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(54) Title: AMORPHOUS VARENICLINE TARTRATE

(57) Abstract: Amorphous varenicline tartrate, amorphous solid dispersions of varenicline tartrate and a pharmaceutical carrier, and processes for the preparation thereof.

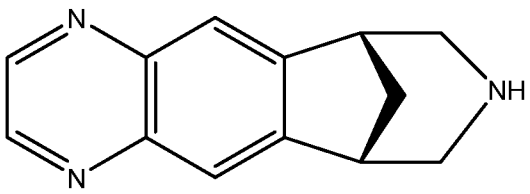
AMORPHOUS VARENICLINE TARTRATE

INTRODUCTION

Aspects of the present invention relate to an amorphous form of varenicline tartrate, an amorphous solid dispersion of varenicline tartrate, and processes for the preparation thereof.

Varenicline is the first approved nicotinic receptor partial agonist and is pharmacologically different from other smoking cessation aids such as nicotinic antagonists (e.g., bupropion) and nicotine replacement therapies (e.g., nicotine patches and nicotine gum).

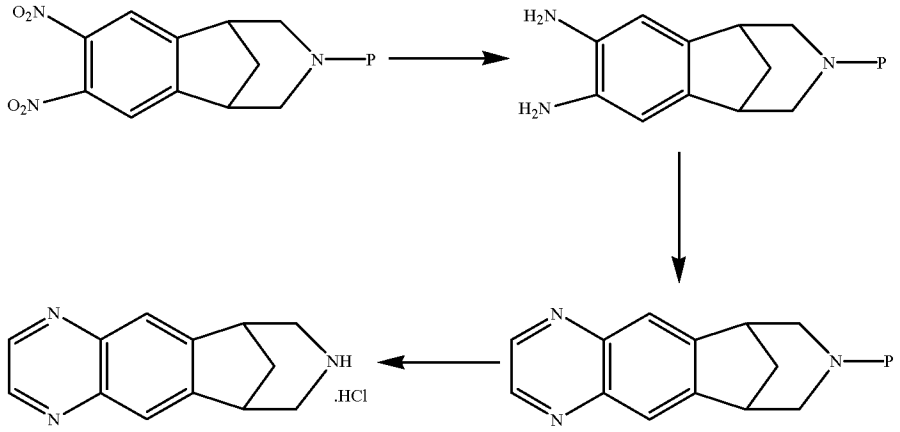
The drug compound having the adopted name "varenicline" has chemical names 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, or 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine, and is structurally represented by Formula I.



Formula I

Varenicline, as a nicotinic receptor partial agonist, reduces both cravings and the pleasurable affects of cigarettes and other tobacco products, and through these mechanisms it assists some patients with quitting smoking. Being known to be useful in modulating cholinergic function, it is indicated for the treatment of smoking cessation. Varenicline is present in the form of a salt with L-tartaric acid, i.e., varenicline tartrate, in products marketed as CHANTIX™ in the U.S. and CHAMPIX™ in Europe and Canada.

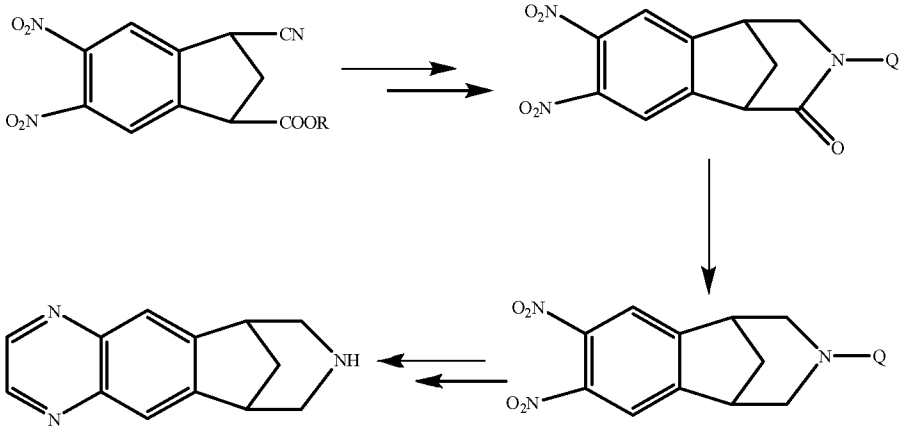
Coe et al., in U.S. Patent No. 6,410,550 disclose several analogues of fused aza polycyclic compounds and process for their preparation. The chemical pathway described for varenicline hydrochloride in this patent is summarized in Scheme I:



Scheme I

wherein P is hydrogen, methyl, $COOR^{16}$ and wherein R^{16} is (C_1-C_6) alkyl, allyl or 2,2,2-trichloroethyl; -C(=O)NR^5 R^6 ; -C(=O)H, -C(=O)(C_1-C_6)alkyl, wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms; -$COOCH_2C_6H_5$, benzyl, t-butoxycarbonyl (t-Boc) or trifluoroacetyl, wherein R^5 and R^6 are each selected, independently, from hydrogen and (C_1-C_6) alkyl, or R^5 and R^6 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, N-(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine wherein the ring sulfur is replaced with a sulfoxide or sulfone.

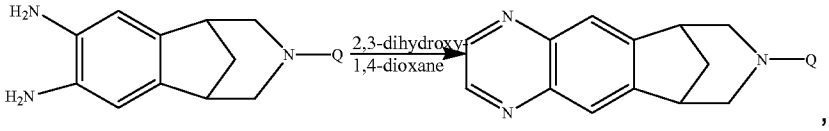
Singer et al,, in U.S. Patent No. 7,091,372, describe another process for the preparation of various 1,3 substituted indene derivatives, which are useful intermediates in the preparation of aryl fused aza polycyclic compounds. The chemical pathway disclosed in this patent for preparation of various indene derivatives and subsequent aza polycyclic compounds is summarized in Scheme II.



Scheme II

wherein Q may be chosen from groups such as $COCF_3$, $COCCl_3$, $COOCH_2CCl_3$, $COO(C_1\text{-}C_6)$alkyl and $COOCH_2C_6H_5$.

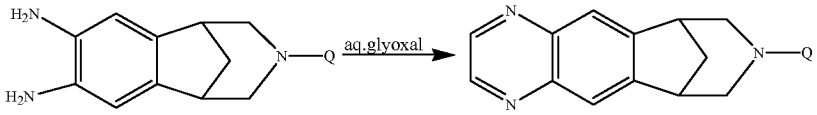
Rainville et al., in International Application Publication No. WO 2004/108725, describe a process for the cyclization of diamino compounds with 2,3-dihydroxy-1,4-dioxane to obtain pyrazine compounds, as summarized in Scheme III.



Scheme III

wherein Q is as nitrogen-protecting group such as a trifluoroacetyl group, an acetyl group, or a t-butoxycarbonyl group.

Robert et al., in International Application Publication No. WO 2006/090236, describe a process for cyclization of diamino compounds with aqueous glyoxal in an alcoholic solvent to form the corresponding quinoxaline derivatives. The process disclosed in this application is summarized in Scheme IV.



Scheme IV

wherein Q is as nitrogen-protecting group such as a trifluoroacetyl group, an acetyl group or a t-butoxycarbonyl group.

Bogle et al., in U.S. Patent No. 6,890,927, state that varenicline tartrate exists in three forms; two anhydrous forms, Form A and Form B, and one hydrate form, Form C, and that Form A is the kinetic polymorph, which will convert under appropriate conditions to the thermodynamically favored Form B. It was further disclosed that Form C of varenicline tartrate is a monohydrate and is relatively stable under ambient conditions.

There is a continuing need to provide stable forms of varenicline tartrate.

SUMMARY

In one embodiment, the invention encompasses an amorphous form of varenicline tartrate. The amorphous form of varenicline tartrate described herein may have residual water content in the range of from about 0.1% to about 10%, by weight.

In an aspect, there are provided processes for the preparation of an amorphous form of varenicline tartrate, comprising removing solvent from a solution of varenicline tartrate.

In an aspect, there are provided pharmaceutical compositions that include a therapeutically effective amount of an amorphous form of varenicline tartrate, which is described herein, and at least one pharmaceutically acceptable excipient.

In an aspect, the present application provides amorphous solid dispersions of varenicline tartrate together with a pharmaceutically acceptable carrier.

In an aspect, the present application provides processes for preparing amorphous solid dispersions of varenicline tartrate together with a pharmaceutically acceptable carrier, comprising removing solvent from a solution of varenicline tartrate and a pharmaceutically acceptable carrier.

In another aspect, the present application provides pharmaceutical compositions comprising amorphous solid dispersions of varenicline tartrate together with at least one pharmaceutically acceptable excipient, optionally with one or more other pharmaceutically acceptable excipients.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an X-ray powder diffraction (XRPD) pattern of an illustrative sample of varenicline tartrate amorphous form.

Fig. 2 is an XRPD pattern of a stabilized amorphous solid dispersion of varenicline tartrate with hydroxypropyl cellulose, prepared according to Example 11.

Fig. 3 is an XRPD pattern of a stabilized amorphous solid dispersion of varenicline tartrate with hydroxypropyl methylcellulose, prepared according to Example 12.

Fig. 4 is an XRPD pattern of a stabilized amorphous solid dispersion of varenicline tartrate with povidone, prepared according to Example 13.

DETAILED DESCRIPTION

New solid forms of pharmaceutically useful compounds provide an opportunity to improve the characteristics of formulated products, such as stability, solubility and formulation processing. Although the existence and preparation of solid forms (e.g., polymorps, amorphous, etc.) for any given chemical compound

cannot be predicted, active pharmaceutical ingredients, like varenicline tartrate, may give rise to a variety of solid forms having different physical characteristics and distinct physicochemical properties, which may be characterized by various analytical methods e.g., X-ray powder diffraction patterns, infrared absorption spectra, solid state NMR spectra, and thermal analysis methods suchas differential scanning calorimetry (DSC) thermograms, thermogravimetric analysis (TGA) curves, etc. In some cases, different forms of the same drug can exhibit different solubility and therefore different dissolution rates. This variation may result in finished dosage forms with different bioavailabilities between various production lots of formulated pharmaceutical products. Since polymorphic forms may vary in their physical and chemical properties, most regulatory authorities require identification of the polymorphic nature of the active pharmaceutical ingredients to minimize variations in the bioavailability of the finished dosage forms.

