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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 March 2008 (06.03.2008)

PCT

(10) International Publication Number
WO 2008/026227 A2

(51) International Patent Classification:
C07C 213/06 (2006.01) *C07C 213/10* (2006.01)

(21) International Application Number:
PCT/IN2007/000408

(22) International Filing Date: 24 August 2007 (24.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1548/CHE/2006 28 August 2006 (28.08.2006) IN

(71) Applicant *(for all designated States except US)*: **MATRIX LABORATORIES LTD** [IN/IN]; 1-1-151/1, IV Floor, Sairam Towers, Alexander Road, Secunderabad 500 003 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RAMANJANEYULU, Gorantla, Seeta** [IN/IN]; Plot N°34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist., Hyderabad 500 055, Andhra Pradesh (IN). **RAMDAS, Chavakula** [IN/IN]; Plot N°34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist., Hyderabad 500 055, Andhra Pradesh (IN). **RAO, Konudula, Babu** [IN/IN]; Plot N°34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist., Hyderabad 500 055, Andhra Pradesh (IN).

(74) Agent: **KAUSHIK, Geetesh**; Plot No 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist., Hyderabad 500 055, Andhra Pradesh (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, 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))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report*

(54) Title: A PROCESS FOR THE PREPARATION OF ATOMOXETINE HYDROCHLORIDE

(57) Abstract: Provided is the process for the preparation of Atomoxetine hydrochloride by the condensation of N,N-dimethyl 3-phenyl-3-chloropropyl amine acid addition salt with o- cresol in presence of a phase transfer catalyst and base followed by demethylation and resolution. Also provided preparation of crystalline Atomoxetine hydrochloride.

WO 2008/026227 A2

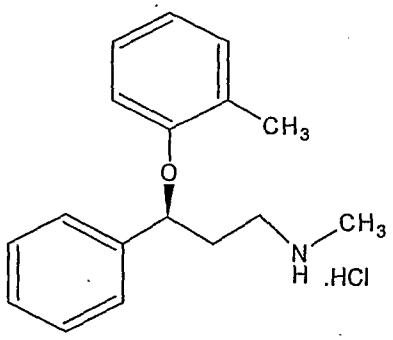
Title: A Process for the preparation of Atomoxetine hydrochloride

Field of the Invention:

The present invention relates to the process for the preparation of crystalline Atomoxetine hydrochloride

Background of the Invention:

Atomoxetine hydrochloride, (R)(-)-N-methyl-3-(o-tolyloxy)-3- phenylpropyl amine hydrochloride has the formula as shown below



Atomoxetine hydrochloride

Atomoxetine is the (R)-(-)enantiomer of Tamoxetine, is an aryloxyphenyl propyl-amine, a selective norepinephrine reuptake inhibitor, marketed as hydrochloride salt under the name of STRATTERA® used for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD).

US 4,314,081 discloses a process for preparation of N-methyl 3-(o-tolyloxy)-3-phenylpropylamine hydrochloride along with other compounds. One of the disclosed process for preparation of N-methyl 3-(o-tolyloxy)-3-phenylpropylamine involves the reaction of N,N-dimethyl 3-phenyl-3-chloro propyl amine hydrochloride with sodium salt of the corresponding phenol in methanol followed by demethylation using cyanogens bromide. The reaction of N, N-dimethyl 3-phenyl-3-halopropyl amine hydrochloride with sodium salt of the corresponding phenol in methanol is a time consuming process, requires about five days for completion of reaction.

The alternate process disclosed involves the bromination of 3-phenylchloropropyl amine with N-Bromosuccinimide, condensation with o-cresol followed by amination with methyl amine. The process requires the dry sodium salt of phenol.

EP 052492 discloses the process for preparation of Atomoxetine hydrochloride from N-methyl 3-(o-tolyloxy)-3-phenylpropylamine by crystallization as (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropylamine (S)-(+)-mandalate, basification in water, extraction with diethyl ether and bubbling the hydrogen chloride gas.

US 4,950,791 discloses a process that involves the condensation of (S)-3-hydroxy-3-phenylpropyl amine with aroyl alkanols using the Mitsunobo reaction which requires the use of reagent diethyl azodicarboxylate, known to be highly carcinogenic and expensive.

US 5,847,214 discloses a process that involves the reaction of N-methyl-3-phenylpropyl amines with aryl halides; the success of reaction depends on the electron withdrawing group on the benzene ring of the aryl halide.

