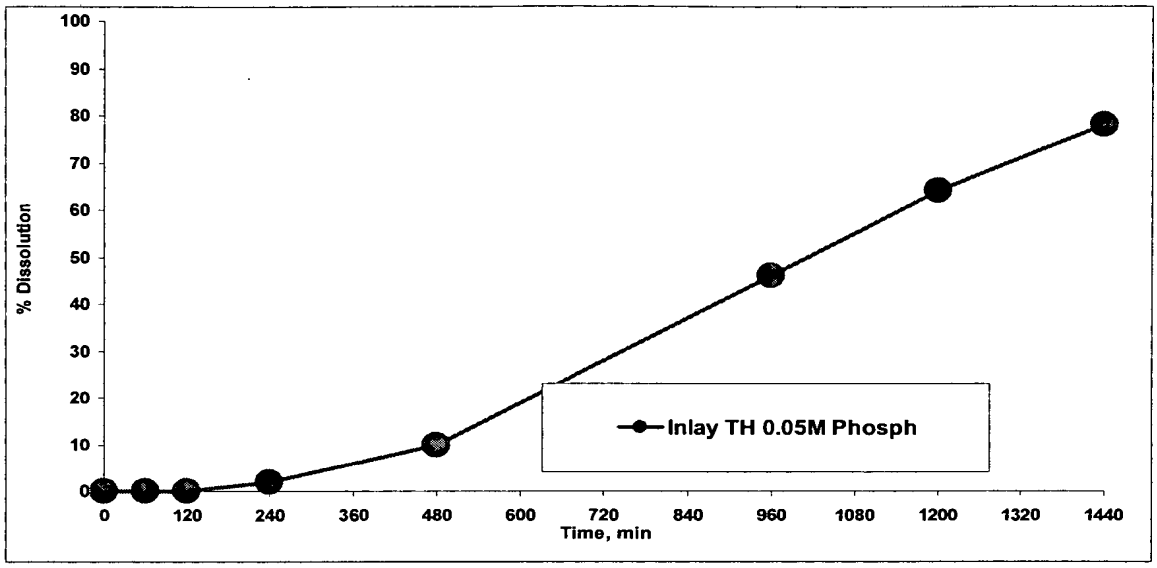


Figure 3

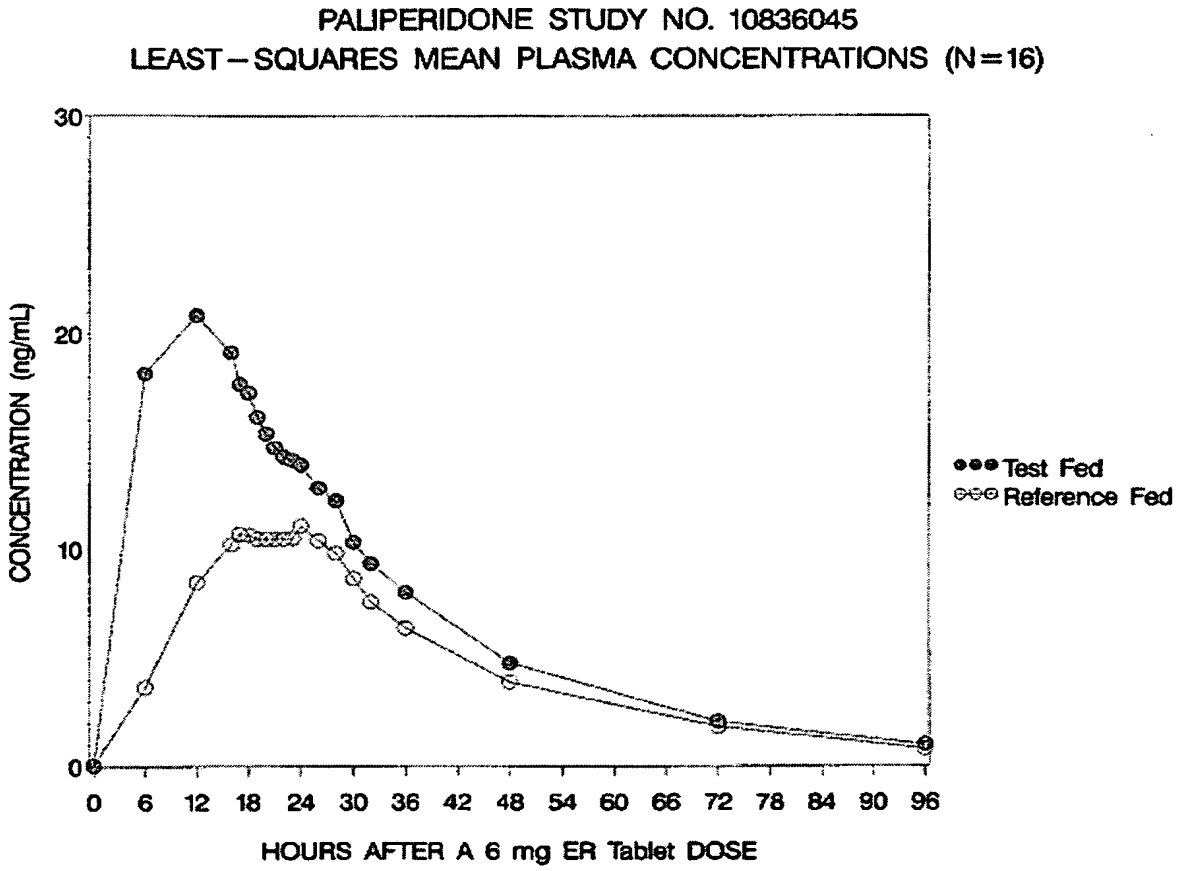
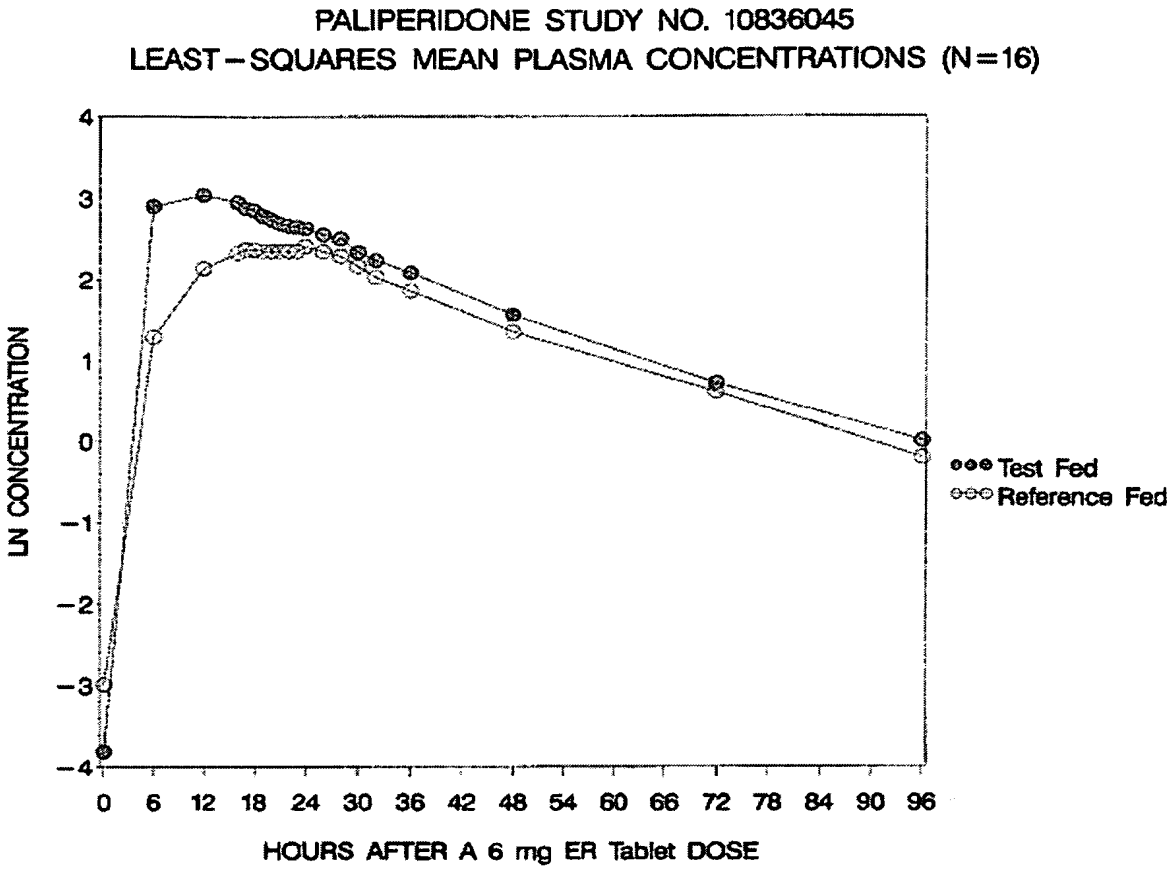

PALIPERIDONE STUDY NO. 10836045
LEAST-SQUARES MEAN PLASMA CONCENTRATIONS (N=16)
CONCENTRATION (ng/mL)
30
20
10
0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
HOURS AFTER A 6 mg ER Tablet DOSE
Test Fed
Reference Fed

Figure 4


PALIPERIDONE STUDY NO. 10836045
LEAST-SQUARES MEAN PLASMA CONCENTRATIONS (N=16)
LN CONCENTRATION
4
3
2
1
0
−1
−2
−3
−4
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
HOURS AFTER A 6 mg ER Tablet DOSE
Test Fed
Reference Fed

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/010014

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K9/50

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/189635 A1 (KRAMER MICHELLE [US] ET AL) 24 August 2006 (2006-08-24) paragraphs [0066], [0084] - [0106], [0117] - [0123], [0131], [0132], [0137], [0138] figures 1,2 examples 6,8,9,19 ----- -/--	1,3,4

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 January 2009	03/02/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schwald, Claudia

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/010014

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/108067 A (SUN PHARMACEUTICAL IND LTD [IN]; DHARMADHIKARI NITIN BHALACHAND [IN];) 16 December 2004 (2004-12-16) abstract page 4, lines 16-34 page 6, lines 6-34 page 13, line 23 page 15, lines 4-27 page 16, lines 4-8 page 16, lines 17-23 examples 1,2	1,3,4
X	US 2006/034927 A1 (CASADEVALL GEMMA [ES] ET AL) 16 February 2006 (2006-02-16) abstract paragraphs [0030], [0041], [0048], [0049] figures 1-6 example 1 example 3	1-3
X	WO 2004/010981 A (ALZA CORP [US]) 5 February 2004 (2004-02-05) paragraphs [0032], [0033], [0038], [0041], [0094], [0099], [0109], [0110] paragraphs [0140] - [0144] example 1	1,3
A	US 2005/232990 A1 (BOEHM GARTH [US] ET AL) 20 October 2005 (2005-10-20) paragraphs [0001], [0010], [0013], [0015], [0134] - [0150], [0278]	5-11, 29-59

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/010014

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

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

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

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

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

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

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

see additional sheet

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

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

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

1-4 (part.), 1-11 (part.) and 29-39, 40-59

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

Remark on Protest

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

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

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4(part.)

A dosage form for sustained release of Paliperidone, comprising at least a first component and a second component located adjacent to the first component, wherein the first component comprises at least one delay layer comprising a polymer, and the second component comprises non-coated Paliperidone,
wherein the first component further comprises non-coated Paliperidone.

---

2. claims: 1-5(part.)

The dosage form of any one of claims 1 to 4, wherein a layer of the second component is partially or completely surrounded by a sub-layer, which is partially or completely surrounded by a layer of the first component.

---

3. claims: 1-5(part.)

The dosage form of any one of claims 1 to 4, wherein a layer of the first component contacts a layer of the second component along one face; further partially or completely surrounded by a coating layer.

---

4. claims: 1-5(part.)

The dosage form of any one of claims 1 to 4, wherein the dosage form comprises three layers, so that two layers of the first component surround a layer of the second component; further partially or completely surrounded by a coating layer.

---

5. claims: 1-5(part.)

The dosage form of any one of claims 1 to 4, wherein a layer of the second component is partially or completely surrounded by a sub-layer, which is partially or completely surrounded by a layer of the first component; further partially or completely surrounded by a coating layer.

---

6. claims: 1-12(part.) and 13-24

The dosage form of any one of claims 1 to 11, comprising a plurality of particulates, wherein each particulate comprises at least the first component and the second component.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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7. claims: 1-12(part.) and 25-28

A process for preparing the dosage form of claim 12, comprising: preparing a particulate by coating a core with a layer comprising non-coated Paliperidone or a salt thereof and applying an extended release layer thereon.

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8. claims: 1-11(part.) and 29-39

The dosage form of any one of claims 1 to 11, comprising a plurality of particulates wherein each of the particulates comprises at least three layers:
a first layer comprising Paliperidone or a salt thereof and a polymer;
a second layer being a delay release layer covering the first layer; and
a third layer comprising Paliperidone and a polymer.

---

9. claims: 40-59

Paliperidone extended release tablet in the form of an inlay tablet comprising:
(a) an inlay core comprising non-coated Paliperidone and at least one polymer capable of delaying the release of Paliperidone from the inlay core and capable of swelling upon hydration; and
(b) an outer layer comprising a pharmaceutical excipient which is substantially water insoluble, wherein the outer layer partially surrounds the inlay core
and the process of preparation thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/010014

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

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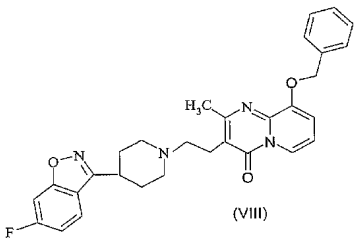
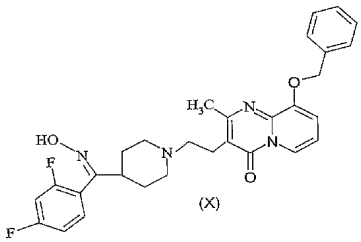
(54) **Title:** PROCESSES FOR THE PREPARATION OF PALIPERIDONE AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF AND INTERMEDIATES FOR USE IN THE PROCESSES



(VIII)



(X)

(57) **Abstract:** The present invention relates to novel compounds of formula (VIII) and (X), processes for their preparation and their use in the preparation of paliperidone or a salt thereof. There is also provided by the present invention novel processes for preparing intermediates for use in the preparation of paliperidone or a salt thereof, and novel processes for preparing paliperione or a salt thereof.

WO 2009/047499 A2

PROCESSES FOR THE PREPARATION OF PALIPERIDONE AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF AND INTERMEDIATES FOR USE IN THE PROCESSES

Field of the Invention

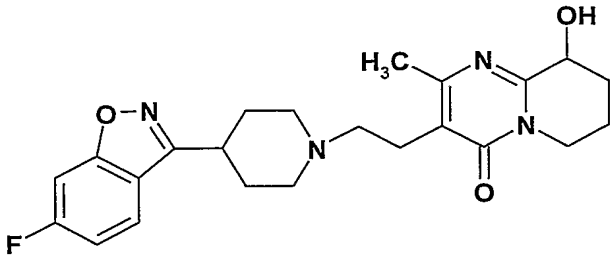
The present invention relates to processes for the preparation of paliperidone or its pharmaceutically acceptable salt, and processes for preparing intermediates useful in the synthesis of paliperidone, or its pharmaceutically acceptable salts.

Background of the Invention

Schizophrenia is a common and disabling psychotic disorder characterized by extreme disturbances of cognition and thought, affecting language, perception and sense of self. Despite the availabilty of a number of agents for the treatment of schizophrenia, it remains a significant burden on healthcare systems. Most of the antipsychotic drugs, although effective against psychosis, do not improve and may even exacerbate the negative symptoms of schizophrenia.

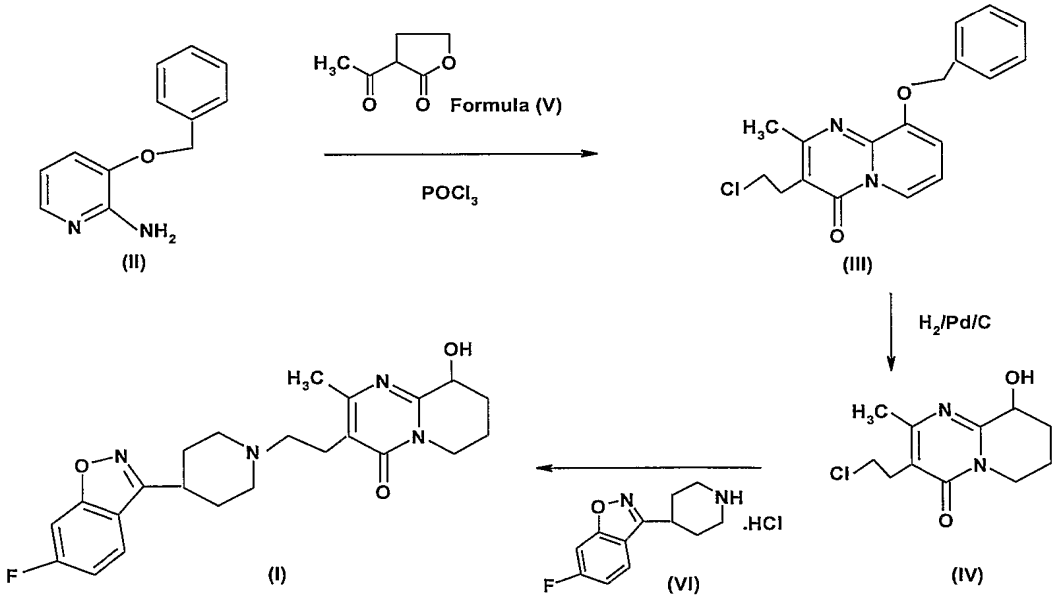
Paliperidone, an atypical antipsychotic, is an active metabolite of risperidone used for the treatment of schizophrenia and bipolar disorder. While its specific mechanism of action is unknown, it is believed that paliperidone and risperidone act via similar, if not the same, pathways.

Paliperidone, i.e 9-hydroxyrisperidone, is chemically known as 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido [1,2-a] pyrimidin-4-one and has the following structural formula (I),



(I)

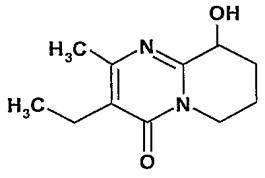
US 5,158,952 and its equivalent EP 368,388 disclose paliperidone, compositions comprising paliperidone and methods of its use. The synthetic process employed is depicted in the following scheme.



wherein the compound of formula (II) is reacted with the compound of formula (V) at 90°C for 5 hours to yield the compound of formula (III) which is purified by column chromatography using trichloromethane and methanol and further recrystallized from isopropanol. The compound of formula (III) is further reduced to the compound of formula (IV) in methanol using a palladium on carbon as catalyst, which is further condensed with the compound of formula (VI) to yield paliperidone of formula (I).

The process disclosed in the US 5,158,952 has several disadvantages. First, the intermediate (III) is obtained as an oily mass. This oily mass contains impurities which

are difficult to separate by crystallization. In this process, a solid product is obtained only after purification by column chromatography thereby making the process non economical on an industrial scale. Second, hydrogenolysis of the compound of formula (III) to the compound of formula (IV) leads to undesirable dechlorination resulting in the des-chloro impurity of compound of formula (VII)



(VII)

Paliperidone thus obtained by condensation of the compound of formula (IV) with the compound of formula (VI) is of poor quality and is further purified by column chromatography and solvent crystallizations, thereby making the process time consuming and expensive.

Therefore, there exists a need for a more economical and efficient method of making pure paliperidone which is suitable for industrial scale up.

Objects of the Invention

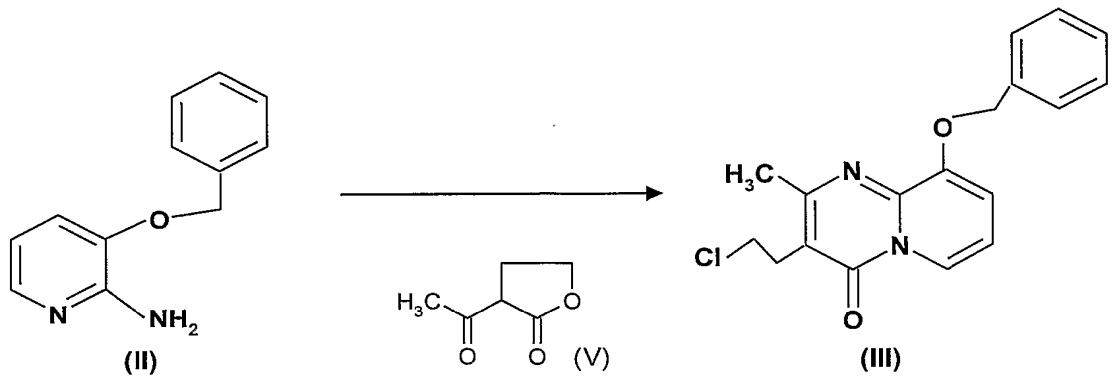
It is an object of the present invention to provide novel intermediates for the synthesis of paliperidone or its pharmaceutically acceptable salts.

It is another object of the present invention to provide processes for the preparation of novel intermediates used in the synthesis of paliperidone or its pharmaceutically acceptable salts.

It is yet another object of this invention to provide novel processes for the preparation of paliperidone or its pharmaceutically acceptable salts using novel intermediates.

Summary of the Invention

According to a first aspect of the present invention, there is provided a process for preparing a compound of formula (III) comprising condensing a 3-benzyloxy-2-aminopyridine (II) with an α-acyl lactone (V).



Advantageously, the condensation is carried out in the presence of a dipolar aprotic solvent. Preferably, the dipolar aprotic solvent is present in a catalytic amount. Preferably, the condensation is carried out in the presence of an activating agent. Most preferably, the condensation is carried out in the presence of an activating agent and a catalytic amount of a dipolar aprotic solvent.

In an embodiment, the dipolar aprotic solvent is selected from the group consisting of N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), 1-methyl-2-pyrrolidinone, pyridine and acetic anhydride. Preferably, the dipolar aprotic solvent is DMF.

In an embodiment, the activating agent is a halogenating reagent, typically a chlorinating agent suitably selected from the group consisting of thionyl chloride, phosphorous oxychloride, phosphorous trichloride, phosphorous pentachloride, oxalyl chloride and phosgene. Preferably, the activating agent is phosphorous oxychloride. Alternatively, other halogenating agents may be used, for example brominating agents. In this case, the chloro moiety in compound (III) above would be replaced with a bromo moiety, i.e. a compound of formula (IIIa).

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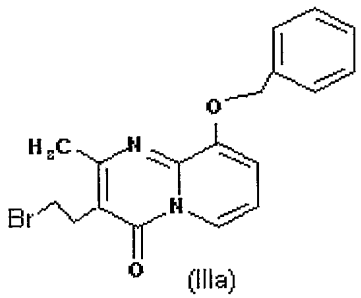
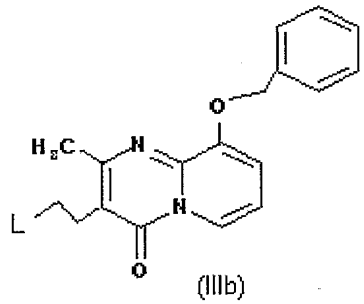


(IIIa)

In another alternative, the reaction conditions of the condensation of compound (II) with compound (V) would be such that a different leaving group were present in place of the chloro moiety on compound (III), i.e. the compound of formula (IIIb) below wherein L is a leaving group.



(IIIb)

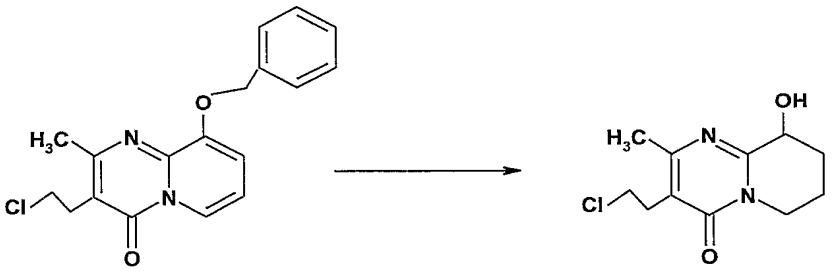
Alternative leaving groups are well known to those skilled in the art. Such modified compounds, i.e. compounds of formula (IIIa) or (IIIb) may also be used in the processes described below.

The condensation may be carried out in the presence of a further solvent. Typically, the further solvent is an inert solvent selected from the group consisting of hydrocarbon solvents such as benzene, cyclohexane, toluene, or xylene; halogenated hydrocarbons such as chlorobenzene, methylene chloride; anisole; or DMF. Alternatively the reaction may be performed in the absence of a further solvent.

The compound (III) obtained by the condensation is optionally purified for example by crystallization using solvents such as isopropyl alcohol, methanol, butanol, ethanol, ethyl acetate or mixtures thereof.

According to another aspect of the present invention, there is provided a process for preparing paliperidone or a salt thereof, the process comprising an intermediate step of condensing a 3-benzyloxy-2-aminopyridine (II) with an α-acyl lactone (V) to form a compound of formula (III) according to the process described above.

According to another aspect of the present invention, there is provided a process for preparing a compound of formula (IV) comprising reducing a compound of formula (III) to the compound of formula (IV).



Formula (III) Formula (IV)

Advantageously, the reduction is carried out in the presence of an acid. Suitably, the acid is selected from the group consisting of: a carboxylic acid such as acetic acid, trifluoro acetic acid, dichloro acetic acid, trichloro acetic acid or formic acid; a mineral acid such as hydrochloric acid, sulfuric acid or phosphoric acid; and a Lewis acid such as boron trihalides. Preferably, the acid is acetic acid.

In an embodiment, the reduction is a catalytic reduction. The catalytic reduction may be carried out in the presence of a noble metal catalyst and hydrogen gas or using transfer hydrogenation.

In an embodiment, the catalyst is selected from the group consisting of palladium, palladium hydroxide, palladium on activated carbon, palladium on alumina, platinum, platinum on activated carbon, platinum dioxide and Raney nickel, preferably palladium-on-carbon. The catalyst may be a combination of catalysts.