The amorphous form of varenicline tartrate described herein may be characterized by its XRPD pattern. The amorphous form of varenicline tartrate described herein has a pattern without intense focused reflections and is featureless except for a halo. Fig. 1 provides an example of the XRPD pattern of the amorphous form of varenicline tartrate.

All X-ray powder diffraction pattern data provided herein were obtained using a Bruker AXS D8 Advance Powder X-ray Diffractometer. XRPD patterns were generated using copper Kα radiation at a wavelength 1.541 Å.

The amorphous form of varenicline tartrate described herein may have a water content in the range of from about 0.1% to about 10%, by weight.

The amorphous varenicline tartrate produces a product with desired characteristics like stability and is suitable for preparing pharmaceutical compositions for pharmaceutical use.

In an embodiment, the present invention provides substantially pure amorphous varenicline tartrate, having less than about 20%, or less than about 10%, or less than about 5%, or less than about 1%, by weight of a crystalline form of varenicline tartrate. The substantially pure amorphous varenicline tartrate can have less than about 20%, or less than about 10%, or less than about 5%, or less than about 1%, by weight of all crystalline forms of varenicline tartrate.

In an aspect, the present application provides processes for the preparation of an amorphous form of varenicline tartrate. In an embodiment, the amorphous form of varenicline tartrate described herein may be prepared by removing the solvent from the solution of varenicline tartrate.

A solution may be provided by forming a solution of varenicline tartrate, alone or together with a soluble pharmaceutically acceptable excipient, in a suitable solvent. If the solution of varenicline tartrate and an excipient is provided, the excipient may be chosen to enable stabilization of the amorphous solid formed upon solvent removal.

Providing a solution of varenicline tartrate in a suitable solvent includes any of:

(i) Direct use of a reaction mixture containing varenicline tartrate and obtained in the course of synthesis, if desired after addition of a pharmaceutically acceptable carrier.

(ii) Dissolution of varenicline tartrate in a suitable solvent, either alone or in combination with a pharmaceutically acceptable carrier.

(iii) Contacting varenicline free base in a suitable solvent with L-tartaric acid, either alone or in combination with a pharmaceutically acceptable carrier.

The solvents that may be utilized for providing a solution of varenicline tartrate include, but are not limited to, alcohol solvents such as methanol, ethanol, isopropyl alcohol and n-propanol; halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform and carbon tetrachloride; ketone solvents such as acetone, ethyl methyl ketone and methyl isobutyl ketone; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate and t-butyl acetate; ether solvents such as diethyl ether, dimethyl ether, diisopropyl ether, methyl t-butyl ether, tetrahydrofuran and 1,4-dioxane; hydrocarbon solvents such as toluene, xylene, n-heptane, cyclohexane and n-hexane; nitrile solvents such as acetonitrile and propionitrile; dimethylsulfoxide (DMSO); N,N-dimethylformamide (DMF); N,N-dimethylacetamide; water; and mixtures thereof. Further, the solvent used to practice the process described herein should be chemically inert, with respect to dissolved solutes.

Amorphous varenicline tartrate together with a pharmaceutically acceptable carrier may be prepared by combining the pharmaceutically acceptable carrier with a solution of varenicline tartrate, or combining varenicline tartrate with a

solution of pharmaceutically acceptable carrier, and removal of the solvent. Alternately, a solution of pharmaceutically acceptable carrier may be dissolved in the same or a different solvent and added to a varenicline tartrate solution.

When amorphous varenicline tartrate is prepared from varenicline free base by reaction with L-tartaric acid, the solvents that are utilized for the dissolution of varenicline free base and L-tartaric acid may be the same or different, and the solutions are then combined for further processing.

Suitable pharmaceutically acceptable carriers which may be used in the processes of the present application include, but are not limited to, hydrophilic carriers like polymers of N-vinylpyrrolidone, commonly known as polyvinylpyrrolidines ("PVP" or "povidone"), gums, cellulose derivatives, cyclodextrins, gelatins, hypromellose phthalate, sugars, polyhydric alcohols, polyethylene glycol, polyethylene oxides, polyoxyalkylene derivatives, methacrylic acid copolymers, polyvinylalcohols, and propylene glycol derivatives. In embodiments, the carriers will stabilize amorphous varenicline tartrate.

The solution of varenicline tartrate obtained above may be formed with heating to obtain a more concentrated solution. Generally the temperature at which dissolution takes place varies from room temperature to the boiling point of the solvent. The temperature at which the dissolution occurs depends on the nature of the solvent and may be determined by person skilled in the art. Any undissolved particles may be removed suitably by filtration, such as passing the solution through paper, glass fiber, or other membrane material, centrifugation, decantation, and other techniques.

In one variant, the solvent may be removed using any of the suitable methods such as evaporation, atmospheric distillation, or distillation under vacuum. Further, the techniques which may be used for the removal of solvent include use of rotational evaporating devices such as a Buchi Rotavapor, spray drying, agitated thin film drying ("ATFD"), lyophilization, freeze drying, and the like.

Distillation of the solvent may be conducted under a vacuum, such as below about 100 mm Hg, or below about 600 mm Hg, at elevated temperatures such as about 20°C to about 70°C. Any temperature and vacuum conditions may be used as long as they do not adversely influence the nature of the product. The vacuum and the temperature used for the removal of the solvent depend on

parameters such as the boiling point of the solvent, and may readily be determined by persons skilled in the art.

Isolation of the product thus obtained includes collection of the material, with or without cooling below the operating temperature, by any techniques such as filtration by gravity or suction, centrifugation, and the like, and optional washing with the solvent. The amorphous varenicline tartrate obtained may also be collected from the equipment using techniques such as by scraping, or by shaking a container.

The solid material obtained by any of the techniques described above may be optionally further dried. Drying may be suitably carried out by any methods such as using a tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer, and the like. The drying may be carried out under reduced pressures and at various temperatures. The temperatures may range from about ambient temperature to about 100°C, for a time period that produces the desired residual solvent content.

Amorphous varenicline tartrate thus obtained may be milled to get a desired particle size distribution. A milling operation can reduce the size of particles and increase surface areas of particles, by colliding particles with each other at high velocities.

In an embodiment, the present application also provides stable amorphous solid dispersions of varenicline tartrate together with a pharmaceutically acceptable carrier, processes for preparation thereof, and pharmaceutical compositions prepared therefrom.

The amorphous solid dispersions of varenicline tartrate together with a pharmaceutically acceptable carrier described herein may be characterized by their XRPD patterns. A completely amorphous solid dispersion of varenicline tartrate together with a pharmaceutically acceptable carrier described herein has a pattern without intense focused reflections, and is generally featureless except for a halo. In particular, peaks characteristic of a solid form of varenicline tartrate are absent.

An amorphous solid dispersion of varenicline tartrate described herein may have a water content in the range of from about 0.1% to about 10%, by weight.

A solid dispersion of amorphous varenicline tartrate together with a pharmaceutically acceptable carrier provides a product with desired

characteristics like stability, and is suitable for preparing pharmaceutical compositions for pharmaceutical use.

In another embodiment, the present invention provides substantially pure amorphous solid dispersions of varenicline tartrate, having less than about 20%, or less than about 10%, or less than about 5%, or less than about 1%, by weight of any crystalline form of varenicline tartrate. The substantially pure amorphous solid dispersions of varenicline tartrate can have less than about 20% , or less than about 10%, or less than about 5%, or less than about 1%, by weight of all crystalline forms of varenicline tartrate.

In an aspect, the present application provides processes for preparing amorphous solid dispersions of varenicline tartrate together with a pharmaceutically acceptable carrier, an embodiment comprising removing the solvent from a solution of varenicline tartrate and a pharmaceutically acceptable carrier.

In embodiments, a solution may be provided by dissolving varenicline tartrate and a soluble pharmaceutically acceptable excipient, in a suitable solvent. The excipient may be chosen to stabilize the amorphous solid formed upon solvent removal.

Providing a solution of varenicline tartrate and a pharmaceutically acceptable excipient in a suitable solvent includes any of:

(i) Direct use of a reaction mixture containing varenicline tartrate that is obtained in the course of synthesis, and which is combined with a pharmaceutically acceptable carrier.

(ii) Dissolution of varenicline tartrate in a suitable solvent, in combination with a pharmaceutically acceptable carrier.

(iii) Contacting varenicline free base with L-tartaric acid, and a pharmaceutically acceptable carrier in presence of a suitable solvent.

Any physical form of varenicline tartrate, such as crystalline, amorphous, and their mixtures, may be utilized for providing a solution of varenicline tartrate along with a pharmaceutically acceptable carrier.

Pharmaceutically acceptable carriers that may be used for the preparation of stabilized amorphous solid dispersions of varenicline tartrate of the present application include, but are not limited to: pharmaceutical hydrophilic carriers such as polyvinylpyrrolidones (homopolymers of N-vinylpyrrolidone, called povidones),

copolymers of N-vinylpyrrolidone, gums, cellulose derivatives (including hydroxypropyl methylcelluloses, hydroxypropyl celluloses, and others), polymers of carboxymethyl celluloses, cyclodextrins, gelatins, hypromellose phthalates, polyhydric alcohols, polyethylene glycols, polyethylene oxides, polyoxyethylene derivatives, polyvinylalcohols, propylene glycol derivatives, and the like; and organic amines such as alkyl amines (primary, secondary, and tertiary), aromatic amines, alicyclic amines, cyclic amines, aralkyl amines, hydroxylamine or its derivative, hydrazine or its derivative, and guanidine or its derivatives. The use of mixtures of more than one of the pharmaceutical excipients to provide desired release profiles or for the enhancement of stability is within the scope of this application. Also, all viscosity grades, molecular weights, commercially available products, their copolymers, and mixtures are all within the scope of this application without limitation.