US 6,541,668 discloses a process that involves the reaction of alkoxide of N-methyl-3-phenyl-3hydroxy propyl amine or a corresponding N-protected derivative with 2-fluoro toluene in presence of solvent.

WO 2006/020348 discloses the crystalline polymorphic forms, Form A, Form B and Form C of Atomoxetine hydrochloride. WO 2006/020348 further discloses that the repetition of the processes disclosed in EP 052,492 and US 6,541,668 yielded a crystalline form of Atomoxetine hydrochloride denominated as Form A.

None of the prior art methods reported the use of phase transfer catalysts for the condensation of aryl alkanols or their alkali salts with aryl 3-halopropyl amine or amine protected derivatives.

The present invention provides a process for preparation of Atomoxetine hydrochloride involves the reaction of N,N-dimethyl 3-phenyl-3-chloro propyl amine acid addition salt with o-Cresol in presence of a phase transfer catalyst followed by demethylation and resolution with (S)-(+)-mandelic acid followed by saltification with hydrochloride.

Summary of the Invention:

The main object of the present invention is to provide a process for the preparation of Atomoxetine and its pharmaceutically acceptable salts.

Another object of the present invention is to provide a process for preparation of Atomoxetine hydrochloride.

Another object of the present invention is to provide a process for preparation of crystalline Atomoxetine hydrochloride.

Another object of the present invention is to provide a process for preparation of Atomoxetine using N, N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine and its salts thereof.

Another object of the present invention is to provide a process for preparation of N, N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine and its salts thereof.

Accordingly in the present invention N,N-dimethyl 3-phenyl-3-chloropropyl amine acid addition salt on reaction with o-cresol in presence of a base and phase transfer catalyst yields the N, N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine, which can be isolated as acid addition salts. Demethylation of N,N-dimethyl 3-(o-tolyloxy)-3-phenyl propylamine on with phenyl chloroformate in presence of diisopropyl ethyl amine and sodium hydroxide in DMSO affords the N-methyl 3-(o-tolyloxy)-3-phenylpropylamine (Tomoxetine), which on treatment with (S)-(+)-mandelic acid in a mixture of toluene and ethyl acetate gives the (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropylamine (S)-(+)-mandalate. Basification of (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropylamine (S)-(+)-mandalate in presence of water followed by extraction with solvent and treatment with hydrogen chloride affords the Atomoxetine hydrochloride, can be purified by dissolution

in an alkanol, treatment with carbon followed by removal of solvent and addition of a second solvent affords the Atomoxetine hydrochloride.

Brief description of the drawings:

Fig: 1 shows the X-ray diffraction pattern of Atomoxetine hydrochloride obtained as per the present invention

Detailed description of the invention:

Thus in accordance with the present invention Atomoxetine hydrochloride is prepared by the following steps;

- Adding N,N-dimethyl 3-phenyl-3-chloropropyl amine acid addition salt slowly to a suspension of o-cresol, sodium hydroxide and a phase transfer catalyst in a mixture of water and a halogenated hydrocarbon
- Maintaining the reaction mass for the complete conversion of N, N-dimethyl 3-phenyl-3-chloropropyl amine hydrochloride to N, N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine
- Isolating the obtained N,N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine
- Demethylating N,N-dimethyl 3-(o-tolyloxy)-3-phenylpropyl amine with phenyl chloroformate in presence of diisopropyl ethyl amine to get N-methyl 3-(o-tolyloxy)-3-phenylpropylamine
- Treating N-methyl 3-(o-tolyloxy)-3-phenylpropylamine with (S)-(+)-mandelic acid in a mixture of toluene and ethyl acetate
- Crystallizing and isolating (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropyl amine (S)-(+)-mandalate
- Basifying (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropylamine (S)-(+)-mandalate and extracting the liberated (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropylamine with an water immiscible solvent
- Saltification with hydrogen chloride to get Atomoxetine hydrogen chloride

- Dissolution of Atomoxetine hydrochloride in an alkanol
- Optionally treating the solution with activated carbon
- Removing the solvent from the solution
- Adding a second solvent and Isolating Atomoxetine hydrochloride

