(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2012 (20.09.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/123963 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/IN2012/000126

(22) International Filing Date:
23 February 2012 (23.02.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
511/MUM/2011 24 February 2011 (24.02.2011) IN

(71) Applicant *(for all designated States except US)*: **MEGAFINE PHARMA (P) LTD.** [IN/IN]; 4th Floor, Sethna 55, Maharshi Karve Road, Marine Lines, Mumbai 400002, Maharashtra (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MATHAD, Vijayavitthal Thippannachar** [IN/IN]; Flat No.5, Nirman Classic, Behind HDFC BANK, Thatte Nagar, Nashik-422005, Maharashtra (IN). **SOLANKI, Pavankumar Vrajlal** [IN/IN]; Megafine Pharma (P) Ltd., Gut No.201, Lakhmapur, Dindori, Nashik - 422202, Maharashtra (IN). **PANDIT, Bhushan Sudhakar** [IN/IN]; Megafine Pharma (P) Ltd., Gut No.201, Lakhmapur, Dindori, Nashik - 422202, Maharashtra (IN). **UPPELLI, Sekhar Babu** [IN/IN]; Megafine Pharma (P) Ltd., Gut No.201, Lakhmapur, Dindori, Nashik - 422202, Maharashtra (IN).

(74) Agent: **GHARVE, Shilpa**; LEGA SOLV, C-302, RNA Regency Park, M.G. Road, Kandivali (West), Mumbai 400067, Maharashtra (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/123963 A2

(54) **Title**: A PROCESS FOR PREPARATION OF ILOPERIDONE AND AMORPHOUS CO- PRECIPITATE OF ILOPERIDONE WITH PHARMACEUTICALLY ACCEPTABLE EXCIPIENT

(57) **Abstract**: A process for preparation of iloperidone wherein 1-(4-(3-chloropropoxy-3- methoxyphenyl)ethanone is reacted with 6-fluoro-3-piperidin-4-yl-1,2 benzisoxazole hydrochloride in a biphasic solvent system in presence of an inorganic base and a phase transfer catalyst. Further, process for preparation of an amorphous co-precipitate of iloperidone or its acid addition salt along with pharmaceutically acceptable excipient is proposed. Further, the present invention also relates to a co-precipitate of amorphous form of iloperidone along with pharmaceutically acceptable excipients.

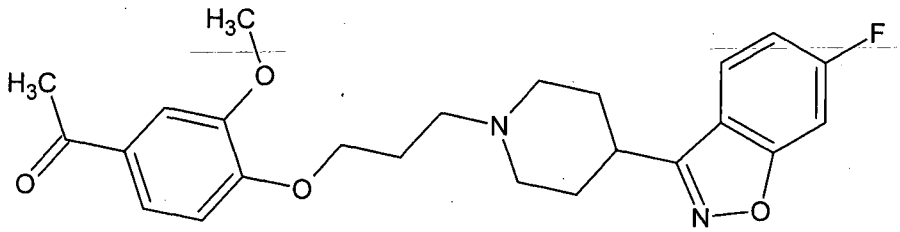
TITLE OF THE INVENTION

A PROCESS FOR PREPARATION OF ILOPERIDONE AND AMORPHOUS CO-PRECIPITATE OF ILOPERIDONE WITH PHARMACEUTICALLY ACCEPTABLE EXCIPIENT

This application claims priority from Indian Patent Application No. 511/MUM/2011 filed on 24th February 2011.

FIELD OF INVENTION:

The present invention relates to a process for preparation of iloperidone of the formula (I);



Formula (I)

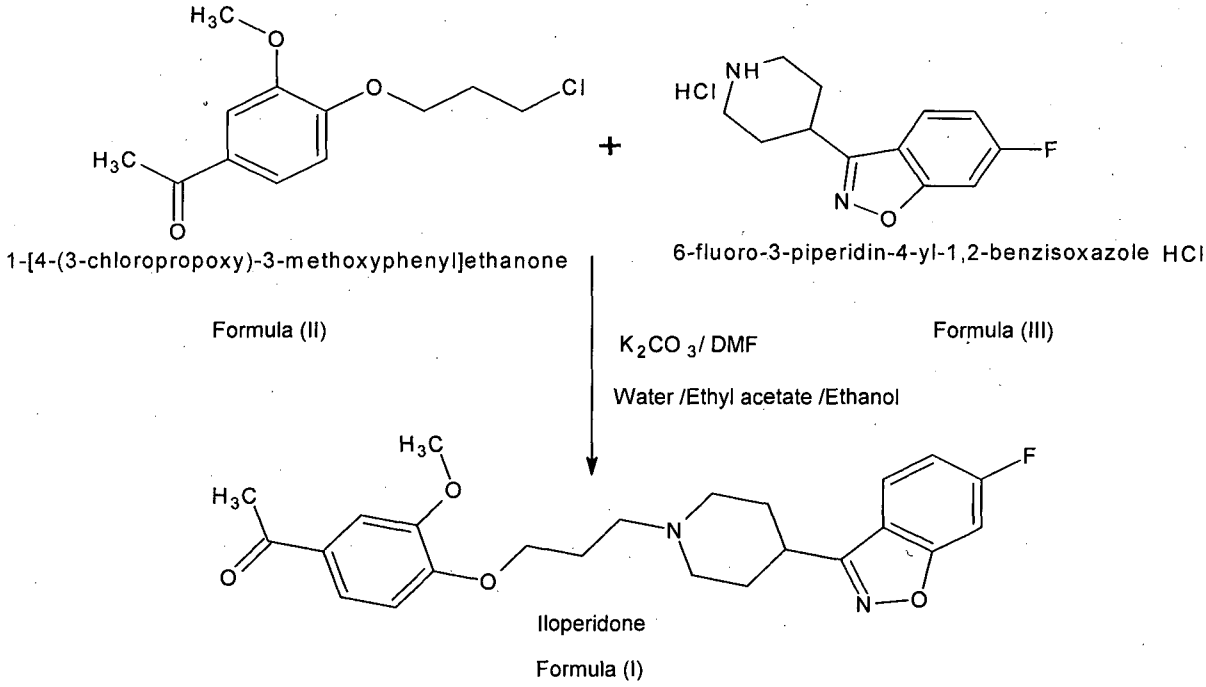
wherein the said process substantially eliminates potential impurities and improves yield. More particularly, the present invention also relates to a co-precipitate of amorphous form of iloperidone along with pharmaceutically acceptable excipients.

The present invention further relates to a process for preparation of co-precipitate of amorphous form of iloperidone along with pharmaceutically acceptable excipients.

BACKGROUND OF THE INVENTION:

Iloperidone, also known as Fanapt, Fanapta, and previously known as Zomaril, is an atypical antipsychotic drug used for the treatment of schizophrenia. The chemical name of iloperidone is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1- piperidinyl]propoxy] -3-methoxyphenyl]ethanone.

EP 0402644 patent discloses first synthetic route of synthesis of iloperidone as shown in Scheme I, which consists of alkylation reaction between 1-(4-(3-chloropropoxy-3-methoxyphenyl)ethanone of the formula (II) and 6-fluoro-3-piperidin-4-yl-1,2 benzisoxazole hydrochloride of the formula (III) in presence of potassium carbonate in N,N dimethyl formamide. The reaction has been subsequently worked up and the compound of formula (I) is extracted from water using ethyl acetate. The compound of formula (I) is purified by crystallization using ethanol. The overall yield of compound of formula (I) is 58%.

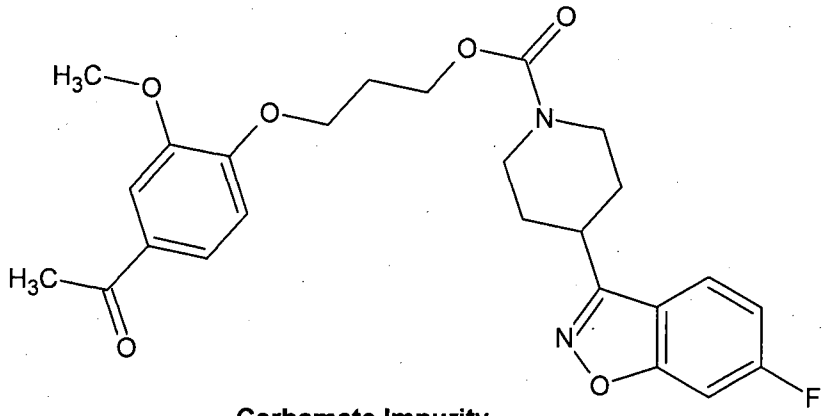


SCHEME 1

Further, we have analyzed the reported synthetic route for synthesis of iloperidone; following limitations have been observed and identified in the reported synthetic route:

a) The yield obtained using said synthetic route as reported in US RE39198 is 58%. Hence, this route of synthesis is not cost efficient at commercial scale due to low yield;

b) Use of potassium carbonate as a base in reaction leads to formation of carbon dioxide as one of the side products during the reaction, which further hinders in the manufacturing process by actively participating in manufacturing process and thereby leads to the formation of carbamate impurity of the formula (IV):



Carbamate Impurity

Formula (IV)

which is in the range of 15-20%, and thereby resulting in low yield of iloperidone;

c) Purification by crystallization using ethanol as a solvent is not effective in eliminating or controlling carbamate impurity below 0.15% as per the ICH guide lines for the known impurities; and

d) Iloperidone obtained by the above synthetic process is beige in colour.