The solvents that may be utilized for providing a solution of varenicline tartrate along with a pharmaceutically acceptable carrier include, but are not limited to: alcoholic solvents such as methanol, ethanol, isopropyl alcohol and n-propanol; halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform and carbon tetrachloride; ketone solvents such as acetone, ethyl methyl ketone and methyl isobutyl ketone; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate and t-butyl acetate; ether solvents such as diethyl ether, dimethyl ether, diisopropylether, methyl t-butyl ether, tetrahydrofuran and 1,4-dioxane; hydrocarbon solvents such as toluene, xylene, n-heptane, cyclohexane and n-hexane; nitrile solvents such as acetonitrile and propionitrile; dimethylsulfoxide (DMSO); N,N-dimethylformamide (DMF); N,N-dimethylacetamide; water; and mixtures thereof. Further, the solvent used to practice the processes described herein should be chemically inert with respect to dissolved solutes.

The solution may be obtained by dissolving varenicline tartrate and the pharmaceutically acceptable carrier in a solvent or in different solvents, optionally with heating. Generally the temperatures at which dissolution takes place vary from room temperature to the boiling point of the solvent. The temperature at which the dissolution occurs depends on the nature of the solvent and may be determined by person skilled in the art. Any undissolved particles may be removed suitably by filtration, such as passing a solution through paper, glass

fiber, or other membrane material, centrifugation, decantation, and other techniques. The solution may optionally be treated with materials such as carbon to remove colour or to improve clarity of the solution.

Removal of the solvent from the solution can be accomplished using any suitable technique. The solvent may be removed by techniques known in art which include but are not limited to: distillation, evaporation, oven drying, tray drying, rotational drying (such as with a Buchi Rotavapor), spray drying, freeze-drying, fluidized bed drying, flash drying, spin flash drying, agitated thin film drying, and the like.

Distillation of the solvent may be conducted under a vacuum, such as below about 100 mm Hg, or below about 600 mm Hg, at elevated temperatures such as about 20°C to about 100°C. Any temperature and vacuum conditions may be used as long as they do not influence the nature of the product. The vacuum and the temperature used for the removal of the solvent depend on parameters such as the boiling point of the solvent, and may readily be determined by persons skilled in the art.

These techniques are applicable to both aqueous and non-aqueous solutions of varenicline tartrate together with a pharmaceutically acceptable carrier.

Isolation of the product thus obtained includes collection of the material, with or without cooling below the operating temperature, by any techniques such as filtration by gravity or suction, centrifugation, and the like, and optionally washing with the solvent. The amorphous solid dispersion obtained may also be collected from the equipment using techniques such as by scraping, or by shaking a container.

The solid material obtained by any of the techniques described above may be optionally further dried. Drying may be suitably carried out by any known methods such as using a tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer, and the like. The drying may be carried out under reduced pressures and at various temperatures. The temperatures may range from about ambient temperature to about 100°C for a time period that produces the desired residual solvent content.

Solid dispersions of varenicline tartrate thus obtained may be milled to get a desired particle size distribution. A milling operation reduces the size of particles

and increases surface areas of particles by colliding particles with each other at high velocities.

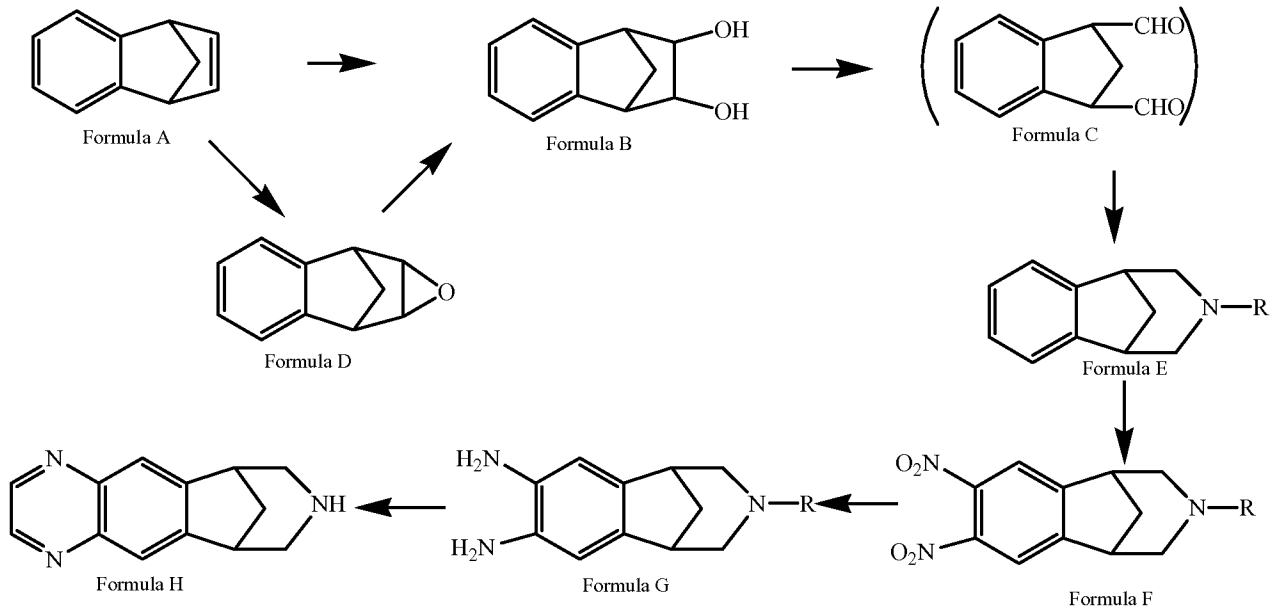
Specific amorphous solid dispersions of varenicline tartrate together with a pharmaceutically acceptable carrier obtained using the above processes are characterized by X-ray powder diffraction ("XRPD") patterns substantially in accordance with Fig. 2, Fig. 3, and Fig.4.

In an embodiment, the present application also provides stabilized amorphous solid dispersions of varenicline tartrate together with a pharmaceutically acceptable carrier, processes for preparation thereof, and pharmaceutical compositions comprising them.

The solid dispersions of amorphous varenicline tartrate together with a pharmaceutically acceptable carrier provide a product with desired characteristics like stability, and are suitable for preparing pharmaceutical compositions for pharmaceutical use.

The starting varenicline tartrate used to prepare an amorphous solid described herein may be prepared, for example, by reacting varenicline free base with L-tartaric acid. The amount L-tartaric acid used for the preparation of varenicline tartrate may vary from about 1 to about 5 molar equivalents, per equivalent of varenicline free base. In a particular variant, the amount L-tartaric acid used for the preparation of varenicline tartrate may vary from about 1 to about 2.3 molar equivalents, per equivalent of varenicline free base. In another variant, the amount L-tartaric acid used for the preparation of varenicline tartrate may vary from about 2.3 to about 5 molar equivalents, per equivalent of varenicline free base.

A chemical pathway for the preparation of varenicline is as shown in Scheme V.



Scheme V

wherein R is hydrogen, methyl, $COOR^{16}$, wherein R^{16} is C_1 -C_6 alkyl, allyl or 2,2,2-trichloroethyl; -C(=O)NR^5 R^6 ; -C(=O)H, -C(=O)(C_1-C_6)alkyl, wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, -$COOCH_2C_6H_5$, benzyl, 4-methoxybenzyl; 3,4-dimethoxybenzyl; t-butoxycarbonyl (t-Boc) or trifluoroacetyl, wherein R^5 and R^6 are, independently, hydrogen and C_1 -C_6 alkyl, or R^5 and R^6, together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, N-(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine wherein the ring sulfur is replaced with a sulfoxide or sulfone, alkylsulfonyl, including C_1 -C_6 alkylsulfonyl, arylsulfonyl, including benzylsulfonyl, p-toluenesulfonyl, etc.

The compound of Formula B may be prepared by treating the compound of Formula A with a hydroxylating reagent in a suitable organic solvent. Non-limiting examples of hydroxylating agents include osmium tetraoxide, potassium permanganate, potassium dichromate, and iodine/silver acetate. When osmium tetraoxide is employed, other oxidants, such as, but not limited to, N-methylmorpholine-N-oxide, pyridine-N-oxide, sodium peroxydisulfate, iodine, hydrogen peroxide, and potassium ferricyanide may also be used. Organic solvents that may be utilized for this step include, but are not limited to: alcoholic solvents such as methanol, ethanol, isopropyl alcohol and n-propanol; halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform and carbon tetrachloride; ketone solvents such as acetone, ethyl methyl ketone

and methyl isobutyl ketone; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate and t-butyl acetate; ether solvents such as diethyl ether, dimethyl ether, diisopropyl ether, methyl t-butyl ether, tetrahydrofuran and 1,4-dioxane; hydrocarbon solvents such as toluene, xylene, n-heptane, cyclohexane and n-hexane; nitrile solvents such as acetonitrile and propionitrile; dimethylsulfoxide (DMSO); N,N-dimethylformamide (DMF); N, N-dimethylacetamide; water; and mixtures thereof. The reaction is typically carried out at room temperature, however, if desired the reaction may be carried out at higher temperatures to enhance the progress of the reaction. The obtained product may be purified using methods such as column chromatography, preparative HPLC purification, and/or crystallization using a solvent or a mixture of solvents.

Alternately, the hydroxylation reaction for the preparation of the compound of formula B may be carried out under ultrasonic conditions which may reduce the reaction time significantly.

Alternately, the compound of Formula B may also be prepared by initially converting the compound of Formula A to an epoxide compound of Formula D, and subsequntly converting the compound of Formula D into the compound of Formula B.

The compound of Formula D may be prepared by treating the compound of Formula A, using methods capable of making epoxides from alkenes as known in the art. This reaction may be accomplished, for example, by using peroxyacids, hydrogen peroxide, sodium hypochloride, perchloric acid, etc.

The compound of Formula D may then be converted to a diol of Formula B. The conversion of compound of Formula D to the compound of Formula B may be carried out in the presence of acids or bases.