N,N-dimethyl 3-phenyl-3-chloropropyl amine acid addition salt is added to a mixture of o-cresol, acid addition salt is selected from hydrochloride, hyrobromide, sulphate, phosphate, nitrate or acetate. The preferred acid addition salt is hydrochloride, base such as sodium hydroxide, potassium hydroxide and a phase transfer catalyst such as tertiary ammonium salts, selected from tetrabutyl ammonium bromide, tetrabutyl ammonium chloride, triethyl benzyl ammonium chloride, tributyl benzyl ammonium chloride and mixtures thereof; phosphonium salts; crown ethers in water and a halogenated hydrocarbon such as methylene chloride, ethylene dichloride, chloroform at a temperature of about 0°C to about 50°C preferably at about 15 to 35°C. Reaction mass is maintained for about 6 hrs to 24 hrs, preferably for about 12 hrs to 16 hrs at a temperature of 0°C to 50°C preferably at 15°C to 35°C. Optionally an additional quantity of same phase transfer catalyst as 2nd lot can be introduced into the reaction mass after initial maintenance of 2 hrs to 6hrs. Reaction mass is allowed to settle and separated the layers. Aqueous layer is extracted with same halogenated hydrocarbon, washed the combined organic layer with sodium hydroxide solution, water and brine solution. Solvent is removed from the organic layer preferably under vacuum at temperature below 60°C affords the N,N-dimethyl 3-(o-tolyloxy)-3-phenylpropyl amine. N,N-dimethyl 3-(o-tolyloxy)-3-phenylpropyl amine is dissolved in an alkyl ester such as ethyl acetate, isopropyl acetate and treated with an acid such as hydrochloric acid, oxalic acid at a temperature of 10°C to 50°C, preferably at 20°C to 40°C for about 30 min to 4hrs followed by cooling to a temperature of 0°C to 20°C, maintained for 15min to 4 hrs followed by isolation and drying afforded the N,N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine acid addition salts.

N,N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine acid addition salt/s is basified with ammonia solution in toluene, separated the layers, treated the organic layer with phenyl

chloroformate in presence of diisopropyl ethyl amine at a temperature of about 40^{0}C to 65^{0}C for about 12 to 4 hrs. Sodium bicarbonate solution is added to the reaction mass, stirred and settled. The organic layer is separated and washed with dilute hydrochloric acid, sodium bicarbonate solution. The organic layer is concentrated to afford residue. The obtained residue is dissolved in DMSO, treated with aqueous sodium hydroxide at 30°C to 60°C, preferably at 40°C to 50°C for about 8 hrs. The reaction mass is transferred into to chilled water, adjusted the pH 5.0 to 6.0 with acetic acid and washed the reaction mass with n-hexane. Again pH is adjusted 10.5 to 11.5 with sodium hydroxide. Extracted the reaction mass with toluene. Toluene layer is washed with water, optionally treated the organic layer with activated carbon. pH of the Toluene layer is adjusted to below 2.0 by addition of hydrochloric acid. Toluene is removed by vacuum distillation preferably at temperature below 60°C. To the obtained residue ethyl acetate is added and stripped off below 55°C. The obtained residue is dissolved in ethyl acetate, maintained the mass for about 2 hrs at temperature of 15 to 25°C, followed by cooling and maintained at temperature of 0°C to 5°C for about 1 hr. The precipitated N-methyl 3-(o-tolyloxy)-3-phenylpropylamine hydrochloride is isolated and dried.

N-methyl 3-(o-tolyloxy)-3-phenylpropylamine hydrochloride is suspended in a mixture of water and toluene. The reaction mass is basified with a base such as sodium hydroxide, ammonia solution and allowed for settling. Toluene layer is separated and the aqueous layer is extracted with toluene. The combined toluene layer is washed with water. Toluene is removed under vacuum at temperature below 75°C affords the N-methyl 3-(o-tolyloxy)-3-phenylpropylamine as a residue. The residue is dissolved in a mixture of toluene, ethyl acetate in a ratio of 1:3, treated with (S)-(+)-mandalic acid at a temperature of 20°C to 50°C preferably 35°C to 45°C for 30 min to 4hrs. The reaction mass is cooled and maintained at a temperature of 25°C to 35°C for 3 to 6 hrs, further cooled to a temperature of 0°C to 10°C. The precipitated product is isolated and dried to get (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropylamine (S)-(+)-mandalate. The (S)-(+)-mandalate salt can be optionally purified in ethyl acetate to get an enantiomeric purity > 99.0%.