CN101768154 discloses the synthesis of iloperidone by N-alkylation reaction between 1-(4-(3-chloropropoxy-3-methoxyphenyl)ethanone of the formula (II) and 6-fluoro-3-piperidin-4-yl-1,2 benzisoxazole hydrochloride of the formula (III) in inorganic alkaline solution, particularly; alkali metal carbonate solution. We have analyzed the reported synthetic route for synthesis of

iloperidone and have observed and identified that the use of alkaline carbonate solution leads to the formation of carbamate impurity in the range of 1 to 1.5%.

Several patents were published after, describing essentially the same synthetic way such as US5364866 and US5663449.

Process research and development in pharmaceutical companies aim to produce a process for the manufacture of a chemical intermediate or an active pharmaceutical ingredient (API) at minimal cost with high yield and better quality.

According to the current state of art, amorphous form of iloperidone is not disclosed in the existing art. Amorphous forms of active pharmaceutical ingredients (APIs) provides an opportunity to improve the performance characteristics, inclusive of solubility, stability, flowability, tractability and compressibility of drug substances, and the safety and efficacy of drug products of a pharmaceutical product. These discoveries enlarge scope available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

Generally, amorphous solids offer opportunities for solubility and bioavailability enhancement since these materials are more soluble than the crystalline form of the same compound. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments.

The problem faced in production of amorphous form is highly unstable nature of these amorphous forms due to extreme hygroscopic nature of the amorphous form and thereby increasing the level of difficulty of preparation of the same and maintaining the integrity of the form throughout their lifecycle.

Hence, there is an urgent need for a solution that overcomes these limitations stated above.

The present invention proposes a process for preparation of iloperidone and a stable co-precipitate of amorphous iloperidone along with pharmaceutically acceptable excipients.

OBJECTS OF THE PRESENT INVENTION :

The primary object of the present invention is to provide a process for preparation of iloperidone of formula (I); wherein the reaction is carried out in a biphasic solvent system in presence of an inorganic base and a phase transfer catalyst.

Another object of the present invention is to provide a process for preparation of iloperidone of formula (I) wherein the yield is improved to 95% thereby making the process efficient, high throughput and cost-effective.

Still another object of the present invention is to provide a process for preparation of iloperidone of formula (I) wherein the said process eliminates laborious workup, extensive purifications, and avoids the exposure of production personnel to pharmaceutical industrial operations. Hence, makes the process simple and easy and user friendly.

Yet another object of the present invention is to provide a process for preparation of iloperidone of formula (I), wherein the iloperidone obtained is substantially free from impurities and thereby substantially eliminating the purification steps required and further making process cost effective and efficient.

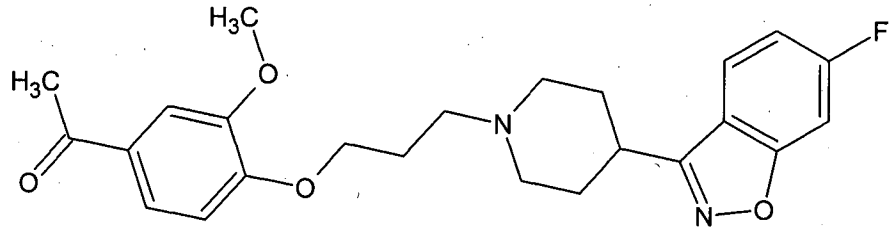
An additional object of the present invention is to provide amorphous form of iloperidone of formula (I).

Still another additional object of the present invention is to provide a stable co-precipitate of amorphous form of iloperidone along with pharmaceutically acceptable excipient.

Yet another additional object of the invention is to provide stable co-precipitate of amorphous form of iloperidone along with pharmaceutically acceptable excipient which can be directly used in pharmaceutical formulation.

SUMMARY OF THE INVENTION:

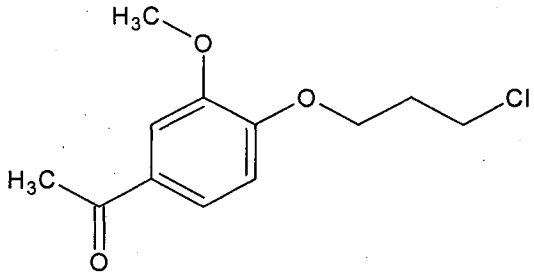
The present invention provides a process for preparation of iloperidone of formula (I);



Formula (I)

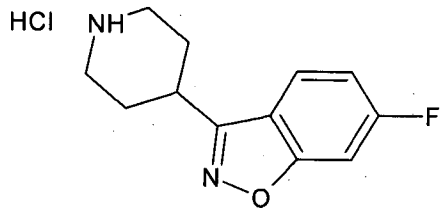
wherein, the said process comprising:

a. reacting 1-(4-(3-chloropropoxy-3-methoxyphenyl)ethanone having structure (formula II):



Formula (II)

with 6-fluoro-3-piperidin-4-yl-1,2 benzisoxazole hydrochloride having structure (formula III)



Formula (III)

in a biphasic solvent system and in presence of an inorganic base and a phase transfer catalyst; and

b. isolating of the said iloperidone of the formula (I) of step (a).

Further, the process of the present invention substantially eliminates potential impurities and thereby improves yield. More particularly, the present invention also relates to amorphous co-precipitate of iloperidone along with pharmaceutically acceptable excipients. The present invention further relates to a process for preparation of amorphous co-precipitate of iloperidone along with pharmaceutically acceptable excipients.

BRIEF DESCRITPION OF DRAWINGS :

Figure 1 of the present invention illustrates X-ray powder diffraction (XRD) pattern of co precipitates of amorphous form of iloperidone of the formula (I) with polyvinylpyrrolidone as a pharmaceutically acceptable excipient, prepared according to example 3.

Figure 2 of the present invention illustrates Infrared spectrum (IR) of co precipitates of amorphous form of iloperidone of the formula (I) with polyvinylpyrrolidone as a pharmaceutically acceptable excipient, prepared according to example 3.

DETAILED DESCRIPTION OF THE INVENTION:

Before the present invention is described, it is to be understood that this invention is not limited to particular methodologies and materials described, as these may vary as per the person skilled

in the art. It is also to be understood that the terminology used in the description is for the purpose of describing the particular embodiments only, and is not intended to limit the scope of the present invention.

Before the present invention is described, it is to be understood that unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Further, it is to be understood that the present invention is not limited to the methodologies and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described, as these may vary within the specification indicated. Unless stated to the contrary, any use of the words such as "including," "containing," "comprising," "having" and the like, means "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations. The described embodiments of the invention and the disclosed examples are given for the purpose of illustration rather than limitation of the invention as set forth the appended claims. Further the terms disclosed embodiments are merely exemplary methods of the invention, which may be embodied in various forms.

The term “coprecipitates” or “co-precipitate” as used herein are synonymous and refers to compositions comprising amorphous iloperidone together with at least one pharmaceutically acceptable excipient, being prepared by removing the solvent from the solution containing both of them.

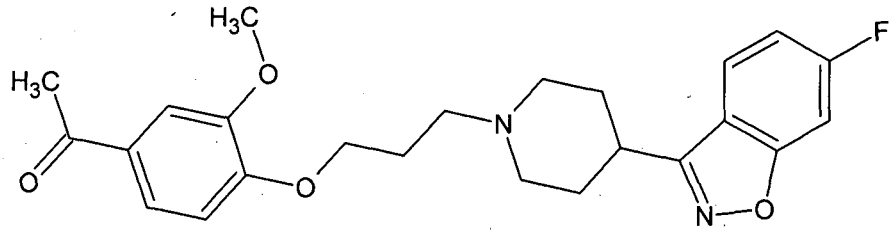
The term "pharmaceutically acceptable" as used herein means that which is useful in preparing a pharmaceutical composition that is generally non-toxic and is not biologically undesirable and includes that which is acceptable for veterinary use and/or human pharmaceutical use.