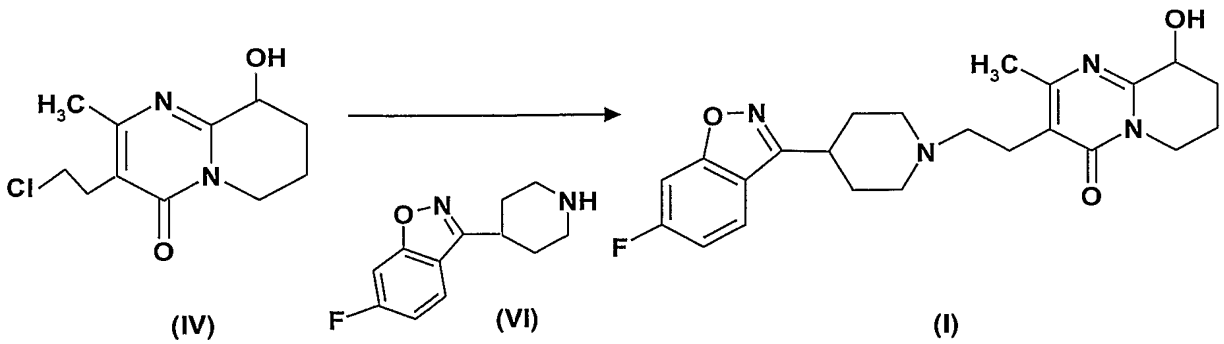
In a particularly preferred embodiment, the amount of catalyst employed ranges from about 1% by weight of compound (III) to about 30% by weight of compound (III), preferably about 10% by weight of compound (III) to about 20% by weight of compound (III), more preferably the amount of catalyst is about 15% by weight of compound (III).

Suitably, the reaction is carried out in the presence of a solvent selected from: a lower alcohol solvent for example a C_1 to C_3 alcohol solvent such as methanol, ethanol, isopropanol or n-butanol; an ether such as tetrahydrofuran or 1,4-dioxane; an ester such as ethyl acetate; a halogenated hydrocarbon such as methylene dichloride, ethylene dichloride; a ketone such as acetone; or a mixture thereof.

In an embodiment, the compound of formula (III) is prepared by the process described above.

According to another aspect of the present invention, there is provided a process for preparing paliperidone or a salt thereof, the process comprising an intermediate step of reducing a compound of formula (III) to a compound of formula (IV) by the process described above.

According to another aspect of the present invention, there is provided a process for preparing paliperidone or a salt thereof comprising condensing chloroethyl derivative (IV) with compound (VI) or a salt thereof to obtain paliperidone (I), and optionally converting paliperidone to a salt thereof.



(IV) (VI) (I)

Preferably, the condensation is carried out in the presence of base. Suitably, the base is an organic base or an inorganic base. The base may be selected from the group consisting of pyridine, triethylamine, diisopropylethylamine, potassium phosphate, sodium carbonate, potassium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, sodium hydroxide and potassium hydroxide, preferably potassium carbonate.

Typically, the condensation is carried out in an inert organic solvent, with or without water. In an embodiment, the solvent is a C1 to C6 straight chain alcohol, tetrahydrofuran, acetonitrile, DMF, DMA, methylene chloride, ethylene chloride, diglyme or toluene like. The preferred solvents are acetonitrile and methanol.

The condensation may be carried out at an elevated temperature. In an embodiment, the condensation is carried out at a temperature ranging from room temperature to the reflux temperature of the solvent, preferably from 40°C to 90°C, more preferably from 75°C to 80°C.

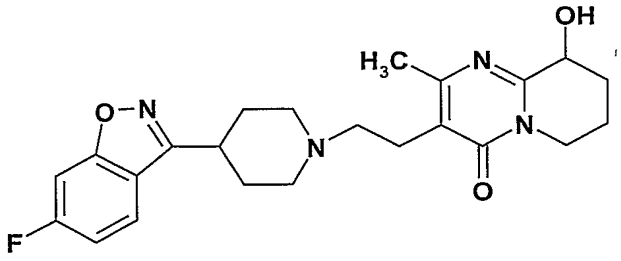
Optionally, the condensation is carried out in the presence of a catalyst such as tetrabutyl ammonium bromide, tetrabutyl ammonium chloride, potassium iodide, sodium iodide, sodium bromide, potassium bromide or lithium iodide.

The paliperidone is produced in a high purity (for example not more than 1.50% total impurities, preferably not more than 1.00% total impurities) but may be further purified for example by crystallization using a solvent or a mixture of solvents.

The optional conversion of paliperidone to a salt thereof may be carried out according to any conventional process.

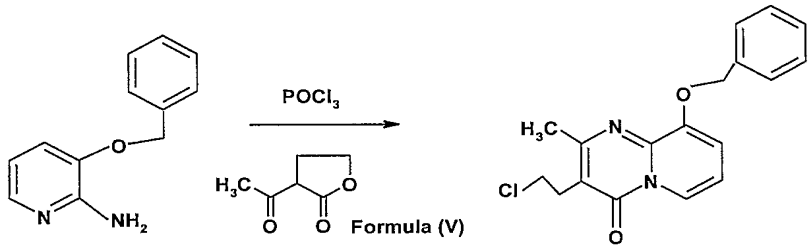
In an embodiment, compound (IV) is prepared by the process described above.

In an embodiment, there is provided a process for preparing paliperidone of formula (I) or a salt thereof



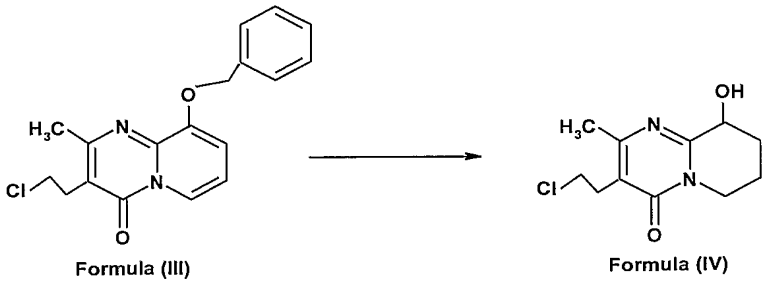
Formula (I)

the process comprising: a) condensing 3-benzyloxy- 2-aminopyridine (II) with an α-acyl lactone (V) in the presence of an activating agent and a catalytic amount of a dipolar aprotic solvent in a suitable inert solvent to obtain compound (III);



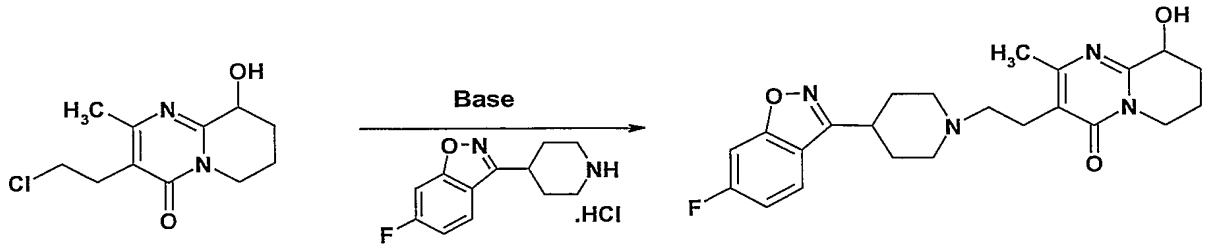
Formula (II) Formula (V) Formula (III)

b) reducing the compound of formula (III) in the presence of an acid to a compound of formula (IV);



Formula (III) Formula (IV)

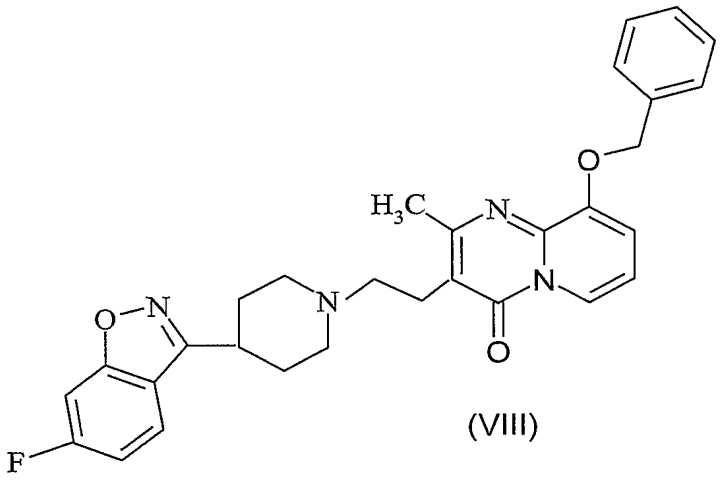
c) condensing the chloroethyl derivative (IV) with compound (VI) or a salt thereof in the presence of a base to obtain paliperidone (I);



Formula (IV) Formula (VI) Formula (I)

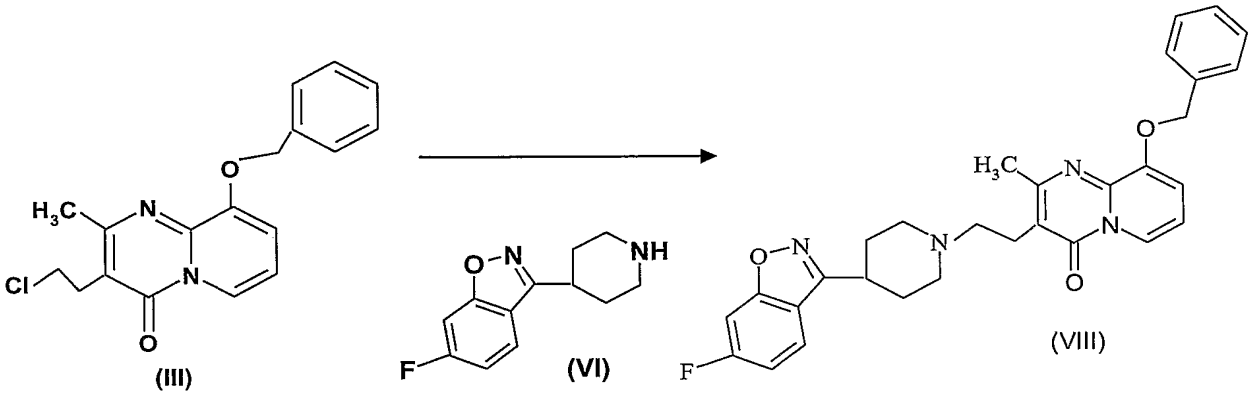
and d) optionally converting paliperidone base to a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention, there is provided a compound of formula (VIII). Compound of formula (VIII) is useful in the preparation of paliperidone of formula (I) or pharmaceutically acceptable salts thereof.



(VIII)

According to another aspect of the present invention, there is provided a process for preparing a compound of formula (VIII) comprising condensing a compound of formula (III) with a compound of formula (VI) or a salt thereof to obtain the compound of formula (VIII).



Typically, the condensation is carried out in the presence of a solvent. The solvent may be selected from the group consisting of toluene, ethyl acetate, acetonitrile, tetrahydrofuran, methylene chloride, ethylene chloride, diglyme, cyclohexane, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), C1 to C6 straight or branched chain alcohols, such as methanol, ethanol, isopropanol, n-propanol, and mixtures thereof.

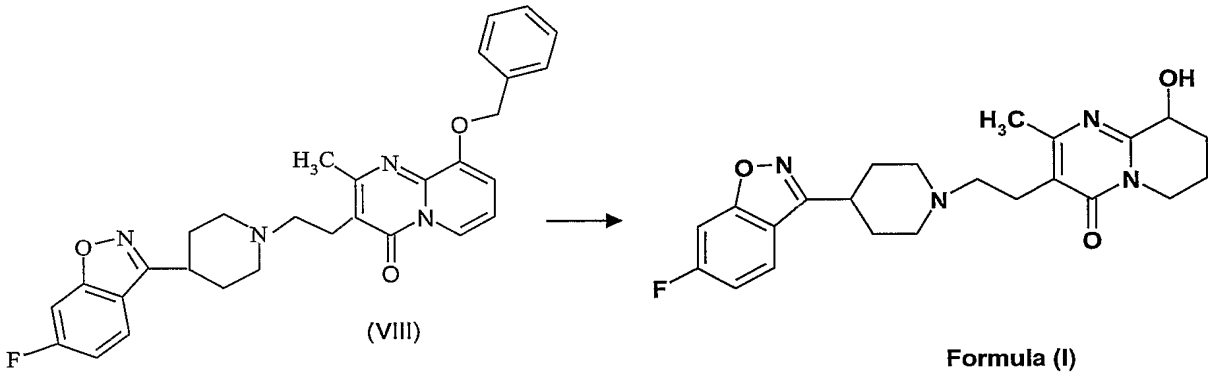
Preferably, the condensation is carried out in the presence of a base. The base may be an organic or inorganic base. The inorganic base may be selected from group the consisting of potassium carbonate, sodium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide and potassium phosphate. The organic base may be selected from the group consisting of diisopropyl ethyl amine, pyridine and triethyl amine. Preferably, the base is potassium carbonate.

Optionally the reaction is carried out in the presence of a catalyst. The catalyst may be selected from the group consisting of tetrabutyl ammonium bromide, tetrabutyl ammonium chloride, potassium iodide, sodium iodide, lithium iodide, sodium bromide and potassium bromide; preferably potassium iodide.

In a preferred embodiment, the condensation is carried out in the presence of a base and a catalyst, more preferably in the presence of potassium carbonate and potassium iodide.

In an embodiment, the compound of formula (III) is prepared by the process described above.

According to another aspect of the present invention, there is provided a process for preparing paliperidone or a salt thereof comprising converting the compound of formula (VIII) to paliperidone and optionally converting the paliperidone to a salt thereof.



In an embodiment, the conversion comprises reduction. Preferably, the conversion of compound (VIII) to paliperidone comprises reducing compound (VIII) using catalytic reduction, suitably in the presence of a noble metal catalyst and hydrogen gas or using transfer hydrogenation.

In an embodiment, the catalyst is selected from the group consisting of palladium, palladium on carbon (preferably in an amount ranging from 1% to 20% of carbon by weight of palladium), platinum, platinum dioxide, platinum on carbon, palladium hydroxide, palladium on alumina or Raney nickel; preferably palladium on carbon (preferably 10% of carbon by weight of palladium) and the amount of catalyst employed ranges from 1% to 30% by weight of compound (VIII), preferably in an amount of 15% by weight of compound (VIII). In an embodiment, the catalytic reduction is carried out a temperature ranging from 20°C to 80°C, preferably from 25°C to 35°C. In another embodiment, the catalytic reduction may be carried out under a hydrogen gas pressure ranging from 1.0 Kg to 8.0 Kg, preferably from 4.0 Kg to 5.0 Kg. A combination of catalysts may also be used.

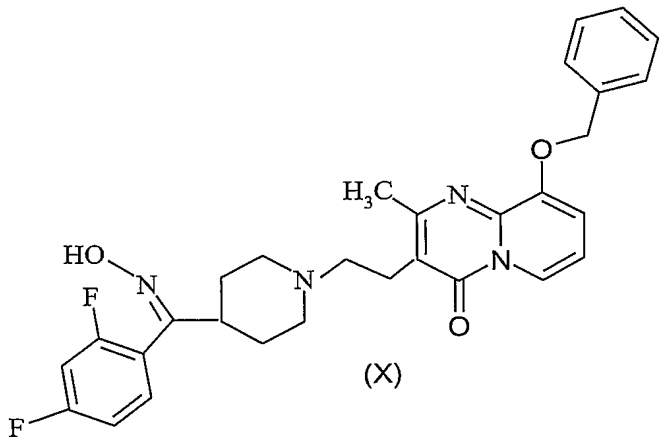
Typically, the reduction is carried out in the presence of a solvent. Preferably, the solvent is selected from the group consisting of ethyl acetate, methanol, ethanol, isopropyl alcohol, n-butanol, tetrahydrofuran, 1,4-dioxane, acetic acid, acetone, a halogenated hydrocarbon such as methylene dichloride or ethylene dichloride, or mixture thereof; preferably methanol.

Optionally, the paliperidone is converted to a salt thereof in accordance with conventional techniques.

In another embodiment, the compound of formula (VIII) has been prepared by the process described above.

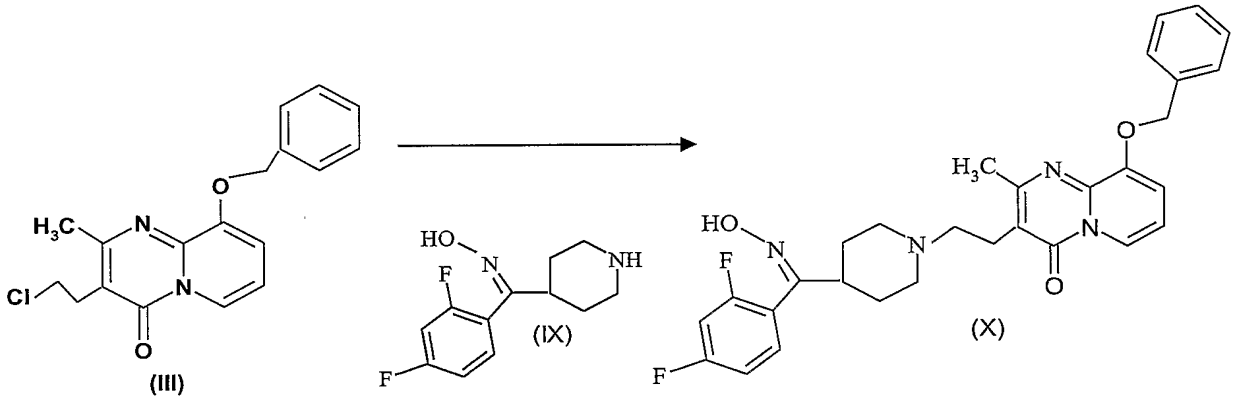
In a preferred embodiment, there is provided a process for preparing paliperidone or a pharmaceutically acceptable salt thereof comprise the following steps: a) condensing 3-benzyloxy-2-aminopyridine of formula (II) with an α-acyl lactone of formula (V) in the presence of an activating agent, preferably phosphorus oxychloride, and a catalytic amount of dipolar aprotic solvent, and in the presence of a further solvent to obtain the compound of formula (III); b) condensing the compound of formula (III) with the compound of formula (VI) in the presence of a base and optionally in the presence of a catalyst to obtain the compound of formula (VIII); and c) reducing the compound of formula (VIII) to obtain paliperidone (I).

According to another aspect of the present invention, there is provided a compound of formula (X). Compound (X) is useful in the preparation of paliperidone of formula (I) or pharmaceutically acceptable salts thereof.



(X)

According to another aspect of the present invention, there is provided a process for preparing a compound of formula (X) comprising condensing a compound of formula (III) with a compound of formula (IX) to obtain the compound of formula (X).



(III) (IX) (X)

Typically, the condensation is carried out in the presence of a solvent. The solvent may be selected from the group consisting of toluene, ethyl acetate, acetonitrile, tetrahydrofuran, methylene chloride, ethylene chloride, diglyme, cyclohexane, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), C1 to C6 straight or branched chain alcohols, such as methanol, ethanol, isopropanol, n-propanol, and mixtures thereof.

Preferably, the condensation is carried out in the presence of a base. The base may be an organic or inorganic base. The inorganic base may be selected from group the consisting of potassium carbonate, sodium carbonate, cesium carbonate, potassium

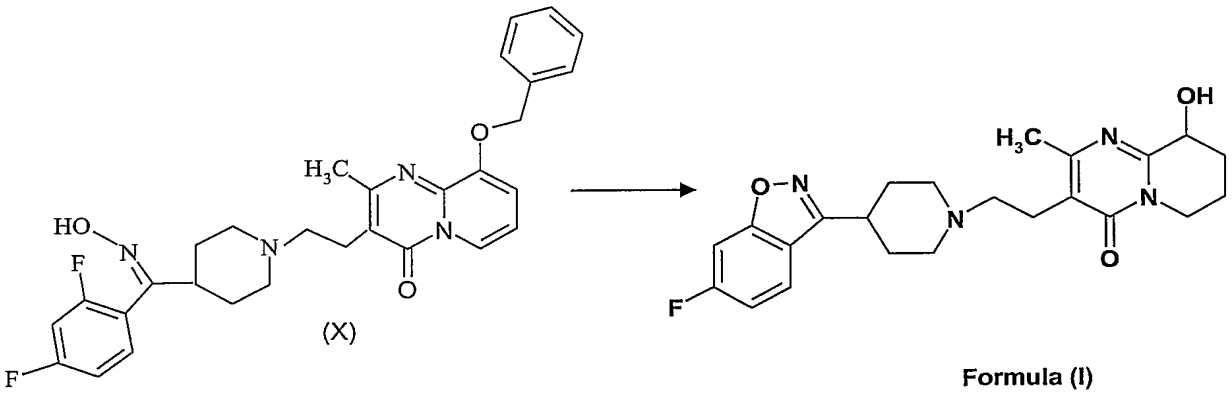
bicarbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide and potassium phosphate. The organic base may be selected from the group consisting of diisopropyl ethyl amine, pyridine and triethyl amine. Preferably, the base is potassium carbonate.

Optionally the reaction is carried out in the presence of a catalyst. The catalyst may be selected from the group consisting of tetrabutyl ammonium bromide, tetrabutyl ammonium chloride, potassium iodide, sodium iodide, lithium iodide, sodium bromide and potassium bromide; preferably potassium iodide.

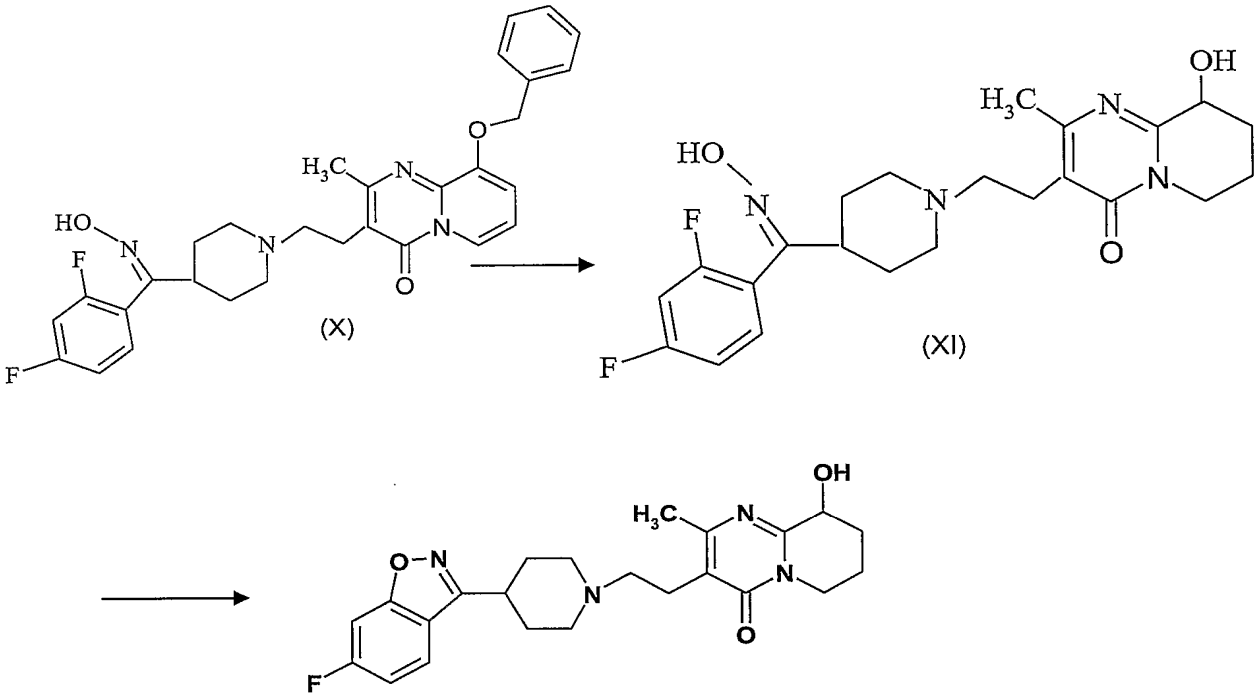
In a preferred embodiment, the condensation is carried out in the presence of a base and a catalyst, more preferably in the presence of potassium carbonate and potassium iodide.

In an embodiment, the compound of formula (III) is prepared according to the process described above.

According to another aspect of the present invention, there is provided a process for preparing paliperidone or a salt thereof comprising converting the compound of formula (X) to paliperidone and optionally converting the paliperidone to the salt thereof.



In an embodiment, the conversion of compound (X) to paliperidone or a salt thereof comprises reducing the compound (X) to a compound of formula (XI) and cyclising the compound (XI) to obtain paliperidone.



Formula (I)

Preferably, the reduction of compound (X) to compound (XI) comprises reducing compound (X) using catalytic reduction, suitably in the presence of a noble metal catalyst and hydrogen gas or using transfer hydrogenation.

In an embodiment, the catalyst is selected from the group consisting of palladium, palladium on carbon (preferably in an amount ranging from 1% to 20% of carbon by weight of palladium), platinum, platinum dioxide, platinum on carbon, palladium hydroxide, palladium on alumina or Raney nickel; preferably palladium on carbon (preferably in an amount of 10% of carbon by weight of palladium) and the amount of catalyst employed ranges from 1% to 30% by weight of compound (X), preferably 15% by weight of compound (X). In an embodiment, the catalytic reduction is carried out a temperature ranging from 20°C to 80°C, preferably from 25°C to 35°C. In another embodiment, the catalytic reduction may be carried out under a hydrogen gas pressure

ranging from 1.0 Kg to 8.0 Kg, preferably from 4.0 Kg to 5.0 Kg. A combination of catalysts may also be used.

Typically, the reduction is carried out in the presence of a solvent. Preferably, the solvent is selected from the group consisting of ethyl acetate, methanol, ethanol, isopropyl alcohol, n-butanol, tetrahydrofuran, 1,4-dioxane, acetic acid, acetone, a halogenated hydrocarbon such as methylene dichloride or ethylene dichloride, or mixture thereof; preferably methanol.

The cyclisation of compound (XI) may be carried out in a solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, toluene, xylene, anisole, tetrahydrofuran, ethyl acetate, acetonitrile, methyl isobutyl ketone or methyl ethyl ketone, preferably toluene.

The cyclisation reaction is preferably carried out in the presence of an inorganic base such as potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, cesium carbonate, lithium carbonate, sodium hydroxide or potassium hydroxide; preferably potassium carbonate.

Optionally, the cyclisation reaction is carried out in the presence of a catalyst such as potassium iodide, sodium iodide, lithium iodide, sodium bromide or potassium bromide; preferably potassium iodide.

Optionally, the paliperidone is converted to a salt thereof in accordance with conventional techniques.

In another embodiment, the compound of formula (X) has been prepared by the process described above.