(R)-(-)N-methyl 3-(o-tolyloxy)-3-phenylpropylamine (S)-(+)-mandalate is neutralized with a base such as alkali hydroxides like sodium hydroxide, potassium hydroxide, alkali carbonates, ammonia solution, preferably sodium hydroxide in water and extracted with water immiscible solvent such as ethyl acetate. The organic layer is separated and the aqueous layer is extracted with same solvent. Combined organic layer is with brine solution and treated with activated carbon. Organic layer is concentrated preferably under vacuum and again fresh solvent is added. Reaction mass is cooled to a temperature of 0°C to 10°C and the pH is adjusted below 2.0 by passing the hydrogen chloride gas at temperature of –10°C to 20°C, preferably at 0°C to 10°C. After pH adjustment the reaction mass is maintained for 30 min to 3 hrs at the same temperature. The precipitated product is isolated and dried to get Atomoxetine hydrochloride.

Atomoxetine hydrochloride is dissolved in an alkanol such as methanol, ethanol, isopropanol and mixtures thereof, preferably methanol at temperature of 20°C to 50°C. The obtained solution is optionally treated with activated carbon and the solvent is removed at temperature below 60°C preferably under vacuum. After distillation a second solvent such as alkyl ester like ethyl acetate, isopropyl acetate is added at temperature of 15°C to 45°C and maintained for 30 min to 2 hrs. The reaction mass is further cooled and maintained at temperature of –10°C to 20°C preferably 0°C to 10°C for 30 min to 3 hrs. The precipitated product is isolate and dried at temperature of 40°C to 60°C preferably under vacuum afforded the crystalline Atomoxetine hydrochloride.

The prepared and purified Atomoxetine hydrochloride is identified as crystalline Atomoxetine hydrochloride polymorphic form-A based on the PXRD.

The invention is further illustrated with a few non-limiting examples.

Example-1: Preparation of N,N-Dimethyl-3-(tolyloxy)-3-phenyl propyl amine oxalate.

O-Cresol (152.5 Gms) is added to aqueous sodium hydroxide (86.5 Gms in 1400 ml) at temperature of 30 to 35°C over 30 minutes. The reaction mixture is stirred for 30 minutes

at 30 to 35°C, Triethyl benzyl ammonium chloride (13.25 Gms) and methylene dichloride (1400 ml) are added 30 to 35°C. N,N-Dimethyl 3-phenyl-3-chloropropyl amine hydrochloride is added to the reaction mixture at a temperature of 25 to 30°C over 1-1½ hours. The reaction mass is maintained at a temperature of 25 to 30°C for 4 hrs. Triethyl benzyl ammonium chloride (13.0 Gms) is added at 25-30°C and maintained the reaction mass at temperature of 25 to 30°C for 8 hours. Reaction completion is checked by HPLC and allowed the reaction mass to settle. Organic layer is separated and the aqueous layer is extracted with dichloromethane (175 ml). The combined organic layer is washed with 10% Sodium hydroxide solution (175 ml), DM Water (2X175 ml), 10% sodium chloride solution (175 ml) and finally with DM Water (175 ml) successively. MDC is distilled off till temperature reaches to 55°C and finally under vacuum to remove traces of MDC at temperature below 55°C. The obtained residue is dissolved in Ethyl acetate (175 ml) and distilled off under vacuum at temperature below 55°C. The obtained residue is dissolved in ethyl acetate (1000 ml) and treated with activated carbon (17.5 gm). Filtered the mass through hyflow bed and washed the bed with ethyl acetate (400 ml). Combined the filtrate and ethyl acetate washings. Oxalic acid (103 gm) is added to the ethyl acetate layer lot wise at temperature of 25 to 35°C over 1 to 2 hours. The reaction mass is maintained for 1 hour at temperature of 25 to 35°C. The reaction mass is cooled to 0°C and maintained for 1 hr at 0 to 5°C. Filter the mass and washed the wet cake with chilled ethyl acetate (175 ml). The wet cake is dried at room temperature and then at temperature of 50-55°C till constant weight.