The term "excipient" as used herein means a component of a pharmaceutical product that is not an active ingredient, such as filler, diluent, carrier, and so on. The excipients those are useful in preparing a pharmaceutical composition are generally safe, non-toxic and neither biologically nor otherwise undesirable, and are acceptable for veterinary use as well as human pharmaceutical use.

The term "a pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

The term "substantially free of" in reference to a composition, as used herein, means that an absent substance cannot be detected in the composition by methods known to those skilled in the art at the time of the filing of this application.

In one of the embodiments, the present invention provides a process for preparation of iloperidone of formula (I);



Formula (I)

wherein, the said process comprising:

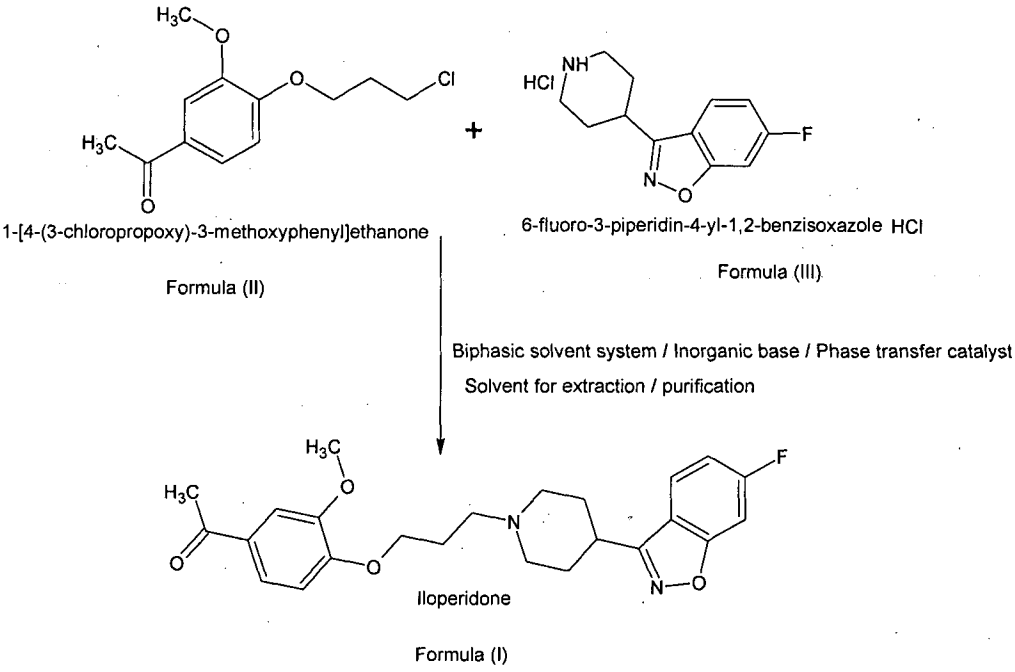
(a) reacting 1-(4-(3-chloropropoxy-3-methoxyphenyl)ethanone of formula (II) with 6-fluoro-3-piperidin-4-yl-1,2 benzisoxazole hydrochloride of formula (III) in a biphasic solvent system and in presence of an inorganic base and a phase transfer catalyst; and; and

(b) isolating iloperidone of the formula (I).

The synthetic route of synthesis of iloperidone of the present invention is shown in Scheme II.

In a preferred embodiment of the present invention, biphasic solvent system comprises of water and a solvent; wherein the said solvent is a water immiscible solvent.

Preferably, the water immiscible solvents comprises of hydrocarbons, chlorinated hydrocarbons, acetates or ethers.



Scheme II

More preferably water immiscible solvent is selected from hydrocarbons such as but not limited to heptane, hexane, cyclohexane, toluene or xylene.

Most preferably, the water immiscible solvent is heptane.

According to yet another preferred embodiment of the present invention, the biphasic solvent system of water: solvent is used in the range of about 8:1 to 1:8.

Most preferably, the biphasic solvent system of water: solvent is used in the ratio of 5:1.

Further, in a preferred embodiment of the present invention, inorganic base comprises of alkali metal hydroxide or alkali metal alkoxides.

More preferably, alkali metal hydroxide is selected from group consisting of sodium hydroxide, potassium hydroxide, lithium hydroxide or cesium hydroxide; and alkali metal alkoxide is selected from group consisting of sodium methoxide or potassium tertiarybutoxide.

Further, the said inorganic base used in reaction of scheme II is in the range of 2.5 to 3.0 equivalents.

According to yet another preferred embodiment of the present invention, the phase transfer catalyst is selected from group comprising of tetrabutyl ammonium bromide, tetrabutyl ammonium chloride, tetrabutyl ammonium sulfate, tetrabutyl ammonium hydroxide, tetrabutyl ammonium iodide, tetraethyl ammonium bromide, tetraethyl ammonium chloride, tetrahexyl ammonium iodide, tetramethyl ammonium chloride, tetramethyl ammonium fluoride, tetramethyl ammonium hydroxide, tetrapropyl ammonium bromide or tetrapropyl ammonium chloride.

The said phase transfer catalyst used is in the range of 0.5 to 0.25 weight percent with respect to 1-(4-(3-chloropropoxy-3-methoxyphenyl)ethanone of formula (II).

Further, the reaction of Scheme - II of the present invention is carried out at temperature in the range of about 50°C to 80°C.

More preferably, the reaction of Scheme - II of the present invention is carried out at temperature of about 65°C to 75°C.

Most preferably, the reaction of Scheme - II of the present invention is carried out at temperature 70°C.

According to another embodiment of the present invention, isolation of iloperidone of the formula (I) in step (b) comprises the steps of:

i. extracting the crude compound of formula (I) from the reaction mass with solvent,
ii. washing the organic layer of step (i) with water,
iii. decolorizing the said organic layer of step (ii) with activated charcoal,
iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (I),
v. optionally, purifying the compound of formula (I) obtained in step (iv) by crystallization using solvent, or
vi. optionally, purifying the compound of formula (I) obtained in step (iv) by acid-base treatment, or
vii. optionally, purifying the compound of formula (I) obtained in step (iv) by crystallization in combination with acid-base treatment.

Further, in a preferred embodiment of the present invention, the solvent used for extraction of the compound of formula (I) in step (i) comprises of dichloromethane, chloroform, ethylacetate or toluene.

More preferably, the solvent used for extraction of the compound of formula (I) in step (i) is dichloromethane.

According to another embodiment of the present invention, isolation of iloperidone of formula (I) from reaction mass can also be alternatively performed by:

1. isolating crude iloperidone from the reaction mass;
2. drying the said crude iloperidone obtained from step (1);
3. crystallizing the said dried crude iloperidone using solvent to obtain purified iloperidone of formula (I).

In a preferred embodiment, the solvent used for purification of iloperidone of the formula (I) by crystallization includes, but does not limited to nitriles, ketones, alkylacetates, dimethyfomamide, dimethylsulfoxide, ethers, alcohols their mixture thereof or mixture with water thereof.

More preferably, said alcohols used for purification of iloperidone of the formula (I) by crystallization comprises of methanol, ethanol, propanol, isopropyl alcohol, butanol; and most preferably isopropyl alcohol.

Further, the overall yield of iloperidone of formula (I) obtained using the process of the present invention is at least about 95% with purity of at least about 99% (by HPLC).

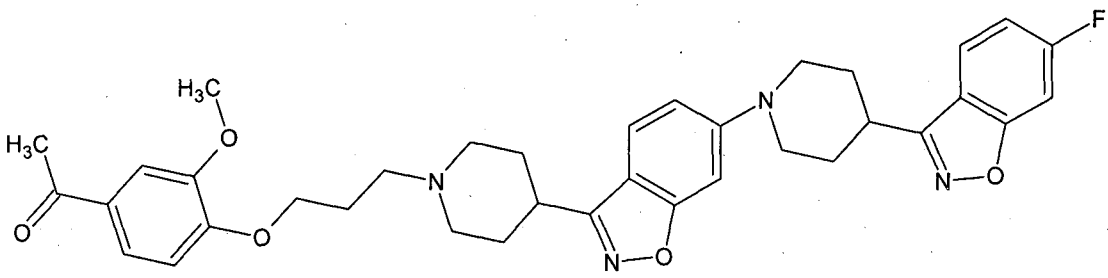
More particularly, the total purity of iloperidone of formula (I) obtained is at least about 99.85% (by HPLC).

Further, the process of the present invention has less than about 0.20% carbamate impurity of the formula (IV) by using inorganic base in reaction.