In a preferred embodiment, there is provided a process for preparing paliperidone or a pharmaceutically acceptable salt thereof comprise the following steps: a) condensing the compound of formula (III) with the compound of formula (IX) in the presence of base to obtain the compound of formula (X); b) reducing the compound of formula (X)

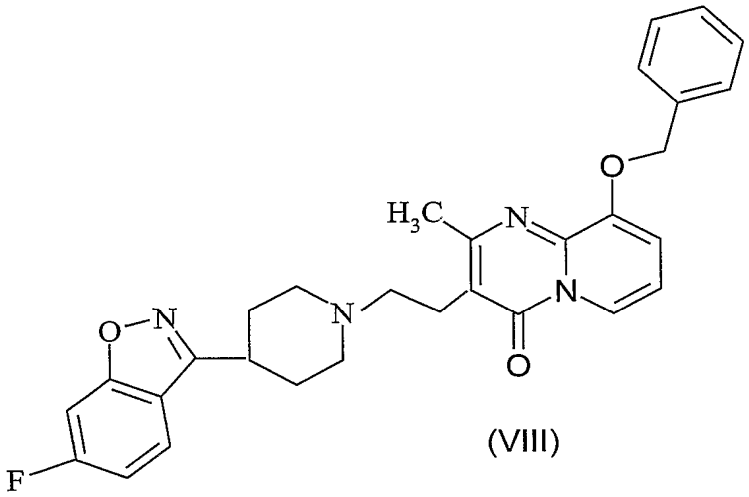
to obtain the compound of formula (XI); and c) cyclising the compound of formula (XI) to obtain paliperidone of formula (I).

In all aspects of the present invention in which paliperidone is optionally converted to a salt thereof, the salt is an acid addition salt formed by treatment with an appropriate acid, such as a hydrohalic acid, for example hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, propanoic acid, hydroxyacetic acid, 2-hydroxypropanoic acid, 2-oxopropanoic acid, ethanedioic acid, propanedioic acid, butanedioic acid, (Z)-2-butenedioic acid, (E)-2-butenedioic acid, 2-hydroxybutanedioic acid, 2,3-dihydroxybutanedioic acid, 2-hydroxy-1,2,3-propanetricarboxylic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, cyclohexanesulfamic acid, 2-hydroxybenzoic acid or 4-amino-2-hydroxybenzoic acid.

According to another aspect of the present invention, there is provided paliperidone or a salt thereof prepared according to any one of the processes described above. According to another aspect of the present invention, there is provided a pharmaceutical composition comprising paliperidone or a salt thereof prepared according to any one of the processes described above and one or more pharmaceutically acceptable excipients. Such pharmaceutical compositions and excipients are well known to those skilled in the art. According to another aspect of the present invention, there is provided the use of paliperidone or a salt thereof prepared according to any one of the processes described above in medicine. According to another aspect of the present invention, there is provided the use of paliperidone or a salt thereof prepared according to any one of the processes described above in the treatment of schizophrenia or bipolar disorder. According to another aspect of the present invention, there is provided a method of treating schizophrenia or bipolar disorder comprising administering to a patient in need thereof a therapuetically effective amount of paliperidone or a salt thereof prepared according to any one of the processes described above.

Detailed Description of the Invention

In one aspect, the present invention relates to novel key intermediates useful in the synthesis of paliperidone or its pharmaceutically acceptable salts. One of the novel compounds has the formula (VIII).



(VIII)

In an embodiment, the present invention provides a process for the preparation of paliperidone or a pharmaceutically acceptable salt thereof, which comprises the following step:

a) condensing 3-benzyloxy-2-aminopyridine of formula (II) with an α-acyl lactone of formula (V) in the presence of an activating agent and catalytic amount of dipolar aprotic solvent, in a suitable inert solvent and at suitable temperature, to obtain compound of formula (III).

It was found that by use of catalytic amount of dipolar aprotic solvent, the formation of impurities was minimized to about 5%. Typically such dipolar aprotic solvent is selected from group comprising of N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), 1-methyl-2-pyrrolidinone, pyridine, acetic anhydride, preferably DMF.

Appropriate activating agent used for the condensation reaction in step a) is halogenating agent selected from group comprising of thionyl chloride, phosphorous

oxychloride, phosphorous trichloride, phosphorous pentachloride, oxalyl chloride, phosgene and the like. In particular, phosphorous oxychloride is preferred.

Suitable inert solvent for the condensation reaction include hydrocarbon solvents such as benzene, cyclohexane, toluene, or xylene; halogenated hydrocarbons such as chlorobenzene, methylene chloride; anisole or DMF. Alternatively the reaction may also be performed in the absence of solvent.

In an attempt to determine which possible initial impurities could cause the large scale deviation, it was observed that by carrying reaction as reported in the prior art, at high temperature of 90°C and adding compound (V) in lots, yields 50% of undesired impurities which impair the desire reaction product.

The suitable temperature at which reaction is carried out ranges from 50°C to 100°C, preferably 60 to 80°C. The reaction is carried out for 1 to 20 hours, preferably for 10 to 15 hours by which the undesired impurity is reduced substantially.

The product obtained is optionally purified by crystallization using solvents selected from group comprising of isopropyl alcohol, methanol, butanol, ethanol, ethyl acetate or mixtures thereof.

In a further embodiment, the process for the preparation of paliperidone or a pharmaceutically acceptable salt thereof, comprises the following step:

b) condensing compound of formula (III) with compound of formula (VI) or a salt thereof in a suitable solvent and in presence of a base to give novel intermediate of formula (VIII). Optionally the reaction is carried out in presence of a catalyst.

The suitable solvent used is selected from group comprising of toluene, ethyl acetate, acetonitrile, tetrahydrofuran, methylene chloride, ethylene chloride, diglyme, cyclohexane, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), Dimethylsulfoxide (DMSO), C_1 to C_6 straight or branched chain alcohols such as but not limited to methanol, ethanol, isopropanol, n-propanol or mixtures thereof.

The base used is organic or inorganic. Inorganic base is selected from group comprising of potassium carbonate, sodium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide, potassium phosphate while organic base is selected from but not limited to diisopropyl ethyl amine, pyridine, triethyl amine. The base preferred is potassium carbonate.

The catalyst is selected from group comprising of tetrabutyl ammonium bromide, tetrabutyl ammonium chloride, potassium iodide, sodium iodide, lithium iodide, sodium bromide, potassium bromide; preferably potassium iodide.

In a further embodiment, the process for the preparation of paliperidone or a pharmaceutically acceptable salt thereof, comprises the following step:

c) reducing intermediate of formula (VIII) using catalytic reduction in the presence of a noble metal catalyst and hydrogen gas or using transfer hydrogenation to obtain paliperidone of formula (I).

Preferred catalysts used are those known in the art such as palladium, palladium on carbon (preferably in an amount ranging from 1% to 20% carbon by weight of palladium), platinum, platinum dioxide, platinum on carbon, palladium hydroxide, palladium on alumina, Raney nickel, preferably palladium on carbon (preferably in an amount of 10% carbon by weight of palladium) and the amount of catalyst employed ranges from 1% to 30% by weight of compound (VIII), preferably 15% by weight of compound (VIII). In an embodiment, the process is carried out in a suitable solvent at a temperature ranging from 20-80°C, preferably 25-35°C under hydrogen gas pressure ranging from 1.0-8.0 Kg, preferably 4.0-5.0 Kg.

A combination of catalysts may also be used. The amount of catalyst employed is reduced to about 15% w/w as compared to 60% w/w as reported in the prior art. This obviates the need for handling large quantity of catalyst on industrial scale, thereby reducing the risk involved.

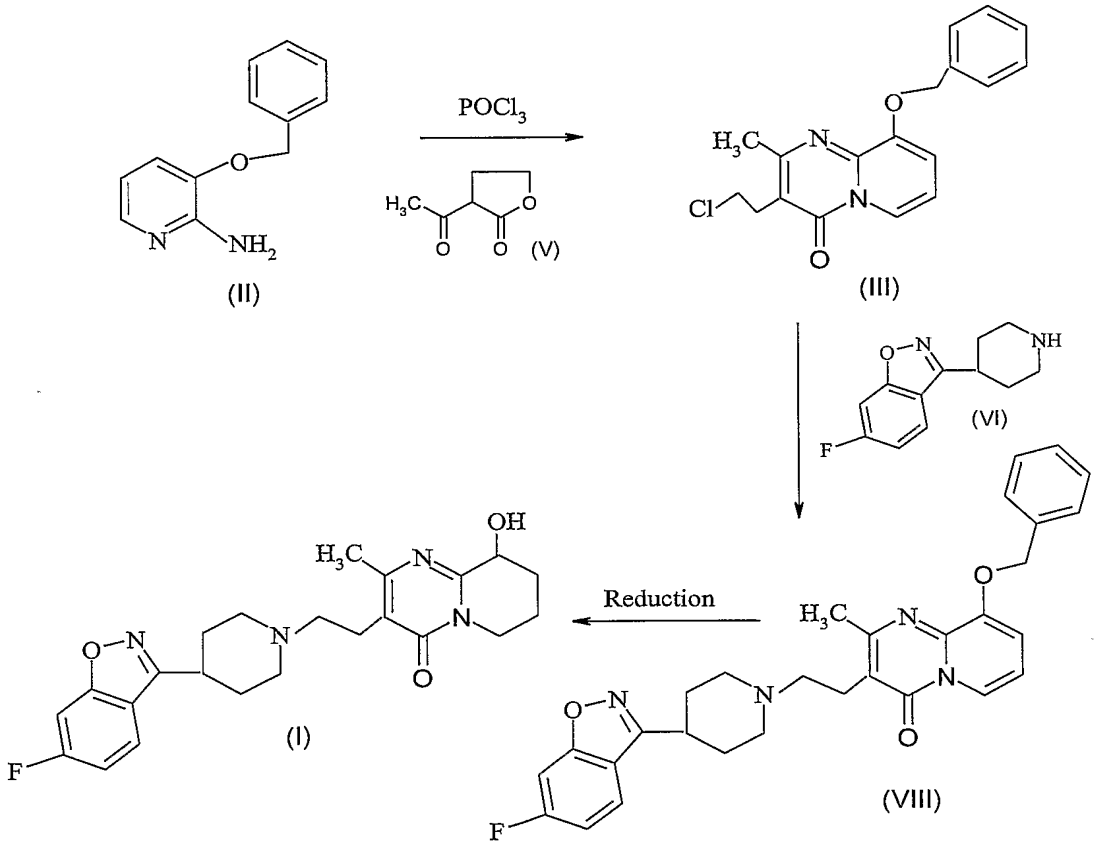
The suitable solvent used is selected from group comprising of ethyl acetate, methanol, ethanol, isopropyl alcohol, n-butanol, tetrahydrofuran, 1,4-dioxane, acetic acid,

acetone, halogenated hydrocarbons such as methylene dichloride, ethylene dichloride or mixture thereof, preferably methanol.

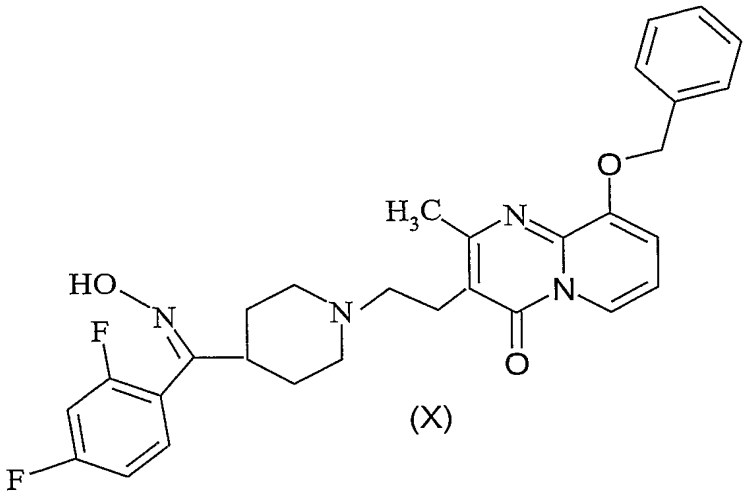
Optionally paliperidone base can be converted to pharmaceutically acceptable salts thereof. Such conversions are well known to those skilled in the art and involve treatment with an acid to form an acid addition salt.

The process is represented by the Scheme I as follows:

Scheme I



In another aspect of the present invention, there is provided a compound of formula (X) which is useful in the synthesis of paliperidone or its pharmaceutically acceptable salts.



(X)

This compound of formula (X) may be used as an intermediate in a process for the preparation of paliperidone or a salt thereof. The process may comprise the following steps: a) condensing a compound of formula (III) with a compound of formula (IX) in a suitable solvent and in the presence of a base to obtain a compound of formula (X); b) reducing the compound of formula (X) to obtain a compound of formula (XI); c) cyclising the ompound of formula (XI) to obtain paliperidone of formula (I); and d) optionally converting the paliperidone of formula (I) to a salt thereof.

The compound of formula (III) may be prepared by the process mentioned above.

The base and solvent used for the preparation of compound (X) may be the same as those used in step b) above for scheme I. Optionally, the preparation of compound (X) is carried out in the presence of a catalyst. The catalyst may be the same as that used in step b) above for scheme I.

The compound of formula (X) may be reduced using a noble metal catalyst and hydrogen gas or using transfer hydrogenation under the conditions mentioned in step c) above for scheme I, to obtain the compound of formula (XI).

The compound of formula (XI) may be cyclised in a solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, toluene, xylene,

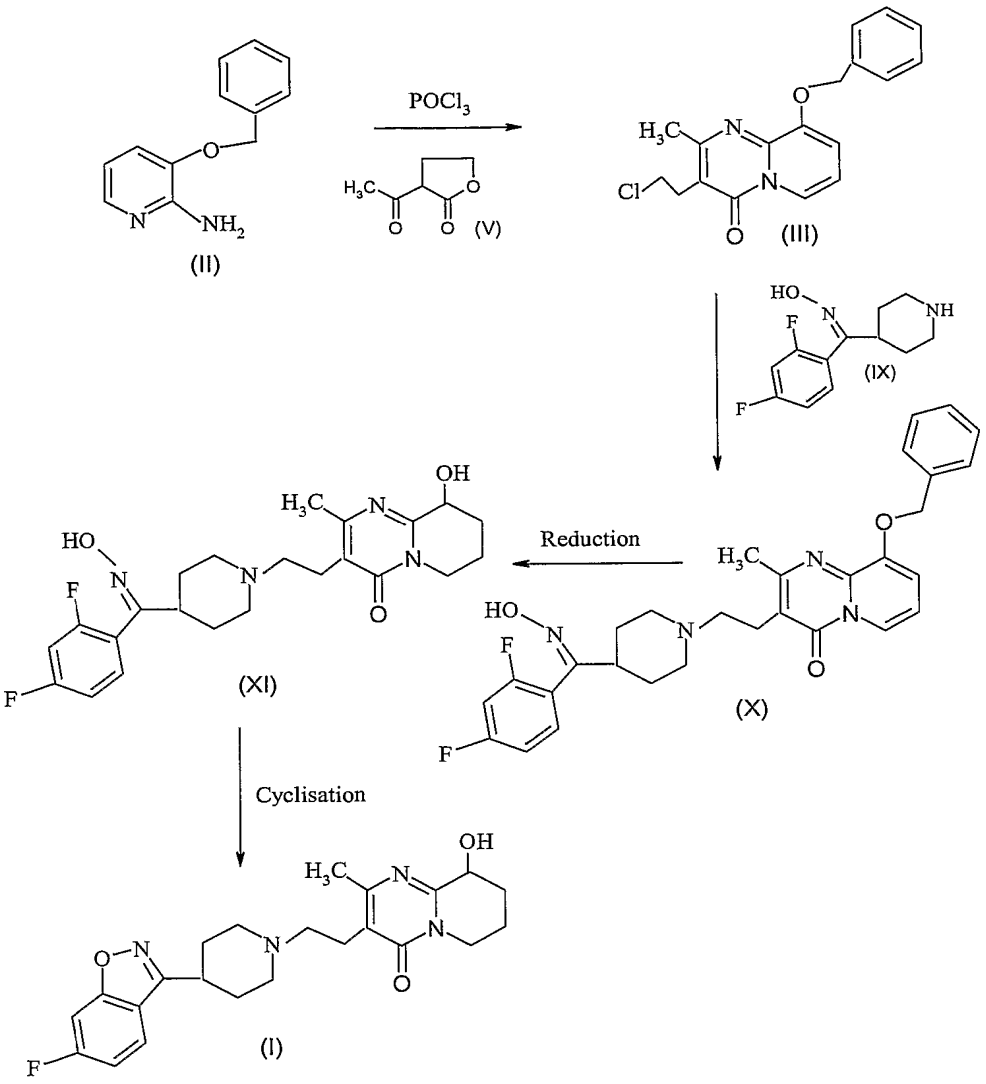
anisole, tetrahydrofuran, ethyl acetate, acetonitrile, methyl isobutyl ketone or methyl ethyl ketone, preferably toluene.

The reaction may be carried out in the presence of an inorganic base such as potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, cesium carbonate, lithium carbonate, sodium hydroxide or potassium hydroxide preferably potassium carbonate.

Optionally, the reaction is carried out in the presence of a catalyst such as but not limited to potassium iodide, sodium iodide, lithium iodide, sodium bromide or potassium bromide, preferably potassium iodide.

The process may be represented by following reaction Scheme II:

Scheme II



In yet another embodiment of the invention, there is provided a process for the preparation of paliperidone or a pharmaceutically acceptable salt thereof. The process may comprise the step of: i) catalytically reducing the compound of formula (III) using a noble metal catalyst and hydrogen gas or using transfer hydrogenation under to obtain chloroethyl derivative of formula (IV).

The conditions used for reduction may be the same as those used in step c) above for Scheme I. The reaction may be carried out in the presence of an acid.

In the process of the present invention, an acid may be employed to reduce the formation of the des-chloro impurity of formula (VII). Typically, this step results in a reduction of the des-chloro impurity to less than 3%. The acid used may be selected from a carboxylic acid such as acetic acid, trifluoro acetic acid, dichloro acetic acid, trichloro acetic acid, formic acid; a mineral acid such as hydrochloric acid, sulfuric acid, phosphoric acid; or a Lewis acid such as boron trihalide and the like. In particular, acetic acid is preferred.

The reaction may be carried out in lower alcohol solvents for example C_1 to C_3 alcohol solvents such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran, 1,4-dioxane; esters such as ethyl acetate; halogenated hydrocarbons; ketones such as acetone or a mixture of such solvents.

The process of this invention has been found to be particularly advantageous over the prior art US `952 process. This prior art process requires large volumes of solvent such as methanol, and a catalyst such as 10% of palladium on charcoal (60% w/w) which tends to produce a significant amount of des-chloro impurity of formula (VII). The deschloro impurity formed not only leads to incomplete reaction but also lowers the yield of the desired product.

The compound of formula (III) may be prepared by the process mentioned in step a) above for Scheme I.

The process for preparing paliperidone or salt thereof may comprise condensing a chloroethyl derivative of formula (IV) with a compound of formula (VI) or a salt thereof in the presence of a base and at an elevated temperature to obtain paliperidone of formula (I).

The base used may be the same as that used in step b) above for scheme I.

In an embodiment, the reaction temperature ranges from room temperature to the reflux temperature of the solvent, preferably from 40°C to 90°C.

This reaction is typically carried out in an inert, organic solvent, with or without water. Appropriate organic solvents are C_1 to C_6 straight chain alcohols, tetrahydrofuran, acetonitrile, DMF, DMA, methylene chloride, ethylene chloride, diglyme, toluene and the like. The preferred solvents are acetonitrile and methanol.

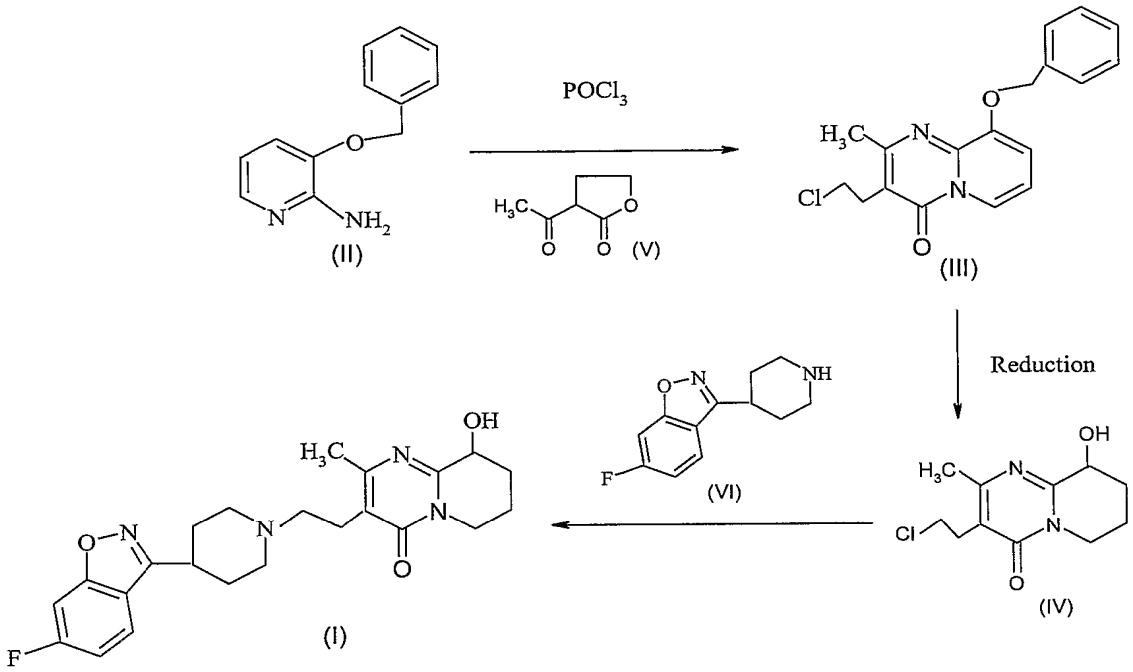
Optionally, the reaction is carried out in presence of a catalyst. The catalyst used may be the same as that used in step b) above for scheme I.

Paliperidone obtained by following the processes of the present invention advantageously has a reduced amount of the des-chloro impurity, to the extent that, in a particularly preferred embodiment, the impurity is not detected. In another particularly preferred embodiment, paliperidone obtained by following the processes of the present invention is substantially free of all impurities. By "substantially free of", it is meant that the paliperidone contains no more than 1.50% total impurities, preferably, no more than 1.00% total impurities. To achieve an even higher purity paliperidone product, the paliperidone prepared according to the processes of the present invention may be further purified by crystallization using a solvent or mixture of solvents.

Optionally paliperidone base may be converted to a pharmaceutically acceptable salt thereof. Such conversions are well known to those skilled in the art and involve treatment with an acid to form an acid addition salt.

The process may be represented by the following Scheme III:

Scheme III



The present invention is now further illustrated by the following examples, which do not, in any way, limit the scope of the invention.

EXAMPLES:

Example 1: Preparation of compound of formula (III)

To a three–necked flask compound (II) (50 g) and toluene (500 ml) were charged. The reaction mixture was cooled to 0-5°C. To this solution dimethyl formamide (5.0 ml) was added followed by slow addition of freshly distilled phosphorus oxychloride (105 ml) at 0-5°C over a period of 2 hours. The contents were heated slowly to 50-55°C and maintained for 30 minutes. A solution of compound (V) in toluene (84 ml in 100 ml) was added slowly to the reaction mass and the reaction mass was heated to 70-75°C, maintained for 30 minutes. The reaction mass was further heated to 80-85°C, maintained for 6-7 hours. After completion of the reaction, the reaction mass was cooled to room temperature, quenched into ice-water mixture (1000 ml) and extracted with methylene chloride (250 ml × 2). The methylene chloride layer was washed with

water (250 ml × 2). To this water (50 ml) was charged and pH of the reaction mass was adjusted to 7.0-7.5 using triethylamine. The organic layer was separated and dried over sodium sulphate (5 g) and distilled off completely under vacuum below 35°C. The residue obtained was dissolved in isopropyl alcohol (85 ml) at 40-45°C, cooled to 0-5°C, filtered, washed with chilled isopropyl alcohol (20 ml) and dried under vacuum at 40-45°C for 6 hours to yield compound (III) (52.5 g), HPLC purity- 99%).

Example 2: Preparation of compound of formula (IV)

Compound (III) (20 g), ethylacetate (1500 ml) and acetic acid (60 ml) were charged in a hydrogenator. To this 10% palladium on carbon (5 g) was added and the reaction mass was hydrogenated by applying hydrogen gas pressure of 3.5-4.0 Kg at 25-30°C for 15 hours to yield 14.5 g of compound (IV) (HPLC purity - 90 %).

Example 3: Preparation of compound of formula (I) [Paliperidone]

In a three necked flask acetonitrile (230 ml), compound (IV) (20 g) and compound (VI) (23.3 g) were charged. To the reaction mass, potassium carbonate (18 g) and potassium iodide (0.5 g) were added. The contents were heated to 76-78°C and maintained for 3 hours at 76-78°C. After completion of reaction, the reaction mixture was cooled to 0-5°C and stirred for 1 hour. The solid, was filtered, washed with water (65 ml). The solid obtained was dissolved in methanol (190 ml) by heating the contents to 60-65°C, treated with activated charcoal (3.5 gm), stirred at 60-65°C for 30 minutes. The reaction mass was filtered hot over hyflo at 60-65°C, washed with hot methanol (20 ml). Methanol was distilled completely under vacuum below 45°C to obtain residue. Ethyl acetate (20 ml) was charged and continued distillation under vacuum to remove traces of methanol. The residue was stirred in (20 ml) ethyl acetate for 1 hour at 25-30°C. The resulting solid was filtered and washed with ethyl acetate (10 ml) and dried under vacuum at 40-45°C for 6 hours to yield 6.5 g of paliperidone.(HPLC purity-99.5%).

Example 4: Preparation of compound of formula (VIII)

Acetonitrile (1000 ml), compound of formula (III) (50 g), compound of formula (VI) (39 g), potassium carbonate (50 g) and potassium iodide (5 g) were charged and refluxed for 20 hours. The reaction mass was cooled to room temperature, chilled to 0-5°C,

filtered, washed with water (100 ml) and then dissolved in methanol (200 ml) by heating the contents to 60-65°C, treated with activated charcoal (4.0 g), stirred at 60-65°C for 30 minutes. The reaction mass was filtered hot over hyflo at 60-65°C, washed with hot methanol (50 ml). Methanol was distilled under vacuum below 45°C to obtain residue, ethyl acetate (50 ml) was charged and stripped out methanol. The residue was stirred in ethyl acetate (50 ml) for 1 hour at 25-30°C. The material so obtained was filtered, washed with ethyl acetate (20 ml) and dried under vacuum at 40-45°C for 6 hours to yield compound of formula (VIII) (50 g).

