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(54) Title: LONG ACTING DEPOT FORMULATION FOR THE CONTINUOUS DOPAMINERGIC STIMULATION

(57) Abstract: A pharmaceutical long acting depot composition is provided for the treatment of Parkinson's disease. The formulation comprises a therapeutically effective amount of rotigotine or its pharmaceutically acceptable derivative and pharmaceutically acceptable excipients. The process of preparation of the formulation is also provided.



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“LONG ACTING DEPOT FORMULATION FOR THE CONTINUOUS DOPAMINERGIC STIMULATION”

CROSS REFERENCE TO RELATED APPLICATIONS:

This application claims priority to co-pending Indian Provisional Patent Application Serial Number 201621040062 filed on November 23, 2016. This application is incorporated herein by reference, in its entirety.

FIELD OF THE INVENTION:

The present invention relates to long-acting depot formulation of dopamine receptor agonists, in particular to aqueous depot suspension, lipid coated aqueous depot suspensions, methods for preparing them and methods of using these long-acting depot pharmaceuticals for the treatment of Parkinson's disease.

BACKGROUND OF THE INVENTION::

Rotigotine is the active ingredient in the product sold as NEUPRO[®] transdermal patch by UCB, Inc. and is available in six strengths of 1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours of Rotigotine. Each patch contains a) a flexible, tan-colored backing film, consisting of an aluminized polyester film coated with a pigment-layer on the outer side. The backing provides structural support and protection of the drug-loaded adhesive layer from the environment b) a self-adhesive drug matrix layer, consisting of the active component rotigotine and the following inactive components: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol c) a protective liner, consisting of a transparent fluoropolymer-coated polyester film. This liner protects the adhesive layer during storage and is removed just prior to application. NEUPRO[®] is indicated for the treatment of Parkinson's disease and Restless Legs Syndrome.

One of the difficulties with the commercially available formulation is that transdermal absorption of rotigotine is affected by low permeability of skin and thus

has low absorption, low bioavailability and exhibits great individual difference limiting therapeutic effects especially for advanced Parkinson's disease patients. During clinical trials, it has been observed that there is an adverse effect of skin reactions at the application site reported with both the rotigotine transdermal patch and placebo patch. Hence because of these site reactions, currently patches are not applied at the same site for more than once every 14 days. Currently transdermal patch is applied once daily. However, considering the age of the patients undergoing treatment it is less convenient and poses problems of adherence to treatment and patient incompliance. These transdermal patches also give discontinuous or pulsatile stimulation of dopamine receptors which in turn lead to onset of drug related motor complications.

Continuous dopaminergic stimulation is a therapeutic concept for the management of Parkinson's disease (PD) that proposes continuous as opposed to discontinuous or pulsatile stimulation of striatal dopamine receptors will delay or prevent the onset of levodopa-related motor complications. This hypothesis has arisen from studies of the normal basal ganglia demonstrating that nigral dopaminergic neurons normally fire continuously and striatal dopamine levels are relatively constant.

U.S. Patent No. 8604076 discloses a method for producing an injectable pharmaceutical composition, comprising preparing an oily suspension of solid-phase rotigotine or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable hydrophobic liquid phase that comprises a wetting agent free of phosphatides; and thermally treating said oily suspension to provide a sterile depot suspension of said rotigotine or salt thereof.

U.S. Patent No. 8691277 discloses long-acting sustained-release dosage forms of dopamine receptor agonists, in particular to injectable sustained-release microspheres, implants and injectable gels of dopaminergic drugs and methods for preparing them, and to methods of using these compounds for the manufacture of long-acting sustained release pharmaceuticals of rotigotine and its salts, especially

microspheres, for the treatment or adjunctive therapy of dopamine receptor associated diseases, and for the treatment of Parkinson diseases.

U.S. Patent No. 9265835 discloses a composition comprising rotigotine or a pharmaceutically acceptable salt thereof; at least one poly(lactide-co-glycolide) (PLGA); and at least one fatty acid, wherein the rotigotine or a pharmaceutically acceptable salt thereof is about 20-40% in weight relative to the total weight of the composition, and wherein the at least one fatty acid is about 1-15% in weight relative to the total weight of the composition, wherein the composition is in the form of microspheres. The composition can be administered by intramuscular injection, subcutaneous injection, intradermal injection, intraperitoneal injection, etc.

U.S. Patent No. 7309497 discloses an injectable pharmaceutical composition comprising at least one pharmacologically active agent in its solid phase; a vehicle essentially consisting of polyol fatty acid esters with an esterification level of over 80%; and a wetting agent comprising polyol fatty acid esters with a monoester content of over 60%, wherein the active agent is an antiparkinsonian agent which is released in the body from the injectable pharmaceutical composition in a therapeutically effective amount over a time period of at least 24 hours.

EP Patent No. 2642993 provides a composition comprising rotigotine or a pharmaceutically acceptable salt thereof; at least one poly(lactide-co-glycolide) (PLGA); and at least one fatty acid, wherein the at least one fatty acid is at least 0.5% in weight relative to the total weight of the composition. The composition as disclosed herein has significantly reduced burst release effect. The disclosure also provides a method of treating Parkinson's disease comprising administering an effective amount of the composition as disclosed to a subject in need thereof.

CN patent No. 1762495 discloses a microsphere formulation comprising rotigotine and degradable polymer auxiliary materials. The rotigotine microsphere

formulation as disclosed in CN1762495A may achieve the effect of long-acting sustained release, but a problem of burst release may occur.

U.S. Patent application No. 2014/0255488 relates to a long-acting sustained-release dosage form for treatment of Parkinson Disease, comprising a dopamine receptor agonist (Rotigotine and salts) and a pharmaceutically acceptable biodegradable polymer accessories, wherein the content of the dopamine receptor agonist in the sustained-release dosage form is 5-50% by weight, and the content of the pharmaceutically acceptable polymer accessories is 50-95% by weight.

Although attempts have been made in the prior art to overcome the problems associated with the oral and transdermal dosage form of rotigotine as well as to overcome the problems associated with patient compliance and discontinuous stimulation of dopamine receptors there is still a need to provide improved pharmaceutical compositions, especially those that allow for continuous dopaminergic stimulation which will ultimately delay or prevent the onset of drug-related motor complications, have long duration of action, less frequency of dosage administration and provide optimum release profile of rotigotine with enhanced bioavailability. These long acting depot formulation of dopamine receptor agonist can maintain a stable release rate for several weeks, several months or longer so as to avoid the above-described drawbacks of both transdermal and oral administration such as poor bioavailability, high frequency of administration, possible toxicity and inadequate individualizable dosing. Aqueous depot suspension of rotigotine and lipid coated aqueous depot suspension rotigotine can address the problems of application site reaction, fluctuating drug concentration and will provide continuous dopaminergic stimulation prolonging the duration of action and thus improving patient compliance.

OBJECT OF THE INVENTION:

The object of the present invention is to provide a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative having improved systemic absorption.

Another object of the present invention is to provide a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative in the dosage form of an aqueous depot suspension injection or lipid coated aqueous depot suspension injection.

Another object of the present invention is to provide a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative in an aqueous depot suspension injection or lipid coated aqueous depot suspension injection wherein the particle size of the drug is about 0.5 -100 μm

Another object of the present invention is to provide a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative in an aqueous depot suspension injection or lipid coated aqueous depot suspension injection wherein the dose of rotigotine is 10 mg- 300 mg.

Yet another object of the present invention is to provide a long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative in an aqueous depot suspension injection or lipid coated aqueous depot suspension injection wherein the said formulation is administered subcutaneously/ intramuscularly about monthly or bimonthly in an injection volume of 0.5 ml to 2.5 ml in a prefilled syringe.