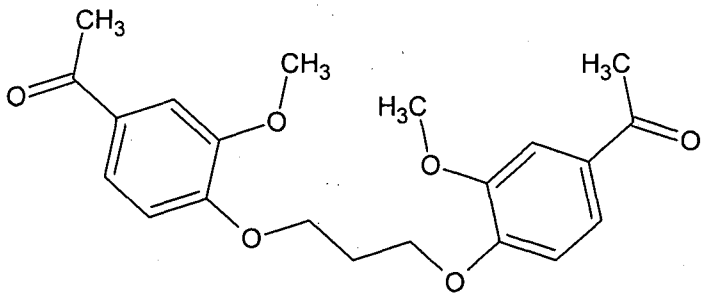
More particularly, the process of the present invention has no carbamate impurity of the formula (IV) by using inorganic base in reaction.

The process of the present invention also controls the dimer impurity of formula (V) and (VII); wherein the said dimer impurities of formula V and VII is less than about 0.20%.

Preferably, the said iloperidone of formula (I) contains less than about 0.06% impurity of dimer of formulae (V) and (VII).

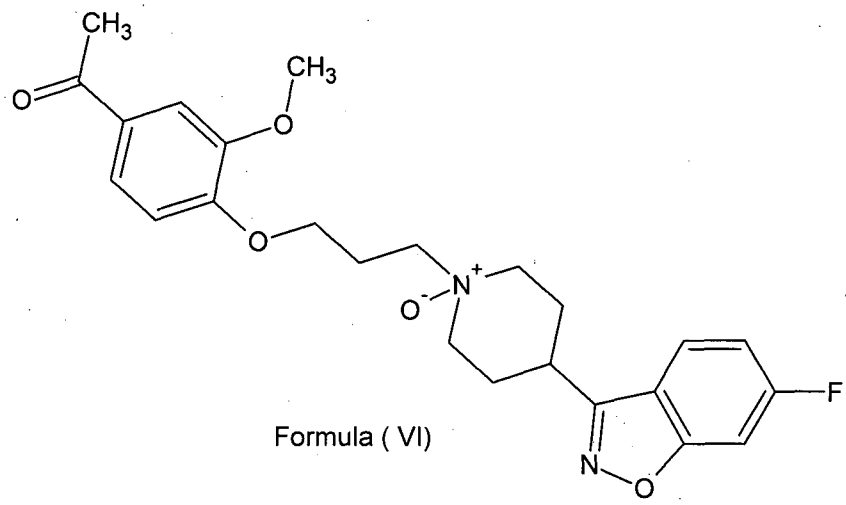


Formula (V)



Formula (VII)

In yet another preferred embodiment of the present invention, the process of the present invention further controls the content of N-oxide impurity of formula (VI); wherein the said N-oxide impurity is less than about 0.20%.



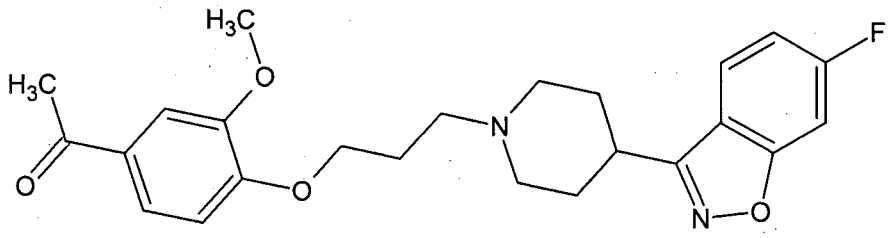
Formula (VI)

More particularly, the process of the present invention has 0.02% N-oxide impurity.

Thereby, process of the present invention improves the yield of iloperidone of formula (I) and simultaneously eliminates carbamate impurity of the formula (IV), controls the dimer impurities of the formula (V) and (VII) and N-oxide impurities (VI); wherein the said impurities is less than about 0.20%, and further makes the process efficient and cost-effective, less laborious, simple and easy to perform, with increased purity.

Since iloperidone of formula (I) obtained is substantially free from impurities, thereby substantially eliminating the several purification requirements and making the process effective and cost efficient.

According to another embodiment, the present invention provides a co-precipitate of amorphous form of iloperidone of formula (I) or its acid addition salt with a pharmaceutically acceptable excipient;



Formula (I)

characterized by their X-ray diffraction (XRD) pattern and infrared absorption (IR) spectrum.

Figure 1 of the present invention illustrates X-ray powder diffraction (XRD) pattern of co precipitate of amorphous form of iloperidone of the formula (I) with polyvinylpyrrolidone as pharmaceutically acceptable excipients is prepared as described in Example 3.

Figure 1 further demonstrates the amorphous nature of the co-precipitate. The X-ray diffractogram was measured on Bruker Axe, DS advance Power X-ray Diffractometer with Cu K alpha-1 Radiation source having the wavelength 1.541A°.

Figure 2 of the present invention illustrates Infrared spectrum (IR) of co precipitates of amorphous form of iloperidone of the formula (I) with polyvinylpyrrolidone as a pharmaceutically acceptable excipient, prepared according to Example 3.

The IR spectrum of co-precipitate of amorphous form of iloperidone of the formula (I) with a pharmaceutically acceptable excipient having characteristic peaks at 3447.92, 2949.72, 1677.01, 1510.03, 1461.77, 1417.03, 1269.86, 1220.47, 1149.83, 1123.17, 1031.56, 955.73, 852.41, 812.52 cm^{-1}.The IR spectra of co-precipitates of the invention has been recorded on a Fourier Transform Infrared Spectroscopy, Perkin Elmer model 100 instrument using potassium bromide pellet method.

The weight ratio of amorphous form of co-precipitate of iloperidone of the formula (I) to pharmaceutically acceptable excipient is in the range from 1:1 to 1: 0.01.

More preferably weight ratio of amorphous form of co-precipitate of iloperidone of the formula (I) to pharmaceutically acceptable excipient is 1:1.

In a preferred embodiment of the present invention, pharmaceutically acceptable excipients used to prepare co-precipitate of iloperidone of formula (I) of the present invention includes, pharmaceutical hydrophilic carriers such as but does not limit to polyvinylpyrrolidone (homopolymers, also called "povidone", or copolymers of N-vinylprrolidone), gums, cellulose derivatives (including hydroxypropyl methylcellulose, hydroxypropyl cellulose and others), cyclodextrins, gelatins, hypromellose phthalate, sugars or polyhydric alcohols.
In yet another preferred embodiment of the present invention, use of mixture of more than one of the pharmaceutical carriers to provide desired release profiles or for the enhancement of stability is within the scope of the invention. Further, all viscosity grades, molecular weight, commercially available products, their copolymers, mixtures are all within the scope of this invention without limitation.

Preferably, the said excipient used in the co-precipitation of iloperidone is polyvinylpyrrolidone (povidone).

The co-precipitate according to the invention comprises of iloperidone of Formula (I) or its acid addition salts; wherein the said acid addition salts comprises of organic and/or inorganic acid addition salts.

In a preferred embodiment of the present invention, organic acid addition salts comprises of fumarate, acetate, succinate, maleate, oxalate or tartarate; preferably organic acid salt is fumarate.

In a preferred embodiment of the present invention, inorganic acid addition salt comprises of hydrochloride, hydrobromide or sulfate; preferably inorganic salt is hydrochloride.

According to yet another embodiment, the present invention provides a process for the preparation of amorphous co-precipitate of iloperidone or its acid addition salts with pharmaceutically acceptable excipients; wherein the said process comprising the steps of:

A. preparing solution of iloperidone or its acid addition salt and pharmaceutically acceptable excipients in at least one solvent;
B. removing solvent from solution obtained from step (A); and
C. drying the solid residue of step (B) to obtain the co-precipitate.

Optionally, treating the solution obtained in step (A) to remove insoluble matter; wherein the treatment for removal of insoluble matter can be done using the following techniques such as but not limited to filtration, centrifugation, and decantation.

Further, based on the equipment used and the solution properties, such as concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid crystallization.

In a preferred embodiment, the solution of iloperidone or its acid addition salt and pharmaceutically acceptable excipients prepared in step (A) can be done by any of the following methods:

D. dissolving iloperidone or its acid addition salt in at least one solvent followed by addition and dissolution of a pharmaceutically acceptable excipient in the said solution; or
E. dissolving pharmaceutically acceptable excipient in at least one solvent followed by addition and dissolution of iloperidone or its acid addition salt in the said solution; or
F. Alternatively, by the following steps:

i. dissolving iloperidone or its acid addition salt in a first solvent to form a solution (M);
ii. dissolving a pharmaceutically acceptable excipient in second solvent to form a solution (L);
iii. combining solution (M) and the solution (L) to obtain solution as desired for step (A).

In a preferred embodiment of the present invention, iloperidone or its acid addition salts used to prepare the solution of step (A) and (D) can be either in crystalline form, or mixture of crystalline and amorphous form, solvates or hydrates form.