Example 5: Preparation of compound of formula (I)

Methanol (1000 ml), compound of formula (VIII) (35 g) and 10% palladium on carbon (5 g) were charged and hydrogenated at hydrogen gas pressure of 4.5-5.0 Kg at 30-35°C for 6 hours. The reaction mass was filtered, the clear filtrate was concentrated. Isopropanol (200 ml) was charged, stirred for 30 minutes at 5-10°C. The material was filtered, washed with chilled isopropanol (20 ml) and was dissolved in methanol (200 ml) at 60-65°C. The reaction mass was treated with activated charcoal (4 g), stirred for 30 minutes, filtered over hyflo when hot, washed with hot methanol (25 ml). The clear filtrate was distilled completely under vacuum below 45°C, methanol was stripped off with ethyl acetate (25 ml). The residue was stirred in ethyl acetate (30 ml) for 1 hour at 25-30°C. The material was filtered, washed with ethyl acetate (15 ml) and dried under vacuum at 40-45°C to yield paliperidone, compound of formula (I) (15.0 g).

Example 6: Preparation of compound of formula (X)

Dimethyl formamide (500 ml), compound of formula (III) (50 g), compound of formula (IX) (44 g), potassium carbonate (50 g) and potassium idodide (5 g) were charged and heated to 90-95°C for 5 hours. The reaction mass was quenched into water (400 ml), extracted with methylene chloride (500 ml × 3). Methylene chloride layer was washed with water (200 ml × 3), dried over sodium sulphate (5 g), concentrated to residue. Isopropanol (200 ml) was added, cooled to 5-10°C, filtered and washed with chilled isopropanol (50 ml) and dried at 40-45°C to yield compound of formula (X) (50.0 g).

Example 7: Preparation of compound of formula (XI)

Ethyl acetate (1000 ml), compound of formula (X) (40 g) and 10% palladium on carbon (5 g) were charged and hydrogenated at hydrogen gas pressure of 4.5-5.0 Kg at 30-35°C for 4 hours. The reaction mass was filtered, the clear filtrate was concentrated. Isopropanol (200 ml) was charged, stirred for 30 minutes at 5-10°C, filtered and washed with chilled isopropanol (20 ml) and dried at 45-50°C to yield compound of formula (XI) (18 g).

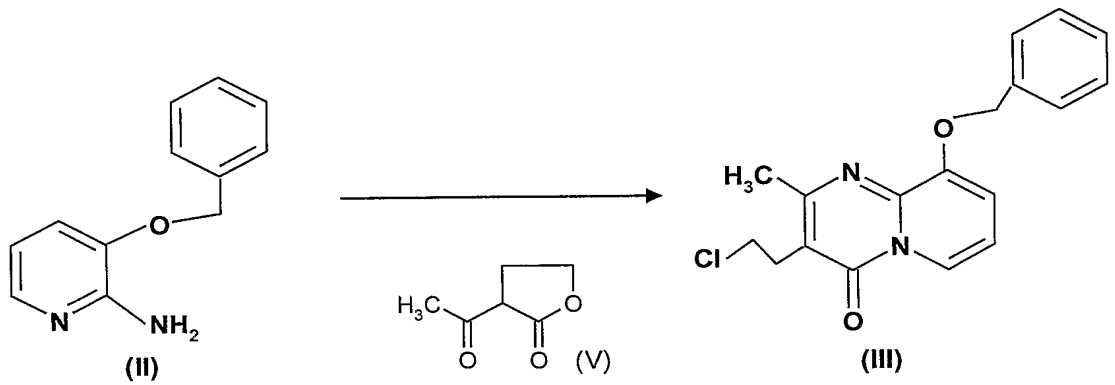
Example 8: Preparation of compound of formula (I)

Toluene (500 ml), compound of formula (XI) (50 g) and potassium carbonate (5 g) were charged and heated to reflux for 4 hours. The reaction mass was cooled to 5-10°C, filtered, washed with chilled toluene (50 ml). The filtered material was dissolved in methylene chloride (500 ml), washed with water (250 ml × 2). Methylene chloride layer was dried with sodium sulphate (5 g), concentrated to residue. Isopropanol (200 ml) was charged, stirred for 30 minutes at 5-10°C, filtered and washed with chilled isopropanol (40 ml). The material was dissolved in methanol (200 ml) at 60-65°C, treated with activated charcoal (4 g), stirred for 30 minutes, filtered over hyflo when hot, washed with hot methanol (25 ml). The clear filtrate was distilled completely under vacuum below 45°C and methanol was stripped off with ethyl acetate (25 ml). The residue was stirred in ethyl acetate (30 ml) for 1 hour at 25-30°C. The material was filtered, washed with ethyl acetate (15 ml) and dried under vacuum at 45-50°C to yield paliperidone, compound of formula (I) (38.0 g).

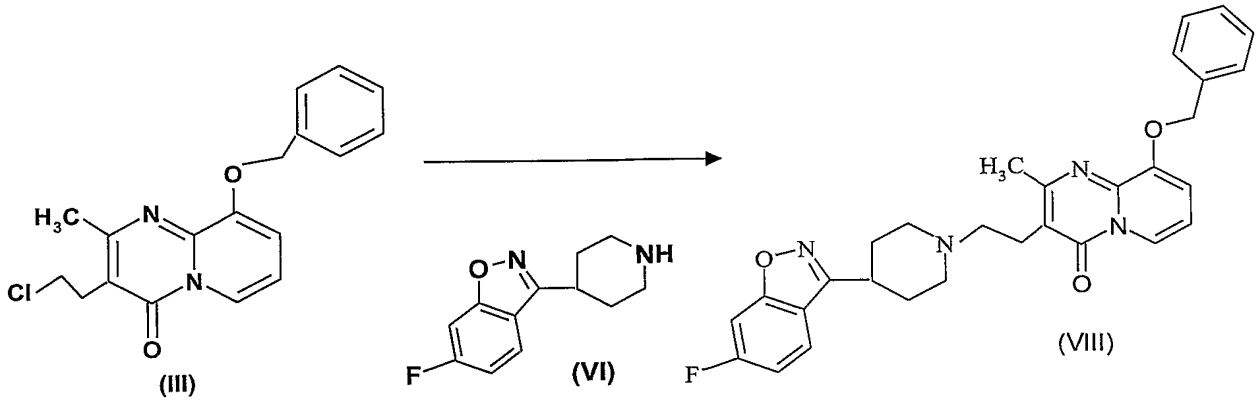
It will be appreciated that the invention may be modified within the scope of the appended claims.

CLAIMS

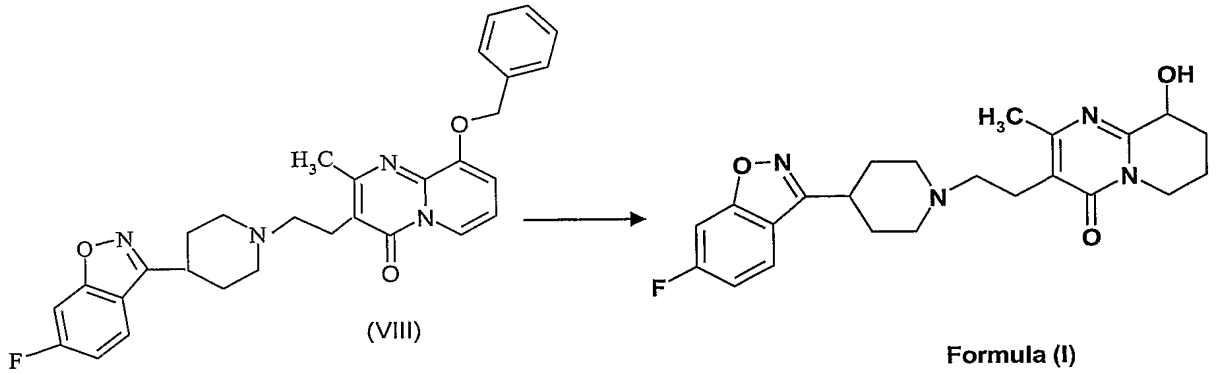
1. A process for preparing paliperidone or a salt thereof comprising: (a) condensing a 3-benzyloxy-2-aminopyridine (II) with an α-acyl lactone (V) in the presence of a catalytic amount of a dipolar aprotic solvent and an activating agent to obtain a compound of formula (III);



(b) condensing the compound of formula (III) with a compound of formula (VI) or a salt thereof to obtain the compound of formula (VIII);

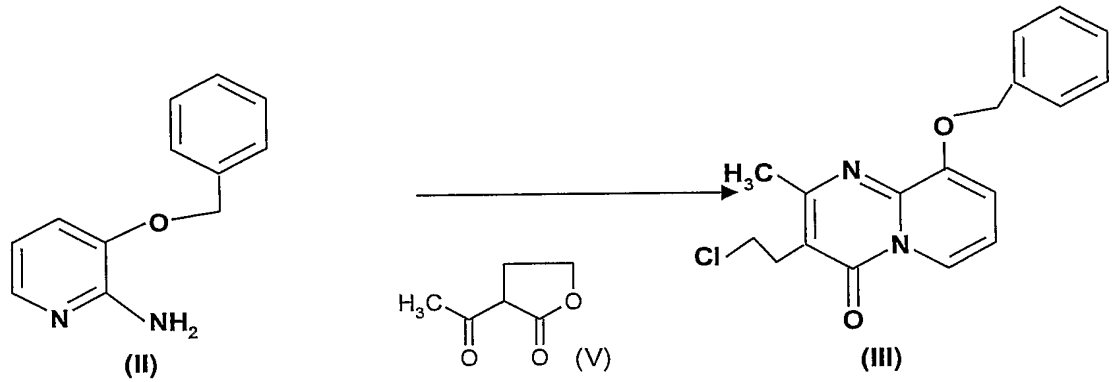


(c) converting the compound of formula (VIII) to paliperidone by catalytic reduction; and

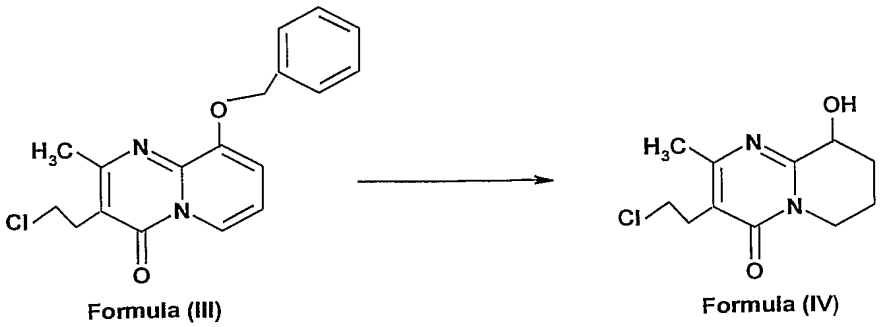


(d) optionally converting paliperidone to a salt thereof.

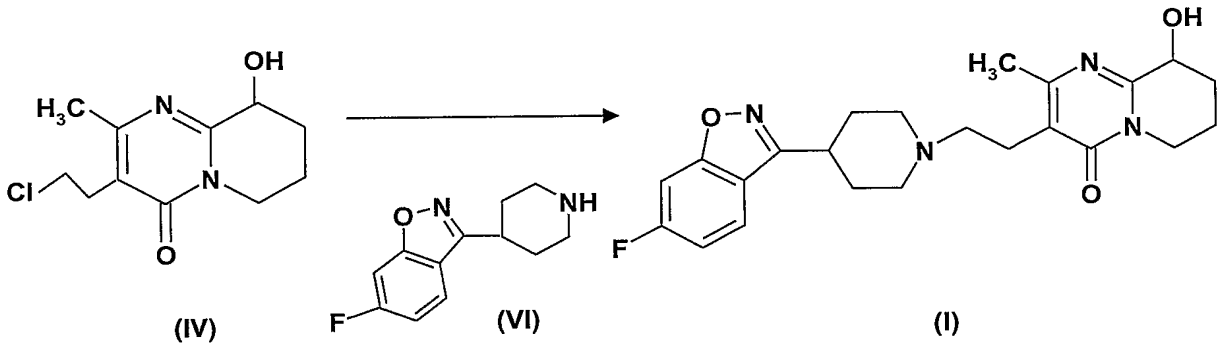
2. A process for preparing paliperidone or a salt thereof comprising: (a) condensing a 3-benzyloxy-2-aminopyridine (II) with an α-acyl lactone (V) in the presence of a catalytic amount of a dipolar aprotic solvent and an activating agent to obtain a compound of formula (III);



(b) catalytically reducing the compound of formula (III) to a compound of formula (IV) in the presence of an acid;

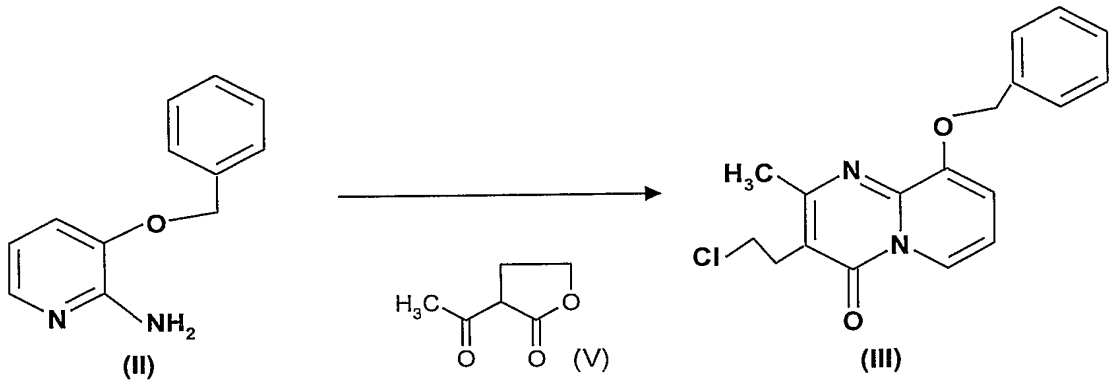


(c) condensing chloroethyl derivative (IV) with compound (VI) or a salt thereof in the presence of a base to obtain paliperidone (I); and

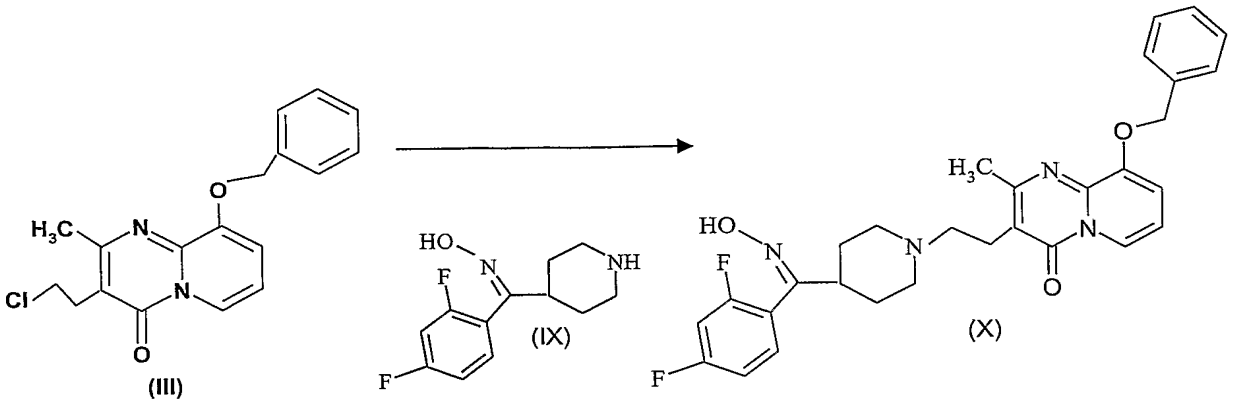


(d) optionally converting paliperidone to a salt thereof.

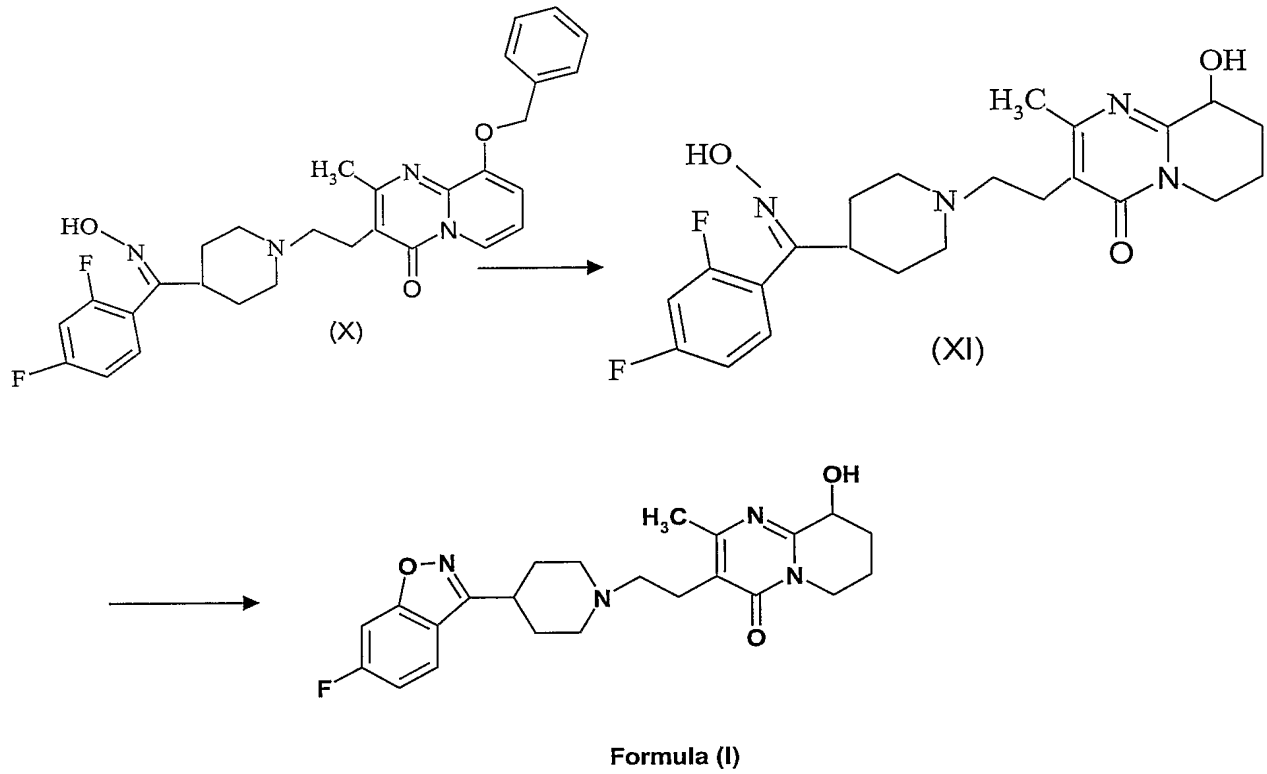
3. A process for preparing paliperidone or a salt thereof comprising: (a) condensing a 3-benzyloxy-2-aminopyridine derivative (II) with an α-acyl lactone (V) in the presence of a catalytic amount of a dipolar aprotic solvent and an activating agent to obtain a compound of formula (III);



(b) condensing the compound of formula (III) with a compound of formula (IX) to obtain a compound of formula (X);



(c) converting the compound (X) to a compound of formula (XI) by catalytic reduction and cyclising the compound (XI) to obtain paliperidone;



Formula (I)

(d) and optionally converting paliperidone to a salt thereof.

4. A process according to claim 1, 2 or 3, wherein the dipolar aprotic solvent is selected from the group consisting of N,N-dimethylformamide (DMF), N,N-

dimethylacetamide (DMA), dimethylsulfoxide (DMSO), 1-methyl-2-pyrrolidinone, pyridine and acetic anhydride.

5. A process according to any preceding claim, wherein the activating agent is a halogenating reagent selected from the group consisting of thionyl chloride, phosphorous oxychloride, phosphorous trichloride, phosphorous pentachloride, oxalyl chloride and phosgene.

6. A process according to claim 2 or any claim dependent on claim 2, wherein the acid is selected from the group consisting of acetic acid, trifluoro acetic acid, dichloro acetic acid, trichloro acetic acid, formic acid, hydrochloric acid, sulfuric acid, phosphoric acid and a boron trihalide.

7. A process according to any preceding claim, wherein the catalytic reduction is carried out in the presence of a noble metal catalyst and hydrogen gas or using transfer hydrogenation.

8. A process according to claim 7, wherein the catalyst is selected from the group consisting of palladium, palladium hydroxide, palladium on activated carbon, palladium on alumina, platinum, platinum dioxide, platinum on activated carbon and Raney nickel.

9. A process according to claim 2 or any claim dependent on claim 2, wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, pyridine, potassium phosphate, sodium carbonate, potassium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, sodium hydroxide and potassium hydroxide.

10. A process according to claim 2 or any claim dependent on claim 2, wherein step (c) is carried out at a temperature ranging from 40°C to 90°C.

11. A process according to claim 2 or any claim dependent on claim 2, wherein the condensation is carried out in the presence of a catalyst selected from tetrabutyl

ammonium bromide, tetrabutyl ammonium chloride, potassium iodide, sodium iodide, sodium bromide, potassium bromide or lithium iodide.

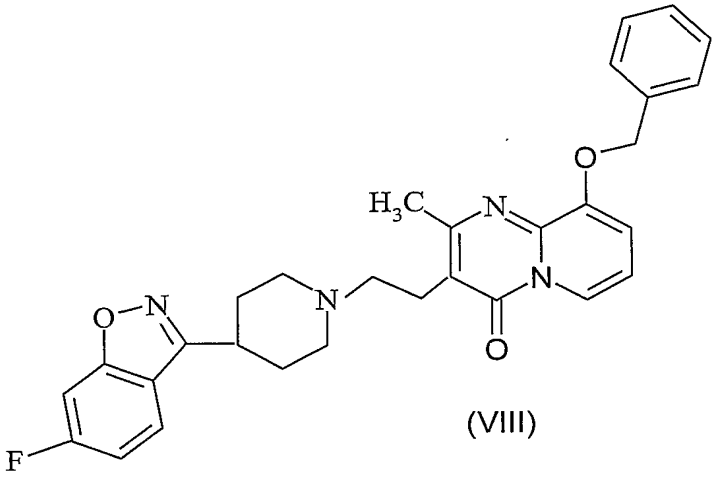
12. A process according to claim 1, 3 or any claim dependent on claim 1 or 3, wherein step (b) is carried out in the presence of a base selected from the group consisting of potassium carbonate, sodium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide, potassium phosphate, diisopropyl ethyl amine, pyridine and triethyl amine.

13. A process according to claim 1, 3 or 12, wherein step (b) is carried out in the presence of a catalyst selected from the group consisting of tetrabutyl ammonium bromide, tetrabutyl ammonium chloride, potassium iodide, sodium iodide, lithium iodide, sodium bromide and potassium bromide.

14. A process according to claim 3 or any claim dependent on claim 3, wherein the cyclisation of compound (XI) is carried out in the presence of an inorganic base selected from the group consisting of potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, cesium carbonate, lithium carbonate, sodium hydroxide or potassium hydroxide.

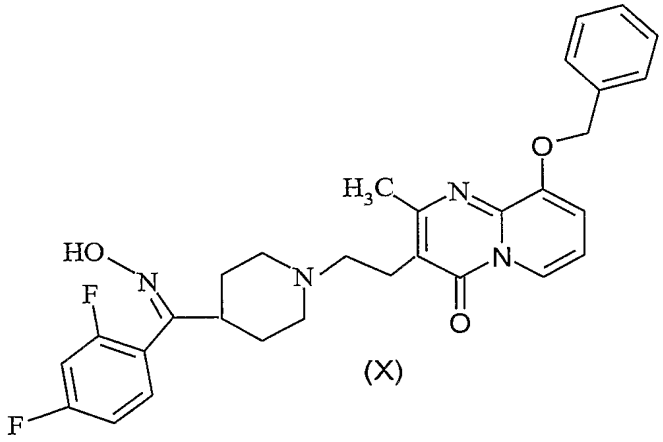
15. A process according to claim 3 or 14, wherein the cyclisation is carried out in the presence of a catalyst selected from potassium iodide, sodium iodide, lithium iodide, sodium bromide or potassium bromide.

16. A compound of formula (VIII)



(VIII)

17. A compound of formula (X)



(X)

18. A process according to any one of claims 1 to 15, wherein the paliperidone is converted to a salt thereof.

19. Compound (VIII) substantially as herein described with reference to the examples.

20. Compound (X) substantially as herein described with reference to the examples.

21. A process for preparing compound (VIII) substantially as herein described with reference to the examples.

22. A process for preparing compound (X) substantially as herein described with reference to the examples.

23. A process for preparing paliperidone substantially as herein described with reference to the examples.

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Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

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

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

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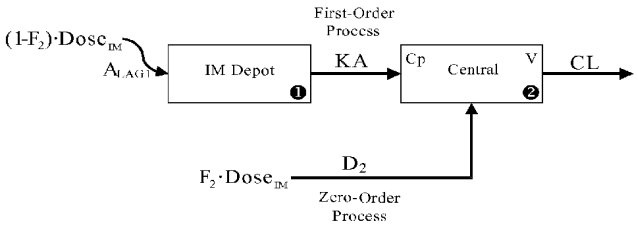
(54) Title: DOSING REGIMEN ASSOCIATED WITH LONG-ACTING INJECTABLE PALIPERIDONE ESTERS

FIGURE 1



(57) Abstract: The present application provides a method for treating patients in need of psychiatric treatment, wherein said patient misses a stabilized dose of a monthly maintenance regimen of paliperidone palmitate. The present application also provides a method for treating psychiatric patients in need of a switching treatment to paliperidone palmitate in a sustained release formulation.

WO 2011/053829 A1

DOSING REGIMEN ASSOCIATED WITH LONG-ACTING INJECTABLE PALIPERIDONE ESTERS

FIELD OF THE INVENTION

This invention relates to a method for treating patients in need of switching treatment from other antipsychotic drug to long-acting injectable paliperidone palmitate formulations.

BACKGROUND OF THE INVENTION

Antipsychotic medications are the mainstay in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorders. Conventional antipsychotics were introduced in the mid-1950s. These typical or first generation drugs are usually effective in controlling the positive symptoms of schizophrenia, but are less effective in moderating the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, typified by risperidone and olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia.

Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine D_2 and serotonin (5-hydroxytryptamine type 2A) antagonism of the second generation, atypical antipsychotic drugs. Paliperidone is the major active metabolite of risperidone. Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) for the treatment of schizophrenia and maintenance of effect.

Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension for the treatment of schizophrenia and other diseases that are normally treated with antipsychotic medications. Because of extreme low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly after an i.m. injection before being hydrolyzed to paliperidone and made available in the systemic circulation.

Many patients with the mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have

difficulty adhering to a daily oral treatment regimen, i.e. compliance problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies. Paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly, which may greatly enhance compliance with dosing. Paliperidone palmitate formulated as an aqueous nanosuspension is described in U.S. Patent Numbers. 6,577,545 and 6,555,544. In addition, a dosing regimen of paliperidone palmitate for treating patients is disclosed in US Patent Application Publication No. 20090163519.

Paliperidone palmitate is an atypical antipsychotic drug administered by injection. Paliperidone palmitate may be administered at flexible injection sites including gluteal or detloid muscle. Previous oil-based antipsychotic agents are indicated for gluteal muscle injection and may be associated with pain on injection, which may cause undesired effects of needle phobia and perceived injection pain. This may reduce patients' acceptance towards these medications and result in a negative influence on the clinical management of these patients. The administration of paliperidone palmitate at flexible injection sites may improve patients' acceptance and compliance to psychotic treatment.

In addition, paliperidone palmitate provides benefits of sustained dose release in plasma without significant concentration variation, regular monitor, reduced side effects and increased treatment efficacy. The administration of paliperidone palmitate may improve effectiveness of psychotic treatment.

Therefore, there may be an increasing demand to switch treatment of patients in need thereof from oral or injectable antipsychotic drugs to paliperidone palmitate. Further, there is a need to reinitiate a dosing regimen for patients who misses their maintenance or stabilized dose. Thus, the objective of the present application is to provide a dosing regimen of paliperidone palmitate for patients in need of a treatment switching from other antipsychotic agents to paliperidone palmitate. Another objective of the present application is to provide a dosing regimen of paliperidone palmitate for patients who have missed the monthly maintenance or stabilized dosing regimen of paliperidone palmitate.

SUMMARY OF THE INVENTION

In one embodiment of the present application a dosing regimen is provided for administering paliperidone palmitate to a patient in need of psychiatric treatment, wherein said patient misses a stabilized monthly maintenance dose for more than about 4 weeks and less than about 6 weeks, comprising administering intramuscularly in the deltoid a first reinitiation loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; and administering intramuscularly in the gluteal a reinitiation maintenance dose of paliperidone as a paliperidone ester in a sustained release formulation on the 23rd day to about the 37th day or between about 30 ± 7 day after said first day of treatment.

In another embodiment of the present application a dosing regimen is provided for administering paliperidone esters to a patient in need of psychiatric treatment, wherein said patient misses a stabilized monthly maintenance dose for more than about 6 weeks, comprising administering intramuscularly in the deltoid a first reinitiation loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid a second reinitiation loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; and administering intramuscularly in the gluteal a reinitiation maintenance dose of paliperidone as a paliperidone ester in a sustained release formulation on about the 23rd day to about the 37th day or between about 30 ± 7 days after said first day of treatment

According to the present application, the first reinitiation dose and the second reinitiaiton dose may be the same dosing as the stabilized monthly maintenance dose. Further, the first reinitiation dose, the second reinitiation dose and the reinitiation maintenance dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation may range from about 39 mg to about 234 mg.

In yet another embodiment of the present application a dosing regimen is provided for administering paliperidone palmitate to a psychiatric patient in need of a switching treatment to paliperidone palmitate, wherein said patient has received injectable antipsychotic drugs other than paliperidone palmitate, comprising administering intramuscularly in the deltoid of said patient a first loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation

on the first day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of said patient a maintenance dose of paliperidone palmitate in a sustained release formulation on about the 23rd day to about the 37th day or between about 30 ± 7 days after said first day of treatment.

In a further embodiment of the present application a dosing regimen is provided for administering paliperidone palmitate to a psychiatric patient in need of a switching treatment to paliperidone palmitate, wherein said patient has received injectable antipsychotic drugs other than paliperidone palmitate, comprising administering intramuscularly in the deltoid of said patient a first loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid or gluteal muscle of said patient a maintenance dose of paliperidone palmitate in a sustained release formulation on about the 23rd day to about the 37th day or between about 30 ± 7 days after said first day of treatment; and administering in the deltoid or gluteal muscle of said patient said maintenance dose of paliperidone palmitate in a sustained release formulation monthly thereafter.

According to the present application, the first dose and the maintenance dose of paliperidone for the switch treatment as a paliperidone palmitate formulated in a sustained release formulation may range from about 39 mg to about 234 mg.

Further according to the present application, the first dose and the maintenance dose of paliperidone for the switch treatment as a paliperidone palmitate formulated in a sustained release formulation may range from about 39 mg to about 234 mg.

This and other objects and advantages of the present invention may be appreciated from a review of the present applications.

DETAILED DESCRIPTION OF FIGURES

Figure 1. Diagram of the final model for paliperidone palmitate.

Figure 2. Simulations for reinitiation treatment of patients who missed the week 4 dose at about weeks 5, 6, 7, and 8 with a single maintenance dose of at day 1.

Figure 3. Simulation of reinitiation treatment of patients who missed the week 4 dose at about weeks 5, 6, 7, and 8 with two maintenance doses at day 1/day 8.

Figure 4: Plasma concentration profiles of steady-state paliperidone palmitate following more than about 6 months of treatment lapse, using various doses of paliperidone palmitate.

Figure 5. Switching treatment from oral paliperidone ER to paliperidone palmitate. Pink shaded areas represent patients stabilized on oral ER paliperidone and continuing oral therapy. (A) Hatched area represents patients switched to paliperidone palmitate on day 1 using the day1/day8 initiation. (B) Hatched area represents patients switched to paliperidone palmitate on day 1 using a single initiation dose alone. Lines & shaded/hatched areas represent median and about 90% prediction intervals; arrows indicate dosing times.

Figure 6. Switching from RISPERDAL® CONSTA® to paliperidone palmitate. Top panel represents the low dose and the bottom panel represents the high dose. Simulations for the middle dose are not shown because those results can be simply interpolated between the 2 panels. Lines and shaded areas (violet region) represent medians and about 90% prediction intervals.

DETAILED DESCRIPTION

The present application provides a dosing regimen for paliperidone palmitate comprising administering a initial dosing at the first day of treatment and administering a maintenance dosing on between 30 ± 7 days after the first day of treatment.

Paliperidone palmitate is the first in the class of long-acting intramuscular injectable atypical antipsychotic. Paliperidone palmitate is an ester of paliperidone which has been approved in the US, Europe and other countries for the acute and maintenance treatment of patients with schizophrenia. Following intramuscular injection, paliperidone is released into the systemic circulation over an extended period of time, allowing for once-monthly dosing without the need for oral supplementation.

U.S. Patent Application No. 20090163519 has disclosed a dosing regimen for treating a psychiatric patient using paliperidone as a paliperidone palmitate ester in a sustained release formulation. To attain a therapeutic plasma level of paliperidone, patients are administered to receive a first dose of paliperidone palmitate on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment. It is preferred that the patients will be administered the first dose on day 1, the second dose on day 8 after the first dose and the third dose on

day 36 of after the first dose. The first two doses may be injected in the deltoid muscle. Thereafter paliperidone palmitate may be administered by injection approximately once a month (e.g. once every four weeks). To assure a potential therapeutic plasma level of paliperidone is attained, at least the first loading dose of about 150 mg-eq. of paliperidone as a paliperidone palmitate ester may be administered on day 1 of treatment. To further assure a potential therapeutic plasma level of paliperidone is attained by the patient, the first loading dose and the second loading dose ranging between from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate ester may be administered. To maintain a therapeutic level in the plasma, the subsequent doses thereafter or the maintenance dose ranging from about 25 mg-eq. to 150 mg-eq. per month may be administered. The maintenance dose may be administered intramuscularly into the deltoid or gluteal muscle, and the gluteal muscle is preferred. Those of ordinary skill in the art will understand that the maintenance dose may be titrated up or down in view of the patients' conditions such as response to the medication and renal function.

Due to the improved drug efficacy, long-acting sustained release formulation, and reduced side effects of paliperidone palmitate, there may be clinical need and increasing demand to switch patients from previous antipsychotic drugs to paliperidone palmitate.

As described herein, various dosing regimen including switching treatment and reinitiation treatment for paliperidone palmitate is generated from comprehensive pharmacokinetic models or simulations on clinical data. The models or simulations provide useful, efficient and cost-effective treatment since there is no systematically collected clinical data to specifically address switching schizophrenia patients from other antipsychotics to paliperidone palmitate or concerning concomitant administration with other antipsychotics. Based on the extensive analysis of Phases I, II and III clinical trials with schizophrenia patients, the pharmacokinetic models provide an optimal effective regimen for switching treatment of patients from other antipsychotic drug to paliperidone palmitate and reinitiation treatment of patients missed their stabilized doses of paliperidone palmitate.

The models have indicated that there may be flexibility in the duration of the second loading dose and the maintenance dose of the maintenance dosing regimen. For example, the second loading dose may be administered within the duration of about the 8^{th} day $\pm$ 2 days after administering of the first loading dose. Therefore, the second

loading dose may be administered from about the 6th to about the 10th day after the first loading dose of the initial dosing. Similarly, the maintenance dose may be administered within the duration of about the 30th day ±7 days after administering of the first loading dose. Therefore, the maintenance dose may be administered from about the 23rd day to about the 37th day after administering of the first loading dose of the initial dosing. The flexible administration timing provides additional treatment benefit for patients who may require earlier administration or have missed their dose, within a short window, of the scheduled treatment without affecting the treatment effectiveness.

The models or simulations also indicate that paliperidone palmitate may be administered by intramuscular injection into either deltoid or gluteal muscle. The first and second loading dose of the initiation regimen may be administered in the deltoid muscle and the maintenance dose of the maintenance regimen may be administered in either the deltoid or gluteal muscle. The injection into the deltoid muscle may be delivered by a 1-inch 23- Gauge (G) or 1.5-inch 22-G needle based on the patient's weight. For the patients whose body weights are less than about 90 kg or 200 lb, a 1-inch 23-G needle may be used for administration, and for those body weights are equal or more than about 90 kg or 200 lb, a 1.5-inch 22-G needle may be used for administration. The injection into the gluteal muscle may be delivered by a 1.5-inch 22-G needle for all body weights.

One aspect of the present application provides a method or dosing regimen for treating patients switching from previous injectable or oral antipsychotic drug to paliperidone palmitate. The previous injectable antipsychotic drug may include but not limited to clopenthixol decanoate, perphenazine enanthate, pipothiazine palmitate, haloperidol decanoate, fluspirilene, zuclopenthixol decanoate, flupenthixol decanoate, fluphenazine decanoate, fluphenazine enanthate, risperidone microspheres, olanzapine pamoate and the like. The previous oral antipsychotic drug may include oral typical antipsychotic such as chlorpromazine, flupenthixol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, trifluoperazine or the like; and oral atypical antipsychotic drug such as amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone active moiety, sertindole, ziprasidone and the like.

For patients who have previously received injectable antipsychotic drugs, a switching treatment to paliperidone palmitate may comprise an initiation dosing regimen and a maintenance dosing regimen. The switching treatment may be initiated in place of the next scheduled injection. It is found herein that one dosing of paliperidone palmitate may be sufficient to attain the desired drug levels or plasma concentration of paliperidone during the initial dosing regimen. Accordingly, the initiation dosing regimen for switching patients from other injectable antipsychotic may comprise administering a first loading dose of paliperidone palmitate. Thereafter, the patients may be administered with the maintenance dosing regimen of paliperidone palmitate at a monthly schedule. The maintenance dosing regimen may comprise administering a maintenance dose of paliperidone palmitate on between days 23 to 37 after the first loading dose.

The dose of the switching treatment from previous injectable antipsychotic may be determined based on the condition of the patient and/or the severity of the disease. The preferred first loading dose may range from about 156 mg to about 234 mg of paliperidone palmitate, and more preferably about 234 mg. The preferred monthly maintenance dose may range from about 39 to about 234 mg, and more preferably about 117 mg. Based on the patient tolerability and/or the drug efficacy, the maintenance dose may be further adjusted monthly to achieve optimal treatment effectiveness.

By way of example, a dosing regimen is provided to switch patients from other injectable antipsychotic drug to paliperidone palmitate comprising administering into the deltoid muscle the initial dosing regimen comprising a first loading dose of about 234 mg of paliperidone palmitate and administering into the deltoid or gluteal muscle the maintenance regimen comprising a monthly maintenance dose of about 39 to about 234 mg of paliperidone palmitate on about the 23rd day to about the 37th day after administering of the first loading dose.

For patients who have previously received oral antipsychotic drugs, a switching treatment to paliperidone palmitate may comprise an initial dosing regimen and a monthly dosing regimen. The initial dosing regimen may comprise administering a first loading dose of paliperidone palmitate and administering a second loading dose of paliperidone palmitate, and the maintenance dosing regimen may comprise administering a maintenance dose of paliperidone palmitate. The previous oral

antipsychotics may be discontinued at the time of initiation of the switching treatment or administration of the first loading dosing of paliperidone palmitate.

To initiate switching treatment from oral antipsychotic drug, paliperidone palmitate may be initiated with the first loading dose on treatment day 1 and the second loading dose one week later, and maintained with the maintenance dose at a monthly schedule. The dose may be determined based on the condition of the patient and/or the severity of the disease. The preferred first loading dose may range from about 156 mg to about 234 mg of paliperidone palmitate, and more preferably about 234 mg. The preferred second loading dose may range from about 78 mg to about 156 mg, and more preferably about 156 mg. The preferred monthly maintenance dose may range from about 39 to about 234 mg, and more preferably about 117 mg. Subsequently, based on the patient tolerability and/or the drug efficacy, the maintenance dose may be further adjusted monthly to achieve optimal treatment effectiveness. The patients may be monitored for several months to ensure the full effect of the dose adjustment because of the prolonged-release characteristic of paliperidone palmitate.

Based on the pharmacokinetic simulations, patients previously stabilized on paliperidone in oral tablets may attain similar paliperidone steady-state exposure during maintenance treatment with paliperidone palmitate intramuscular injection monthly. For example, patients stabilized on oral paliperidone of about 3 mg may attain similar paliperidone steady-state exposure with the intramuscular injection of paliperidone palmitate of about 39 mg to about 78 mg. Similarly, patients stabilized on oral paliperidone of about 6 mg and about 9 mg may attain similar paliperidone steady-state exposure with the intramuscular injection of paliperidone palmitate of about 117 mg and about 234 mg, respectively. Therefore, during the maintenance regimen, the patients previously stabilized on paliperidone in oral tablets may be administered with the appropriate dose of paliperidone palmitate in injectable formulation corresponding to the stabilized dose of oral paliperidone.

Another aspect of the present application provides a method for treating patients who have missed the stabilized dosing regimen. As generally recommended in the medical field, a missed dose during treatment regimen should be avoided. Because of the flexibility in the duration of the initiation dosing regimen and the maintenance dosing regimen as discussed above, the second loading dose of the initial regimen may be administered at about the 8^{th} day $\pm$ 2 days after administering of the first loading

dose. Similarly, the maintenance dose of the maintenance regimen may be administered at about the 30th day ± 7 days after administering of the first loading dose. This may avoid or reduce the frequency of a missed dose of paliperidone palmitate during the treatment.

Using the pharmacokinetic model or simulation, a dosing regimen is provided for the reinitiation regimen for administering paliperidone palmitate to patients who have missed the monthly maintenance dose by more than about 4 weeks. The reinitiation regimen may depend upon the duration of time lapsed since the last injection of paliperidone palmitate. By way of example, a reinitiation regimen may be provided for treating patients who have missed a dose for more than about 4 weeks and less than about 6 weeks, for more than about 6 weeks and less than about 6 months, and for more than about 6 months.

When more than about 4 weeks and less than about 6 weeks have elapsed since a patient received the last dosing of paliperidone palmitate, the reinitiation regimen may comprise a first loading dose and a maintenance dose. The first dose of may be administered as soon as possible and the maintenance dose may be administered at monthly intervals after the first loading dose. The duration of the maintenance dose may be flexible, e.g. the maintenance dose may be administered 30 days ±7 days or the 23rd day to the 37th day after the first loading dose. It is found herein that the administration of a single dose of paliperidone palmitate at the treatment day 1 provides sufficient drug levels or plasma concentrations of paliperidone. Therefore, a second loading dose at day 8 is not needed for treating the patients who missed stabilized dose for less than about 6 weeks.

The first dose and the maintenance dose may be the same dosing amount as the previously stabilized dose of the maintenance regimen prior to the missed dose. Each of the first and the maintenance doses of the reinitiation regimen for less than about 6 weeks may range from about 39 mg to about 234 mg of paliperidone palmitate. Additionally, the maintenance dosing of the reinitiation regimen for less than about 6 weeks may be injected in either deltoid or gluteal muscle.

In one embodiment, a method of reinitiation regimen is provided for treating patients who have missed a dose for more than about 4 weeks and less than about 6 weeks, comprising administering into the deltoid muscle a first loading dose and administering into the deltoid or gluteal muscle a maintenance dose on about the 23rd to

about the 37th day after the first loading dose. Thereafter, the maintenance may be administered into the deltoid or gluteal muscle at a monthly schedule.

When more than 6 weeks and less than about 6 months have elapsed since a patient received the last dosing of paliperidone palmitate, the reinitiation regimen may comprise a first loading dose, a second loading dose, and a maintenance dose. The first dose of may be administered as soon as possible, the second dose may be administered at about the 8th days after the first loading dose, and a maintenance dosing may be administered at about the 30th day after the first loading dose. Thereafter, the maintenance dose may be administered at monthly intervals. The duration of the second loading dose and the maintenance dose may be flexible. For example, the second loading dose may be administered 7 days ± 2 days or the 6th day to the 10th day after the first loading dose and the maintenance dose may be administered 30 day ±7 days or the 23rd day to the 37th day after the first loading dose. The first dose and the second dose of the reinitiation regimen for more than about 6 weeks and less than 6 months may be injected in deltoid muscle to provide a quick attainment to the desired drug levels or plasma concentrations of paliperidone. The first dose and the second dose may depend on the stabilized dose prior to the missed dose. By way of example, when the stabilized dose prior to the missed dose is less than about 234 mg of paliperidone palmitate, the first loading dose and the second loading dose may be the same dosing amount as the stabilized dose prior to the missed dose. For example, each of the first loading dose and the second loading dose may range from about 39 mg to about 156 mg of paliperidone palmitate. By way of another example, when the stabilized dose prior to the missed dose is about 234 mg of paliperidone palmitate, the first loading may be administered at about 156 mg and the second loading dose may be administered at about 156 mg. Thereafter, the maintenance dosing may range from about 39 mg to about 234 mg of paliperidone palmitate and may be injected in either deltoid or gluteal muscle.

In another embodiment, a method of reinitiation regimen is provided for treating patients who have missed a dose for more than about 6 weeks and less than 6 months, comprising administering into the deltoid muscle a first loading dose, administering into the deltoid muscle a second loading dose on about the 6th day to the 10th day after the first loading dose, and administering into the deltoid or gluteal muscle a

maintenance dose on about the 23rd day to the 37th day after the first loading dose. Thereafter, the maintenance dose may be administered at monthly intervals.

When more than about 6 months have elapsed since a patient received the last dosing of paliperidone palmitate, the reinitiation regimen may comprise a first loading dose, a second loading dose and a maintenance dose. The first dose may be administered as soon as possible, the second dose may be administered on about the 8th day after the first loading dose, and a maintenance dosing may be administered on about 30th day after the first loading dose. The duration of the second loading dose and the maintenance dose of the reinitiation regimen may be flexible. For example, the second loading dose may be administered 7 day ± 2 days or the 6th day to the 10th day after the first loading dose and the maintenance dose may be administered 30 day ±7 days or the 23rd day to the 37th day after the first loading dose.

The dose of the reinitiaiton regimen for more than about 6 months may be determined based on the condition of the patient and/or the severity of the disease. The preferred first loading dose may range from about 156 mg to about 234 mg of paliperidone palmitate, and more preferably about 234 mg. The preferred second loading dose may range from about 78 mg to about 156 mg, and more preferably about 156 mg. The preferred monthly maintenance dose may range from about 39 to about 234 mg, and more preferably about 117 mg. Subsequently, based on the patient tolerability and/or the drug efficacy, the maintenance dose may be further adjusted monthly to achieve optimal treatment effectiveness. The patients may be monitored for several months to ensure the full effect of the dose adjustment because of the prolonged-release characteristic of paliperidone palmitate. Further, the first dose and the second dose of the reinitiation regimen for patients who have missed the dose for more than about 6 months may be injected in deltoid muscle. The maintenance dose of the reinitiation regimen for patients who have missed the dose for more than about 6 weeks may be injected in either deltoid or gluteal muscle.

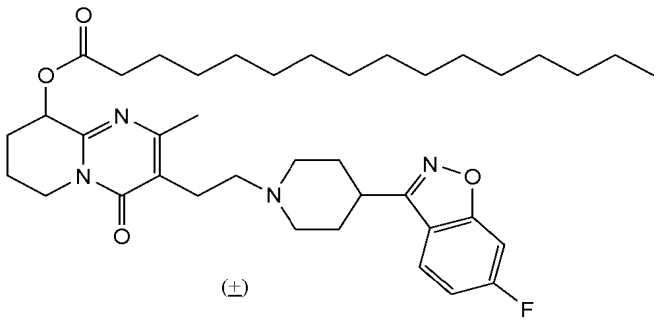
In yet another embodiment, a method of reinitiation regimen is provided for treating patients who have missed a dose for more than about 6 months, comprising administering into the deltoid muscle a first loading dose, administering into the deltoid muscle a second loading dose on about the 6th to about the 10th day and administering into the deltoid or gluteal muscle a maintenance dose on about the 23rd day to about the

37th day after administering of the first loading dose. Thereafter, the maintenance dose may be administered at monthly intervals.

As used herein, the term "stabilized dose" refers to the dose which is to be administered according the established dosing regimen. Preferably, the stabilized dose may the maintenance dose of the monthly maintenance dosing regimen prior to a missed dose.

Also used herein, the terms "the first loading dose of the reinitiation regimen", "the first dose of the reinitiation regimen", "the first reinitiation dose" or variant thereof refer to the dose to be administered on day 1 when patients return to treatment. Similarly, the terms "the second loading dose of the reinitiation regimen", "the second dose of the reinitiation regimen", "the second reinitiation dose" or variant thereof refer to the dose to be administered after a week after the treatment day 1; and the terms "the maintenance dose of the reinitiation regimen", "the reinitiation maintenance dose" or variant thereof refer to the dose to be administered monthly after the treatment day 1.

Paliperidone esters are psychotic agents belonging to the chemical class of benzisoxazole derivatives, which contains a racemic mixture of (+)- and (-)-paliperidone, which are described in US Patent No. 5,254,556 (incorporated herein by reference). The chemical name for paliperidone palmitate is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate. The structural formula is:



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Paliperidone esters may be formulated with pharmaceutical excipients into injectable dosage forms as described in US Patent Nos. 5,254,556 and 6,077,843 both of which are incorporated herein by reference. Injectable formulations may be formulated in aqueous carriers.

Suitable aqueous depot formulations are described in US Patent No. 6,077,843 which is incorporated herein by reference. The aqueous formulation would preferably be a nano particle suspension of wherein the nano particles would be of an averages size of less than about 2,000 nm to about 100 nm. Preferably the nano particles would have an average particle size (d50) of from about 1,600 nm to about 400 nm and most preferably about 1,400 nm to about 900 nm. Preferably the d90 will be less than about 5,000 nm and more preferably less than about 4,400 nm. As used herein, an effective average particle size (d50) of less than about 2,000 nm means that at least 50% of the particles have a diameter of less than about 2,000 nm when measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation. With reference to the effective average particle size, it is preferred that at least about 90%, e.g. about 5,000 nm. Most preferably, about 90% of the particles have a size of less than about 4,400 nm.

Suitable aqueous nanoparticle depot formulations are described in US Patent No. 6,555,544 which is incorporated herein by reference. In one embodiment of the present invention the formulation would comprise nanoparticles, a surfactant, a suspending agent, and optionally one or more additional ingredients selected from the group consisting of preservatives, buffers and an isotonizing agent.

Useful surface modifiers are believed to include those that physically adhere to the surface of the active agent but do not chemically bond thereto. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available TWEENS™, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phtalate, noncrystalline

cellulose, magnesium aluminate silicate, triethanolamine, polyvinyl alcohol (PVA), poloxamers, tyloxapol and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

Particularly preferred surface modifiers include polyvinylpyrrolidone; tyloxapol; poloxamers, such as PLURONIC™ F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide available from BASF; poloxamines, such as TETRONIC™ 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF; dextran; lecithin; Aerosol OT™ (AOT) which is a dioctyl ester of sodium sulfosuccinic acid available from Cytec Industries; DUPONOL™ P which is a sodium lauryl sulfate available from DuPont; TRITON™ X-200 which is an alkyl aryl polyether sulfonate available from Rohm and Haas; TWEEN™ 20, 40, 60 and 80 which are polyoxyethylene sorbitan fatty acid esters available from ICI Speciality Chemicals; SPAN™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids; ARLACEL™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids available from Hercules, Inc.; CARBOWAX™ 3550 and 934 which are polyethylene glycols available from Union Carbide; CRODESTA™ F110 which is a mixture of sucrose stearate and sucrose distearate available from Croda Inc.; CRODESTA™ SL-40 which is available from Croda, Inc.; hexyldecyl trimethyl ammonium chloride (CTAC); bovine serum albumin and SA90HCO which is $C_{18}H_{17}CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$. The surface modifiers which have been found to be particularly useful include tyloxapol and a poloxamer, preferably, Pluronic™ F108 and Pluronic™ F68.

Pluronic™ F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula $HO[CH_2CH_2O]_x[CH(CH_3)CH_2O]_y[CH_2CH_2O]_zH$ in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag NONIONIC™ 1108-F available from Hodag, and SYNPERONIC™ PE/F108 available from ICI Americas.