Yet another object of the present invention is to provide a method for treatment of Parkinson's disease by continuous dopaminergic stimulation for prolonged time, the said method comprises administering a pharmaceutical long-acting depot composition comprising rotigotine in an aqueous depot suspension injection or lipid coated aqueous depot suspension injection.

Yet another object of the present invention is to provide the use of a pharmaceutical long-acting depot composition comprising rotigotine in an aqueous depot

suspension injection or lipid coated aqueous depot suspension injection for the treatment of Parkinson's disease by continuous dopaminergic stimulation for prolonged time.

SUMMARY OF THE INVENTION:

According to an aspect of the present invention, there is provided a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative having improved systemic absorption.

According to another aspect of the invention, there is provided a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative in aqueous depot suspension injection or lipid coated aqueous depot suspension injection.

According to another aspect of the invention, there is provided a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative in an aqueous depot suspension injection or lipid coated aqueous depot suspension injection wherein the particle size of the drug is about 0.5 -100 μm .

According to yet another aspect of the invention, there is provided a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative in an aqueous depot suspension injection or lipid coated aqueous depot suspension injection wherein the dose of rotigotine or its pharmaceutically acceptable derivative is 10 mg to 300 mg.

According to yet another aspect of the invention, there is provided a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative in an aqueous depot suspension injection or lipid coated aqueous depot suspension injection wherein the said composition is administered

subcutaneously/intramuscularly about monthly or bimonthly in an injection volume of 0.5 ml to 2.5 ml in a prefilled syringe.

According to yet another aspect of the invention, there is provided a method for treatment of Parkinson's disease, the said method comprises administering a pharmaceutical long-acting depot composition comprising rotigotine in an aqueous depot suspension injection or lipid coated aqueous depot suspension injection by continuous dopaminergic stimulation for prolonged time.

According to yet another aspect of the invention, there is provided the use of a pharmaceutical long-acting depot composition comprising rotigotine or its pharmaceutically acceptable derivative in an aqueous depot suspension injection or lipid coated aqueous depot suspension injection for the treatment of Parkinson's disease by continuous dopaminergic stimulation for prolonged time

BRIEF DESCRIPTION OF THE FIGURES:

Fig 1: In-vitro drug release profile of formulation in example 1 in phosphate buffer at pH 4.5

Fig 2: In-vitro drug release profile of formulation in example 2 in phosphate buffer at pH 4.5

Fig. 3: In-vitro drug release profile of formulation in example 6 in phosphate buffer at pH 4.5

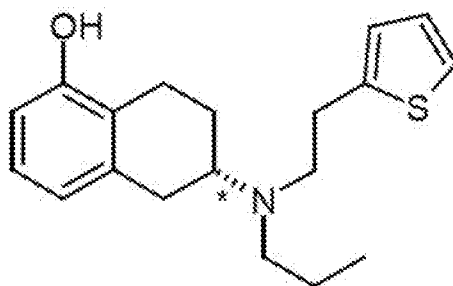
Fig.4: In-vivo release profile of formulation of example 1

Fig. 5: In-vivo release profile of formulation of example 2

DETAILED DESCRIPTION OF THE INVENTION::

Aspects of the present application relate to pharmaceutical compositions comprising rotigotine, or its pharmaceutically acceptable derivatives thereof, in the form of an aqueous depot suspension injection or lipid coated aqueous depot suspension injection.

The drug compound "Rotigotine" has a chemical name (6S)-6-{propyl [2-(2-thienyl) ethyl] amino}-5,6,7,8-tetrahydro-1-naphthalenol and its structural formula is shown below



Rotigotine has the molecular formula of $C_{19}H_{25}NOS$ and has molecular weight of 315.48. Rotigotine is a white to off-white powder. Its water solubility and lipophilicity are pH dependent: at neutral pH it is poorly water-soluble and lipophilic (neutral form) and at more acidic pH rotigotine's water solubility increases and its lipophilicity decreases (protonated form). It contains one chiral centre and it is synthesised solely as the S-isomer. No polymorphism has been observed during development. Rotigotine appears to be sensitive to oxidation and it is not hygroscopic.

Rotigotine is a potent and selective dopamine D2 agonist playing a significant role in the treatment of all diseases associated with a dopamine-related metabolic disorder such as Parkinson's disease and Restless Leg syndrome. It was found, however, that due to a distinct first-pass effect the bioavailability after oral administration is merely about 0.5% (Swart and Zeeuw, *Pharmazie* 47 (1992) 613), ruling out oral administration of N-0923 (Rotigotine).

The term "Rotigotine" is used in broad sense to include not only "Rotigotine" *per se* but also its pharmaceutically acceptable derivatives thereof. Suitable pharmaceutically acceptable derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable anhydrides, pharmaceutically acceptable enantiomers,

pharmaceutically acceptable esters, pharmaceutically acceptable isomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc.

In some embodiments, the dose of rotigotine ranges from about 1 mg to about 10 mg per day. In an embodiment, the typical recommended monthly dosage regimen ranges from about 10 mg to about 300 mg.

Preferably, rotigotine may be administered to the subject in need thereof once a month or bimonthly.

In an embodiment, the amount of rotigotine in the composition of present invention is about 10 mg to about 300 mg. In preferred embodiment, the amount of rotigotine in composition of present invention is about 25 mg to about 200 mg.

The term "therapeutically effective amount" or "effective amount" is such that when administered, the pharmaceutical composition results in the inhibition of the systemic infection. The dosage administered to a patient can be as single or multiple doses depending upon a variety of factors, including the drug's administered pharmacokinetic properties, the route of administration, patient conditions and characteristics (sex, age, body weight, health, size, etc.), and extent of symptoms, concurrent treatments, frequency of treatment and the effect desired.

The term "treatment" or "treating" of a disease, virus or condition refers to executing a protocol that may include administering one or more drugs to a patient, in an effort to alleviate signs or symptoms of the disease, virus or condition. Alleviation can occur prior to signs or symptoms of the disease, virus or condition appearing, as well as after their appearance. Thus, treating or treatment includes reducing, preventing or prevention of the disease, virus or condition. In addition, treating or treatment does not require complete alleviation of signs or symptoms,

does not require a cure, and specifically includes protocols that have only a marginal effect on the patient.

The term “reduced initial burst release” as per the present invention means the reduction in release of active ingredient from the dosage form at initial time points. The release of active ingredient in first hour according to the present invention is less than 35% and preferably less than 30%. The formulations of the present invention are preferably injectable preparations. Injectable formulations of the present invention are typically formulated as aqueous suspensions. Sterile injectable formulations can be prepared according to techniques known in the art using suitable carriers, excipients, dispersing or wetting agents, and suspending agents. The injectable formulations may be sterile injectable suspensions in a nontoxic, parenterally acceptable diluent or solvent. Among the acceptable vehicles and diluents or solvents that may be employed are water for injection, isotonic dextrose solution, Ringer's solution, isotonic sodium chloride solution, and suitable aqueous solvents and the like useful and safe for parenteral administration. In addition, sterile fixed oils or fatty esters are conventionally employed as solvents or suspending media.

The compositions of the present application are particularly suited for use in parenteral administration, but it will be understood that the solutions may have alternative uses. Injectable formulations may be administered via any route including intramuscular or subcutaneous.