In a preferred embodiment of the present invention, first solvent and second solvent of above disclosed steps can be either same or different as long as the solvents have mutual solubility and form a single phase.

Further, in any event, iloperidone or its acid addition salt should be completely soluble in the solvents used and should provide a clear solution. The presence of un-dissolved crystals could lead to the formation of a material that is not completely amorphous.

Further, the solution of step (A) can be obtained directly from a reaction in which iloperidone or its acid addition salts is formed.

According to yet another preferred embodiment of the present invention, the solvent (first and second) used for preparation of solution of steps (A), (D), (E) and (F) includes solvents such as but does not limit to:

- **Alcohols:** such as methanol, ethanol, isopropanol, and the like;
- **Halogenated hydrocarbons:** such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like;
- **Ketones:** such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like;

- **Esters**: such as ethyl acetate, n-propyl acetae, n-butyl acetate, t-butylacetate and the like;
- **Ethers**: such as diethyl ether, dimethyl ether, diisopropyl ether and the like;
- **Hydrocarbons**: such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like;
- **Nitriles**: such as acetonitriles, propionitrile and the like;
- or mixtures of the above said solvents.

Further, the dissolution temperature to prepare solution of steps (A), (D), (E) and (F) is in the range from about 20°C to 120°C or reflux temperature of the solvent/mixture of solvents used for dissolution. Further, the temperature used for dissolution can be of any temperature as long as the solution obtained is a clear solution.

As used herein, "reflux temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

The quantity of solvent used for dissolution depends on the kind of solvent and the dissolution temperature adopted to prepare the solution of steps (A), (D), (E) and (F).

In a preferred embodiment of the present invention, the concentration of iloperidone or its acid addition salt in the solution is in the range from about 0.1 g/ml to about 10 g/ml in the solvent, and the volume of the solvent is kept to a minimum so as to facilitate effective solvent removal.

The removal of solvent in step (B) can be accomplished by using any of the following techniques such as but not limited to filtration, distillation, evaporation, atmospheric distillation, concentration and distillation, under vacuum such as rotary evaporator, lyophilization, freeze drying, spray drying, agitated thin film drying (ATFD), or the like.

The removal of the solvent from the solution of iloperidone or its acid addition salts and a pharmaceutical excipient in step (B) may be affected at increased temperature, preferably at reflux temperature, and/or reduced pressure.

Further, in step (C), drying of the residue is carried out at atmospheric pressure or reduced pressures, such as below about 200 mm/Hg, or below about 50 mm/Hg, at temperatures such as about 35°C to about 70°C.

Further, the drying may be carried for about 1 to 15 hours depending on the product specifications.

In a preferred embodiment of the present invention, temperatures and pressures can be variable and chosen based up on volatility of the solvent used in the preparation of solution.

The co-preceipitate of the invention makes the amorphous form of iloperidone or its acid addition salt stable and thus they can be handled easily. Further, a process for the preparation of co-precipitate of amorphous form of iloperidone or its acid addition salts with pharmaceutically acceptable excipients is simple and easy to carry out.

BEST MODE OR EXAMPLES FOR WORKING OF THE INVENTION

The present invention is described in the examples given below; further these are provided only to illustrate the invention and therefore should not be construed to limit the scope of the invention.

EXAMPLE 1:

Tetrabutyl ammonium bromide (2.40 gm) was added to a stirred solution of Potassium hydroxide (0.724 kg) in mixture of Heptane (2.0L) and water (10.0L), followed by addition of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (2, 1.0kg) and 6-fluoro-3-piperidin-4-yl-1,2-benzisoxazole hydrochloride(3, 1.11kg) at 30°C. This reaction mass was stirred for 15 to 20 min.

The temperature of the reaction mass was raised to 70°C and was maintained for 8 to 10 hours. After completion of reaction (by TLC, Mobile Phase: Toluene/Acetone/Ethyl acetate = 6:2:2 mL), the mixture was cooled to 30°C, diluted with dichloromethane (2.5 L) and stirred for 30 minutes. The dichloromethane layer was separated. The aqueous layer was re-extracted with dichloromethane (1.0L). The combined dichloromethane layer was washed with water (1.5L) and decolorized with activated charcoal (0.05 kg). The solvent was distilled off completely to obtain the residue. The residue obtained was dissolved in isopropyl alcohol (5.0L) at reflux temperature to obtain the clear solution. The clear solution obtained was cooled to 30°C followed by 0°C and stirred for 60 min to precipitate out crystals. The colorless crystals of compound (I) obtained were filtered. The crystalline solid was dried under vacuum (650-700 mm/Hg) to obtain pure compound (I) as a crystalline solid. HPLC analysis was performed for the crystalline solid obtained. The purity of Iloperidone, impurity profile and yield are shown in table 1 below.

Table 1: Analysis data of iloperidone i.e. purity, yield and impurity profile.

Purity %	**Yield Kg (%)**	**Impurity profile**			
		Carbamate (IV)	**Dimer**		**N-Oxide (VI)**
			(V)	(VII)	
99.85	1.67 kg (95%)	Not detected	0.06	0.06	Not Detected

EXAMPLE 2:

Tetrabutyl ammonium bromide (2.40 gm) was added to a stirred solution of Potassium hydroxide (0.724 kg) in mixture of Heptane (2.0L) and water (10.0L), followed by addition of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (2, 1.0kg) and 6-fluoro-3-piperidin-4-yl-1,2-benzisoxazole hydrochloride(3, 1.11kg) at 30°C. This reaction mass was stirred for 15 to 20 min. The temperature of the reaction mass was raised to 70°C and maintained for 8 to 10 hours. After

completion of reaction (by TLC, Mobile Phase: Toluene/Acetone/Ethyl acetate = 6:2:2 mL), the mixture was cooled to 30°C, the reaction mixture was filtered to obtain wet crude iloperidone. Further, the obtained wet crude was dried at 60-65°C under vacuum to furnish crude iloperidone (1.72 kg). The dried crude iloperidone was dissolved in isopropyl alcohol (5.0 L) at reflux temperature and decolorized with activated charcoal (0.05 kg). Obtained filtrate was cooled to 30°C followed by 0°C and stirred for 60 min to precipitate out crystals. The colorless crystals of compound (I) obtained were filtered. The crystalline solid was dried under vacuum (650-700 mm/Hg) to obtain pure compound (I) as a crystalline solid. HPLC analysis was performed for the crystalline solid obtained. The purity of Iloperidone, impurity profile and yield are shown in table 2 below.

Table 2: Analysis data of iloperidone i.e. purity, yield and impurity profile.

Purity %	**Yield Kg (%)**	**Impurity profile**			
		Carbamate (IV)	**Dimer**		**N-Oxide (VI)**
			(V)	**(VII)**	
99.87	1.66 kg (95%)	Not detected	0.03	0.06	0.02

EXAMPLE-3:

Iloperidone (5.0 gm) and povidone (PVP K30) (5.0 gm) was dissolved in 50 ml of dichloromethane at room temperature. The solution was filtered and dichloromethane was removed under vacuum using buchi rotavapour apparatus. Dried co-precipitate of iloperidone with povidone (9.0 gm) was obtained.

The XRD pattern of the amorphous form of iloperidone of the formula (I) with polyvinylpyrrolidone as a pharmaceutically acceptable excipient is illustrated in figure 1, which demonstrates the amorphous nature of the co-precipitate.

Infrared spectrum (IR) of co precipitates of amorphous form of iloperidone of the formula (I) with polyvinylpyrrolidone as a pharmaceutically acceptable excipient is illustrated in figure 2, demonstrated the amorphous nature of the co-precipitate.

EXAMPLE - 4:

Crude iloperidone (2.0 gm, 1 equivalent) as obtained from example - 2 was charged to methanol (25 ml), followed by addition of conc. HCl (0.6 gm, 1.3 equivalents). The reaction mass was heated to reflux temperature and maintained for 30 min. The reaction mass was cooled to 30°C, followed by 0 – 5 °C, and stirred for 60 min at 0 - 5°C to precipitate crystals of hydrochloride salt of iloperidone. The colorless crystals of hydrochloride salt of iloperidone obtained were filtered. The crystalline solid was dried under vacuum (650-700 mm/Hg) to obtain pure hydrochloride salt of iloperidone as a crystalline solid. HPLC analysis was performed for the crystalline solid obtained. The purity of Iloperidone, impurity profile and yield are shown in table 3 below.

Table 3: Analysis data of hydrochloride salt of iloperidone i.e. purity, yield and impurity profile.