Acids that are useful for the conversion of compound of formula D into compound of formula B include, but are not limited to, hydrochloric acid, sulfuric acid, etc. Bases that are useful for such conversion include, but are not limited to, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, etc. Other acids and bases known to a person skilled in the art are also contemplated, without limitation.

The solvents and the conditions contemplated for the conversion of compound of formula A into the compound of formula B may also be useful for the conversion of the compound of formula A into D, and from D into B.

The compound of Formula B may be further converted to a compound of Formula E through the compound of Formula C, such as using the process given in U.S. Patent No. 6,410,550.

The compound of Formula B may be reacted with sodium periodate in a mixture of a chlorinated hydrocarbon, such as dichloroethane (DCE), and water, or with lead tetraacetate in a chlorinated hydrocarbon solvent, at a temperature from about 0°C to about room temperature, to generate a dialdehyde or glycal compound of Formula C. The compound of Formula C thus obtained may be then reacted with benzylamine and sodium triacetoxyborohydride in a chlorinated hydrocarbon solvent at a temperature from about 0°C to about room temperature, to form the desired compound of Formula E. Removal of the benzyl group from the compound of Formula E yields the compound of Formula E, where R is hydrogen. This may be accomplished using methods well known to those of skill in the art, for example, optionally reacting the free base with one equivalent of acid, e.g., hydrochloric acid, to form the corresponding acid addition salt, followed by reacting with hydrogen and a palladium on charcoal or palladium hydroxide catalyst in methanol at about room temperature to 75^{O}C in an autoclave.

In the reductive animation step described above for the preparation of the compound of Formula E, alternatives to benzylamine such as ammonia, hydroxylamine, alkoxyamines, methylamine, allylamine, and substituted benzylamines (e.g., diphenylmethylamine and 2- and 4-alkoxy substituted benzylamines) may also be used. They may be used as free bases, or as their salts, preferably their acetate salts, and can be subsequently removed by methods described in the literature.

The compound of Formula E, wherein R is hydrogen, may be reacted with a protecting group such as trifluoroacetic anhydride to form the compound of Formula E, where R is -$COCF_3$. This reaction is typically conducted in an inert organic solvent such as methylene chloride at a temperature from about 0°C to about room temperature. The reaction may be optionally conducted in the presence of a base. The base used for the reaction may be an organic or inorganic base. Other suitable amine-protecting groups that can be used,

alternatively, in the procedure described herein include $COOR^{16}$ wherein R^{16} is a C_1-C_6 alkyl, allyl or 2,2,2-trichloroethyl; $-C(=O)NR^5R^6$; -C(=O)H, $-C(=O)(C_1$-$C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halogen atoms; $-COOCH_2C_6H_5$, t-butoxycarbonyl (t-Boc), wherein R^5 and R^6 are each, independently, hydrogen or C_1-C_6 alkyl, or R^5 and R^6 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, N-$(C_1$-$C_6)$alkylpiperazine or thiomorpholine ring, or a thiomorpholine wherein the ring sulfur is replaced with a sulfoxide or sulfone; alkylsulfonyl, including (C_1 -C_6)alkylsulfonyl; arylsulfonyl, including benzylsulfonyl, p-toluenesulfonyl; and the like.

The compound of Formula E may be subjected to nitration to obtain a dinitro compound of Formula F. The compound of Formula E may be added to a mixture of trifluoromethanesulfonic acid (CF_3SO_2OH) and nitric acid, in a chlorinated hydrocarbon solvent, such as chloroform, dichoroethane, or methylene chloride. The resulting mixture may be allowed to react for about 5 to 24 hours. This reaction is generally conducted at a temperature ranging from about -78°C to about 0°C for about 2 hours, and then allowed to warm to room temperature for the remaining time.

The amount of nitric acid used for this step may vary from about 1 to about 6 molar equivalents, per equivalent of the compound of Formula E. In a particular variant, the amount of nitric acid used for this step may vary from about 2 to about 3 molar equivalents, per equivalent of the compound of Formula E. In another variant, the amount of nitric acid used for this step may vary from about 3 to about 6 molar equivalents, per equivalent of the compound of Formula E.

The amount of trifluoromethanesulfonic acid (CF_3SO_2OH) used for this step may vary from about 1 to about 6 molar equivalents , per equivalent of the compound of Formula E. In a particular variant, the amount trifluoromethanesulfonic acid used for this step may be about 4 or more molar equivalents, per equivalent of the compound of Formula E. In another variant, the amount trifluoromethanesulfonic acid used for this step may vary from about 1 to about 4 molar equivalents, per equivalent of the compound of Formula E. Alternatively, the reaction may also be carried out using sulfuric acid instead of trifluoromethanesulfonic acid.

Reduction of the compound of Formula F, using methods well known to those of skill in the art, yields the compound of Formula G. This reduction may be accomplished, for example, using hydrogen and a palladium catalyst such as palladium hydroxide in methanol at about room temperature.

Alternatively, this reduction of the compound of Formula F may be accomplished using Raney nickel, which is inexpensive and easy to handle in commercial production quantities. The process includes contacting the compound of Formula E with Raney nickel in a suitable solvent with hydrogen. Suitable solvents that may be used for this reduction include, but are not limited to: alcoholic solvents such as methanol, ethanol, isopropyl alcohol and n-propanol; halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform and carbon tetrachloride; ketone solvents such as acetone, ethyl methyl ketone and methyl isobutyl ketone; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate and t-butyl acetate; ether solvents such as diethyl ether, dimethyl ether, diisopropyl ether, methyl t-butyl ether, tetrahydrofuran and 1,4-dioxane; hydrocarbon solvents such as toluene, xylene, n-heptane, cyclohexane and n-hexane; nitrile solvents such as acetonitrile and propionitrile; dimethylsulfoxide (DMSO); N,N-dimethylformamide (DMF); N,N-dimethylacetamide; water; and mixtures thereof. In embodiments, the reaction may be carried out in an autoclave vessel. The compound of Formula F, Raney nickel and an organic solvent may be mixed together and stirred under hydrogen pressure until the reaction is complete. The reaction time typically varies from about 5 hours to 20 hours. Optionally, the reaction may be conducted at higher temperatures to enhance progress of the reaction as may be determined by person skilled in the art. After the completion of the reaction, the product may be isolated by conventional techniques known in the art.

The obtained product of Formula G may be subjected to cyclization to obtain the compound of Formula H. The cyclization may be accomplished by following the processes described in the literature, using reagents such as 2,3-dihydroxy-1,4-dioxane, glyoxal or glyoxal sodium bisulfite hydrate.

The compound of Formula H obtained according to the process described herein may have a nitrogen-protecting group, which may be removed by suitable reagents depending upon the nature of the protecting group to obtain varenicline. Deprotection may be accomplished using methods well known to those of skilled

in the art, for example, reacting the protected compound with a lower alkanol and an aqueous alkali metal, alkaline earth metal, or ammonium hydroxide or carbonate, such as aqueous sodium carbonate, at a temperature from about 50°C to about 100°C, such as at about 70°C, for about two to about six hours.

The varenicline free base thus obtained may be converted in to varenicline tartrate by a process such as:

i) providing a solution of varenicline free base in an organic solvent;

ii) treating the solution with between about 1 and about 5 equivalents of L-tartaric acid, per equivalent of varenicline, to cause precipitation of a solid; and

iii) collecting the precipitating solid, which is varenicline tartrate.

Providing a solution of varenicline tartrate in a suitable solvent includes either of:

(i) direct use of a reaction mixture containing varenicline free base and obtained in the course of synthesis; and

(ii) dissolution of varenicline free base in a suitable solvent.

As set forth above, in a particular variant, the amount L-tartaric acid used for the preparation of varenicline tartrate may vary from about 1 to 2.3 molar equivalents, per equivalent of varenicline free base. In another variant, the amount L-tartaric acid used for the preparation varenicline tartrate may vary from about 2.3 to about 5 molar equivalents, per equivalent of varenicline free base.

The solvents that may be used in this process include: C_1-C_6 alkyl alcohols such as methanol and ethanol; C_1 -C_6 alkyl ketones such as acetone, methyl ethyl ketone; C_1-C_6 alkyl ethers such as diethyl ether, methyl ethyl ether, and diisopropyl ether; nitriles such as acetonitrile; C_1 -C_6 alkyl esters such as ethyl acetate and isopropyl acetate; etc.

Optionally, the intermediates of varenicline tartrate obtained may be converted into acid-addition salts by reacting with a pharmaceutically acceptable acid. Examples of such acids include: inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid, and the like; and organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, and the like. The conversion of a intermediate into its salt increases the stability of the compound and hence these salts may be stored for an extended time depending on their stability after their manufacture.

The intermediates of varenicline tartrate that are obtained may have sufficient purity which may be used in the subsequent step without further purification. If desired, the intermediates may be purified by any of the general techniques such as recrystallization, crystallization, slurry washing, distillation, column chromatography, etc., to produce substantially pure intermediates having greater than about 90%, or greater than about 95%, or greater than about 98%, by weight purity, such as can be determined using high performance liquid chromatography (HPLC).

Amorphous varenicline tartrate, or solid dispersions of amorphous varenicline tartrate or crystalline varenicline tartrate, of the present application may contain less than about 0.5% by weight of total impurities, as determined by HPLC. In another embodiment, the total impurities are less than about 0.2%, or less than about 0.1%, or less than about 0.05%, by weight.

In another embodiment of the present application, there are provided pharmaceutical compositions that include a therapeutically effective amount of an amorphous form of varenicline tartrate or a solid dispersion of amorphous varenicline tartrate, and at least one pharmaceutically acceptable excipient.

Amorphous varenicline tartrate, or a solid dispersion of amorphous varenicline tartrate or crystalline varenicline tartrate, described herein may be formulated into solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, pills and capsules, liquid oral dosage forms such as but not limited to syrups, suspensions, dispersions, and emulsions, and injectable preparations such as but not limited to solutions, dispersions, and freeze-dried compositions. Formulations may be in the form of immediate release, delayed release or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combinations of matrix and reservoir systems. The compositions may be prepared using techniques such as direct blending, dry granulation or wet granulation, or by extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated or modified release coated. Compositions of the present

application may further comprise one or more pharmaceutically acceptable excipients.