It is known that water-soluble drugs are readily injectable. However, water-insoluble drugs such as rotigotine are not readily injectable and thus for such drugs, the preparation of injectable formulations represents a substantial problem. The Pharmacopeia contains many examples of water-insoluble drugs which must be taken orally because no adequate injectable form exists for them. It's been a challenge to design and deliver water insoluble drugs as injectable dosage form that too in depot form. Present art is limited in terms of the drug concentration and total volume which can be injected. Its application is limited by problems of local

irritation, tissue destruction, etc. (in IM injection) and thrombophlebitis, thromboembolism, pulmonary capillary blockage, etc. (in IV injection). Water-insoluble drugs are rendered injectable by formulation as aqueous suspensions or aqueous suspensions of phospholipid-coated microcrystals. The crystalline drug is reduced to 50 nm to 100 μ m dimensions by sonication or other processes inducing high shear in the presence of phospholipid or other membrane-forming amphipathic lipid. The membrane-forming lipid stabilizes the microcrystal by both hydrophobic and hydrophilic interactions, coating and enveloping it and thus protecting it from coalescence, and rendering the drug substance in solid form less irritating to tissue. Various methods have been used and proposed for the sustained release of biologically active agents. Such methods include slow-release, orally administered compositions, such as coated tablets, formulations designed for gradual absorption, such as transdermal patches, and slow-release implants such as "sticks" implanted under the skin. One method by which the gradual release of a bioactive agent has been proposed is a so-called "depot" injection. In this method, a bioactive agent is formulated with carriers providing a gradual release of active agent over a period of a number of hours or days or months. These are often based upon a degrading matrix which gradually disperses in the body to release the active agent.

A depot formulation is specially formulated to provide slow absorption of the drug from the site of administration, often keeping therapeutic levels of the drug in the patient's system for days or weeks at a time. Alternatively, a depot formulation may provide convenience for a patient in need of chronic medication. By delivering drug without exposure to the GI tract, the potential issue of drug degradation is avoided. Moreover, a depot formulation may provide better compliance due to the infrequent dosing regimen and convenience. Additional characteristics of a depot formulation that will enhance patient compliance are good local tolerance at the injection site and ease of administration. Good local tolerance means minimal irritation and inflammation at the site of injection; ease of administration refers to the size of needle and length of time required to administer a dose of a particular drug formulation.

In embodiment, the present invention provides parenteral pharmaceutical long acting depot compositions of rotigotine in an aqueous suspension.

In some embodiments, the formulation is an aqueous based suspension formulation and the size distribution of the rotigotine particles has a d_{10} of about 0.5micron to about 10.0 micron, d_{50} of about 1 micron to about 40 microns and d_{90} of about 20 microns to about 100 microns. In other embodiments, the size distribution of the rotigotine particles in the formulation has a d_{10} of about 1 micron to about 5 microns, d_{50} of about 5 microns to about 30 microns and d_{90} of about 40 microns to about 80 microns. Without being bound to any theory, it is believed that decrease in particle size of rotigotine will decrease the initial burst release of rotigotine from the formulation.

In another embodiment, aqueous compositions according to the present invention further comprise a wetting agent or suspending agent, matrix forming agent, viscosity enhancing agent and optionally one or more of a preservative, a buffer and an isotonicizing 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 isotonicizing agent.

The wetting agent or suspending agent are present in the present invention to ensure complete wetting of the microparticles by the injection vehicle. Suitable wetting agents or suspending 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 Preferred wetting agents include polysorbate 20 (Tween 20), polysorbate 40 (Tween 40), and polysorbate 80 (Tween 80). Other suspending agents suitable for use include various polymers, low molecular weight oligomers, natural products, and surfactants, including nonionic and ionic surfactants, such as cetyl pyridinium chloride, gelatin, casein, lecithin

(phosphatides), dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol 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[®] such as e.g., Tween 20[®] and Tween 80[®] (ICI Specialty Chemicals)); polyethylene glycols (e.g., Carbowaxs 3350[®] and 1450[®], and Carbopol 934[®] (Union Carbide)), dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses (e.g., HPC, HPC-SL, and HPC-L), methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronic F68[®] and F108[®], which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic 908[®], also known as Poloxamine 908[®], which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); a charged phospholipid such as dimyristoyl phosphatidyl glycerol, dioctylsulfosuccinate (DOSS); Tetronic 1508[®] (T-1508) (BASF Wyandotte Corporation), dialkylesters of sodium sulfosuccinic acid (e.g., Aerosol OT[®], which is a dioctyl ester of sodium sulfosuccinic acid (American Cyanamid)); Duponol P[®], which is a sodium lauryl sulfate (DuPont); Tritons X-200[®], which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-1100, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-10G[®] or Surfactant 10-G[®] (Olin Chemicals, Stamford, Conn.); Crodestas SL-40[®] (Croda, Inc.); and SA9OHCO, which is C₁₈H₃₇CH₂(CON(CH₃))—CH₂(CHOH)4(CH₂OH)₂ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-

glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; and the like.

Most of these suspending agents are known pharmaceutical excipients and 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 Society of Great Britain (The Pharmaceutical Press, 1986), specifically incorporated by reference. The suspending agents are commercially available and/or can be prepared by techniques known in the art.

The suspending agent or wetting agent will be present in an amount within the range from about 0.2 to about 10 % by weight, preferably for about 0.5 to about 5 % by weight based on the total weight of the sterile injectable formulation. Preferably, the amount of wetting agent or suspending agent in present invention are from 1 mg to 10 mg of the total formulation.

The injection vehicle may comprise a matrix forming agent. A preferred matrix forming agent is polyethylene glycol, sodium carboxymethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, hydroxypropylethyl cellulose, hydroxypropylmethyl cellulose, polyethylene glycols, polyoxyethylene and polyoxy-propylene ethers and polyvinylpyrrolidone, with sodium carboxymethyl cellulose and polyvinylpyrrolidone being preferred, although other suitable matrix forming agents may also be used.

The injection vehicle may also comprise a viscosity enhancing agent that increases the viscosity of the injection vehicle. A preferred density enhancing agent is sorbitol, glycerine, propylene glycol and such other solvents may also be used.

The injection vehicle may also comprise a tonicity adjusting agent to adjust the tonicity to preclude toxicity problems and improve biocompatibility. A preferred tonicity adjusting agent is sodium chloride, although other suitable tonicity adjusting agents may also be used.

Pharmaceutically acceptable preservatives are antimicrobials and anti-oxidants used in the present invention can be selected from the group consisting of benzyl alcohol, methyl paraben, propyl paraben benzoic acid, butylated hydroxyanisole, butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl- γ -piccolinium chloride, phenylmercuric acetate and thimerosal. In particular, it is benzyl alcohol which can be used in a concentration up to 2% (w/v), preferably up to 1.5% (w/v). In some preferred embodiment, methyl paraben and propyl paraben are also used in an amount of about 0.01% to about 1.0 %.

Suitable buffering agents used in present invention are salt of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to pH 8.5), preferably in the pH range of 7 to 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.

Pharmaceutically acceptable isotonicizing agents used in present invention are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. The suspensions conveniently comprise from 1 to 10 % (w/v) isotonicizing agent. Preferably, mannitol is used in a concentration from 2 to 7 %, more preferably about 5 %. Most 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 addition, electrolytes have the further advantage of buffering

the aqueous suspension. 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)) for rendering the solution isotonic, neutral and less prone to flocculation of the suspended ester therein.

Suitable vehicle used in present invention are water for injection, mixture of glycerine and water for injection.

One preferred injection vehicle of the present invention is an aqueous injection vehicle that comprises 0.2% polysorbate 80, 3% PEG3350, 1% benzyl alcohol, 0.9% sodium chloride and water for injection.