Purity %	**Yield g (%)**	**Impurity profile**			
		Carbamate (IV)	**Dimer**		**N-Oxide (VI)**
			(V)	**(VII)**	
99.94	1.75 g (80.64%)	Not detected	0.03	0.03	Not detected

EXAMPLE - 5:

Crude iloperidone (2.0 gm, 1 equivalent) as obtained from example - 2 was charged to isopropyl alcohol (15 ml), followed by addition of IPA.HCl (0.6 gm, 1.3 equivalents). The reaction mass was heated to reflux temperature and maintained for 30 min. The reaction mass was cooled to 30°C, followed by 0 – 5 °C, and stirred for 60 min at 0 - 5°C to precipitate crystals of hydrochloride salt of iloperidone. The colorless crystals of hydrochloride salt of iloperidone obtained were filtered. The crystalline solid was dried under vacuum (650-700 mm/Hg) to obtain pure hydrochloride salt of iloperidone as a crystalline solid. HPLC analysis was performed for the crystalline solid obtained. The purity of Iloperidone, impurity profile and yield are shown in table 4 below.

Table 4: Analysis data of hydrochloride salt of iloperidone i.e. purity, yield and impurity profile.

Purity %	**Yield g (%)**	**Impurity profile**			
		Carbamate (IV)	**Dimer**		**N-Oxide (VI)**
			(V)	**(VII)**	
99.91	1.95 g (89.86%)	Not detected	0.04	0.05	Not detected

EXAMPLE - 6:

Crude iloperidone (2.0 gm, 1 equivalent) as obtained from example - 2 was charged to methanol (16 ml), followed by addition of fumaric acid (0.55 gm, 1 equivalent). The reaction mass was heated to reflux temperature and maintained for 30 min. The reaction mass was cooled to 30°C, followed by 0 – 5 °C, and stirred for 30 min at 0 - 5°C to precipitate crystals of fumarate salt of iloperidone. The colorless crystals of fumarate salt of iloperidone obtained were filtered. The crystalline solid was dried under vacuum (650-700 mm/Hg) to obtain pure fumarate salt of

iloperidone as a crystalline solid. HPLC analysis was performed for the crystalline solid obtained. The purity of fumarate salt of Iloperidone, impurity profile and yield are shown in table 5 below.

Table 5: Analysis data of fumarate salt of iloperidone i.e. purity, yield and impurity profile.

Purity %	**Yield g (%)**	**Impurity profile**			
		Carbamate (IV)	**Dimer**		**N-Oxide (VI)**
			(V)	**(VII)**	
99.96	2.14 g (84.86%)	Not detected	0.01	0.02	Not detected

EXAMPLE - 7:

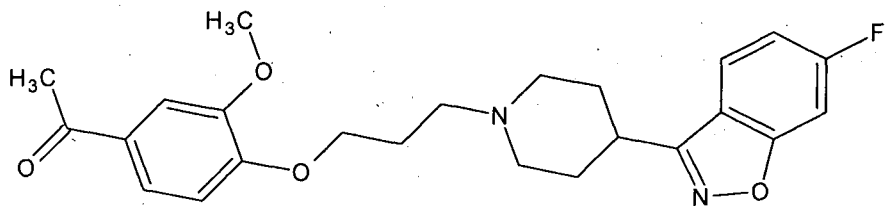
Hydrochloride salt of iloperidone (2.0 gm) was charged to purified water (30 ml), followed by addition of liquor ammonia until pH 7.8 was obtained. The reaction mass was stirred at room temperature for 30 min maintaining pH at about 7-8. The reaction mass was then filtered to obtain pure colorless crystals of iloperidone. The crystalline solid was dried under vacuum (650-700 mm/Hg) till constant weight was achieved. HPLC analysis was performed for the crystalline solid obtained. The purity of Iloperidone, impurity profile and yield are shown in table 6 below.

Table 6: Analysis data of iloperidone i.e. purity, yield and impurity profile.

Purity %	**Yield g (%)**	**Impurity profile**			
		Carbamate (IV)	**Dimer**		**N-Oxide (VI)**
			(V)	**(VII)**	
99.96	1.65 g (89.13%)	Not detected	0.02	0.02	Not detected

WE CLAIM:

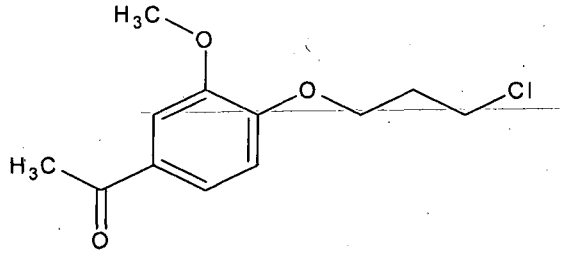
1. A process for preparation of iloperidone of formula (I);



Formula (I)

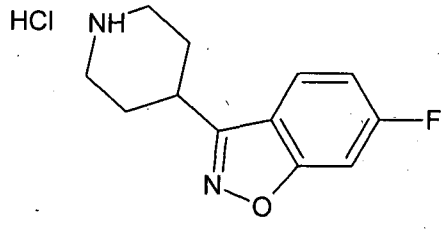
wherein, the said process comprises of:

a. reacting 1-(4-(3-chloropropoxy-3-methoxyphenyl)ethanone having structure (formula II):



Formula (II)

with 6-fluoro-3-piperidin-4-yl-1,2 benzisoxazole hydrochloride having structure (formula III):



Formula (III)

in a biphasic solvent system and in presence of an inorganic base and a phase transfer catalyst; and

b. isolating said iloperidone of the formula (I) from reaction mass of step (a).

2. The process as claimed in claim 1, wherein the said biphasic solvent system comprises of water and solvent.

3. The process as claimed in claim 2, wherein the said solvent is water immiscible solvent.

4. The process as claimed in claim 3, wherein the said water immiscible solvent is selected from the group consisting of hydrocarbons, chlorinated hydrocarbons, acetates and ethers.

5. The process as claimed in claim 4, wherein the said hydrocarbon solvent comprises of heptane, hexane, cyclohexane, toluene or xylene.

6. The process as claimed in claim 2, wherein the said biphasic solvent system of water: solvent is in the range of about 8:1 to about 1:8.

7. The process as claimed in claim 6, wherein the said biphasic solvent system of water: solvent is used in the ratio 5: 1.

8. The process as claimed in claim 1, wherein the said inorganic base is alkali metal hydroxide or alkali metal alkoxide; the said base used in the range of 2.5 to 3.0 equivalents.

9. The process as claimed in claim 8, wherein the alkali metal hydroxide is selected from the group consisting of sodium hydroxide, potassium hydroxide, lithium hydroxide or cesium hydroxide.

10. The process as claimed in claim 8, wherein the alkali metal alkoxide is selected from the group consisting of potassium tertiarybutoxide or sodium methoxide.

11. The process as claimed in claim 1, wherein the said phase transfer catalyst is selected from the groups consisting of tetrabutyl ammonium bromide, tetrabutyl ammonium chloride, tetrabutyl ammonium sulfate, tetrabutyl ammonium hydroxide, tetrabutyl ammonium iodide, tetraethyl ammonium bromide, tetraethyl ammonium chloride, tetrahexyl ammonium iodide, tetramethyl ammonium chloride, tetramethyl ammonium fluoride, tetramethyl ammonium hydroxide, tetrapropyl ammonium bromide or tetrapropyl ammonium chloride.

12. The process as claimed in claim 1, wherein the said phase transfer catalyst used is in the range of 0.5 to 0.25 weight percent with respect to 1-(4-(3-chloropropoxy-3-methoxyphenyl)ethanone of the formula (II).

13. The process as claimed in claim 1, wherein the said reaction is carried out at temperature in the range of about 50°C to 80°C.

14. The process as claimed in claim 13, wherein the said the reaction is carried out at temperature of about 65°C to 75°C.

15. The process as claimed in claim 1, wherein isolation of said iloperidone of formula (I) of step (b) of claim 1 comprises the steps of:

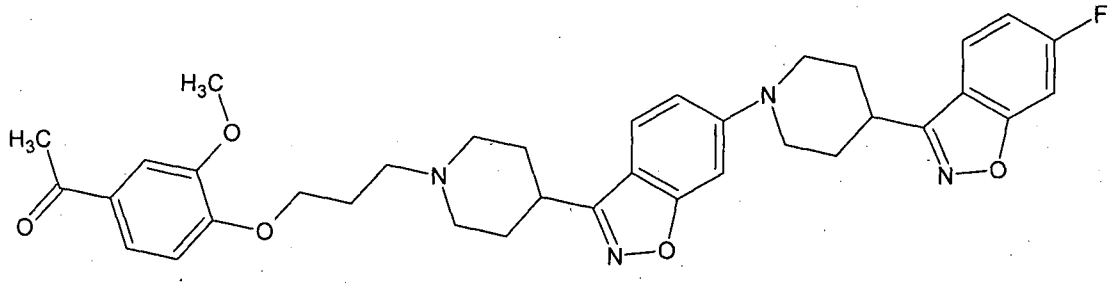
i. extracting the crude compound of formula (I) from the reaction mass with ~~first~~ solvent,
ii. washing the organic layer of step (i) with water,
iii. decolorizing the said organic layer of step (ii) with activated charcoal,
iv. concentrating the said organic layer of step (iii) to obtain the residue comprising the compound of formula (I),
v. optionally, purifying the compound of formula (I) obtained in step (iv) by crystallization using solvent, or
vi. optionally, purifying the compound of formula (I) obtained in step (iv) by acid-base treatment or

vii. optionally, purifying the compound of formula (I) obtained in step (iv) by crystallization in combination with acid-base treatment.