The dry weight of N,N-Dimethyl-3-(tolyloxy)-3-phenyl propyl amine oxalate is 230 Gms

Example-2: Preparation of N-Methyl-3-(2-methyl phenoxy)-3-phenyl propyl amine hydrochloride

Charged toluene (1000 ml), N,N-Dimethyl-3-(tolyloxy)-3-phenyl propyl amine oxalate (200 gm) and DM Water (1000 ml) at 25-35°C. Raised the temperature to 40 - 45°C, Ammonia solution (260 ml) is added at 40–45°C and maintained for 30 min. Reaction mass allowed to settle. Organic layer is separated and the aqueous layer is extracted with toluene (200 ml) at 30-40°C. Combined the organic layer, and washed with DM water (2

X 200 ml) at 30-35°C. Distilled off toluene (200 – 250 ml) azeotropically to remove the water and make up final volume to 1200 ml with fresh toluene. Cooled the reaction mass to 35 - 40°C and added Diisopropyl ethyl amine (8.4 gm). Raised the reaction mass temperature to 50-55°C. Slowly added Phenylchloroformate (90.4 gms) at 50 – 55°C over 1 ½ - 2hrs. Maintained the reaction mass at 50-60°C for 1½ hours. Checked the reaction completion by TLC. Cooled the reaction mass to 30-35°C and washed the reaction mass with 1% Sodium bicarbonate solution (2000 ml), 0.5 N HCl (2 X 100 ml) and 1% Sodium bicarbonate solution (1500 ml) at 25-35°C. Toluene is distilled off under vacuum below 65°C. DMSO (2000 ml) is added to the residue and maintained for 5- 10 min to get clear solution. Reaction mass temperature is raised to 40°C and slowly added Sodium hydroxide solution (62.6 g sodium hydroxide + 395 ml of DM Water) at 40-45°C. Maintained the reaction mass at 40-50°C for 8 hrs. Checked the reaction completion by TLC and cooled the reaction mass to 18 - 25°C.

Charged DM Water (2000 ml) in another flask and cooled to 18-25°C. Slowly transfered the above reaction mass to cold water at temperature of 18-25°C. Adjusted the pH of the reaction mass to 5.6 – 6.0 with Acetic acid at 18-25°C. Washed the reaction mass with n-Hexane (2 X 150 ml). Adjusted the pH of reaction mass to 10.5 – 11.5 with 50% w/w Sodium hydroxide solution and stirred for 15 minutes at 20-25°C. Added toluene (1000 ml) and maintained for 15 – 30 min at 20 – 25°C. Reaction mass is allowed to settle and separated the organic layer. Extracted the aqueous layer with toluene (200 ml). Combined toluene layer is washed with DM water (3 x 200ml) and treated with activated carbon (20 Gms). Stirred for 30 min. at 25-35°C and filtered through hyflow bed. Washed the bed with toluene (100 ml). Adjusted the pH of the toluene layer to below 2.0 with CP HCl at 25-30°C. Stirred for 30 min. at 25-30°C. Toluene is distilled off completely under vacuum at 50-55°. Charged ethyl acetate (100 ml) to the residue and distilled off completely under vacuum at 50-55°C. Added ethyl acetate (600 ml) to the above residue and maintained at 15 – 20°C for 2 hrs. Cooled the reaction mass to 0-2°C and maintained for 60 min at 0-5°C. Filtered the mass and washed the wet cake with chilled ethyl acetate (200 ml). Dried the material at 50-55°C till constant weight.

Output : 110 Gms

Example 3: Preparation of Atomoxitine HCl

Step-1: (R) (-) N-Methyl-3-(2-methylphenoxy)-3-phenylpropylamine(S)-(+) mandelate

N-Methyl-3-(2-methyl phenoxy)-3-phenyl propyl amine hydrochloride (100 Gms) is added to a mixture of DM water (400ml) and Toluene (400 ml) at 25-35°C.

Temperature is raised to 40-45°. Slowly added ammonia solution (110 ml) at 40-45°C and maintained for 30 min at 40 - 45°C. Allowed the reaction mass to settle for 30 min and separated the layers.Organic layer is separated and the aqueous layer is extracted with toluene (100 ml). Combined the organic layer and washed with DM water (2 X 100 ml). Toluene is distilled of under vacuum at 60-65°C and to the obtained residue toluene (90 ml) and Ethyl acetate (270 ml) are added. Charged S(+)-Mandelic acid (26 gm) at 28-32°C and maintained for 30 minutes at 25-30°C Slowly raised the temperature to 40-45°C over a period of 1.0 hour and maintained the mass at 40 - 45°C for 2.0 hours. Slowly cooled the mass to 28-32°C over a period of 1.0 hr and maintained at 28-32°C for 4-5 hrs. Again cooled the reaction mass to 0-5°C and maintained at 0-5°C for 1.0 hr. filtered the material and washed the wet cake with chilled ethyl acetate (100 ml). Dried the material at 40-45°C for 1.0 hour.