One preferred injection vehicle is an aqueous injection vehicle that comprises 1.5% sodium carboxymethyl cellulose, 30 % sorbitol, and 0.2 % polysorbate 20. Another preferred injection vehicle is an aqueous injection vehicle that comprises 0.2 % polysorbate 80, 3% PEG 3350, 1% sodium carboxymethyl cellulose, 0.015% methyl paraben and propyl paraben and 0.9% sodium chloride.

In yet another embodiment, the present invention provides parenteral pharmaceutical long-acting depot compositions of rotigotine in a lipid coated aqueous suspension.

In another embodiment, the invention provides a pharmaceutical composition comprising rotigotine, lipid carrier/ coat, complexing agent, one or more stabilizer, along with the excipients selected from wetting agent or suspending agent and matrix forming agent and optionally one or more of a preservative, a buffer and an isotonicizing agent as discussed above. 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 isotonicizing agent.

In an embodiment, the pharmaceutical composition of the present invention comprise aqueous solvent systems, or suitable mixtures thereof.

In some embodiments, the pharmaceutically acceptable lipid based carrier system comprise of physiological lipids such as phospholipids, cholesterol, cholesterol esters and triglycerides. Lipid carriers owing to the biological origin of the carrier material offer a number of advantages making it an ideal drug delivery vehicle.

Pharmaceutically acceptable lipid carriers may be selected from Lecithin (phosphatidyl choline), Sphingomyelin, Synthetic zwitterionic phospholipids or phospholipid analogues, Phosphatidic acid, Phosphatidyl serine, Phosphatidyl inositol, Cardiolipin (diphosphatidyl glycerol), Phosphatidyl glycerol, Phosphatidyl ethanolamine, Semi-lipoidal molecules can be incorporated into the phospholipid or glycerol lipid membrane and change the surface activity of the microdroplet. Molecules included in this class are the following: Stearylamine or other long-chained alkyl amines which can be primary, secondary, tertiary or quaternary substituted. These give the microcrystal coating a positive charge and make them more reactive with cell membranes. Membrane-active agents, glycolipids and glycoproteins to modify surface properties. Examples of membrane-active agents include nystatin, amphotericin B and gramicidin which are surface-active antibiotics. Mono-glycerides, these are not phospholipids, but they have been shown capable of forming oriented monolayers and bilayers in the presence of decane (Benz et al. Biochim. Biophys. Acta 394:323-334, 1975). Examples of these lipids include, but are not limited to, the following:

1-monopalmitoyl-(rac)-glycerol (Monopalmitin), 1-monocapryloyl-(rac)-glycerol (Monocaprylin) 1-monooleoyl-(rac)-glycerol (C18:1, cis-9) (Monoolein)

1-monostearyl-(rac)-glycerol (Monostearin)

Commercially available Membrane-Forming Lipids: Several forms of lecithin are contemplated. As an example, egg lecithin (Sigma Chemical Co.) is used in all of the presented examples. It is preferred for its low price and low degree of unsaturation. Lecithin is also available from bovine heart. Soy bean lecithin is less

expensive. It has a higher degree of unsaturation. Several synthetic varieties of lecithin are available which differ in chain length from 4 to 19 carbons (Supelco, Inc.). It is believed that lecithins with chain lengths in the biological range (10-18) are useful in various applications. Unsaturated lecithins (dioleoyl, dilinoleoyl; beta oleoyl; alpha-palmito beta oleoyl; alpha palmitoyl beta linoleoyl and alpha oleoyl beta palmitoyl) are also available. Diarachidonyl lecithin (highly unsaturated and a prostaglandin precursor) is also available.

Phosphatidic acid is available from egg or as synthetic compounds (dimyristoyl, dipalmitoyl or distearoyl, Calbiochem). Bovine phosphatidyl serine is available (Supelco or Calbiochem).

Phosphatidyl inositol is available from plant (Supelco) or bovine (Calbiochem) sources. Cardiolipin is available (Supelco) from bovine or bacterial sources. Phosphatidyl glycerol is available from bacterial (Supelco) sources or as synthetic compounds (dimyristoyl or dipalmitoyl; Calbiochem).

Phosphatidyl ethanolamine is available as egg, bacterial, bovine or plasmalogen (Supelco) or as synthetic compounds dioctadecanoyl and dioleoyl analogues and dihexadecyl, dilauryl, dimyristoyl and dipalmitoyl (Supelco and Calbiochem).

Monoglycerides are available from Sigma Chemical Co. (1-monopalmitoyl-(rac)-glycerol, monopalmitin; 1-monocapryloyl-(rac)-glycerol, monocaprylin; 1-monooleoyl-(rac)-glycerol (C18:1, cis-9), monoolein; 1-monostearyl-(rac)-glycerol, monostearin).

The solvents used to dissolve the lipid component of the present invention are non-polar solvents such as dichloromethane.

One preferred injection vehicle is a pharmaceutical lipid coated aqueous injection formulation that comprises about 140mg egg yolk lecithin, dichloromethane and water for injection.

The pharmacokinetic properties of the aqueous suspensions according to the present invention further may depend to a limited extent on the physico-chemical properties of the drug, such as the particle size and crystal form.

A particularly desirable feature for an injectable depot composition 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 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 21 G 11/2, 26 G 1, 22 G 2 or 22 G 11/4 needle).

In some embodiments, methods used for preparation of the present invention may be selected from high sheer homogenization, Ultrasonication /high speed homogenization, solvent emulsification/evaporation etc. A preferred method is high sheer homogenization. In another embodiment, the method used for particle size reduction of rotigotine of present invention may be selected from sonication, cryomilling or other processes inducing high shear in the presence of phospholipid or other membrane-forming amphipathic lipid. A preferred method is cryomilling for particle size reduction of rotigotine.

In some embodiments, the pharmaceutical long-acting depot composition in the form of an aqueous suspension or lipid coated aqueous suspension of rotigotine is supplied in an injection volume of 0.5 ml to 2.5 ml in a prefilled syringe.

A person skilled in the art for preparing formulations according to the present invention will understand that the proportions of components with respect to each other will vary depending on the specific components used. For example, the use of different solubilizers and stabilizers will require some straightforward modifications to the proportions, depending on the compatibility and miscibility of a particular stabilizer in a particular vehicle.

In embodiments, the excipients for the present invention may be selected from but not limited to the range of pharmaceutically acceptable excipients, which are soluble in the aqueous solvent system and which are also compatible with the active ingredient. The excipients selected for the purpose of the present invention should not create any degenerative effect on the active ingredient such as Rotigotine.

The following example is for the purpose of illustration of the invention only and is not intended in any way to limit the scope of the present invention.

Approach 1: Aqueous depot suspension

Example 1: Rotigotine aqueous depot formulation

Table 1: Composition of Rotigotine aqueous depot formulation

S. No.	Ingredient	Quantity (%w/v)
1.	Rotigotine	1-10%
2.	PEG 3350	1- 5%
3.	Polysorbate 80	(0.1%-2%)
4.	Sodium chloride	0.8-1.0%
5.	Benzyl alcohol	0.5- 1.5%
6.	NaOH/HCl	pH 3-7
7.	Water for Injection (WFI)	q. s. 1 mL

Process:

1. Water for injection was heated to 90-95°C.
2. Polylobate 80 and benzyl alcohol were dissolved in sufficient quantity of water on magnetic stirrer.
3. PEG3350 was added to the above step while stirring.
4. Sodium chloride was added to the above solution while stirring.
5. Pre-micronized Rotigotine (particle size about $d_{90} = 80\mu\text{m}$) was added to the above solution and stirred.
6. The pH was adjusted with NaOH/ HCl and volume was made up with required quantity of water for injection.
7. Above suspension of step 6 was homogenized using in line homogenizer/Ultraturrex before dispensing.