In these compositions, the active product according to the invention is mixed with one or more pharmaceutically acceptable excipients. The drug substance may be formulated as liquid compositions for oral administration including for example solutions, suspensions, syrups, elixirs and emulsions, containing solvents or vehicles such as water, sorbitol, glycerine, propylene glycol or liquid paraffin etc.

The compositions for parenteral administration may be suspensions, emulsions, aqueous or non-aqueous sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g., ethyl oleate, may be employed. These compositions may contain adjuvants, especially wetting, emulsifying and dispersing agents. Sterilization may be carried out in several ways, e.g., using a bacteriological filter, by incorporating sterilizing agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions, which may be dissolved at the time of use in sterile water or any other sterile injectable medium.

Pharmaceutically acceptable excipients that find use in the present application include, but are not limited to: diluents such as starches, pregelatinized starches, lactose, powdered celluloses, microcrystalline celluloses, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses, hydroxypropyl methylcelluloses, pregelatinized starches, and the like; disintegrants such as starches, sodium starch glycolate, pregelatinized starches, crospovidones, croscarmellose sodium, colloidal silicon dioxides, and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxides, and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants; complex-forming agents such as various grades of cyclodextrins and resins; and release rate-controlling agents such as hydroxypropyl celluloses, hydroxymethyl celluloses, hydroxypropyl methylcelluloses, ethyl celluloses, methyl celluloses, various grades of methyl methacrylates, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but are not limited

to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants, and the like.

Having described the invention with reference to certain embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

The following examples further describe certain specific aspects and embodiments of the invention. These examples are provided solely for purposes of illustration and are not intended to limit the scope of the invention in any manner.

EXAMPLE 1

1A: Preparation of 1,2,3,4-tetra hydro-1,4-methanonaphthalene-2,3-diol.

1,4-Dihydro-1,4-methanonaphthalene (100 g), acetone (1006 mL), water (126 mL), N-methylmorpholine-N-oxide (85 mL), and osmium tetroxide (90 mL, 2% in t-butanol) were placed into a flask at 28°C. The reaction mixture was stirred vigorously until completion of the reaction at 28°C (7 days, with an additional 20 mL of osmium tetroxide and 85 mL of N-methylmorpholine-N-oxide being added after 3 days). The reaction mass was filtered at 28°C and the solid was dried (yield, 53.5 g).

Water (500 mL) was added to the filtrate and then extracted with methylene chloride (2×500 ml) at 28°C. The organic layers were combined, washed with water (250 mL) and the solvent was completely distilled under vacuum below 37°C. To the obtained mass, petroleum ether (120 mL) was added and it was stirred for 60 minutes at 30°C. The obtained solid was collected by filtration and dried at 30°C for 3 hours to obtain additional product (yield, 46 g).

The overall yield is 99.5 g.

1B: Preparation of 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol.

1,4-Dihydro-1,4-methanonaphthalene (5 g) and acetone (50 mL) were placed into a flask at 28°C. Water (6.2 mL), N-methylmorpholine-N-oxide (8.5 g), and osmium tetraoxide (1.1 mL, 2% in t-butanol) were added at 28°C. The reaction mixture was placed in a sonicator at 28-34°C for 6 hours. An aqueous solution of

sodium sulfite (2.5 g in 50 mL water) was added to the reaction mixture. Dichloromethane (100 mL) was added to the reaction mass and the organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane (50 mL). The organic layers were combined, washed with water and the solvent was completely distilled under vacuum below 32°C. To the obtained mass, petroleum ether (30 mL) was added and the mixture was stirred for 30 minutes at 27°C. The obtained solid was collected by filtration, washed with petroleum ether and dried at 48°C for 3 hours (yield, 5.1 g).

1C: Preparation of 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol.

1,4-Dihydro-1,4-methanonaphthalene (2 g), methylene chloride (22 mL) and 40% aqueous NaOH solution (22 mL) were placed into a flask at 28°C. Triethylbutylammonium chloride (0.3 g) was charged and the reaction mass and then cooled to 4°C. $KMnO_4$ (2.3 g) was added in increments over 2 hours at 3-4°C. After maintenance of the reaction mixture at 4°C for 9 hours, water (50 mL) and t-butyl methyl ether (100 mL) were charged into the reaction mass. The reaction mass was stirred for 10 minutes and filtered through a Hyflow (flux-calcined diatomaceous earth) bed. The aqueous and organic layers were separated and the aqueous layer was extracted with t-butyl methyl ether (100 mL). The organic layers were combined and distilled under vacuum at 40°C to obtain a residue. Petroleum ether (10 mL) was added to the residue at 28°C, stirred for 25 minutes and filtered to obtain the product (yield, 0.5 g).

EXAMPLE 2

2A: Preparation of 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-triene hydrochloride.

1,2,3,4-Tetrahydro-1,4-methanonaphthalene-2,3-diol (50 g) was placed into a flask. Water (1312.5 mL) and dichloroethane (525 mL) were added at 26°C and the reaction mass was cooled to 10°C. Sodium periodate (63.75 g) and triethylbenzylammonium chloride (62.5 g) were added and the stirring was continued at 9-10°C for an additional hour and then organic and aqueous layers were separated. The aqueous layer was extracted with dichloroethane (100 mL). The organic layers were combined, dried over sodium sulphate, and then filtered.

To the solution, benzylamine (31.875 g) was added and the mixture was added to another flask containing a solution of sodium triacetoxyborohydride (192.5 g) in dichloroethane (1000 mL) at 5°C. The reaction mixture was allowed to warm to 25°C and stirred until completion of the reaction at 25-26°C (45 minutes). To the reaction mass, saturated sodium carbonate (375 mL) was slowly added and it was further stirred for an hour (pH ~9) at 26°C. Aqueous and organic layers were separated. The aqueous layer was extracted with dichloroethane (2×150 mL). The organic solvent was distilled completely under vacuum below 48°C.

The obtained residue was dissolved in dichloromethane (75 mL) and combined with silica gel (10 g), then solvent was evaporated under vacuum followed by drying the solid at 40-45°C for 15 minutes. The product was purified by column chromatography through silica gel by eluting with a mixture of ethyl acetate and petroleum ether (4:96 by volume). The pure drug fractions were combined, the solvent was distilled under vacuum, and the drug compound in the obtained residue was dissolved in ethyl acetate.

The ethyl acetate solution was cooled to 9-10°C and hydrogen chloride gas was passed through for 1 hour. The reaction mass was maintained for 1 hour, then the solid was filtered and washed with ethyl acetate. It was dried at 53°C for 3 hours (yield, 52.3 g).

2B: Preparation of 10-benzyl-10-aza-tricyclo [6.3.1.$0^{2,7}$] dodeca-2 (7), 3,5-triene hydrochloride

1,2,3,4-Tetrahydro-1,4-methanonaphthalene-2,3-diol (100 g) was placed into a flask. Water (1300 mL) and dichloromethane (500 mL) were added at 28°C, triethylbenzylammonium chloride (200 mg) was added, the mass was cooled to 10°C and sodium metaperiodate (146 g) was added. The reaction mass was maintained at 10–13°C for about one hour, 20 minutes and then cooling was discontinued. The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (500 mL). The combined organic layer was washed with water (3×500 mL), dried over sodium sulphate and then filtered to make reaction solution 1.

In another flask, dichloromethane (500 mL) and benzyl amine (61 g) were combined and cooled to 2°C. Sodium triacetoxyborohydride (364 g) was charged

into the mixture, then reaction solution 1 (prepared above) was added at 0-1°C and the mass was maintained for 15 minutes at 1-4°C, followed by maintenance at 25-27°C for about 2 hours, 30 minutes. The pH of the mass was adjusted with 5% sodium hydroxide solution (2.3 L) to 8.8 and then the mass was maintained for about one hour at 28°C. Aqueous and organic layers were separated and the aqueous layer was extracted with dichlromethane (500 mL) and the combined organic layer was washed with water (2×500 mL). The solvent was distilled from the organic layer under vacuum below 50°C to obtain the product (yield, 131 g).

EXAMPLE 3

3A: Preparation of 10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride.

10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trienehydrochloride (50 g), methanol (175 mL) and 20% palladium hydroxide on carbon (5 g) were charged into an autoclave vessel at 25°C and the mixture was stirred under hydrogen pressure (5 Kg/cm^2) for about 18 hours at 20-25°C. The mixture was filtered to remove the catalyst and the solid washed with methanol (50 mL). The solvent was removed from the filtrate under vacuum below 45°C. The solid obtained was washed with acetone (25 mL) and then dried at 45°C for 2 hours (yield, 32 g).

3B: Preparation of 10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride.

10-Benzyl-10-aza-tricyclo [6.3.1.$0^{2,7}$] dodeca-2 (7), 3,5-triene (30 g), methanol (400 mL) and 5% palladium on charcoal (9 g) were charged into an autoclave vessel at 25°C. The mixture was stirred under hydrogen pressure (5 Kg/cm^2) for about 5 hours at about 70°C and then cooled to 30°C. The mixture was filtered through a Hyflow bed to remove the catalyst and the solid was washed with methanol (100 mL). The solvent was removed from the filtrate under vacuum below 50°C. The residue was dissolved in dichloromethane (150 mL) at 28°C and the solution was dried over sodium sulphate (30 g) . The solvent was removed under vacuum below 50°C to obtain the product (yield, 16.0 g).

EXAMPLE 4: Preparation of 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone

The hydrochloride salt of 10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (18 g) was placed into a flask at 25°C and dichloromethane (225 mL) was added. The mixture was cooled to 4°C and pyridine (15.3 mL) was slowly added at 4°C. Trifluoroacetic anhydride (20.3 mL) was added slowly to the reaction mass at 3°C. The reaction mass was stirred at 3-5°C for 3 hours. 0.5 N HCl solution (100 mL) was added to the reaction mass slowly and the layers were separated. The aqueous layer was extracted with dichloromethane (3×50 mL). The organic layers were combined and washed with HCl (0.5 N, 50 mL), water (2×75 mL) and aqueous sodium bicarbonate (75 mL). The solvent was distilled completely under vacuum below 40°C to obtain the product (yield, 21 g).