Output: 60 Gms

Suspended the above obtained material in Ethyl acetate (270 ml) and raised the reaction mass to reflux for dissolution. Maintained at reflux for 20 – 30 minutes. Cooled the reaction mass to 25-30°C and maintained for 1.0 hour at 25-30°C. Filtered the product and washed the wet cake with Ethyl acetate (60 ml). Dried the material at 40- 45°C till constant weight.

Output: 55 Gms

Step-2: Preparation of Atomoxetine hydrochloride

(R)(-)N-Methyl-3-(2-methylphenoxy)-3-phenylpropylamine(S)-(+) mandelate (100 gm) is suspended in DM water (500ml) at room temperature. 10% Sodium Hydroxide solution (15gms Sodium hydroxide in 150 ml DM Water) is added at 25-35°C in 30 - 40 min and pH is checked. The reaction mixture is extracted with ethyl acetate (500 ml + 200 ml). Combined ethyl acetate layer is washed with 10% sodium chloride solution (2 x 200 ml) and treated with activated carbon (10 gm) for 30 min at 25-35°C. Filtered the mass through hyflow bed and washed the bed with ethyl acetate (100 ml). Ethyl acetate is distilled under vacuum below 45°C to get residue. The obtained residue is dissolved in ethyl acetate (310 ml) and HCl gas is passed slowly to the reaction mass till pH becomes below 2.0. The reaction mass is cooled to 0-5°C and maintained for one hour at 0-5°C. The product is filtered and washed the wet cake with chilled ethyl acetate (100 ml) and dried the material at 40-45°C under vacuum till LOD becomes below 1.0%.

Output: 60 Gms

Step-3: Purification of Atomoxetine hydrochloride

Atomoxetine hydrochloride (60 gm) is dissolved in methanol (120 ml) at 40 - 45°C and treated with activated Carbon (6.0 gm). Filtered the reaction mass through Hyflow bed and washed the bed with methanol (60 ml). Methanol is distilled off below 45°C under vacuum and cooled the reaction mass to 25 to 35°C. Ethyl acetate (600 ml) is charged and maintained the reaction mass at 25-35°C for one hour. The reaction mass is cooled to 0-5°C and maintained for one hour at 0-5°C. Filtered the material and washed the wet cake with chilled ethyl acetate (60 ml). The wet material is dried at room temperature for 2.0 hours followed by at 45-55°C under vacuum till LOD is less than 0.5%.

Output: 57 Gm

We claim;

1. A process for the preparation of Atomoxetine hydrochloride comprising the steps;

   - Reacting N,N-dimethyl 3-phenyl-3-chloropropyl amine acid addition salt with o-cresol in presence of phase transfer catalyst and base to get N,N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine,
   - Demethylating N,N-dimethyl 3-(o-tolyloxy)-3-phenylpropylamine to get N-methyl 3-(o-tolyloxy)-3-phenylpropylamine,
   - Treating N-methyl 3-(o-tolyloxy)-3-phenylpropylamine with (S)-(+)-mandelic acid in a mixture of toluene and ethyl acetate to get (S)-(+)-mandalate,
   - Isolating (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropyl amine (S)-(+)-mandalate,
   - Basifying (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropylamine (S)-(+)-mandalate and extracting the liberated (R)-(-) N-methyl 3-(o-tolyloxy)-3-phenylpropylamine with an water immiscible solvent and
   - Saltification with hydrochloric acid to get Atomoxetine hydrochloride.

2. The process as claimed in claim 1, wherein acid addition salt is selected from hydrochloride, hydrobromide, sulphate, phosphate, nitrate or acetate.

3. The process as claimed in claim 1, wherein the phase transfer catalyst is selected from tetrabutyl ammonium bromide, tetrabutyl ammonium chloride, triethyl benzyl ammonium chloride, tributyl benzyl ammonium chloride and mixtures thereof.

4. The process as claimed in claim 1, wherein the phase transfer catalyst is selected from phosphonium salts and crown ethers.

5. The process as claimed in claim 1, wherein the base is selected from alkali hydroxides, carbonates like sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate.