The optimal relative amount of paliperidone palmitate and the surface modifier depends on various parameters. The optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the antipsychotic agent, etc. The specific surface modifier preferably is present in an amount of about 0.1 to about 1 mg per square meter surface area of the paliperidone palmitate. It is preferred in the case of paliperidone palmitate (9-hydroxyrisperidone palmitate) to use PLURONIC™ F108 as a surface modifier, a relative amount (w/w) of both ingredients of approximately 6:1 is preferred.

The particles of this invention can be prepared by a method comprising the steps of dispersing paliperidone palmitate in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the antipsychotic agent to an effective average particle size of less than about 2,000 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention includes (a) obtaining paliperidone palmitate in micronized form; (b) adding the micronized paliperidone palmitate to a liquid medium to form a premix; and (c) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the effective average particle size.

The paliperidone palmitate in micronized form may be prepared using techniques known in the art. It is preferred that the particle size of the micronized paliperidone palmitate be less than about 100 μm as determined by sieve analysis. If the particle size of the micronized paliperidone palmitate is greater than about 100 μm, then it is preferred that the particles of paliperidone palmitate be reduced in size to less than 100 μm.

The micronized paliperidone palmitate can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of paliperidone palmitate in the liquid medium (weight by weight percentage) can vary widely and depends on the selected antipsychotic agent, the selected surface modifier and other factors. Suitable concentrations of paliperidone palmitate in compositions vary from about 0.1% to about 60%, preferably is from about 0.5% to about 30%, and more preferably, is approximately 7% (w/v). It is currently preferred to use a concentration

of about 100mg eq of paliperidone per ml or about 156 mg of paliperidone palmitate per ml.

A more preferred procedure involves the addition of a surface modifier to the premix prior to its subjection to mechanical means to reduce the effective average particle size. The concentration of the surface modifier (weight by weight percentage) can vary from about 0.1% to about 90%, preferably from about 0.5% to about 80%, and more preferably is approximately 7% (w/v).

The premix can be used directly by subjecting it to mechanical means to reduce the effective average particle size in the dispersion to less than about 2,000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the antipsychotic agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation such as, for example, a roller mill or a Cowles type mixer, until a homogeneous dispersion is achieved.

The mechanical means applied to reduce the effective average particle size of the antipsychotic conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills--such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is anywhere between about 0.1 Pa•s and about 1 Pa•s. For ball milling, the apparent viscosity of the premix preferably is anywhere between about 1 mPa•s and about 100 mPa•s.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of the material for the grinding media is believed not to be critical. However, about 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles which are acceptable for the preparation of pharmaceutical compositions. Further, other media, such as polymeric beads, stainless steel, titania, alumina and about 95% ZrO stabilized with yttrium, are useful. Preferred grinding media have a density greater than about 2.5 g/cm^3 and include about 95% ZrO stabilized with magnesia and polymeric beads.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For rolling mills, processing times of up to two days or longer may be required.

The particles must be reduced in size at a temperature which does not significantly degrade the antipsychotic agent. Processing temperatures of less than about 30°C to about 40°C are ordinarily preferred. If desired, the processing equipment may be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed by, for example, shaking vigorously. Optionally, the dispersion can be subjected to a sonication step using, for example, an ultrasonic power supply.

Aqueous compositions according to the present invention conveniently further comprise a suspending agent and a buffer, and optionally one or more of a preservative and an isotonizing agent. Particular ingredients may function as two or more of these agents simultaneously, e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonizing agent.

Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylene- and polyoxy-propylene ethers. Preferably sodium carboxymethyl cellulose is used in a concentration of about 0.5 to about 2%, most preferably about 1% (w/v). Suitable wetting agents for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate. Preferably polysorbate 20 is used in a concentration of about 0.5% to about 3%, more preferably about 0.5% to about 2%, most preferably about 1.1% (w/v).

Suitable buffering agents are salt of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to the pH value of about 8.5), preferably in the pH range of about 7 to about 7.5. Particularly preferred is

the use of a mixture of disodium hydrogen phosphate (anhydrous) (typically about 0.9% (w/v)) and sodium dihydrogen phosphate monohydrate (typically about 0.6% (w/v)). This buffer also renders the dispersion isotonic and, in addition, less prone to flocculation of the ester suspended therein.

Preservatives are antimicrobials and anti-oxidants which can be selected from the group consisting of benzoic acid, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-gamma-piccolinium chloride, phenylmercuric acetate and thimerosal. In particular, it is benzyl alcohol which can be used in a concentration up to about 2% (w/v), preferably up to about 1.5% (w/v).

Isotonizing agents are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. The suspensions conveniently comprise from about 0% to about 10% (w/v) isotonizing agent. Mannitol may be used in a concentration from about 0% to about 7% More preferably, however, from about 1% to about 3% (w/v), especially from about 1.5% to about 2% (w/v) of one or more electrolytes are used to render the suspension isotonic, apparently because ions help to prevent flocculation of the suspended ester. In particular, electrolytes of the buffer serve as isotonizing agent.

A particularly desirable feature for an injectable depot formulation relates to the ease with which it can be administered. In particular such an injection should be feasible using a needle as fine as possible in a span of time which is as short as possible. This can be accomplished with the aqueous suspensions of the present invention by keeping the viscosity below about 75 mPa•s, preferably below about 60 mPa•s. Aqueous suspensions of such viscosity or lower can both easily be taken up in a syringe (e.g. from a vial), and injected through a fine needle (e.g a 21G $1^1/_2$ inch, 22G 2 inch, 22G $1^1/_4$ inch or 23G 1 inch needle). The preferred needles for injection are 22G 22G 1 ½ inch regular wall and 23G 1 inch regular wall needles.

Ideally, aqueous suspensions according to the present invention will comprise as much prodrug as can be tolerated so as to keep the injected volume to a minimum, and as little of the other ingredients as possible. In particular, such a composition will comprise by weight based on the total volume of the composition: (a) from about 3% to 20% (w/v) of the prodrug; (b) from about 0.5% to 2% (w/v) of a wetting agent; (c) one

or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5); (d) from about 0.5% to about 2% (w/v) of a suspending agent; (e) up to about 2% (w/v) preservatives; and (f) water q.s. ad 100%. Preferably the aqueous suspension will be made under sterile conditions and no preservatives will be used. Appropriate methods to aseptically prepare paliperidone palmitate are described in WO 2006/114384 which is hereby incorporated by reference herein.

The preferred aqueous dosage form contains inactive ingredients that are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection. The mg of compound delivered in such a dosage form to the patient may be from about 25 to about 150 mg (e.g. 25 mg, 50 mg, 75 mg, 100 mg, 150 mg,) injectable dosage form.

As used herein, a dose or dosing is expressed as milligrams (mg) of paliperidone palmitate. Paliperidone palmitate dosing may also be expressed as mg equivalents (mg eq.) of paliperidone with about 39, 78, 117, 156, and 234 mg of paliperidone palmitate being equivalent to about 25, 50, 75, 100 and 150 mg eq., of paliperidone, respectively.

The term **"antipsychotics"** or **"antipsychotic drug medication"** as used herein means any medication used to decrease or ameliorate the symptoms of psychosis in a person with a psychotic disorder and includes, but is not limited to the following compounds: Acetophenazine Maleate; Alentemol Hydrobromide; Alpertine; Azaperone; Batelapine Maleate; Benperidol; Benzindopyrine Hydrochloride; Brofoxine; Bromperidol; Bromperidol Decanoate; Butaclamol Hydrochloride; Butaperazine; Butaperazine Maleate; Carphenazine Maleate; Carvotroline Hydrochloride; Chlorpromazine; Chlorpromazine Hydrochloride; Chlorprothixene; Cinperene; Cintriamide; Clomacran Phosphate; Clopenthixol; Clopimozide; Clopipazan Mesylate; Cloroperone Hydrochloride; Clothiapine; Clothixamide Maleate; Clozapine; Cyclophenazine Hydrochloride; Droperidol; Etazolate Hydrochloride; Fenimide; Flucindole; Flumezapine; Fluphenazine Decanoate; Fluphenazine Enanthate; Fluphenazine Hydrochloride; Fluspiperone; Fluspirilene; Flutroline; Gevotroline Hydrochloride; Halopemide; Haloperidol; Haloperidol Decanoate; Iloperidone; Imidoline Hydrochloride; Lenperone; Mazapertine Succinate; Mesoridazine;

Mesoridazine Besylate; Metiapine; Milenperone; Milipertine; Molindone Hydrochloride; Naranol Hydrochloride; Neflumozide Hydrochloride; Ocaperidone; Olanzapine; Oxiperomide; Penfluridol; Pentiapine Maleate; Perphenazine; Pimozide; Pinoxepin Hydrochloride; Pipamperone; Piperacetazine; Pipotiazine Palmitate; Piquindone Hydrochloride; Prochlorperazine Edisylate; Prochlorperazine Maleate; Promazine Hydrochloride; Quetiapine; Remoxipride; Remoxipride Hydrochloride; Risperidone; Rimcazole Hydrochloride; Seperidol Hydrochloride; Sertindole; Setoperone; Spiperone; Thioridazine; Thioridazine Hydrochloride; Thiothixene; Thiothixene Hydrochloride; Tioperidone Hydrochloride; Tiospirone Hydrochloride; Trifluoperazine Hydrochloride; Trifluperidol; Triflupromazine; Triflupromazine Hydrochloride; and Ziprasidone Hydrochloride.

The term "**psychiatric patient**" as used herein, refers to a human, who has been the object of treatment, or experiment for a "mental disorder" and "mental illness" refer to those provided in the Diagnostic and Statistical Manual (DSM IV), American Psychological Association (APA). Those of ordinary skill in the art will appreciate that paliperidone esters (e.g. paliperidone palmitate) can be administered to psychiatric patients for all the known uses of risperidone. These mental disorders include, but are not limited to, schizophrenia; bipolar disorder or other disease states in which psychosis, aggressive behavior, anxiety or depression is evidenced. Schizophrenia refers to conditions characterized as schizophrenia, schizoaffective disorder and schizophreniform disorders, in DSM-IV-TR such as category 295.xx**.** Bipolar Disorder refers to a condition characterized as a Bipolar Disorder, in DSM-IV-TR such as category 296.xx including Bipolar I and Bipolar Disorder II. The DSM-IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. Pathologic psychological conditions, which are psychoses or may be associated with psychotic features include, but are not limited to the following disorders that have been characterized in the DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress. Examples of pathologic psychological conditions which may be treated include, but are not limited to, Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation

(318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusions (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not

Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS

(312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83). The numbers in parenthesis refer to the DSM-IV-TR categories.

The term "**therapeutically effective amount**" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Those of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above. By way of example, an effective amount of paliperidone for the treatment of mental disorders would be from about 0.01mg/kg to about 2 mg/kg body weight. For the present invention it is preferred to dose patients with about 25 mg- eq. to about 150 mg eq. paliperidone or about 39 mg to about 234 mg paliperidone palmitate. The amount of paliperidone palmitate is provided in sufficient amount to provide the equivalent dose of paliperidone after the palmitic acid moiety is removed from the ester (e.g. 156 mg corresponds to paliperidone 100mg). In one embodiment of present invention wherein paliperidone palmitate is administered by intramuscular injection once per month is preferred.

When asked, approximately half of patients in a 13-week study stated that they preferred deltoid to gluteal injections, with the most common reasons for this preference being that it was easier, less embarrassing and faster than an injection in the gluteal muscle. Moreover, it may be beneficial for patients who favour only deltoid injections due to paranoia and other psychiatric symptomatology. When dosing frequency, aqueous-based formulation and flexibility of injection site to accommodate patients' preference are considered in combination, paliperidone palmitate may provide the advantages of improved convenience and acceptability compared with previous antipsychotic medications. With the availability of paliperidone palmitate, the clinicians may need to manage patients switching treatment from other antipsychotic drugs to paliperidone palmitate.

The following non-limiting examples are provided to further illustrate the present invention.

Example 1. Methodology

Population Pharmacokinetics Models

A comprehensive population pharmacokinetics (PK) model was developed for paliperidone palmitate based on data from previous studies of subjects with schizophrenia. Briefly, a 1-compartment model with first-order elimination best described the PK of paliperidone following intramuscular administration of the paliperidone palmitate ester. As shown in Figure 1, the absorption component of the model allowed a fraction (F2) of the dose to enter the central compartment relatively quickly via a zero-order process with duration D2. After a certain lag-time, the remaining fraction (1-F2) entered the systemic circulation via a first-order process (KA) that determines the shape of the plasma concentration-time curve following injection. NONMEM® Version V (Icon Development Solutions, Ellicott City, MD) running with NM-TRAN version III was used to conduct all population PK analyses and simulations in accordance to the NONMEM Users Guides (Icon Development Solutions, Ellicott City, MD). NONMEM was run using the J&JPRD computational grid using Intel FORTRAN 9.0 compiler for Windows. Generation of data sets for NONMEM simulations and visualization of results were performed using S Plus® 6.0 professional release 2 software (Insightful Corporation, Seattle, WA). The model

building included pooled data from about 1,795 subjects from six Phase 1 studies and five Phase 2 and 3 studies. A total of 18,530 PK samples with valid concentration time-points were part of the population PK database. The final model from the historical population PK analysis [(Pop PK Report Paliperidone Palmitate)], including all significant subject covariates was used as simulation machinery for assessing various dosing regimens for paliperidone palmitate including missed dose treatment and switching treatment.

Additionally, a comprehensive population PK model was developed for the extended release oral formulation of paliperidone or INVEGA. The model was constructed using pooled data from about 1,368 subjects with about 21,183 paliperidone concentrations from all phases of the INVEGA drug development. The PK of paliperidone in plasma was best captured using an open 2-compartment disposition model with linear elimination from the central compartment. The absorption was modeled with a sequential zero-order input into a depot compartment and first-order absorption with a lag-time from the depot to the central compartment. The relatively faster absorption of paliperidone from the oral route allowed identification of the distributive peripheral compartment, which is not discernible in the flip-flopped paliperidone palmitate PK data. The final paliperidone model from this historical analysis, including all significant subject covariates, was used for simulating PK exposure from oral paliperidone at various dose levels.

The PK profiles for about 5,000 subjects were simulated for subjects receiving injectable paliperidone palmitate (INVEGA® SUSTENNA™) and oral paliperidone (INVEGA®). For each data set, the covariates of interest were obtained by resampling from the subject covariates (resampling unit was the subject) available in the subject PK database for paliperidone palmitate and the joint distribution of subject-specific characteristics was maintained. To evaluate the outcome of the simulations, the population median and about 90% prediction interval of the simulated plasma concentration vs. time profiles were plotted together.

A compartmental model was also developed for RISPERDAL® CONSTA® which included a one-compartment disposition submodel characterized by clearance and volume of distribution and three parallel absorption pathways: an immediate pathway describing the absorption of non-encapsulated risperidone, and a fast and a slow sustained-release pathway. For the model building, data for the RISPERDAL®

CONSTA® originating only from the final 20-kg manufacturing scale used in Phase-III trials and "to be marketed" formulation was used as the source information. A two stage approach had to adopted for modeling RISPERDAL® CONSTA® PK because the active moiety profile after intramuscular administration of risperidone depot microsphere formulations was extremely complex (immediate release of a small amount of non-encapsulated risperidone followed by two sustained-release processes differing in the rate of release along with variable delay in release initiation). The model was fitted to individual concentration-time profiles of active moiety. However, the mixed-effects version of the model which included interindividual variability in parameters could not be fitted due to numerical problems with the NONMEM software. Thus, at the first stage, individual estimates of active moiety (risperidone + paliperidone) PK parameters were obtained using clinical studies where intensive blood sampling occurred in about 56 subjects. These estimates were used as part of the second step in a non-parametric approach to perform population simulations.
For the simulation data set, the parameters of interest were obtained by resampling the individual estimates (n=5,000 subjects) where the resampling unit was the subject. This method was able to retain the joint distribution of subject-specific parameters. It was also noted that a depiction of inter-subject variability computed using this method would be an underestimate due to the small size that was used in building this model. Therefore, the prediction interval for RISPERDAL® CONSTA® simulations should be interpreted with caution. To evaluate the outcome of the simulations, the population median and about 90% prediction interval of the simulated plasma concentration vs. time profiles were plotted together. Oral supplementation used during the first few weeks of RISPERDAL® CONSTA® therapy is ignored in this modeling to simplify this complex exercise.

To add credence to the simulation exercise for the initiation regimens, model based projections were compared with the limited and/or sparse observed data from clinical studies.

Example 2. Missed Doses

To manage patients missed the dose of the treatment, simulations were used to evaluate reinitiation treatment in patients who had missed a week 4 dose of paliperidone palmitate and returned to treatment at weeks 5, 6, 7 or 8. The simulations

were also used to evaluate re-initiation treatment in patients who had a prolonged lapse of more than about 6 months. The patient may be administered a single dose at day 1 using the maintenance one that would have been administered at exactly the 4th week, or two doses at day1/day 8 using the same dose as the maintenance dose. Both possibilities were investigated for the about 5, 6, 7, and 8 week scenarios using the doses of about 39, 78, 117, 156, and 234 mg of paliperidone palmitate. The time point at which re-initiation with 2 doses could be appropriate was judged based on visual inspection of simulated curves. The profiles after a missed dose were assessed empirically and proximity to the steady-state levels was the criterion for judging the utility of these dosing schemes.

These results in Figures 2 to 4 indicated that the reinitiation treatment after patients missed their Week 4 maintenance dose or the stabilized dose, re-initiation depended upon the time lapse since the last injection. For example, patients who missed their week 4 maintenance dose and returned to re-initiation at week 5 or 6 (i.e., time lapse since last injection is more than about 4 weeks and less than about 6 weeks) may be administered with single re-initiation dose at the previously stabilized dose followed by monthly injections (Figures 2 and 3). The doses may be administered in either the deltoid muscle with a 1.0 inch 23-G needle for the patients weighting less than about 90 kg or a 1.5 inch 22-G for those weighting equal or more than about 90 kg, or the gluteal muscle with a 1.5-inch 22-G needle for all weights. Additionally, [Figure 6, Panel A and B] This is recommended as the models showed that reinitiation with two doses at day 1/day 8 resulted in a higher than desired plasma concentration (Figure 3).

The simulations also showed that patients who missed their week 4 maintenance dose and returned to re-initiation at week 7 or 8 (i.e., time lapse since last injection is more than about 6 weeks and less than about 6 months) may be administered with two re-initiation doses at the previously stabilized dose followed by monthly injections. The two doses at day 1/day 8 allow re-attainment of steady-state plasma concentration quickly (Figure 3). Additionally, the two reinitiation doses were injected into the deltoid muscle with a 1.0 inch 23-G needle for the patients weighting less than about 90 kg or a 1.5 inch 22-G for those weighting equal or more than about 90 kg. Each of the two re-initiation doses was the previously stabilized dose, except when the patient was stabilized on a dose of about 234 mg. For the patient stabilized on a dose of about 234

mg of paliperidone palmitate, the model recommended each of the first two doses of about 156 mg of paliperidone palmitate.

The simulations further recommended that patient who missed their week 4 maintenance dose and returned more than about 6 months were required to re-initiate the treatment de novo (Figure 4). That is, patients were administered with paliperidone palmitate of about 234 mg on day 1 and about 156 mg on day 8. Each dose was administered into the deltoid muscle with needle selection based upon patient weight as discussed above. The re-initiation doses were followed by monthly paliperidone palmitate injections using maintenance dose recommendations as discussed above. Finally, the simulation models indicated that there is a ±2 day dosing window for the administration of the second dose, if needed, and a ±7 day dosing window for the administration of the monthly maintenance doses (data not shown).

Example 3. Switch Treatment From Oral Antipsychotic

Pharmacokinetic models or simulations were developed to examine drug levels when patients were switched from extended release (ER) oral paliperidone to paliperidone palmitate. The models also determined whether pervious oral antipsychotics such as paliperidone ER could be discontinued at the time of initiation of treatment with paliperidone palmitate.

The models examined patients who were treated with a daily dosing of about 6 mg paliperidone ER and initiated with paliperidone palmitate on the first day after the last oral dose of paliperidone ER. The simulated concentrations of paliperidone from its palmitate ester were added to the drug levels from paliperidone ER using the superposition principles. The simulation models analyzed two scenarios: (A) patients switched from the dose of about 6 mg paliperidone ER to paliperidone palmitate using the two initiation doses of about 150 mg-eq. in the deltoid muscle on treatment day 1 and about 100 mg-eq. in the deltoid muscle one week later; and (B) patients switched from the dose of about 6 mg paliperidone ER to paliperidone palmitate using a single day 1 injection of about 150 mg-eq. dose. The results of the simulations were summarized in Figure 5.

As shown in Figure 5A, the desired paliperidone plasma levels were maintained during the first week of the switching treatment from about 6 mg paliperidone ER to day 1/day 8 initiation regimen of paliperidone palmitate. Though the palperidone

plasma levels decline rapidly from the oral treatment, the plasma levels or concentration increased due to the intramuscular administering of paliperidone palmitate at day 1. Afterward, the administration of the 2nd dose of about 100 mg-eq. dose on day 8 maintained the drug levels in the desired therapeutic range.

On the contrary, the results of Figure 5B showed that when the day 8 injection was skipped, the paliperidone plama levels began to decline and became lower than the desired therapeutic range at about 2 weeks after the day1 injection. Therefore, the initiation regimen of day 1/day 8 of paliperidone palmitate provided an effective treatment for switching patients from oral antipsychotics.

In addition to the simulation based analysis, a literature search was performed to evaluate the pharmacokinetic characteristics of other oral antipsychotics. The results of literature search for typical and atypical antipsychotics were summarized in Tables 1 and 2, respectively.

Table 1. Terminal Half-life of Oral Typical Antipsychotics

Oral Typical Antipsychotic	Terminal Half-life
Chlorpromazine	8-35 hours [a]
Flupenthixol	22-36 hours [a]
Fluphenazine	14-24 hours [a]
Haloperidol	12-36 hours [a]
Loxapine	4 hours [b]
Molindone	1.5 hours [b]
Perphenazine	8-21 hours [a]
Pimozide	2-3 days [b]
Prochlorperazine	4-8 hours [b]
Thioridazine	9-30 hours [a]
Thiothixene	34 hours [a]
Trifluoperazine	10-20 hours [b]

[a] Ereshefsky L. Pharmacokinetics and drug interactions: update for new antipsychotics. J Clin Psychiatry. 1996;57 Suppl 11:12-25.
[b] "Typical antipsychotic" in *Wikipedia: The Free Encyclopedia*, Wikimedia Foundation Inc [Encyclopedia on-line]; retrieved August 6, 2009.

Table 2. Terminal Half-life of Oral Atypical Antipsychotics

Oral Atypical Antipsychotic	Terminal Half-life
Amisulpride	12 hours [c]
Aripiprazole	47-68 hours [c]
Clozapine	9-17 hours [c]
Olanzapine	33 hours [c]
Paliperidone (9-hydroxy-risperidone)	25 hours [d]
Quetiapine	6 hours [c]
Risperidone active moiety [e]	22 hours [c]
Sertindole	70 hours [c]
Ziprasidone	8-10 hours [c]

[c] Mauri MC, Volonteri LS, Colasanti A, Fiorentini A, De Gaspari IF, Bareggi SR. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet. 2007;46(5):359-88.
[d] Vermeir M, Naessens I, Remmerie B, Mannens G, Hendrickx J, Sterkens P, Talluri K, Boom S, Eerdekens M, van Osselaer N, Cleton A. Absorption, metabolism, and excretion of paliperidone, a new monoaminergic antagonist, in humans. Drug Metab Dispos. 2008 Apr;36(4):769-79.
[e] Active moiety is the sum of parent drug plus it's active metabolite 9-hydroxy-risperidone

As shown in the tables, all oral antipsychotics have half-life of less than about 3 days. Given the short half-life of the oral antipsychotics, the drug levels of the previous oral antipsychotic would be decline rapidly during the first week of initiation with paliperidone palmitate. Additionally, more than about 75% of the drug from the oral therapy would be washed out from the systemic circulation within the first week. These results further supported the simulations that a second loading dose of paliperidone palmitate after 7 days or on the 8th day after the treatment day 1 would attain the paliperidone concentrations within the desired therapeutic range.

Example 4. Switch Treatment From Other Long Acting Injectable Antipsychotic

Pharmacokinetic models or simulations were also developed to examine the drug levels when patients were switched from RISPERDAL® CONSTA® to paliperidone palmitate. The modeling also determined whether the treatment with paliperidone palmitate could be initiated at the next scheduled injection of other injectable antipsychotic such as RISPERDAL® CONSTA®.

The models examined patients who were treated with a bi-weekly administration schedule of RISPERDAL® CONSTA® and switched to paliperidone palmitate for about two weeks after their last RISPERDAL® CONSTA® injection. The

simulated concentrations of paliperidone from its palmitate ester were added to the active moiety profile from RISPERDAL® CONSTA® using the superposition principles, as RISPERDAL® CONSTA® has the same active moiety as paliperidone palmitate.

Plasma concentrations were simulated with paliperidone palmitate injection at about two weeks after the last RISPERDAL® CONSTA® injection followed by monthly injections of paliperidone palmitate. The simulation models analyzed two scenarios: (A) a low dose scenario where patients were switched from about 25 mg RISPERDAL® CONSTA® to about 50 mg-eq. paliperidone palmitate followed by monthly injections of about 50 mg-eq. paliperidone palmitate; and (B) a high dose scenario where patients were switched from about 50 mg RISPERDAL® CONSTA® to about 100 mg-eq. paliperidone palmitate followed by monthly injections of about100 mg eq. paliperidone palmitate. These results were summarized in Figure 6.

Figure 6 showed that, for both low and high dose cases, the drug levels were maintained close to the steady-state concentrations right after the switch from RISPERDAL® CONSTA® to paliperidone palmitate. Additionally, after the last injection of RISPERDAL® CONSTA®, the steady state concentrations were maintained for about 4-5 weeks and declined thereafter with a mean plasma half-life of about 4-6 days. Therefore, at the time of switching treatment, only a single injection of paliperidone palmitate was sufficient. This simulation indicated that when switching patients from previous treatment of other long-acting injectable antipsychotics, paliperidone palmitate therapy may be initiated in place of the next scheduled injection and continued at monthly intervals. Also, the simulation indicated that the second dose of initiation dosing regimen and oral supplement were not required when switching from other long acting injectable antipsychotics.

In addition to the simulation based analysis, a literature search was conducted to evaluate the pharmacokinetic characteristics of other long acting injectable antipsychotics. The results were summaried in Table 3.