EXAMPLE 5

5A: Preparation of 1-(4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoroethanone.

Trifluoromethanesulphonic acid (49.6 mL) and dichloromethane (221 mL) were placed into a flask at 28°C and cooled to 5°C. Fuming nitric acid (12.4 mL) was added at the same temperature and maintained for 30 minutes at 4-5°C. A solution of 1-(10-Azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone (31 g) in dichloromethane (217 mL) was added over 10 minutes at 4-10°C. The reaction mixture was stirred at 4-7°C for 2 hours. The temperature of the reaction mass was raised to 28°C and it was then stirred for 5 hours. Water (442 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (147 mL). The organic layers were combined and washed with aqueous sodium bicarbonate solution (147 mL). The solvent was distilled completely under vacuum below 35°C. To the obtained mass, acetone (40 mL) and petroleum ether (40 mL) were added and stirred for 40 minutes at 28°C. The solid was collected by filtration, washed with acetone and then dried at 28°C for 2 hours (yield, 24 g).

5B: Preparation of 1-(4,5-dinitro-10-aza-tricyclo [6.3.1.$0^{2,7}$] dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoro-ethanone.

Sulphuric acid (151 mL) was placed into a flask at 29°C and cooled to 1-2°C. Fuming nitric acid (56 mL) was added at the same temperature and maintained for 30 minutes at 0-2°C. Dichloromethane (700 mL) was added to the reaction mass. A solution of 1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (140 g) in dichloromethane (700 mL) was added to the reaction mass over about 60 minutes at 1-3°C and maintained at 3-6°C for 15 minutes . The temperature of the reaction mass was raised to 25°C and stirred for about 1 hour at 25-28°C. Water (700 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (280 mL). The organic layers were combined and washed with water (2×700 mL). The solvent was distilled from the organic layer under vacuum below 45°C. Acetone (140 mL) and n-hexane (280 mL) were added to the residue at 28°C and stirred for about 25 minutes at 0-5°C. The solid was isolated by filtration, washed with a mixture of acetone (70 mL) and n-hexane (140 mL) and the product was dried at 50°C for about 4 hours (yield, 119.0 g).

EXAMPLE 6

6A: Preparation of 1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoroethanone.

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoro-ethanone (10 g) and ethyl acetate (100 mL) were placed into an autoclave at 28°C. Raney nickel (10 g) was added and the reaction mixture was stirred under hydrogen pressure (5 Kg/cm^2) for 12 hours at the same temperature. The reaction mixture was filtered to remove the catalyst and washed with ethyl acetate (50 mL). The solvent was distilled from the filtrate completely under vacuum below 50°C to obtain the product in the form of an oil (yield, 8.3 g).

6B: Preparation of 1-(4,5-Diamino-10-aza-tricyclo [6.3.1.$0^{2,7}$] dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoroethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoroethanone (70 g) and methanol (700 mL) were placed into an autoclave at

28°C. Palladium hydroxide (7 g) was added and the reaction mixture was stirred under hydrogen pressure (4-5 Kg/cm^2) for about 4 hours at the same temperature. The reaction mixture was filtered to remove the catalyst and the solid washed with methanol (150 mL). The solvent was distilled from the filtrate under vacuum below 50°C and methanol (105 mL) was added at 32°C. The mixture was cooled and maintained at 0-4°C for about 40 minutes. The compound was isolated by filtration, washed with methanol (25 mL) and dried at 58°C for about 4 hours (yield, 46.0 g).

EXAMPLE 7

7A: Preparation of 1-(5,8,14-triazatetracyclo[10.3.1.0$^{2,11.}$ 0^{4,9}]hexadeca-2(11),3,5,9-pentaene)-2,2,2-trifluoroethanone.

1-(4,5-Diamino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoroethanone (22.5 g) and tetrahydrofuran (90 mL) were placed into a flask and stirred for 10 minutes at 28°C to produce a clear solution. Water (90 mL) and glyoxal sodium bisulfite hydrate (45 g) were added to the reaction mass and heated to 64°C. The reaction mixture was stirred at 55-64°C for 3 hours. The reaction mixture was cooled to 27°C and then extracted with ethyl acetate (3×150 mL). The combined organic layer was washed with water and dried over sodium sulfate (15 g), and then was distilled completely under vacuum below 45°C (yield, 19.5 g).

7B: Preparation of 1-(5,8,14-triazatetracyclo [10.3.1.0$^{2,11.}$ 0^{4,9}] hexadeca-2 (11), 3,5,9-pentaene) - 2,2,2-trifluoroethanone

1-(4,5-Diamino-10-aza-tricyclo [6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoroethanone (50 g) and methanol (200 mL) were placed into a flask and stirred for 5 minutes at 28°C. Water (200 mL) and glyoxal sodium bisulfite hydrate (56 g) were added and the mixture was heated to 63°C. The mixture was stirred at 60-63°C for about 2 hours. Water (400 mL) was added at about 63°C. The mixture was cooled to 43°C and maintained for about 40 minutes at the same temperature. The solid obtained was filtered and washed with a mixture of methanol (100 mL) and water (200 mL) and then dried at 62°C for about 5 hours (yield, 44.0 g).

EXAMPLE 8

8A: Preparation of 1-(5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene (varenicline free base).

1-(5,8,14-triazatetracyclo[10.3.1.$0^{2,11}0^{4,9}$]hexadeca-2(11),3,5,9-pentaene)-2,2,2-trifluoroethanone (19 g), methanol (114 mL) and water (114 mL) were placed into a flask at 27°C. Sodium carbonate (12.9 g) was added and the reaction mixture was heated to 70°C and maintained for 2 hours at 70-71°C, then was cooled to 27°C and water (200 mL) was added to the reaction mass. The mass was extracted with dichloromethane (3×150 mL). The combined organic layer was washed with water (200 mL), dried over sodium sulfate and the solvent was removed completely under vacuum below 37°C (yield, 12 g).

8B: Preparation of 1-(5,8,14-triazatetracyclo [10.3.1.02,11. 04,9] hexadeca-2 (11), 3,5,7,9-pentaene (varenicline free base).

1-(5,8,14-triazatetracyclo [10.3.1.$0^{2,11}$.$0^{4,9}$] hexadeca-2 (11), 3,5,9-pentaene) - 2,2,2-trifluoroethanone (12 g) and methanol (60 mL) were placed into a flask at 28°C. Sodium carbonate (6.6 g) and water (60 mL) were added under stirring. The mixture was heated to about 77°C and maintained for about 2 hours at about the same temperature. The solvent was distilled under vacuum below 65°C. The residue was cooled to 27°C and water (120 mL) and dichloromethane (120 mL) were added and stirred for 10 minutes. Organic and aqueous layers were separated. The aqueous layer was extracted with dichloromethane (3×60 ml). The organic layers were combined and the solvent was distilled under vacuum below 48°C. n-Heptane (85 mL) was added to the residue at 48°C and then residual dichloromethane was removed by distillation below 49°C. The mixture was stirred for one hour at 28°C and filtered. The isolated solid was washed with n-heptane (25 mL) and dried at 62°C for about 5 hours (yield, 6.8 g).

EXAMPLE 9

9A: Preparation of crystalline varenicline tartrate.

Varenicline free base (10 g) and methanol (75 mL) were placed into a flask at 27°C and stirred for 5 minutes for complete dissolution. A solution of L-tartaric

acid (8.0 g) in methanol (75 mL) was added into the above reaction mass slowly over 30 minutes at 27°C. The reaction mixture was stirred at 28°C for 1 hour, 45 minutes. The precipitated solid was collected by filtration and washed with methanol (10 mL) and then dried at 45°C for 3 hours (yield, 13 g).

9B: Preparation of crystalline varenicline tartrate.

Varenicline free base (70 g) and methanol (400 mL) were placed into a flask at 28°C and stirred for 10 minutes for complete dissolution, and carbon (14 g) was added. The mixture was stirred for about 30 minutes and filtered, and the bed was washed with methanol (70 mL). To the filtrate, a solution of L-tartaric acid (55 g) in methanol (350 mL) was added slowly over 45 minutes at 28-33°C. The mixture was stirred at 28°C for about 1 hour, 15 minutes. The precipitated solid was isolated by filtration and washed with methanol (210 mL) and then dried at 60-63°C for about 7 hours (yield, 105 g).

EXAMPLE 10

10A: Preparation of amorphous varenicline tartrate.

Varenicline tartrate (1 g) and water (5 mL) were placed into a flask and stirred at 25°C for 10 minutes. Water (5 mL) was added and stirred for 15 minutes for complete dissolution. The solution was then subjected to freeze-drying at -10°C for 5 hours, followed by further drying at 60°C for about 4 hours (yield, 1 g).

10B: Preparation of amorphous varenicline tartrate.

Varenicline tartrate (0.514 g) and water (10 mL) were charged into a beaker and stirred for 10 minutes at 28°C for dissolution. The solution was spray dried in a Mini Buchi spray dryer under the conditions: feed rate, 3 mL/minute; aspirator 70%; inlet temperature 122°C; outlet temperature 71°C; and nitrogen pressure 6.5 Kg/cm^2; to produce 0.062 g of amorphous varenicline tartrate.

10C: Preparation of amorphous varenicline tartrate.

Varenicline tartrate (1 g), methanol (50 mL) and water (8 mL) were charged into a beaker and stirred for 10 minutes at 28°C for dissolution. The solution was filtered and the filtrate was spray dried in a Mini Buchi spray dryer under the conditions: feed rate, 3 mL/minute; aspirator 70%; inlet temperature 122°C; outlet

temperature 73°C; and nitrogen pressure 6.5Kg/cm^2; to produce 0.302 g of amorphous varenicline tartrate.

EXAMPLE 11: Preparation of amorphous solid dispersion of varenicline tartrate with hydroxypropyl cellulose (HPC).