In-vitro dissolution study: The in-vitro dissolution release profile of formulation of example 1 was studied in phosphate buffer pH 4.5 at 37°C. The data is tabulated as under in table 2 and represented in Fig. 1.

Table 2: In-vitro dissolution profile of formulation of example 1

Time (in mins)	% drug release (SD)
10	28 (± 8)
30	47(± 14)
60	56(± 17)
120	60(± 20)
360	62(± 21)
720	62(± 20)

Conclusion: The release of drug from formulation of example 1 was for longer period.

Example 2: Rotigotine aqueous depot formulation**Table 3: Composition of Rotigotine aqueous depot formulation**

S. No.	Ingredient	Quantity (%w/v)
1.	Rotigotine	1-10%
2.	PEG 3350	1-5%
3.	Polysorbate 80	0.1%-2%
4.	Sodium chloride	0.8-1.0%
5.	Benzyl alcohol	0.5- 1.5%
6.	NaOH/HCl	pH 3-7
7.	Water for Injection (WFI)	q. s. 1 mL

Process:

1. Rotigotine was cryomilled to obtain the reduced particle size to around $d_{90} = 40 \mu\text{m}$.
2. Water for injection was heated to 90-95°C.
3. Polysorbate 80 and benzyl alcohol were dissolved in sufficient quantity of water on magnetic stirrer.
4. PEG3350 was added to the above step while stirring.
5. Sodium chloride was added to the above solution while stirring.
6. Pre-micronized Rotigotine (particle size about $d_{90} = 80 \mu\text{m}$) was added to the above solution and stirred.
7. The pH was adjusted with NaOH/ HCl and volume was made up with required quantity of water for injection.
8. Above suspension of step 7 was homogenized using in line homogenizer/Ultraturrex before dispensing.

Observation:

In-vitro dissolution study: The in-vitro dissolution release profile of formulation of example 2 was studied in phosphate buffer pH 4.5 at 37°C. The data is tabulated as under in table 4 and represented in Fig.2.

Table 4: Invitro dissolution profile of formulation of example 2

Time (in mins)	% drug release (SD)
10	22 ($\pm$ 8)
30	25($\pm$ 9)
60	25($\pm$ 10)
120	25($\pm$ 10)
360	26($\pm$ 10)
720	26($\pm$ 10)

Conclusion: The release of drug from formulation of example 1 was for longer period.

Example 3: Rotigotine aqueous depot formulation

Table 5: Composition of Rotigotine aqueous depot formulation

S. No.	Ingredient	Quantity (%w/v)
1.	Rotigotine	2-10%
2.	PEG 3350	2.5-3.5%
3.	Polysorbate 80	0.1 – 2%
4.	Methyl paraben	0.01-1.0%
5.	Propyl paraben	0.01-1.0%
6.	NaOH/HCl	pH 3-7
7.	Glycerin + Water for Injection	q. s. 1 mL

Process:

1. Mixture of glycerin and water (1:1) was prepared.
2. Methyl paraben and propyl paraben were dissolved at 55°C to 60°C to some amount of the above mixture.
3. Polysorbate 80 was added to the above solution while stirring.
4. PEG3350 was added to the above step while stirring.

5. Sodium chloride was added to the above solution and stirred.
6. Rotigotine (particle size about $d_{90} = 80 \mu\text{m}$) was added to the above solution and stirred.
7. Final volume was made up with glycerine + water mixture to obtain the Rotigotine aqueous depot formulation.

Example 4: Rotigotine aqueous depot formulation

Table 6: Composition of Rotigotine aqueous depot formulation

S. No.	Composition	Quantity (%w/v)
1.	Rotigotine	2-15%
2.	Polysorbate 80	0.1 – 2%
3.	PEG 3350	2.5-3.5%
4.	Sodium carboxymethyl cellulose 12M8P	0.5- 2%
5.	Methyl paraben	0.01-1.0%
6.	Propyl paraben	0.01-1.0%
7.	NaOH/HCl	pH 3-7
8.	Water for Injection	q. s. 1 mL

Process:

1. Sodium carboxymethyl cellulose 12M8P, methyl paraben and propyl paraben were dissolved at 55°C to 60°C in sufficient quantity of water.
2. Polysorbate 80 was added to the above solution while stirring.
3. PEG 3350 was added to the above mixture and stirred.
4. Sodium chloride was added to the above mixture and stirred.
5. Rotigotine (particle size about $d_{90} = 94\mu\text{m}$) was added to the above solution and stirred.
6. Final volume was made up with water for injection to obtain the Rotigotine aqueous depot formulation.

Example 5: Rotigotine aqueous depot formulation**Table 7: Composition of Rotigotine aqueous depot formulation**

S. No.	Composition	Quantity (%w/v)
1.	Rotigotine	2-15%
2.	Polysorbate 80	0.1 – 2%
3.	PEG 3350	2.5-3.5%
4.	Sodium carboxymethyl cellulose 7L2P	0.5- 2%
5.	Methyl paraben	0.01-1.0%
6.	Propyl paraben	0.01-1.0%
7.	NaOH/HCl	pH 3-7
8.	Water for Injection	q. s. 1 mL

Process:

1. Sodium carboxymethyl cellulose 7L2P, methyl paraben and propyl paraben were dissolved at 55°C to 60°C in sufficient quantity of water.
2. Polysorbate 80 was added to the above solution while stirring.
3. PEG 3350 was added to the above mixture and stirred.
4. Sodium chloride was added to the above mixture and stirred.
5. Rotigotine (particle size about $d_{90} = 50\mu\text{m}$) was added to the above solution and stirred.
6. Final volume was made up with water for injection to obtain the Rotigotine aqueous depot formulation.

Approach 2: Lipid coated aqueous depot suspension**Example 6: Rotigotine lipid coated aqueous depot formulation****Table 8: Composition of Rotigotine lipid coated aqueous depot formulation**

S. No.	Composition	Quantity (mg)
1.	Rotigotine	30mg
2.	Purified egg yolk lecithin (lipoid E80S)	144mg

3.	Water for Injection	q. s. 1 mL
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Process of preparation:

1. Purified egg yolk lecithin (lipoid E80S) and rotigotine were dissolved in dichloromethane in a round bottom flask. Dichloromethane was evaporated using rotavac.
2. The rotigotine (particle size d_{90} 80 μ ?) lipid complex film was removed from the round bottom flask with water for injection and transferred into a stainless steel container and homogenize.

Observation:

In-vitro dissolution study: The in-vitro dissolution release profile of formulation of example 6 was studied in phosphate buffer pH 4.5 at 37°C. The data is tabulated as under in table 9 and represented in Fig. 3:

Table 9: Invitro dissolution profile of formulation of example 6

Time (in mins)	% drug release (SD)
10	9 ($\pm$ 2.41)
30	19($\pm$ 4.31)
60	28($\pm$ 6.15)
120	43($\pm$ 6.23)
360	74($\pm$ 6.28)
720	80($\pm$ 5.20)

Example 7: Rotigotine lipid coated aqueous depot formulation

Table 10: Composition of Rotigotine lipid coated aqueous depot formulation

S. No.	Composition	Quantity (%w/v)
1.	Rotigotine	2-15%
2.	Cholesterol/Cholesterol Sulfate	10-80%
3.	Fatty acids (e.g. Oleic acid)	2-50%

4.	Lecithin	0.5-20%
5.	Polysorbate 80	0.1%
6.	Sodium Hydroxide	pH 3-7
7.	Hydrochloric acid/ Citric acid/ Glacial Acetic acid	pH 3-7
8.	Water for Injection	q. s. 1 mL-2.5ml

Process:

1. Cholesterol and lecithin were dissolved in Oleic acid at an elevated temperature. The oil phase was cooled to room temperature and Rotigotine (particle size $d_{90} = 80\mu$) was dissolved in it.
2. Polysorbate 80 was dissolved separately in Water for injection.
3. Oil phase of step 1 was added to aqueous phase of step 2 water under stirring.
4. Suspension of step 3 was homogenized in homogenizer before dispensing to achieve uniform suspension.
5. pH of the suspension of step 4 was adjusted using citric acid, Glacial acetic acid or hydrochloric acid if required.
6. Volume of suspension of step 5 was adjusted with sterile-filtered Water for injection.