Table 3. Summary of the properties of depot intramuscular antipsychotics

Drug	Administration interval	$t_{1/2}$ [f]
Clopenthixol decanoate [a]	2-4 weeks	19 days

Perphenazine enanthate [a]	2 weeks	4–6 days
Pipothiazine palmitate [a]	4 weeks	15–16 days
Haloperidol decanoate [a]	4 weeks	21 days
Fluspirilene [a]	1 week	7 days
Zuclopenthixol decanoate [a]	2-4 weeks	19 days
Flupenthixol decanoate [b]	2-4 weeks	17 days
Fluphenazine decanoate [b]	2-5 weeks	14 days
Fluphenazine enanthate [c]	1 week	4 days
Risperidone Microspheres [d]	2 weeks	4-6 days
Olanzapine pamoate [e]	2-4 weeks	30 days

[a] Altamura AC, Sassella F, Santini A, Montresor C, Fumagalli S, Mundo E. Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. Drugs. 2003; 63(5): 493-512.

[b] Kane JM, Aguglia E, Altamura AC, Ayuso Gutierrez JL, Brunello N, Fleischhacker WW, Gaebel W, Gerlach J, Guelfi JD, Kissling W, Lapierre YD, Lindström E, Mendlewicz J, Racagni G, Carulla LS, Schooler NR. Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. Eur Neuropsychopharmacol. 1998; 8(1): 55-66.

[c] Levron JC, Ropert R. Clinical pharmacokinetics of haloperidol decanoate. Comparison with other prolonged-action neuroleptics. Encephale. 1987; 13(2): 83-7.

[d] Gefvert O, Eriksson B, Persson P, Helldin L, Björner A, Mannaert E, Remmerie B, Eerdekens M, Nyberg S. Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Consta) in patients with schizophrenia. Int J Neuropsychopharmacol. 2005; 8(1): 27-36.

[e] Eli Lilly. Zypadhera. Summary of product characteristics. The Netherlands: Eli Lilly Nederland B.V. 2008. Available Online at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/Zypadhera/H-890-PI-en.pdf. Accessed September 1, 2009.

[f] $t_{1/2}$ = apparent terminal half-life after multiple dosing

The results in Table 3 showed that, for all depot antipsychotics, the administration interval was in the range of about 1-2 half-life for each product. Based on the simple first-order elimination pharmacokinetic principles, it may take about 4 to 5 half-life for such drugs to be eliminated from the systemic circulation. Therefore, there would be sustained therapeutic levels of the prior drug in the systemic circulation when paliperidone palmitate is administered in place of the next scheduled injection of the previous antipsychotic. Given that significant levels of the previous antipsychotic would be present in the systematic circulation, there would be no need to use the 2nd initiation dose of paliperidone palmitate on day 8.

What is claimed is:

1. A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with a monthly injectable paliperidone palmitate depot, wherein said patient misses the next scheduled maintenance dose of the monthly injectable paliperidone palmitate depot, comprising:

(1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of the monthly injectable paliperidone palmitate depot; and

(2) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation maintenance dose of the monthly injectable paliperidone palmitate depot on about the 23rd day to about the 37th day after administering of said first reinitiation loading dose.

2. The method of claim 1, further comprising administering in the deltoid or gluteal muscle of said patient said reinitiation maintenance dose monthly.

3. The method of claim 1, wherein said patient misses the next scheduled maintenance dose of the monthly injectable paliperidone palmitate depot for more than about 4 weeks and less than about 6 weeks.

4. The method of claim 1, wherein said patient misses the next scheduled maintenance dose of the monthly injectable paliperidone palmitate depot for more than about 6 weeks and less than about 6 months.

5. The method of claim 1, wherein said patient misses the next scheduled maintenance dose of the monthly injectable paliperidone palmitate depot for more than about 6 months.

6. The method of claim 3, wherein said first reinitiation loading dose is the same amount as said scheduled maintenance dose.

7. The method of claim 3, wherein said first reinitiation loading dose is about 39 mg to about 234 mg.

8. The method of claim 3, wherein said reinitiation maintenance loading dose is about 39 to about 234 mg.

9. The method of claim 3, wherein said patient is in need of treatment for psychosis.

10. The method of claim 3, wherein said patient is in need of treatment for schizophrenia.

11. The method of claim 3, wherein said patient is in need of treatment for bipolar disorder.

12. The method of claim 4, further comprising administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation loading dose of the monthly injectable paliperidone palmitate depot on about the 6th day to about the 10th day after administering of said first reinitiation loading dose.

13. The method of claim 12, further comprising administering in the deltoid or gluteal muscle of said patient said reinitiation maintenance dose monthly.

14. The method of claim 12, wherein said first reinitiation loading dose is about 39 mg to about 117 mg.

15. The method of claim 12, wherein said second reinitiation loading dose is about 39 mg to about 117 mg.

16. The method of claim 5, further comprising administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation loading dose of the monthly injectable paliperidone palmitate depot on about the 6th day to about the 10th day after administering of said first reinitiation loading dose.

17. The method of claim 16, further comprising administering in the deltoid or gluteal muscle of said patient said reinitiation maintenance dose monthly.

18. The method of claim 16, wherein said first reinitiation loading dose is about 39 mg to about 117 mg.

19. The method of claim 16, wherein said second reinitiation loading dose is about 39 mg to about 117 mg.

20. A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with injectable antipsychotic drugs other than paliperidone palmitate, wherein said patient is switched from said injectable antipsychotic drugs to injectable paliperidone palmitate depot, comprising:

(1) administering intramuscularly in the deltoid muscle of said patient a first loading dose of said injectable paliperidone palmitate depot; and

(2) administering intramuscularly in the deltoid or gluteal muscle of said patient a maintenance dose of said injectable paliperidone palmitate depot on about the 23rd day to about the 37th day after administering of said first reinitiation loading dose.

21. The method of claim 20, further comprising administering in the deltoid or gluteal muscle of said patient said maintenance dose monthly.

22. The method of claim 20, wherein said first loading dose is about 78 mg to about 234 mg.

23. The method of claim 20, wherein said maintenance dose is about 39 mg to about 234 mg.

24. The method of claim 20, wherein said patient is in need of treatment for psychosis.

25. The method of claim 20, wherein said patient is in need of treatment for

schizophrenia.

26. The method of claim 20, wherein said patient is in need of treatment for bipolar disorder.

FIGURE 1

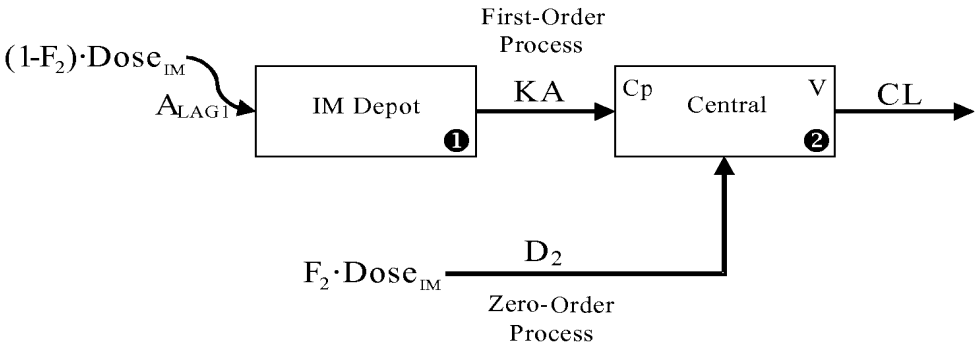

First-Order
Process
(1-F2)·DoseIM
ALAG1
IM Depot
1
KA
Cp
Central
V
2
CL
F2·DoseIM
D2
Zero-Order
Process

FIGURE 2

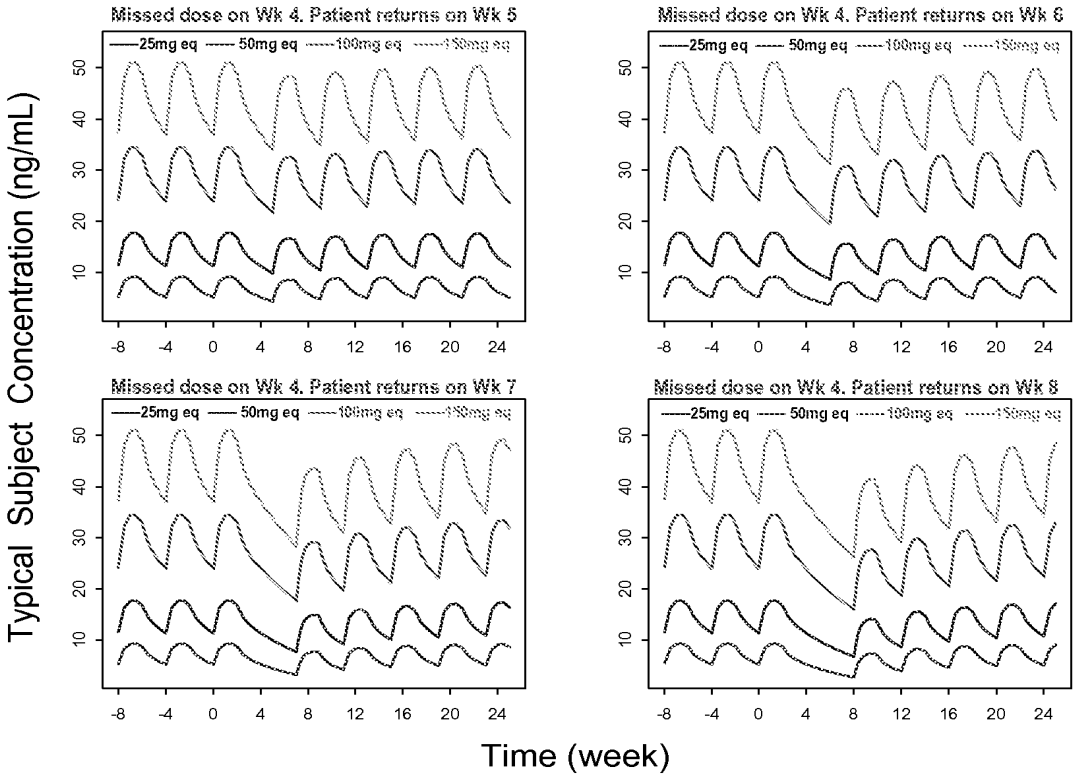

Missed dose on Wk 4. Patient returns on Wk 5
Missed dose on Wk 4. Patient returns on Wk 6
Missed dose on Wk 4. Patient returns on Wk 7
Missed dose on Wk 4. Patient returns on Wk 8
25mg eq
50mg eq
100mg eq
150mg eq
Typical Subject Concentration (ng/mL)
Time (week)

FIGURE 3

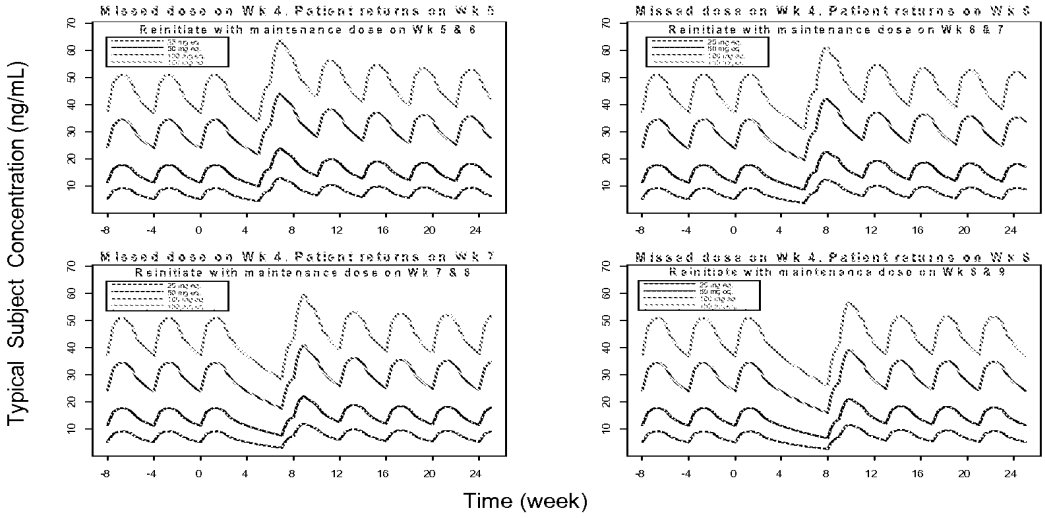

Missed dose on Wk 4, Patient returns on Wk 5
Reinitiate with maintenance dose on Wk 5 & 6
Missed dose on Wk 4, Patient returns on Wk 6
Reinitiate with maintenance dose on Wk 6 & 7
Missed dose on Wk 4, Patient returns on Wk 7
Reinitiate with maintenance dose on Wk 7 & 8
Missed dose on Wk 4, Patient returns on Wk 8
Reinitiate with maintenance dose on Wk 8 & 9
Typical Subject Concentration (ng/mL)
Time (week)

FIGURE 4

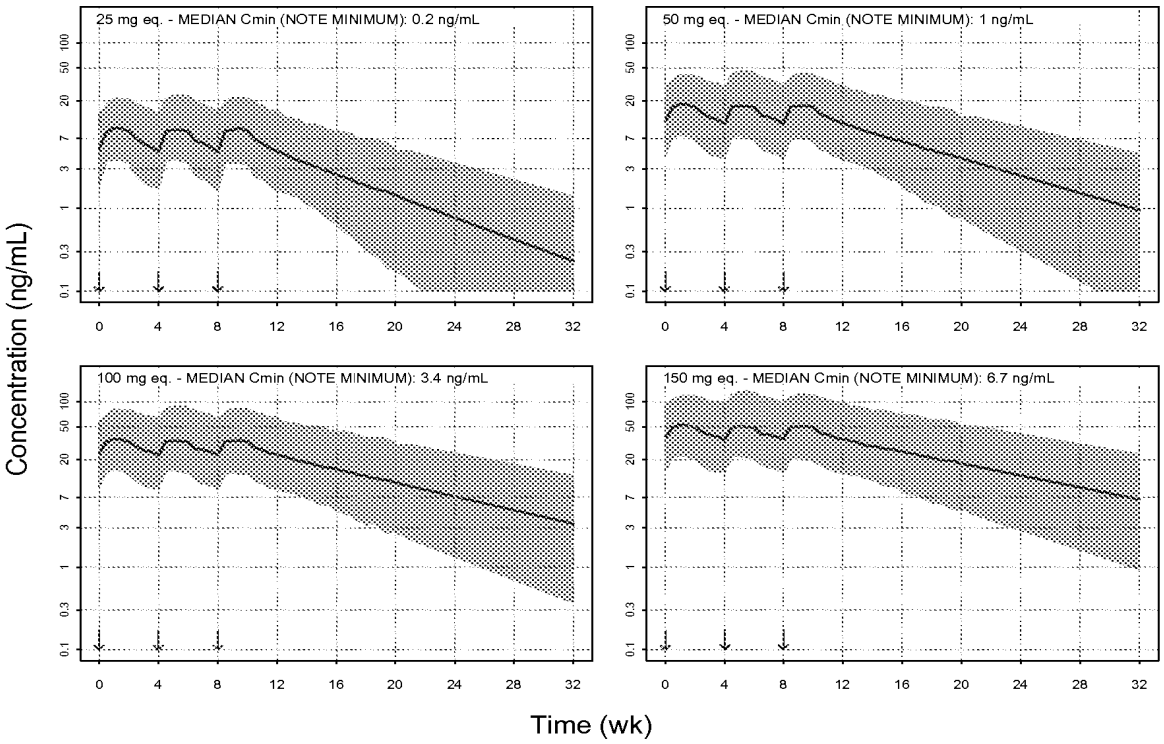

25 mg eq. - MEDIAN Cmin (NOTE MINIMUM): 0.2 ng/mL
50 mg eq. - MEDIAN Cmin (NOTE MINIMUM): 1 ng/mL
100 mg eq. - MEDIAN Cmin (NOTE MINIMUM): 3.4 ng/mL
150 mg eq. - MEDIAN Cmin (NOTE MINIMUM): 6.7 ng/mL
Concentration (ng/mL)
0.1
0.3
1
3
7
20
50
100
0
4
8
12
16
20
24
28
32
Time (wk)

FIGURE 5

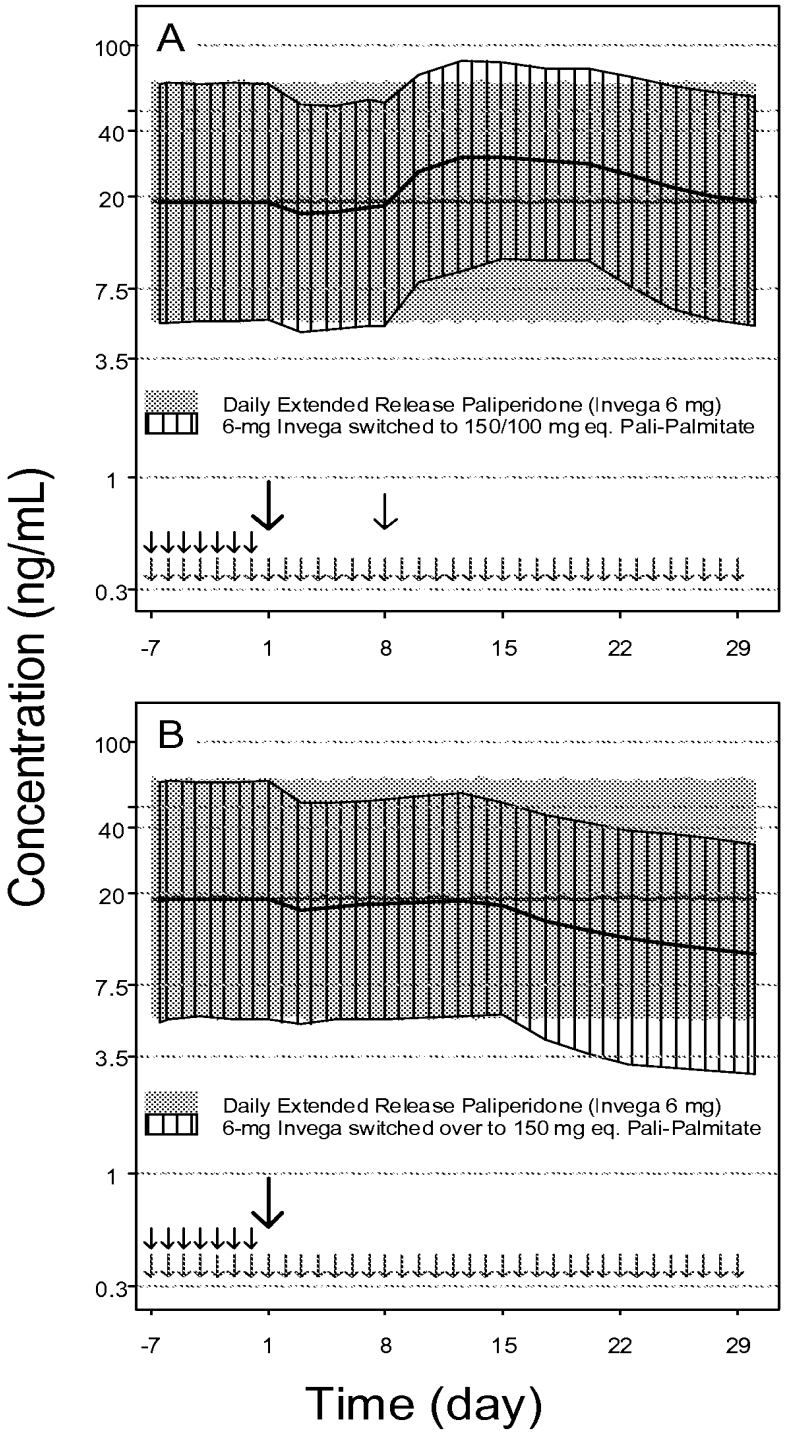
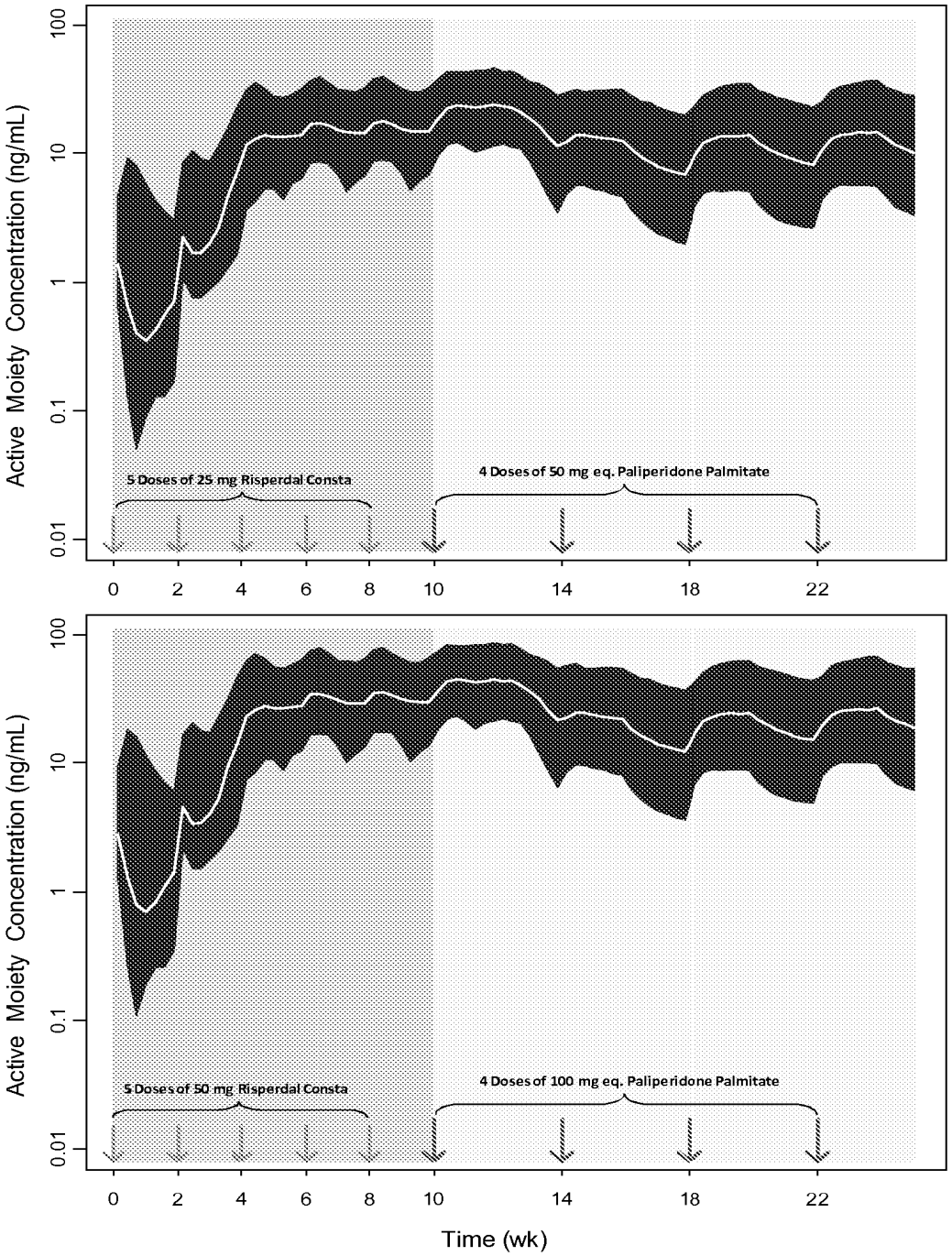

A
100
40
20
7.5
3.5
1
0.3
Daily Extended Release Paliperidone (Invega 6 mg)
6-mg Invega switched to 150/100 mg eq. Pali-Palmitate
-7
1
8
15
22
29
B
100
40
20
7.5
3.5
1
0.3
Daily Extended Release Paliperidone (Invega 6 mg)
6-mg Invega switched over to 150 mg eq. Pali-Palmitate
-7
1
8
15
22
29
Concentration (ng/mL)
Time (day)

FIGURE 6


Active Moiety Concentration (ng/mL)
100
10
1
0.1
0.01
5 Doses of 25 mg Risperdal Consta
4 Doses of 50 mg eq. Paliperidone Palmitate
0
2
4
6
8
10
14
18
22
Active Moiety Concentration (ng/mL)
5 Doses of 50 mg Risperdal Consta
4 Doses of 100 mg eq. Paliperidone Palmitate
Time (wk)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/054807

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/519 A61P25/18
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/080651 A1 (JANSSEN PHARMACEUTICA NV [BE]; VERMEULEN AN MARGRIET CORNELIA [BE]; WO) 2 July 2009 (2009-07-02) page 9, line 3 - page 9, line 19 example 7 claims 1,4,15 page 17 - page 20	1-26
Y	US 2007/197591 A1 (BOOM SANDRA [NL] ET AL) 23 August 2007 (2007-08-23) paragraphs [0016] - [0018] paragraph [0020]	1-26

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
3 January 2011	11/01/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Loher, Florian

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	REVILL P ET AL: "Paliperidone - Antipsychotic agent, treatment of bipolar disorder, dual dopamine D2/5-HT2A receptor antagonist", DRUGS OF THE FUTURE, PROUS SCIENCE, ES, vol. 31, no. 7, 1 July 2006 (2006-07-01), pages 579-584, XP008096915, ISSN: 0377-8282, DOI: DOI:10.1358/DOF.2006.031.07.1008562 page 580, left-hand column, last paragraph	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/054807

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009080651 A1	02-07-2009	AU 2008340101 A1	02-07-2009
		CN 101932327 A	29-12-2010
		EC SP100289 A	30-07-2010
		EP 2234617 A1	06-10-2010
		KR 20100099292 A	10-09-2010
		US 2009163519 A1	25-06-2009
US 2007197591 A1	23-08-2007	AR 058328 A1	30-01-2008
		UY 30007 A1	30-03-2007

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/054807

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/519 A61P25/18
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/080651 A1 (JANSSEN PHARMACEUTICA NV [BE]; VERMEULEN AN MARGRIET CORNELIA [BE]; WO) 2 July 2009 (2009-07-02) page 9, line 3 - page 9, line 19 example 7 claims 1,4,15 page 17 - page 20	1-26
Y	US 2007/197591 A1 (BOOM SANDRA [NL] ET AL) 23 August 2007 (2007-08-23) paragraphs [0016] - [0018] paragraph [0020]	1-26

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 January 2011	11/01/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Loher, Florian