Varenicline tartrate (3.0 g) and hydroxypropyl cellulose (3.0 g) were charged into a flask at 28°C and then 16% aqueous methanol (193.2 mL of methanol and 36.8 mL of water) was charged. The mixture was heated to 60°C to produce a solution, the solution was filtered, and the filtrate was spray dried using a Mini Buchi spray dryer under the conditions: feed rate 10% (3 mL/minute); aspirator 70%; inlet temperature 80°C; outlet temperature 55°C; and nitrogen pressure 5.0-kg/cm^2; to produce 2.8 g of an amorphous solid dispersion of varenicline tartrate with HPC.

The product obtained was found to be stable for at least 20 days at room temperature, and for at least 35 days at 0-5°C, when stored in a double polyethylene container.

EXAMPLE 12: Preparation of amorphous solid dispersion of varenicline tartrate with hydroxypropyl methylcellulose (HPMC).

Varenicline tartrate (4.0 g) and HPMC (4.0 g) were charged into a flask at 28°C and then 16% aqueous methanol (containing 168 mL of methanol and 32 mL of water) was charged. The mixture was heated to 60°C to produce a solution. The solution was filtered and the filtrate was spray dried using a Mini Buchi spray dryer under the conditions: feed rate 20% (6 mL/minute); aspirator 70%; inlet temperature 80°C; outlet temperature 46°C; and nitrogen pressure 5.0 Kg/cm^2; to produce 5.24 g of an amorphous solid dispersion of varenicline tartrate with HPMC.

The product obtained was found to be stable for at least 10 days at 0-5°C, when stored in a double polyethylene container.

EXAMPLE 13: Preparation of amorphous solid dispersion of varenicline tartrate with povidone (PVP).

Varenicline tartrate (4.0 g) and povidone K-30 (4.0 g) were charged into a flask at 28°C and then 16% aqueous methanol (containing 168 mL of methanol

and 32 mL of water) was charged. The mixture was heated to 60°C to produce a solution. The solution was filtered and the filtrate was spray dried using a Mini Buchi spray dryer under the conditions: feed rate 20% (6 mL/minute); aspirator 70%; inlet temperature 80°C; outlet temperature 46°C; and nitrogen pressure 5.0 Kg/cm^2; to produce 4.8 g of an amorphous solid dispersion of varenicline tartrate with PVP.

The product obtained was found to be stable for at least 50 days at room temperature, and at least 111 days at 0-5°C, when packaged under a nitrogen atmosphere.

CLAIMS:

1. Amorphous varenicline tartrate.

2. The amorphous varenicline tartrate of claim 1, having an X-ray powder diffraction pattern substantially in accordance with Figure 1.

3. The amorphous varenicline tartrate of claim 1, having a water content in the range of about 0.1 to about 10 percent, by weight.

4. A process for preparing amorphous varenicline tartrate, comprising removing solvent from a solution of varenicline tartrate.

5. The process of claim 4, wherein the solvent comprises water, an organic solvent, or a mixture of water and an organic solvent.

6. The process of claim 4, wherein a solvent comprises water, an alcohol, a ketone, a halogenated solvent, an ester, an ether, a hydrocarbon, a nitrile, or any mixture of two or more thereof.

7. The process of claim 4, wherein a solvent comprises water, methanol, ethanol, isopropyl alcohol, or a mixture of two or more thereof.

8. An amorphous solid dispersion comprising varenicline tartrate and a pharmaceutically acceptable carrier.

9. The solid dispersion of claim 8, wherein a pharmaceutically acceptable carrier comprises hydroxypropyl cellulose, hydroxypropyl methylcellulose, or povidone.

10. A process for preparing an amorphous solid dispersion of varenicline tartrate, comprising removing solvent from a solution comprising varenicline tartrate and a pharmaceutically acceptable carrier.

11. The process of claim 10, wherein a solvent comprises water, an organic solvent, or a mixture of water and an organic solvent.

12. The process of claim 10, wherein a solvent comprises water, an alcohol, a ketone, a halogenated solvent, an ester, an ether, a hydrocarbon, a nitrile, or any mixture of two or more thereof.

13. The process of claim 10, wherein a solvent comprises water, methanol, ethanol, isopropyl alcohol, or a mixture of two or more thereof.

14. The process of any of claims 4-7 or 10-13, wherein removing solvent comprises spray drying, freeze drying, agitated thin film drying, or lyophilization.

15. A pharmaceutical composition containing amorphous varenicline tartrate of any of claims 1-3, or an amorphous solid dispersion comprising varenicline tartrate of either of claims 8 or 9, and one or more pharmaceutically acceptable excipients.

FIG. 1

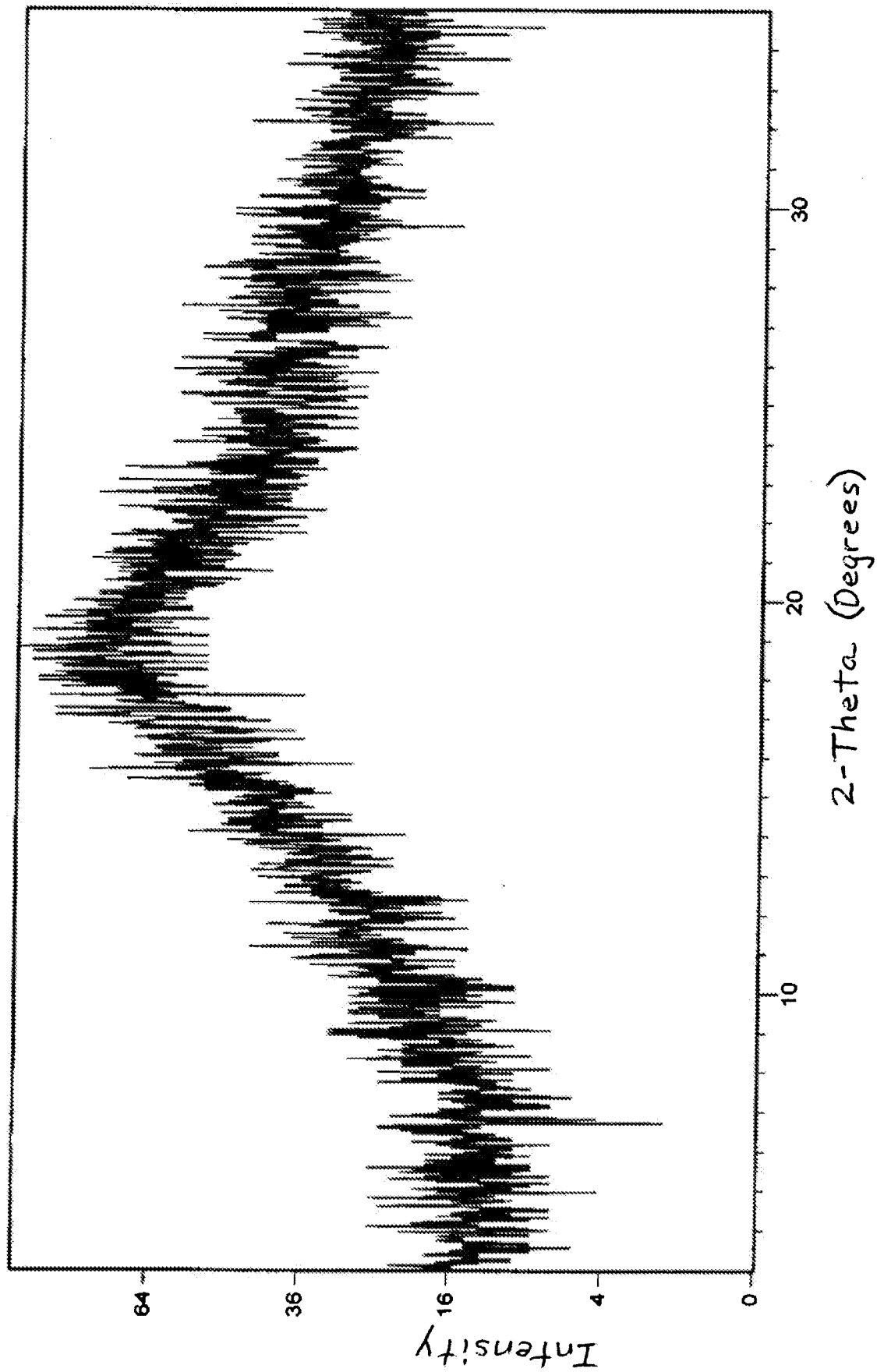
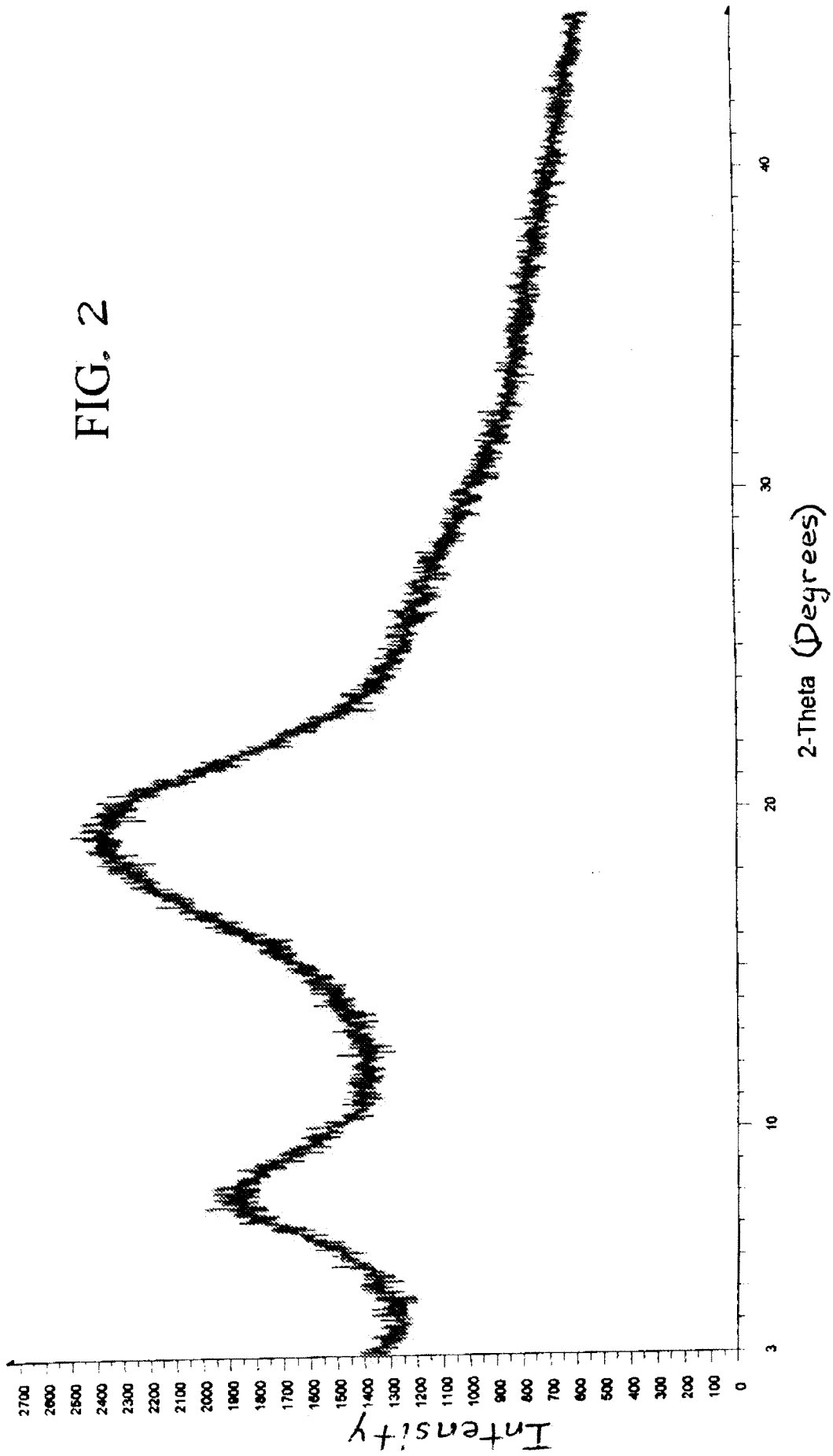