Example 8: Stability study

The formulations of example 1 and example 2 were studied for stability of suspension with respect to rotigotine content and physical appearance to evaluate rotigotine precipitation. The results are shown in table 11 below. The formulations of example 1 and example 2 indicated no precipitation of rotigotine in the composition.

Table 11: Stability study result of formulations of example 1 and 2

Example No	Condition	Time interval	Description	Assay		Related substance					
				mg/ml	% LC	Imp 1 (%)	Imp 2 (%)	USMI (%)	UI1 (%)	TKI (%)	TI (%)
1	40°C /75% RH	1 month	Off white suspension	29.3	97.5	0.09	ND	0.09	Below 0.5	0.09	0.22
2	40°C /75% RH	1 month	Off white suspension	30.5	101.8	0.1	ND	0.15	Below 0.5	0.10	0.26

The above-mentioned comparison of data confirms that the formulations of present invention are stable.

Example 9: Single dose pharmacokinetic study in rats

METHOD AND MATERIAL:

Test System	SD Rat
Sex	Male
Rationale	SD rats are used, as it is commonly used rodent
	species in the phannacokinetic evaluation of
	drugs, and acceptable to the regulatory
	authorities.
Source of Animals	Vivo Biotech, Hyderabad.
Total no of Animals	24
Age at study/	8 to 12 weeks / 250 g ($\pm$ 10% variation accepted)

	at the time of dosing)
Body Weight	accepted at the time of dosing)
Veterinary	Prior to the final assignment to the study, rats
Examination	will be subjected to veterinary examination to
	ensure that the selected rats are in a good state of
	health.
Animal	Animals will be uniquely identified by tail
Identification	marking with permanent marker.
Acclimatization	On receipt from supplier, the animals will be
	examined for external signs of ill health prior to
	acceptance. After health examination, animals
	will be acclimatized for one week under test
	conditions. Only animals without any visible
	signs of illness will be used for the study.
Grouping and	The animals for the experiment will be
Randomization	weighed and arranged in ascending order of
	their body weights. These stratified body weight
	of rat will be distributed by randomization
	procedure using Microsoft excel spreadsheet to
	all the experimental groups, such that body
	weight variation of animals selected for the
	study does not exceed $\pm 10\%$ of the mean body weight
Animal	Under isoflurane anesthesia, all animals were
catheterization	cannulated in right external jugular vein and
	femoral vein (for intravenous infusion, PE-10

	tubing). Rats were surgically implanted with
	a catheter (external jugular vein, PE-50
	tubing) for repeated withdrawal of blood
	samples (~0.300 mL volume per predetermined
	blood collection time). For each group, one
	standby animal was catheterized as backup.
	Rats were allowed to recover for minimum of
	72 h after cannulation before inclusion in
	study and drug administration. General animal
	health and cannula patency was confirmed prior
	to dose administration.

Test dose: The formulation of example 1 and example 2 administered by subcutaneous route at ~2 mL/kg dose volume with 60 mg/kg dose.

Group	Animal I.D	Dose (mg/kg)
Formulation of example 1	1-12	60
Formulation of example 2	13-24	60

Blood Collection and Storage of Samples:

Site of blood collection	Retro orbital plexus using unheparinised capillaries
Anesthesia	Isoflurane anesthesia
Volume of blood	0.30 mL (approx.) at each time point

collected	
Anticoagulant	Na ₂ EDTA (stock strength: 0.2 mg/mL and volume 10 µl/mL blood)
	10 µL/0.30 mL blood)
Blood collection	0.0 (within 1 hour prior to dosing) 1, 2, 4, 6, 8, 10, 12,
time points	24, 48, 72*, 96, 120, 144, and till 432 hours post-dose (Total 15 bleedings/ rat).
Blood	4000 rpm for 10 minutes at 4°C
centrifugation	
Plasma storage	-70°C until analysis (two aliquots of~ 75 µL each)
Plasma vials labeling details	Study No. animals ID No. time point, group, aliquot no. etc

Note:

- A pre-dose sample (two animals from each group) were collected at predose within 1.0 h prior to dose administration.
 - Blood samples were kept on ice bath till centrifugation and centrifugation was done within 30 minutes of collection.
 - *Interim bio-analysis was performed following 72 hours blood collection and was completed before 432 hour. Based on plasma concentration up to 72 hours decision was made for further time point sample collection.
- On completion of last blood sampling, animals were sacrificed without any further investigation.

Bioanalysis

Plasma samples were analyzed for Rotigotine. Bioanalysis was performed by the validated fit-for-purpose bioanalytical method using LC-MS/MS.

Pharmacokinetic data analysis and Evaluation

Pharmacokinetic Software used: Phoenix[®] WinNonlin Software, version 7.0, USA.

Pharmacokinetic parameters: Mean and SD values of C_{max}, AUC_{0-t}, AUC_{0-∞}, T_{max}, Ket, T_{1/2}, VD, Geometric means etc.

Results:

In-vivo release profile: The in-vivo release profile was studied by administering the formulation by subcutaneous route at ~2 mL/kg dose volume. Blood collection was done at time points of 0.0 (within 1 hour prior to dosing) 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144 till 432 hours post-dose and analyzed for amount of Rotigotine in blood. The data is tabulated as under in table 12 and represented in Fig. 4 and Fig. 5:

Table 12: Plasma pharmacokinetic parameters study results of formulations of example1 and example 2

Plasma pharmacokinetic parameters of rotigotine after Subcutaneous injection administration in male SD rats (all values in mean + SD)			
PK Parameter	Unit	Formulation of Example 1	Formulation of Example2
T _{1/2}	(hr)	82.2±29.9	108.0±31.6
C _{max}	(ng/ml)	96.1±50.3	31.9±12.8
T _{max}	(hr)	2(1.0-10.0)	1(1.0-12.0)
AUC _{last}	(hr*ng/ml)	4643.9±1218.4	3694.4±467.0
AUC _{INF_Obs}	(hr*ng/ml)	5036.0±1175.3	4291.7±581.1
AUC_%Extrap_Obs	(%)	8.2±4.7	13.7±4.6

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to fall within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" includes a single excipient as well as two or more different excipients, and the like.