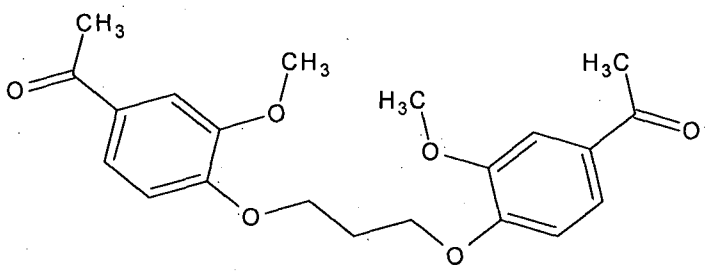
16. The process as claimed in claim 15, wherein the solvent used for extraction of the compound of formula (I) in step (i) is selected from the group comprising of dichloromethane, chloroform, ethylacetate or toluene.

17. The process as claimed in claim 15, wherein the said solvent used for purification of the compound of formula (I) is selected from the group comprising of but does not limited to nitriles, ketones, alkylacetates, dimethyfomamide, dimethylsulfoxide, ethers, alcohols their mixture thereof or mixture with water thereof.

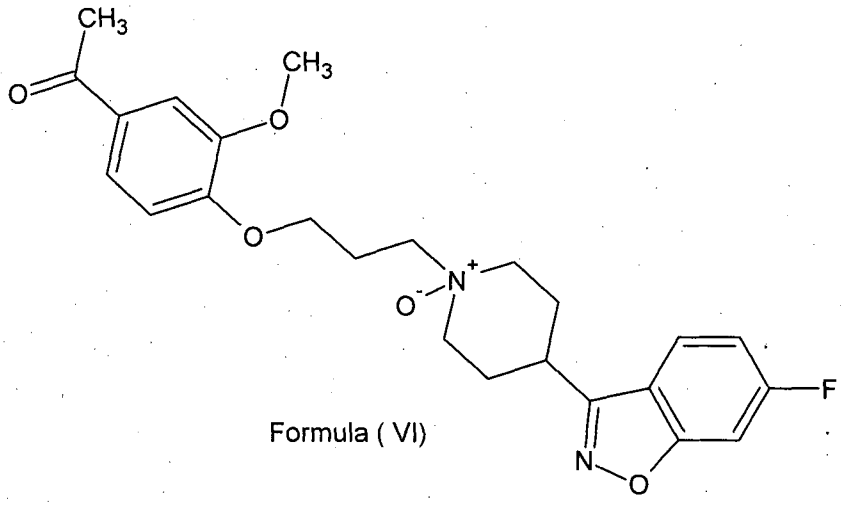
18. The process as claimed in any of the preceding claims, wherein the said iloperidone of formula (I) contains less than about 0.20% impurity of dimer of the formulae (V) and (VII) and N-oxide impurity of formula (VI).



Formula (V)



Formula (VII)

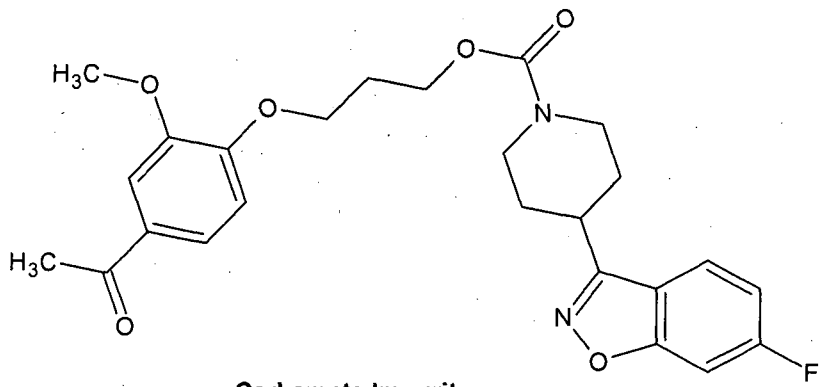


Formula (VI)

19. The process as claimed in any of the preceding claims, wherein the said iloperidone of formula (I) contains less than about 0.06% impurity of dimer of formulae (V) and (VII).

20. The process as claimed in any of the preceding claims, wherein the said iloperidone of formula (I) has 0.02% N-oxide impurity (VI).

21. The process as claimed in any of the preceding claims, wherein the said iloperidone of formula (I) contains less than about 0.20% carbamate impurity of formula IV.

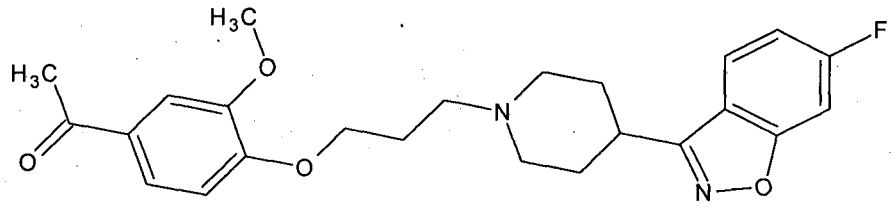


Carbamate Impurity

Formula (IV)

22. The process as claimed in any of the preceding claims,, wherein the said iloperidone of formula (I) has no carbamate impurity of formula IV.

23. A co-precipitate of amorphous form of iloperidone of the formula (I) or its acid addition salt with a pharmaceutically acceptable excipient; characterized by their X-ray diffraction (XRD) pattern as shown in figure 1.



Formula (I)

24. The co-precipitate as claimed in claim 23, wherein the weight ratio of amorphous form of iloperidone of the formula (I) to the pharmaceutically acceptable excipient is in the range of about 1:1 to 1: 0.01.

25. The co-precipitate as claimed in claim 23, wherein the said pharmaceutically acceptable excipients is selected from pharmaceutical hydrophilic carriers consisting of polyvinylpyrrolidone; gums; cellulose derivatives including hydroxypropyl methylcellulose

and hydroxypropyl cellulose; cyclodextrins; gelatins; hypromellose phthalate; sugars and polyhydric alcohols.

26. The co-precipitate as claimed in claim 23, wherein acid addition salts of iloperidone of Formula (I) comprises of organic and/or inorganic salts.

27. The co-precipitate as claimed in claim 26, wherein organic acid addition salts of iloperidone of Formula (I) comprises of fumarate, acetate, succinate, maleate, oxalate or tartarate.

28. The co-precipitate as claimed in claim 26, wherein inorganic acid addition salts of iloperidone of Formula (I) comprises of hydrochloride, hydrobromide or sulfate.

29. A process for preparation of co-precipitate of an amorphous form of iloperidone or its acid addition salts with a pharmaceutically acceptable excipient, the said process comprising the steps of:

A. preparation of a solution of the said iloperidone or its acid addition salt and pharmaceutically acceptable excipients in at least one solvent;
B. removal of solvent from solution obtained in step (A); and
C. drying solid residue obtained from step (B) to obtain the said amorphous co-precipitate of iloperidone or its acid addition salts with the said pharmaceutically acceptable excipient.

30. The process as claimed in claim 29, wherein the said iloperidone or its acid addition salts can be either in crystalline form, or mixture of crystalline and amorphous form, solvates form or hydrates form thereof.

31. The process as claimed in claim 29, wherein the said solvent used in step (A) is selected from the group consisting of alcohols comprising methanol, ethanol or isopropanol; halogenated hydrocarbons comprising dichloromethane, 1,2-dichloroethane, chloroform or carbon tetrachloride; ketones comprising acetone, ethyl methyl ketone or methyl isobutyl ketone;

esters comprising ethyl acetate, n-propyl acetae, n-butyl acetate or t-butylacetate; ethers comprising diethyl ether, dimethyl ether or di-isopropyl ether; hydrocarbons comprising toluene, xylene, n-heptane, cyclohexane or n-hexane; nitriles comprising acetonitriles or propionitrile; and mixtures thereof.