FIG. 2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2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
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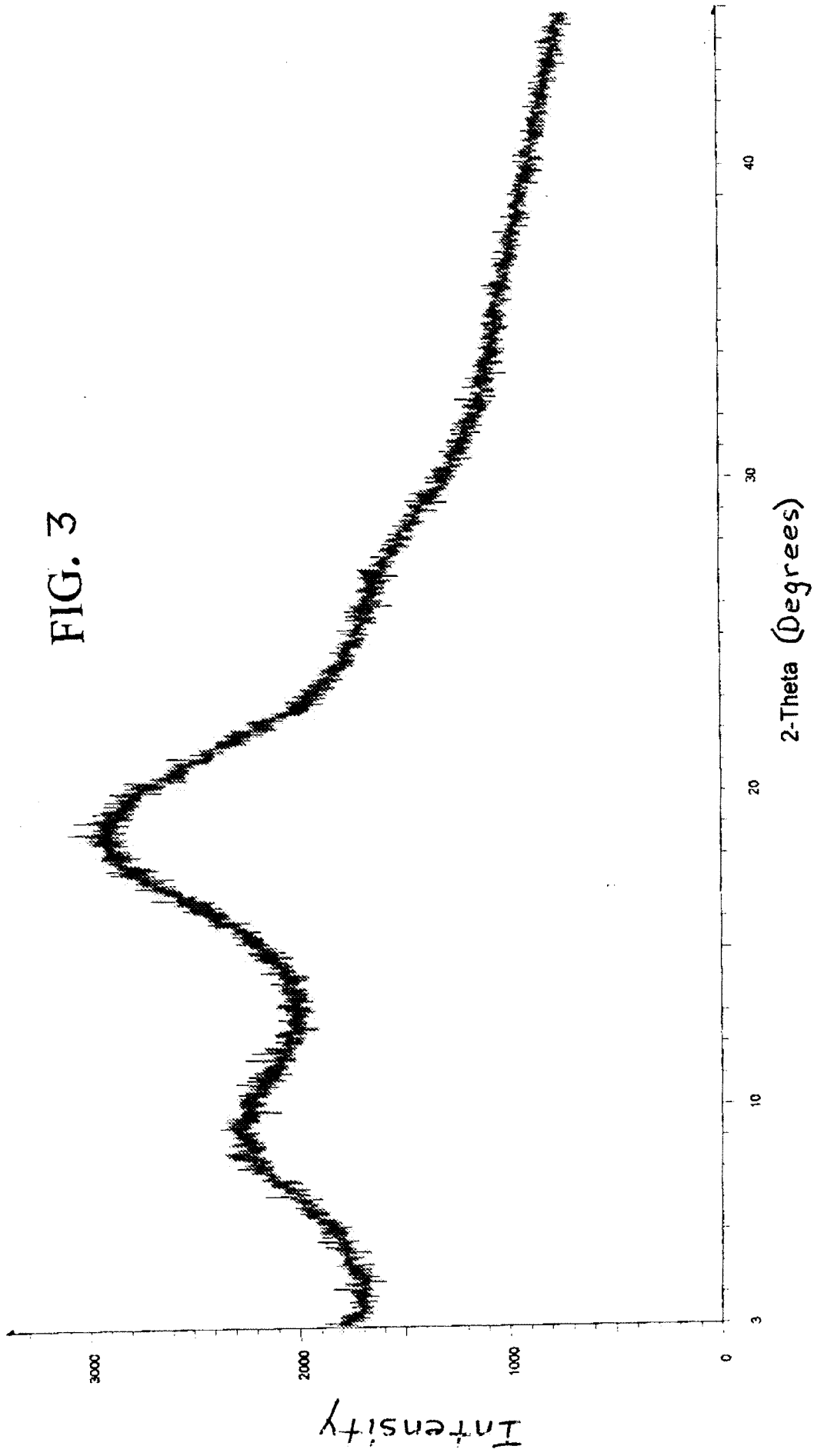
500
400
300
200
100
0
3
10
20
30
40
2-Theta (Degrees)

FIG. 3



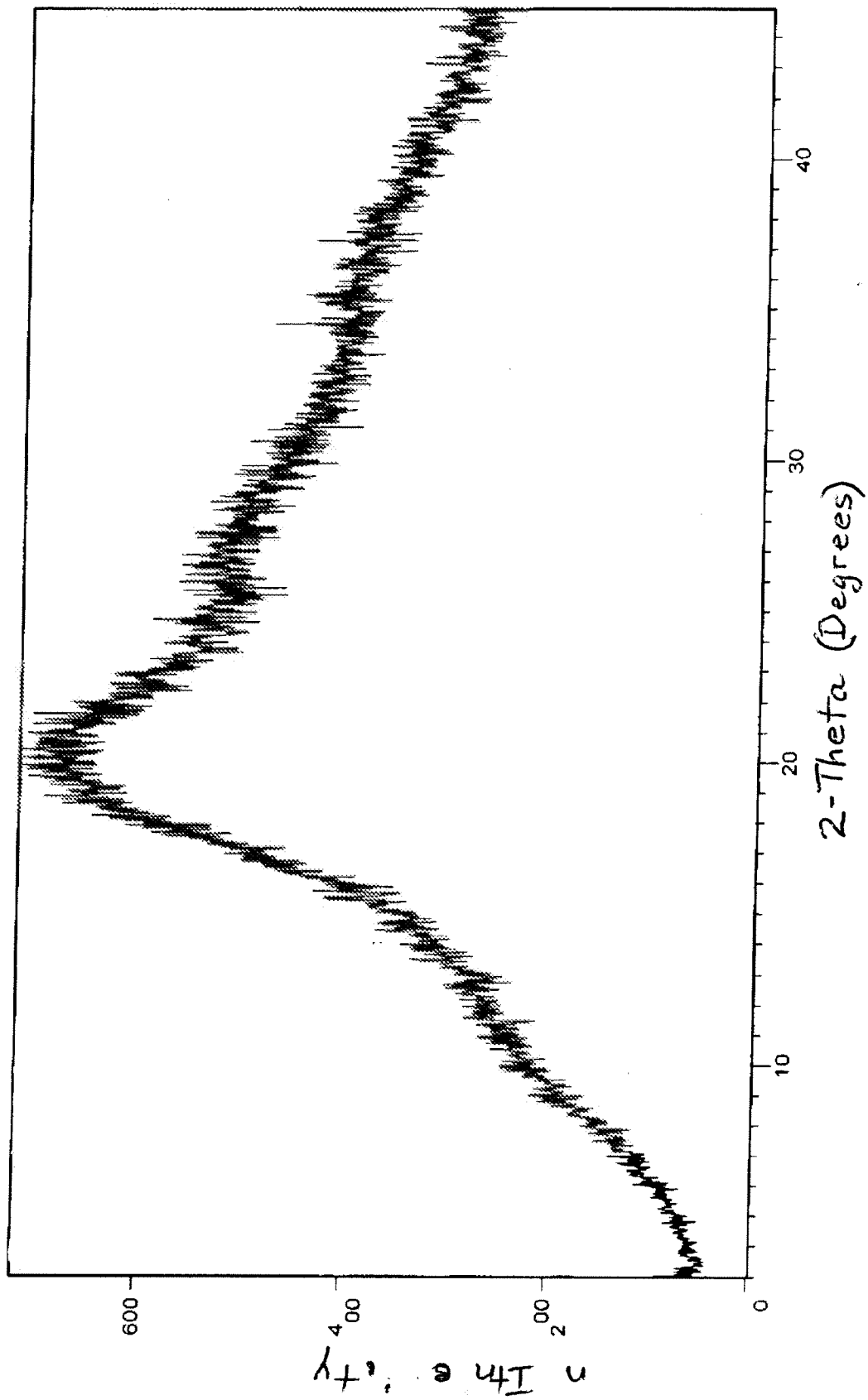


FIG. 4