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	REVILL P ET AL: "Paliperidone - Antipsychotic agent, treatment of bipolar disorder, dual dopamine D2/5-HT2A receptor antagonist", DRUGS OF THE FUTURE, PROUS SCIENCE, ES, vol. 31, no. 7, 1 July 2006 (2006-07-01), pages 579-584, XP008096915, ISSN: 0377-8282, DOI: DOI:10.1358/DOF.2006.031.07.1008562 page 580, left-hand column, last paragraph	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/054807

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009080651 A1	02-07-2009	AU 2008340101 A1	02-07-2009
		CN 101932327 A	29-12-2010
		EC SP100289 A	30-07-2010
		EP 2234617 A1	06-10-2010
		KR 20100099292 A	10-09-2010
		US 2009163519 A1	25-06-2009
US 2007197591 A1	23-08-2007	AR 058328 A1	30-01-2008
		UY 30007 A1	30-03-2007

Electronic Patent Application Fee Transmittal

Application Number:	12337144
Filing Date:	17-Dec-2008
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Filer:	Hal Brent Woodrow/Kristin Miele
Attorney Docket Number:	PRD2901USNP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE - 2nd and Subsequent Request	1820	1	1700	1700
		Total in USD ($)		**1700**

Electronic Acknowledgement Receipt

EFS ID:	16891182
Application Number:	12337144
International Application Number:	
Confirmation Number:	3172
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Customer Number:	27777
Filer:	Hal Brent Woodrow/Kristin Miele
Filer Authorized By:	Hal Brent Woodrow
Attorney Docket Number:	PRD2901USNP
Receipt Date:	18-SEP-2013
Filing Date:	17-DEC-2008
Time Stamp:	16:32:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

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Payment Type	Deposit Account
Payment was successfully received in RAM	$1700
RAM confirmation Number	3829
Deposit Account	100750
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	PRD2901USNP_RCE_09_18_13.pdf	697811 e01bd230277b5b1fa285eb17f5e21013d555548d	no	3
Warnings:					
Information:					
2	Transmittal Letter	PRD2901USNP_SupplIDS_09_18_13.pdf	286076 8def3bcfe8e1b8468ef1f074955ea9f3184fb78a	no	4
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	PRD2901USNP_SupplDS1449_09_18_13.pdf	296187 caad3e81dfb5b76a73e603658661b48d88d26669	no	3
Warnings:					
Information:					
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4	Non Patent Literature	PRD2901USNP_IDS609d_09_18_13.pdf	196702 278f1fadf504e8911d79aeccea4137264caf81e6	no	1
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Information:					
5	Foreign Reference	WO2004010981.pdf	3097418 783ae2d5b35a80e433c814cc66f9f9db8133beb7	no	62
Warnings:					
Information:					
6	Foreign Reference	WO2008021342.pdf	2344059 9132383661f9d486b42b54a2f4a0d386aaf34eba	no	66
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Information:					
7	Foreign Reference	WO2009025859.pdf	1856568 557f6f0a7e443f8a701d5eaf0c1a6508332354ad	no	45
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8	Foreign Reference	WO2009047499.pdf	1473212 8f1389271e235f6a47274ec18270cbc189101143	no	40
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9	Foreign Reference	WO2011053829.pdf	2414575 6b2f77a291a90d2a86980aad114703b2ef0852ba	no	47
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10	Non Patent Literature	Alphs_1_10.pdf	325449 342793e29e17f35e5fba8fae0564632d48f644f7	no	10
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11	Non Patent Literature	Altamura_493.pdf	23871191 c28da38f6cf47c42157f305e32c45246fccaab1c	no	20
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12	Non Patent Literature	Berwaerts_247.pdf	480218 02de8c5dd9b335c3b73495651c9896256ab3ab55	no	12
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13	Non Patent Literature	Canuso.pdf	982565 a7336933824cbc4725448c5bf58e8b4de550eb7c	no	11
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14	Non Patent Literature	Cleton_ClinPharmTher_S31_PI_74.pdf	43926 39e35e6ebd10975f4a708942bcc9f64009fb326b	no	1
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15	Non Patent Literature	Ereshefsky_12.pdf	1194875 2cf429bcb7857ca4b63fc6cd1dd161e9fcda65c5	no	14
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16	Non Patent Literature	Gefvert_27.pdf	115139 0385f50a1542faaad84605d0dd797693a09cac47	no	10
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18	Non Patent Literature	Levron_83.pdf	611339 8e290977ca37010fae4228819ddaab4c8abcb726	no	5
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19	Non Patent Literature	NDA_ApprovalLetter_PP.pdf	262224 a70d16691dbb69b576ca2c9fe6a56f87219e13c2	no	51
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20	Non Patent Literature	sNDA_ApprovalLetter_PP.pdf	275351 46621eb8c4841d0f376860270d86422e6dc9f120	no	54
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21	Non Patent Literature	Markowitz_poster_2011_HI.pdf	294733 3a6bc7eb2ee16284dbef5dea7d4b670a499fe1f4	no	6
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22	Non Patent Literature	Pandina_218.pdf	355125 812f315f8007b0e5748a6cd8ad0b483d94d121f2	no	9
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23	Non Patent Literature	Sheehan_17.pdf	114283 e6f546eacc6fd41c960d541fba9ac46ee1d7404d	no	7
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Information:					
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Information:					
25	Non Patent Literature	PRD3131WOPCT_ISR.pdf	85759 1633ad239de493f1317f85580848adb8b281703b	no	3
Warnings:					
Information:					

26	Other Reference-Patent/App/Search documents	PRD3131USNP_OA_02_28_13.pdf	626474 be9c2e9b7b3509670925b395bc2d7ef6d4305e3f	no	15
Warnings:					
Information:					
27	Non Patent Literature	Mauri_359.pdf	11223598 5a0f22e1214de5f19fa5565a8010e02049ec5e68	no	30
Warnings:					
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28	Fee Worksheet (SB06)	fee-info.pdf	30425 d84088e3d09a41ebffe74114648b2ad9f3c5a92a	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	54190615	

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NOTICE OF ALLOWANCE AND FEE(S) DUE

27777 7590 08/15/2014

BERNARD F. PLANTZ
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER
CLAYTOR, DEIRDRE RENEE

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 08/15/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

TITLE OF INVENTION: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/17/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

27777 7590 08/15/2014
BERNARD F. PLANTZ
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

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12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

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nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/17/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
CLAYTOR, DEIRDRE RENEE	1627	514-257000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 12/337,144	Applicant(s) VERMEULEN ET AL.	
	Examiner Renee Claytor	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the RCE filed on 9/18/2013*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-5,13,15-20,22 and 24*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

The present application is being examined under the pre-AIA first to invent provisions.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/18/2013 has been entered.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: please see the reasons for the Notice of Allowance given on 6/25/2013.

It is noted that Applicants have filed an IDS, which has been considered and no art was found to be relevant to the present invention.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Renee Claytor/
Primary Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	Art Unit
	Renee Claytor	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	257, 323, 360, 379	8/11/2014	RC

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventor Search	8/11/2014	RC
EAST (updated)	8/11/2014	RC

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	257, 323, 360, 379	8/11/2014	RC

PTO/SB/08A (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 3

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear
		2002-0082245		Yelle, William E.	06/27/2002	
		2003-0157180		Francois et al.	08/21/2003	
		2011-0105536		Lewyn-Briscoe et al.	05/05/2011	
		2012-0263795-		Francois et al.	10/18/2012	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Foreign Patent Document Office[3]	Number[4]	KindCode[5]	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document mm-dd-yyyy	Pages, Columns, Lines, where relevant passages or relevant figures appear	T[6]
		WO	2004/010981		ALZA Corporation	02/05/2004		
		WO	2008/021342		Teva Pharmaceutical Industries, LTD.	02/21/2008		
		WO	2009/025859		Teva Pharmaceutical Industries, LTD.	02/26/2009		
		WO	2009/047499		CIPLA Limited	04/16/2009		
		WO	2011/053829		Janssen Pharmaceutica NV	05/05/2011		

Examiner Signature	/Renee Claytor/	Date Considered	08/07/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Unique citation designation number. 2 See attached Kinds of U.S. Patent Documents. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.C./

PTO/SB/08A (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 3

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
		New Drug Application (NDA) dated October 25, 2007 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invega Sustenna (paliperidone palmitate) 39mg, 78mg, 117mg, 156mg, and 234 mg extended-release injectable suspension date of letter is 7/31/2009	
		Supplemental New Drug Application (sNDA) dated March 14, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invega Sustenna (paliperidone palmitate) extended-release injectable suspension, 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg	
		Alphs et al. Annals of General Psychiatry 2011, 10:12	
		Altamura et al., Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. Drugs. 2003; 63(5): 493-512	
		Berwaerts et al., Journal of Affective Disorders 138 (2012) 247–258	
		Canuso et al. 2010, Expert Opinion Pharmacother., Volume 11 (15), pages 2557-2567.	
		Cleton et al., ASSESSMENT OF THE DOSE PROPORTIONALITY OF PALIPERIDONE PALMITATE 25, 50, 100 AND 150 MG EQ., A NEW LONG-ACTING INJECTABLE ANTIPSYCHOTIC FOLLOWING ADMINISTRATION IN THE DELTOID OR GLUTEAL MUSCLES, PI-74, Clinical Pharmacology & Therapeutics, Volume 83, Supplement 1, MARCH 2008, S31	
		Ereshefsky L., Pharmacokinetics and drug interactions: update for new antipsychotics. J Clin Psychiatry. 1996;57 Suppl 11:12-25	
		Gefvert et al. Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Consta) in patients with schizophrenia. Int J Neuropsychopharmacol. 2005; 8(1): 27-36	
		Kane et al., Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. Eur Neuropsychopharmacol. 1998; 8(1): 55-66	
		Levron et al., Clinical pharmacokinetics of haloperidol decanoate. Comparison with other prolonged-action neuroleptics. Encephale. 1987; 13(2): 83-7 [see English Summary as provided]	
		Markowitz et al., "Benefit-Risk Assessment of Maintenance Therapy in Schizophrenia Comparing Long-Acting Injectable (LAI) Paliperidone Palmitate with Paliperidone ER", Presented at the 164th Annual Meeting of the American Psychiatric Association, May 14-18, 2011, Honolulu, HI, USA	

Examiner Signature	/Renee Claytor/	Date Considered	08/07/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.C./

PTO/SB/08A (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 3 of 3

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
		Mauri et al., Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet. 2007;46(5):359-88	
		Pandina et al., Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 218–226	
		Sheehan et al., Comparison of the Peak-to-trough Fluctuation in Plasma Concentration of Long-acting Injectable Antipsychotics and Their Oral Equivalents, *Innov Clin Neurosci*. 2012;9(7–8):17–23	
		Vermeir et al., Absorption, metabolism, and excretion of paliperidone, a new monoaminergic antagonist, in humans. Drug Metab Dispos. 2008 Apr;36(4):769-79	

Examiner Signature	/Renee Claytor/	Date Considered	08/07/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.C./

SUBMISSION UNDER MPEP 609.06 Page 1 of 1	*Application Number*	12/337,144
	Filing Date	12/17/2008
	First Named Inventor	An Vermeulen
	Group Art Unit	1627
	Examiner Name	Claytor, Deirdre
	Attorney Docket Number	PRD2901USNP

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Name of Patentee or Applicant of Cited Document	U.S. Patent Document Number	Kind Code[2] (if known)	Pages, Columns, Lines, where relevant passages or relevant figures appear
		Lewyn-Briscoe et al.	13/903,638 (PRD3131USDIV1)		

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.[1]	Name of Patentee or Applicant of Cited Document	Foreign Patent Document Office[3]	Number[4]	KindCode[5]	Pages, Columns, Lines, where relevant passages or relevant figures appear	T[6]

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITOL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
		International Search Report Re: International Application No.: PCT/US2010/054807 dated January 11, 2011 (PRD3131WOPCT).	
		Office Action mailed February 28, 2013 in US Serial No. 12/916910; Attorney Docket No. PRD3131USNP	

Examiner Signature	/Renee Claytor/	Date Considered	08/07/2014

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.C./

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	RENEE CLAYTOR	1627

CPC						
Symbol					**Type**	**Version**
A61K		31	/	519	F	2013-01-01
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CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	14	
/RENEE CLAYTOR/ Primary Examiner.Art Unit 1627	8/11/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	RENEE CLAYTOR	1627

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
514	257

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	323	360	379		

INTERNATIONAL CLASSIFICATION														
CLAIMED					**NON-CLAIMED**									
C	0	7	D	471 / 04 (2006.01.01)										
A	6	1	K	31 / 445 (2006.01.01)										
A	6	1	K	31 / 41 (2006.01.01)										
A	6	1	K	31 / 42 (2006.01.01)										

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	14	
/RENEE CLAYTOR/ Primary Examiner.Art Unit 1627	8/11/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	RENEE CLAYTOR	1627

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	9	17		33										
2	2	10	18												
3	3	11	19												
4	4	12	20												
5	5		21												
	6	13	22												
	7		23												
	8	14	24												
	9		25												
	10		26												
	11		27												
	12		28												
6	13		29												
	14		30												
7	15		31												
8	16		32												

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	14	
/RENEE CLAYTOR/ Primary Examiner.Art Unit 1627	8/11/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1217	paliperidone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2014/08/11 13:55
L2	187	L1 and @ad<="20071219"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2014/08/11 13:55
L3	50743	schizophren$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2014/08/11 13:55
L4	103	L2 and L3	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2014/08/11 13:55
L5	103	L4	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2014/08/11 13:55
L6	50743	schizophren$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2014/08/11 13:56
L7	103	l5 and L6	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2014/08/11 13:56
S1	414	paliperidone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:00
S2	4	S1 and @ad="20071219"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:01
S3	169	S1 and @ad<="20071219"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:01
S4	37089	schizophren$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:01
S5	93	S3 and S4	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 14:02
S6	9	dosing adj escalation	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 16:24
S7	0	S1 and S6	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 16:24
S8	31	"5254556"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 19:03
S9	19	"6077843"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 19:31
S10	11	"6555544"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/11/29 19:35
S11	20655	psychiatri$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:28
S12	417	paliperidone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:29
S13	139	S12 and S11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:29
S14	14	S11 same S12	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2010/12/03 10:29
S15	895	paliperidone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/06/14 08:53

S16	185	S15 and @ad<="20071219"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/06/14 08:53
S17	46189	schizophren$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/06/14 08:53
S18	102	S16 and S17	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/06/14 08:53
S19	102	S18	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/06/14 08:53

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L8	158	paliperidone	USPAT; UPAD	OR	OFF	2014/08/11 13:58
L9	13509	schizophren$2	USPAT; UPAD	OR	OFF	2014/08/11 13:58
L10	101	l8 and l9	USPAT; UPAD	OR	OFF	2014/08/11 13:58

8/11/2014 1:59:15 PM
H:\EASTBackup\337144.wsp

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12337144	VERMEULEN ET AL.
	Examiner	**Art Unit**
	RENEE CLAYTOR	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/01/2010	12/03/2010	06/28/2011	06/14/2013	08/11/2014				
1	1	÷	✓	✓	=	=				
2	2	÷	✓	✓	=	=				
3	3	÷	✓	✓	=	=				
4	4	÷	✓	✓	=	=				
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	6	÷	✓	✓	-	-				
	7	÷	✓	✓	-	-				
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	10	÷	✓	✓	-	-				
	11	÷	✓	✓	-	-				
	12	÷	N	N	-	-				
6	13	÷	✓	✓	=	=				
	14	÷	N	-	-	-				
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	30	÷	N	N	-	-				
	31	÷	✓	✓	-	-				
	32	÷	N	-	-	-				
	33	÷	✓	✓	-	-				

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12/337,144	Filing Date	2008-12-17	Docket Number (if applicable)	PRD2901USNP	Art Unit	1627
First Named Inventor	An Vermeulen			Examiner Name	Claytor, D. Renee		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 100750

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Hal Brent Woodrow/	Date (YYYY-MM-DD)	2014-11-17
Name	Hal. B. Woodrow	Registration Number	32501

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

CERTIFICATE OF EFS TRANSMISSION		
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via the "Electronic Filing System" in accordance with 37 C.F.R. § 1.6(a)(4).		
Kristin Miele	/Kristin Miele/	November 17, 2014
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: An Vermeulen et al. **Art Unit:** 1627

Serial No.: 12/337,144 **Examiner:** Claytor, D.

Filed: 12/17/2008 **Confirmation Number:** 3172

For: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

Mail Stop: IDS
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir:

This copy is supplemental to the Information Disclosure Statements filed on April 11, 2011, December 12, 2011 and September 18, 2013.

Pursuant to 37 C.F.R. §1.56 and in accordance with 37 C.F.R. §§1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 C.F.R. §1.56(b).

Applicant(s) reserve(s) the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

☒ In accordance with §1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified national application (other than a continued prosecution application under §1.53(d)), within three months of the date of entry into the national stage of the above identified application as set forth in §1.491, or before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of a request for continued examination under §1.114, no additional fee is required.

☐ In accordance with §1.129(a), this Information Disclosure Statement is being filed in connection with ☐ the first or ☐ second After Final Submission, therefore:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☐ Please charge Deposit Account No. 10-0750/ the fee of $180.00 as set forth in §1.17(p).

☐ In accordance with §1.97(c), this Information Disclosure Statement is being filed after the period set forth in §1.97(b) above but before the mailing date of either a Final Action under §1.113 or a Notice of Allowance under §1.311, or an action that otherwise closes prosecution and that it is accompanied by one of:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☐ Please charge Deposit Account No. 10-0750/ the fee of $180.00 as set forth in §1.17(p).

☐ In accordance with §1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under §1.113 or a Notice of Allowance under

§1.311 but before the payment of the Issue Fee. Applicant(s) hereby petition(s) for consideration of this Information Disclosure Statement. Included are: Statement in Accordance with §1.97(e) (attached) and the fee of $180.00 as set forth in §1.17(p).

☐ Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.

☐ Copies of references listed on the attached Form PTO-1449 are enclosed herewith EXCEPT THAT:

- ☐ In view of the voluminous nature of references [list as appropriate], and the likelihood that these references are available to the Examiner, copies are not enclosed herewith.
- ☐ If any of the foregoing publications are not available to the Examiner, Applicant will endeavor to supply copies at the Examiner's request.

☒ Copies of only foreign patent documents and non-patent literature are enclosed in accordance with 37 CFR 1.98 (a)(2).

☐ There are no listed references which are not in the English language.

☒ The relevance of those listed references which are not in the English language is as follows: For YAMADA et al., Future Potentiality of Pharmacotherapy for Schizophrenia in Acute Phase, Clinical Psychopharmacology, Vo. 8, No. 10 (2005), pp.1563-1568, see English translation.

☒ Attached are copies of search report(s) from corresponding patent application(s), which are listed on the attached Submission Under MPEP 609 D.

☐ Attached are the following non-published pending patent applications and/or nonpatent literature which may be deemed relevant, which are listed on the attached Submission Under MPEP 609 D.

Please charge any deficiency or credit any overpayment to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: 17 November 2014

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

PTO/SB/08A (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
		Kazuo YAMADA et al., Future Potentiality of Pharmacotherapy for Schizophrenia in Acute Phase, Clinical Psychopharmacology, Vo. 8, No. 10 (2005), pp.1563-1568	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Electronic Patent Application Fee Transmittal

Application Number:	12337144
Filing Date:	17-Dec-2008
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Filer:	Hal Brent Woodrow/Kristin Miele
Attorney Docket Number:	PRD2901USNP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE - 2nd and Subsequent Request	1820	1	1700	1700
		Total in USD ($)		**1700**

Electronic Acknowledgement Receipt

EFS ID:	20718633
Application Number:	12337144
International Application Number:	
Confirmation Number:	3172
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Customer Number:	27777
Filer:	Hal Brent Woodrow/Kristin Miele
Filer Authorized By:	Hal Brent Woodrow
Attorney Docket Number:	PRD2901USNP
Receipt Date:	17-NOV-2014
Filing Date:	17-DEC-2008
Time Stamp:	16:42:36
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1700
RAM confirmation Number	3555
Deposit Account	100750
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	PRD2901USNP_RCE_11_17_14.pdf	697821 1e86b4af09cfdbb5fd1f5776f003b3dc992f0a1a	no	3
Warnings:					
Information:					
2	Transmittal Letter	PRD2901USNP_SupplIDS_11_17_14.pdf	118130 a6aed7a1b9a25ff476e3a8093237295cbb86b8c6	no	4
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	PRD2901USNP_SuppIDS1449_11_17_14.pdf	150186 ff9ad642a623ee9322ff039cebd739945c08cb28	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Non Patent Literature	Yamada_1563.pdf	1383083 927a3f969c31bc73c36dad126d493d76a4c87042	no	7
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30425 3e48c7673cb0e472b3ef0df53daec7bbb37d081d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2379645		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08A (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Application Number	12/337,144
Filing Date	12/17/2008
First Named Inventor	An Vermeulen
Group Art Unit	1627
Examiner Name	Claytor, Deirdre
Attorney Docket Number	PRD2901USNP

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
		Kazuo YAMADA et al., Future Potentiality of Pharmacotherapy for Schizophrenia in Acute Phase, Clinical Psychopharmacology, Vo. 8, No. 10 (2005), pp.1563-1568	
		Takashi YOSHIO, Sustained-release Antipsychotic Drugs (depot drugs), Psychiatric Nursing, Vol. 33, No.4 (2006), pp.64-67	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Electronic Acknowledgement Receipt

EFS ID:	20882497
Application Number:	12337144
International Application Number:	
Confirmation Number:	3172
Title of Invention:	DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS
First Named Inventor/Applicant Name:	An Vermeulen
Customer Number:	27777
Filer:	Hal Brent Woodrow/Kristin Miele
Filer Authorized By:	Hal Brent Woodrow
Attorney Docket Number:	PRD2901USNP
Receipt Date:	05-DEC-2014
Filing Date:	17-DEC-2008
Time Stamp:	16:40:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	PRD2901USNP_SupplIDS_12_05_14.pdf	118549 395b3581cac965b4d83a0c7eee75555cbdec8aeb	no	4

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	PRD2901USNP_SupplDS1449_12_05_14.pdf	153149 d871c946883252fda16d3b5bd4c99b6e5564169d	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Yamada_1563_FullTrans_JPagent.pdf	458561 afaafbe914b2b89ace0d0e9f2eff53f908d6fc53	no	9
Warnings:					
Information:					
4	Non Patent Literature	Yoshio_FullTrans_JPagent.pdf	352556 f7f89e9e6b4ce500b6df158be000caf9d80e54db	no	8
Warnings:					
Information:					
		Total Files Size (in bytes):	1082815		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
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CERTIFICATE OF EFS TRANSMISSION		
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted to the United States Patent and Trademark Office on the date shown below via the "Electronic Filing System" in accordance with 37 C.F.R. § 1.6(a)(4).		
Kristin Miele	/Kristin Miele/	December 5, 2014
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: An Vermeulen et al. **Art Unit:** 1627

Serial No.: 12/337,144 **Examiner:** Claytor, D.

Filed: 12/17/2008 **Confirmation Number:** 3172

For: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

Mail Stop: IDS
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Dear Sir:

This copy is supplemental to the Information Disclosure Statements filed on April 11, 2011, December 12, 2011, September 18, 2013 and November 17, 2014.

Pursuant to 37 C.F.R. §1.56 and in accordance with 37 C.F.R. §§1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 C.F.R. §1.56(b).

Applicant(s) reserve(s) the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

☒ In accordance with §1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified national application (other than a continued prosecution application under §1.53(d)), within three months of the date of entry into the national stage of the above identified application as set forth in §1.491, or before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of a request for continued examination under §1.114, no additional fee is required.

☐ In accordance with §1.129(a), this Information Disclosure Statement is being filed in connection with ☐ the first or ☐ second After Final Submission, therefore:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☐ Please charge Deposit Account No. 10-0750/ the fee of $180.00 as set forth in §1.17(p).

☐ In accordance with §1.97(c), this Information Disclosure Statement is being filed after the period set forth in §1.97(b) above but before the mailing date of either a Final Action under §1.113 or a Notice of Allowance under §1.311, or an action that otherwise closes prosecution and that it is accompanied by one of:

- ☐ Statement in Accordance with §1.97(e) (attached); or
- ☐ Please charge Deposit Account No. 10-0750/ the fee of $180.00 as set forth in §1.17(p).

☐ In accordance with §1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under §1.113 or a Notice of Allowance under

§1.311 but before the payment of the Issue Fee. Applicant(s) hereby petition(s) for consideration of this Information Disclosure Statement. Included are: Statement in Accordance with §1.97(e) (attached) and the fee of $180.00 as set forth in §1.17(p).

☐ Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.

☐ Copies of references listed on the attached Form PTO-1449 are enclosed herewith EXCEPT THAT:

- ☐ In view of the voluminous nature of references [list as appropriate], and the likelihood that these references are available to the Examiner, copies are not enclosed herewith.
- ☐ If any of the foregoing publications are not available to the Examiner, Applicant will endeavor to supply copies at the Examiner's request.

☒ Copies of only foreign patent documents and non-patent literature are enclosed in accordance with 37 CFR 1.98 (a)(2).

☐ There are no listed references which are not in the English language.

☒ The relevance of those listed references which are not in the English language is as follows: For Takashi YOSHIO, Sustained-release Antipsychotic Drugs (depot drugs), Psychiatric Nursing, Vol. 33, No.4 (2006), pp.64-67, see English translation; and for Kazuo YAMADA et al., Future Potentiality of Pharmacotherapy for Schizophrenia in Acute Phase, Clinical Psychopharmacology, Vo. 8, No. 10 (2005), pp.1563-1568, see full English translation.

☐ Attached are copies of search report(s) from corresponding patent application(s), which are listed on the attached Submission Under MPEP 609 D.

☐ Attached are the following non-published pending patent applications and/or nonpatent literature which may be deemed relevant, which are listed on the attached Submission Under MPEP 609 D.

Please charge any deficiency or credit any overpayment to Deposit Account No. 10-0750/PRD2901USNP/HBW.

Respectfully submitted,

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
Phone: (732) 524-2976
Dated: 5 December 2014

By: /Hal Brent Woodrow/
Hal B. Woodrow, Reg. No. 32,501

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NOTICE OF ALLOWANCE AND FEE(S) DUE

27777 7590 03/13/2015

BERNARD F. PLANTZ
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER
CLAYTOR, DEIRDRE RENEE

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 03/13/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

TITLE OF INVENTION: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/15/2015

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

27777 7590 03/13/2015
BERNARD F. PLANTZ
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/337,144	12/17/2008	An Vermeulen	PRD2901USNP	3172

TITLE OF INVENTION: DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/15/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
CLAYTOR, DEIRDRE RENEE	1627	514-257000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____