32. The process as claimed in claim 29, wherein the dissolution temperature to prepare the solution of step (A) is from about 20°C to about 120°C or reflux temperature of at least one solvent used for dissolution.

33. The process as claimed in claim 29, wherein the concentration of iloperidone or its acid addition salt is from about 0.1 g/ml to about 10 g/ml of the solvent.

34. The process as claimed in claim 29, wherein the said pharmaceutically acceptable excipients is selected from pharmaceutical hydrophilic carriers consisting of polyvinylpyrrolidone; gums; cellulose derivatives including hydroxypropyl methylcellulose and hydroxypropyl cellulose; cyclodextrins; gelatins; hypromellose phthalate; sugars and polyhydric alcohols.

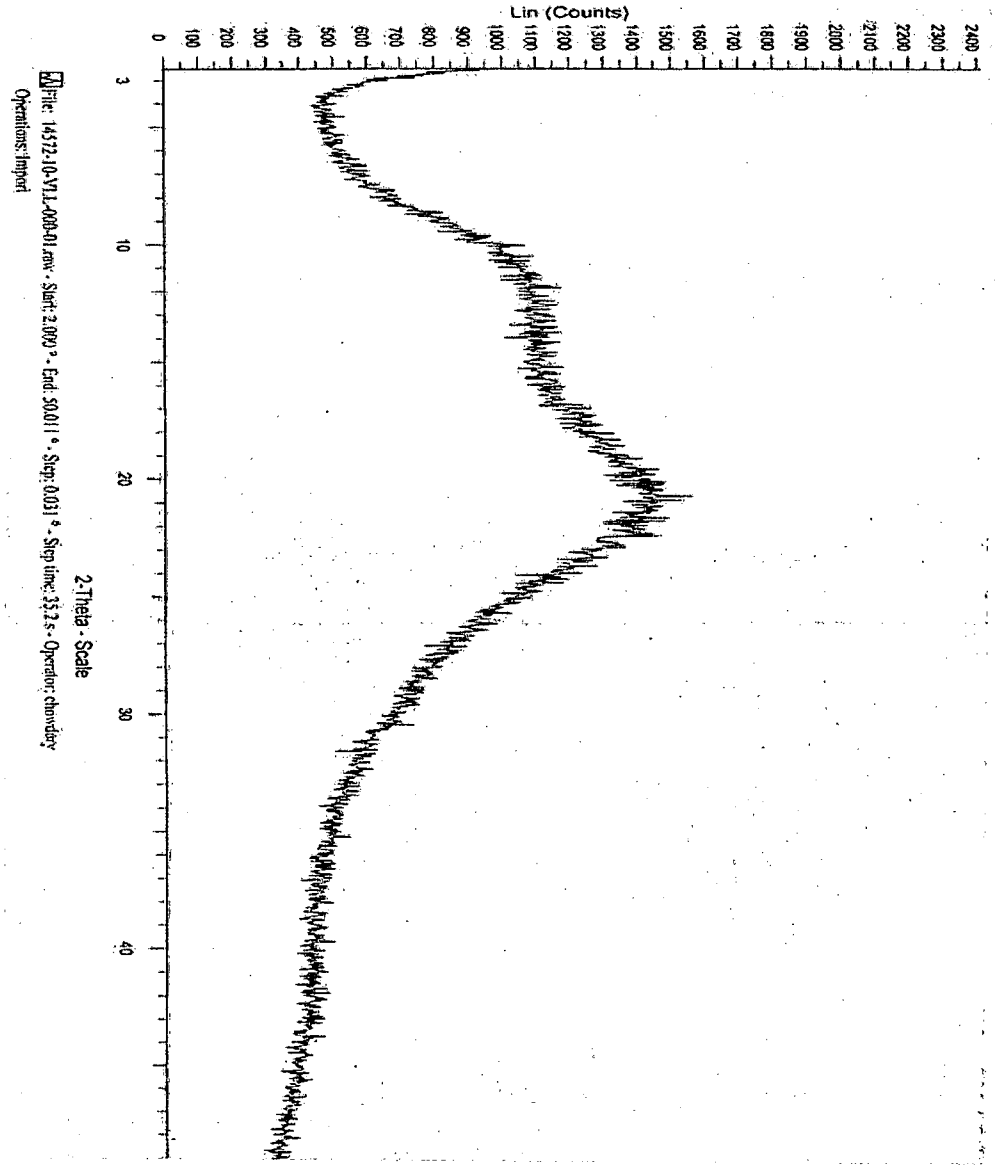

Lin (Counts)
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2100
2200
2300
2400
3
10
20
30
40
2-Theta - Scale
File: 14572-10-VJL-000-01.raw - Start: 2.009 ° - End: 50.011 ° - Step: 0.031 ° - Step time: 35.2 s - Operator: chowdary
Operations: Import

Figure 1

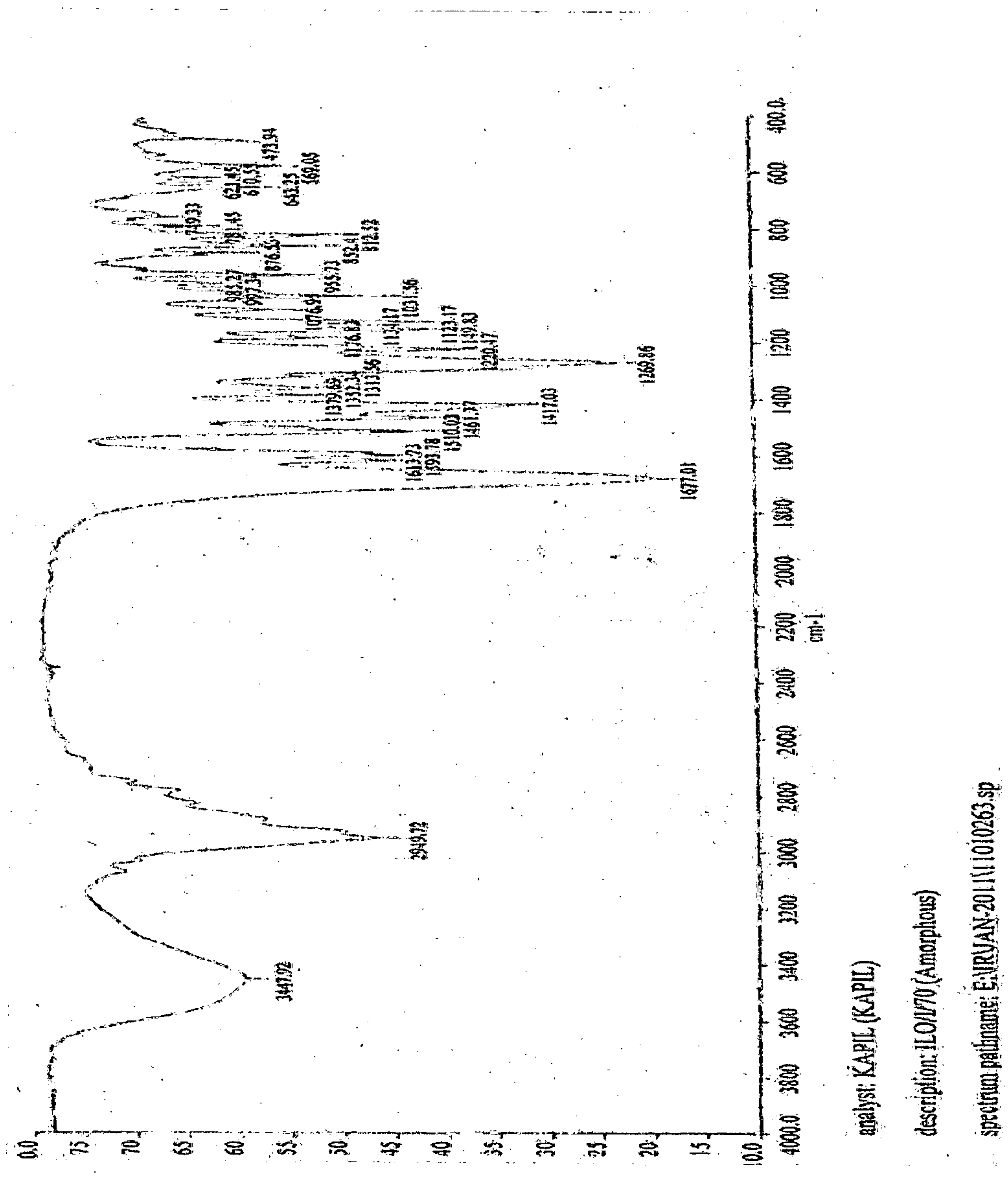

3447.92
2949.72
1677.01
1417.03
1269.86
cm-1
analyst: KAPIL (KAPIL)
description: ILO/I/70 (Amorphous)

Figure 2