We claim,

1. A pharmaceutical long-acting depot composition comprising a therapeutically effective amount of rotigotine or its pharmaceutically acceptable derivative and one or more pharmaceutically acceptable excipients.
2. The pharmaceutical long-acting depot composition according to claim 1, wherein the amount of rotigotine in the composition is from about 10 mg to about 300 mg.
3. The pharmaceutical long-acting depot composition according to claim 1, wherein the particle size (d_{90}) of rotigotine in the composition is from about 20 microns to about 100 microns.
4. The pharmaceutical long-acting depot composition according to claim 1, wherein the particle size (d_{90}) of rotigotine in the composition is from about 40 microns to about 80 microns.
5. The pharmaceutical long acting depot composition according to claim 1, wherein the composition is an aqueous depot injection comprising rotigotine or its pharmaceutically acceptable derivative and one or more pharmaceutically acceptable excipients.
6. The pharmaceutical long-acting aqueous depot injection according to claim 5, wherein the one or more pharmaceutically acceptable excipients are selected from wetting agent or suspending agent, matrix forming agent, viscosity enhancing agent, preservative, buffering agent, isotonicizing agent, injection vehicle, or mixtures thereof.
7. The pharmaceutical long acting depot composition according to claim 1, wherein the composition is a lipid coated aqueous depot injection comprising rotigotine or its pharmaceutically acceptable derivative and one or more pharmaceutically acceptable excipients.
8. The pharmaceutical long-acting aqueous depot injection according to claim 7, wherein the one or more pharmaceutically acceptable excipients are selected from lipid carrier, complexing agent, stabilizer, suspending agent,

wetting agent, preservative, buffering agent, viscosity enhancing agent, density enhancing agent, injection vehicle, isotonicizing agent or mixtures thereof.

9. The long-acting sustained-release depot pharmaceutical composition according to claim 1, wherein the composition is administered subcutaneously or intramuscularly.
10. The long acting sustained release depot pharmaceutical composition according to claim 1, wherein the composition is administered bimonthly or monthly.
11. The long depot sustained release depot pharmaceutical composition according to claim 1, wherein the composition is supplied in an injection volume of 0.5 ml to 2.5 ml in a prefilled syringe.
12. A long-acting aqueous depot suspension injection comprising:
 - a. rotigotine or its pharmaceutically acceptable derivative in an amount from about 10mg to about 300mg and particle size range (d_{90}) from 20 microns to 100 microns,
 - b. polysorbate 80 in an amount from about 0.1 % to about 5 % of the total formulation,
 - c. polyethylene glycol in an amount from about 1 % to about 5 % of total formulation,
 - d. preservative selected from benzyl alcohol, methyl paraben, propyl paraben or mixtures thereof in an amount from about 0.5 % to about 2 % of total formulation
 - e. buffering agent in an amount from about 0.5 % to about 1.5 % of total formulation and
 - f. water for injection vehicle,supplied in an injection volume of 0.5 ml to 2.5 ml in a prefilled syringe.
13. A long-acting lipid coated aqueous depot suspension injection comprising:
 - a. 30 mg rotigotine or its pharmaceutically acceptable derivative
 - b. 144 mg Purified egg yolk lecithin

- c. dichloromethane and
- d. water for injection vehicle

supplied in an injection volume of 0.5 ml to 2.5 ml in a prefilled syringe.

14. The long acting sustained release depot pharmaceutical composition according to claim 1, wherein the composition is for use in the treatment of Parkinson's disease.
15. A method of treatment of Parkinson's disease comprising administration of long acting aqueous depot suspension injection comprising rotigotine and its pharmaceutically acceptable derivative and one or more pharmaceutically acceptable excipients selected from suspending agent, wetting agent, preservative, buffering agent, viscosity enhancing agent, density enhancing agent, injection vehicle, isotonicizing agent or mixtures thereof.
16. A method of treatment of Parkinson's disease comprising administration of long acting lipid coated aqueous depot suspension injection comprising a therapeutically effective amount of rotigotine or its pharmaceutically acceptable derivative and one or more pharmaceutically acceptable excipients selected from lipid carrier, complexing agent, stabilizer, suspending agent, wetting agent, preservative, buffering agent, viscosity enhancing agent, density enhancing agent, injection vehicle, isotonicizing agent or mixtures thereof.