6. The process as claimed in claim 1, wherein condensation reaction of 3-phenyl-3-chloropropyl amine acid addition salt with o-cresol is carried out in a mixture of water and a halogenated hydrocarbon.

7. The process as claimed in claim 1, wherein demethylation takes place with phenyl chloroformate in the presence of diisopropyl ethyl amine.

8. The process as claimed in claim 1, wherein the isolated (R)-(-) N-methyl 3-(o-tolyloxy) -3-phenylpropyl amine (S)-(+)-mandalate is further purified in ethyl acetate.

9. The process as claimed in claim 1, wherein the saltification of Atomoxetine is carried out in Ethyl acetate.

10. A process for preparation of crystalline Atomoxetine hydrochloride comprising the steps:

- Dissolving Atomoxetine hydrochloride in a lower alkanol
- Optionally treating the solution with activated carbon
- Removing the solvent from the solution
- Adding a second solvent and Isolating Atomoxetine hydrochloride

11. The process as claimed in claim 10, wherein the preferable lower alkanol is selected from methanol, ethanol, isopropanol and mixtures thereof.

12. The process as claimed in claim 11, wherein the second solvent is selected from ethyl acetate, isopropyl acetate and mixture thereof.

X-Ray Diffraction Spectrum

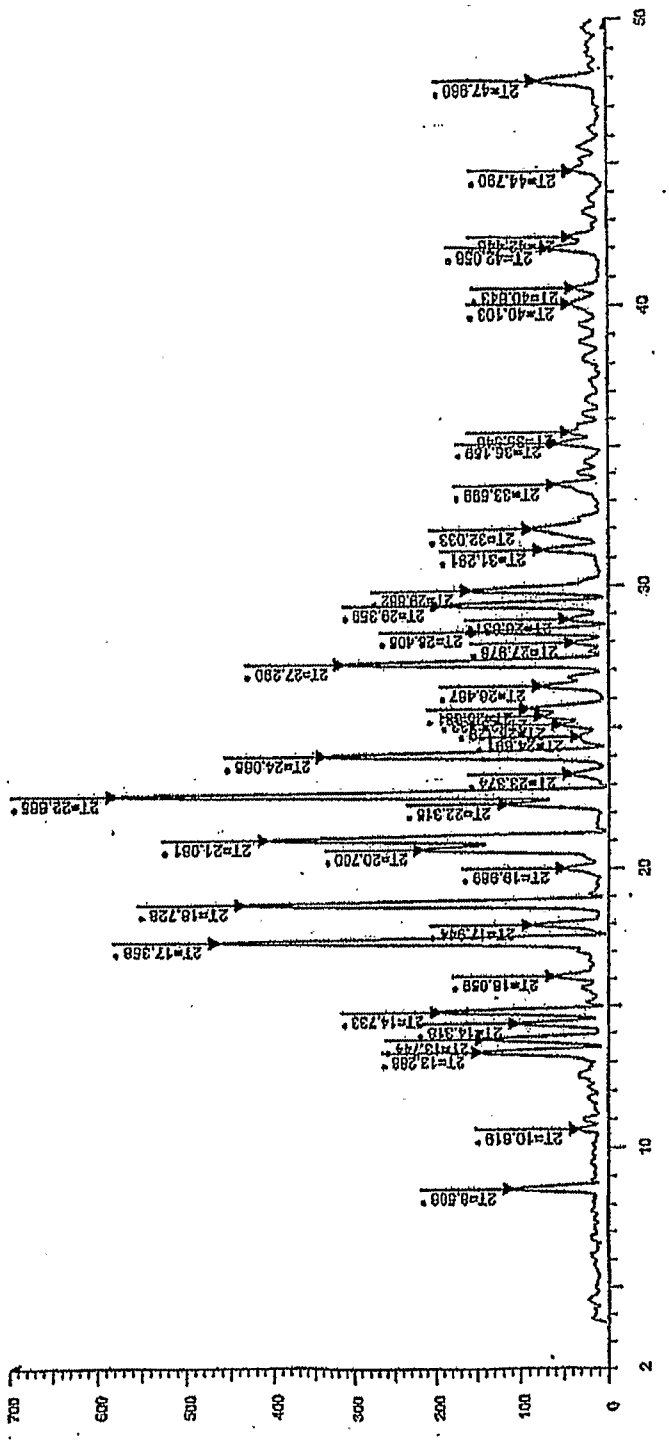


Figure - 1