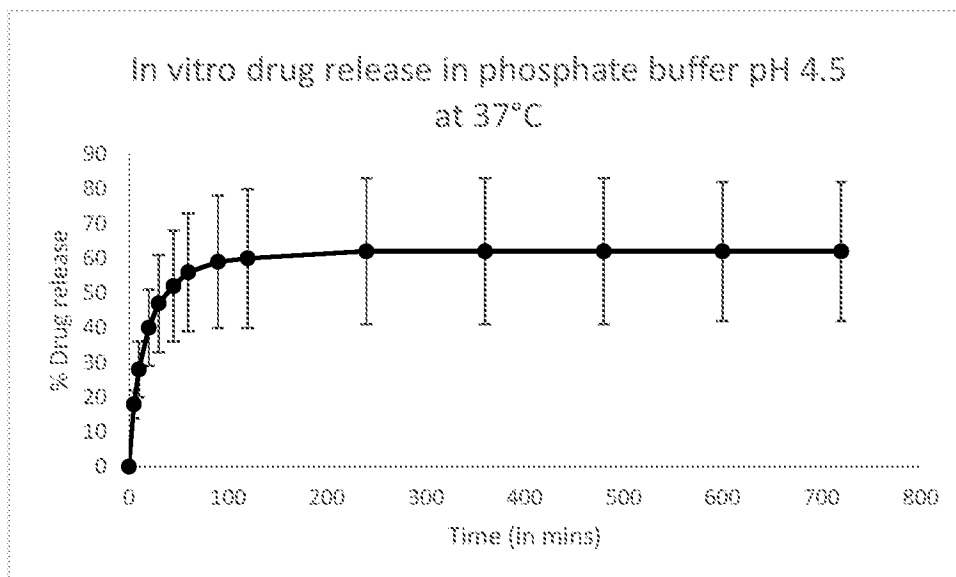


Fig 1: invitro drug release profile of formulation of example 1

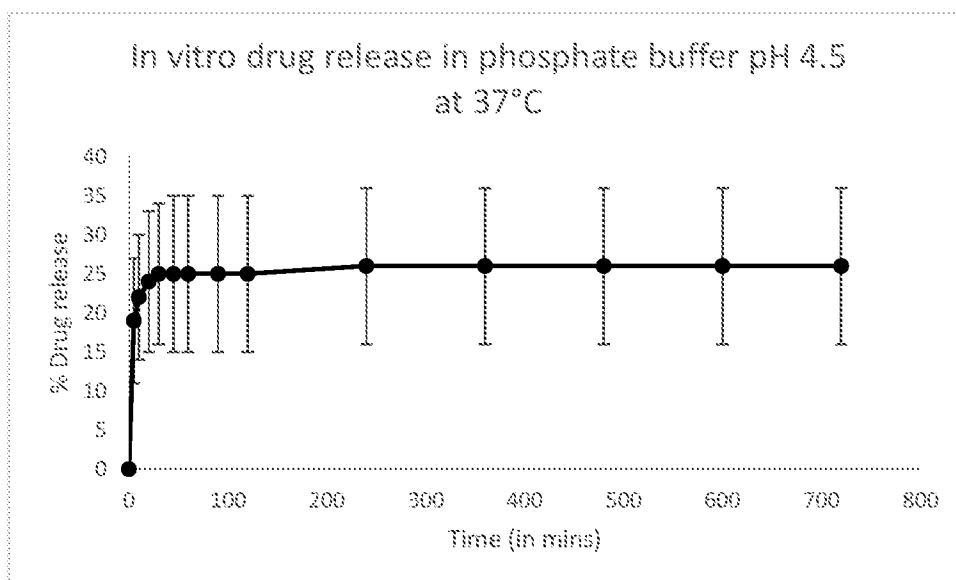


Fig 2: invitro drug release profile of formulation of example 2

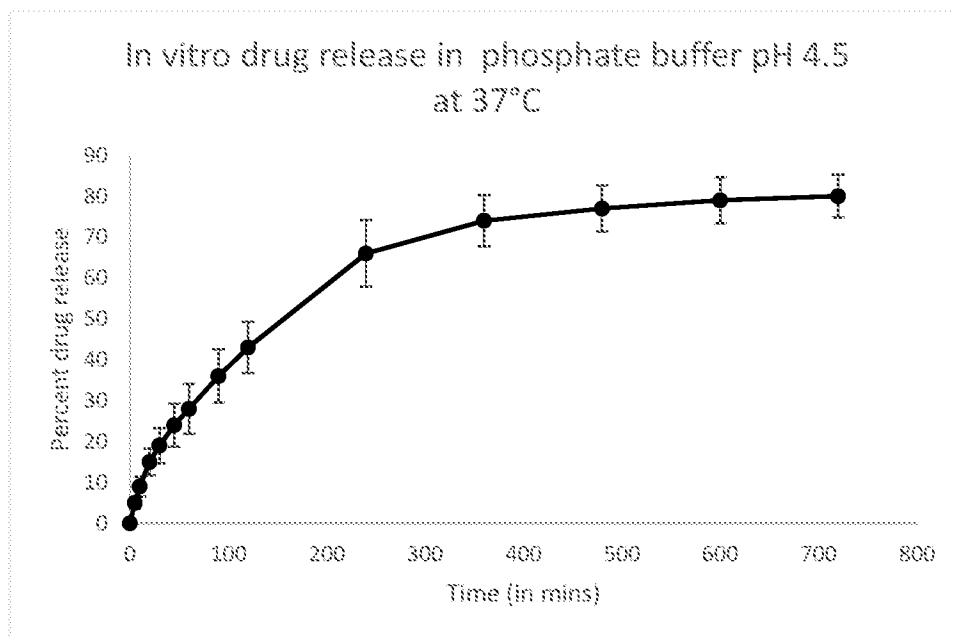


Fig 3: Invitro drug release profile of formulation of example 6

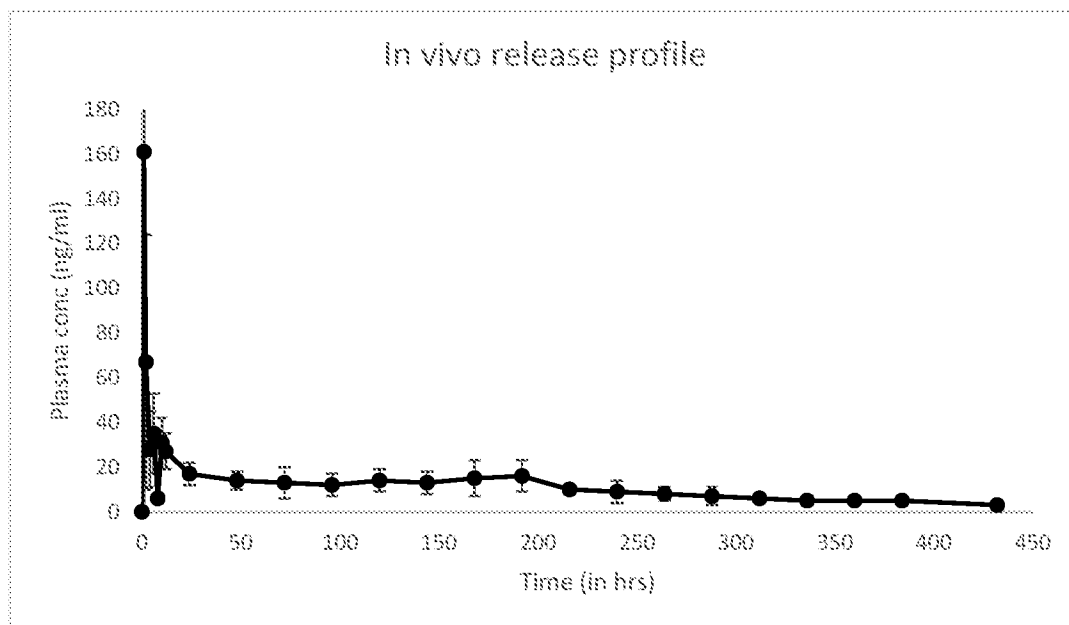


Fig. 4: Invivo release profile of formulation of example 1

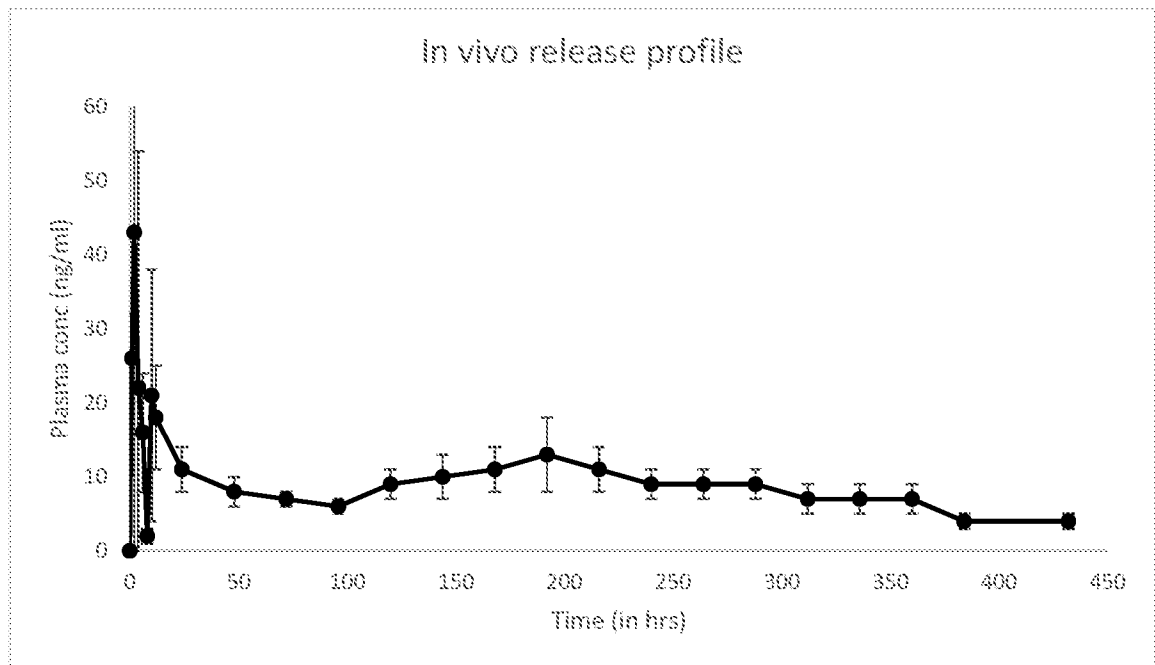


Fig. 5: In vivo release profile of formulation of example 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2017/050550

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/00 A61K9/10 A61K9/16 A61K47/10 A61K31/381 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		
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 practicable, search terms used) EPO-Internal, WPI Data, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 105 963 253 A (ZHU WUXIN) 28 September 2016 (2016-09-28) claims 1,5-8 examples 1-4	1-16
X	----- US 2013/309314 A1 (LI YOUXIN [DE] ET AL) 21 November 2013 (2013-11-21) cited in the application	1,5-10, 14-16
A	paragraphs [0035], [0057] - [0060], [0058], [0143] table 4 claims 1,2,26-28 ----- -/-	2-4, 11-13
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
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13 February 2018	26/02/2018	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Hedegaard, Anette	

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