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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 May 2013 (16.05.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/069025 A1

(51) **International Patent Classification:**
C07D 233/58 (2006.01) ***C07B 57/00*** (2006.01)
BOW 9/02 (2006.01)

(21) **International Application Number:**
PCT/IN2012/000013

(22) **International Filing Date:**
5 January 2012 (05.01.2012)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
3202/MUM/2011 11 November 2011 (11.11.2011) IN

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(81) **Designated States** ***(unless otherwise indicated, for every kind of national protection available):*** AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, 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(H))***

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

— ***of inventorship (Rule 4.17(iv))***

Published:

– *with* international search report (Art 21(3))

WO 2013/069025 A1

(54) **Title:** "PROCESS FOR THE PREPARATION OF DEXMEDETOMIDINE"

(57) **Abstract:** The invention discloses a novel process for preparation of dexmedetomidine in higher yield and with enantiomeric purity more than 99%.

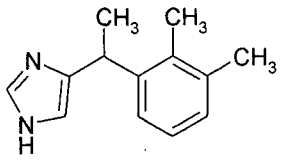
"PROCESS FOR THE PREPARATION OF DEXMEDETOMIDINE"

TECHNICAL FIELD:

The present invention relates to a novel process for resolution of medetomidine to provide dexmedetomidine in high yield and high enantiomeric purity.

BACKGROUND AND PRIOR ART:

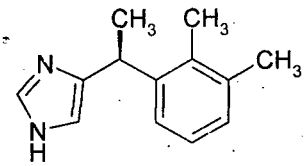
Medetomidine which is chemically named as 4(5)-[l-(2,3-dimethylphenyl)ethyl] imidazole) is known as sedative and potent alpha 2-receptor agonist. It has been described in the European patent EP72615 as an antihypertensive agent and in the European patent EP 187471 as a veterinary sedative-analgesic agent.



Medetomidine

Dexmedetomidine is the (S)-enantiomer of medetomidine. It is a very potent alpha-2 adrenoreceptive agonist which is currently evaluated in clinics as anesthetic. It is relatively unique in its ability to provide sedation without causing respiratory depression. It has further been observed that dexmedetomidine also possesses anxiolytic effects and can therefore be used in the treatment of general anxiety, panic disorder and various kinds of withdrawal symptoms.

Dexmedetomidine has following structure;



Dexmedetomidine was first described in U.S. patent number 4910214. The patent discloses the preparation of dexmedetomidine by resolution of medetomidine using (+)-tartaric acid in presence of methanol. It is also disclosed in the patent that resolution can also be carried out using (-)-malic acid, (-)-mandelic acid or (+)-camphor-10-sulphonic acid. However, the patent does not disclose the yield and enantiomeric purity of dexmedetomidine.

Synthetic communication 26(8), 1585 - 1593 (1996) discloses preparation of dexmedetomidine where resolution of medetomidine was carried out by using (+)-tartaric acid in absolute ethanol. The suspension was heated to reflux until complete dissolution and stirred for 20 hours at room temperature before filtration of white solid. The solid was suspended by stirring for 18 hours in ethanol and filtered. The new solid was suspended by stirring for 66 hours in ethanol and filtered. The solid was dissolved in water and the solution was neutralized with IN NaOH. The solution was extracted with ether, dried and evaporated under pressure. The residue was dissolved in hot ethanol and treated with (+)-tartaric acid and the resulting solution was stirred at room temperature overnight. The solid was filtered to get dexmedetomidine (+)-tartrate in greater than 99% enantiomeric excess and 21% overall. As the process requires 5 days to provide dexmedetomidine in very low overall yield it is industrially uneconomical.

The Chinese patent CN101671305 also discloses preparation of dexmedetomidine where medetomidine was resolved by using S-(+)-phosphoric acid-hydro- l,l'-di-2,2'-naphthyl ester [S-(+)BNP], D-(+)-dibenzoyl tartrate [D-(+)-DBTA], L-(-)-dibenzoyl tartrate [L-(-)-DBTA] or R-(-)-phosphoric acid-hydro- l,l'-di-2,2'-naphthyl ester [R-(-)BNP]. This process is also time consuming and requires highly expensive reagents thus making the process industrially uneconomical.

Needless to say it is advantageous to develop a short, high yielding and industrially viable process for preparation of highly pure dexmedetomidine which eliminates use of expensive reagents.

OBJECT OF THE INVENTION:

It is therefore an object of the invention to overcome or ameliorate at least one disadvantage of the prior art or to provide a useful alternative.

Another object of the invention is to provide a novel, concise, high yielding, commercially viable and industrially applicable process for resolution of medetomidine to provide dexmedetomidine in high yield and with high enantiomeric excess.

Yet another object of the present invention is to provide a process for preparation of dexmedetomidine having desirable pharmacological activity and broad safety margins, without toxicity or unfavorable side effects.

SUMMARY OF THE INVENTION:

In accordance with the above objectives, the present invention provides a process for preparation of dexmedetomidine comprising reacting medetomidine with D-(-)-tartaric acid; filtering the resulting solution; neutralizing the filtrate with a base; reacting the resulting product with L-(+)-tartaric acid to provide dexmedetomidine L-(+)-tartrate; and reacting dexmedetomidine L-(+)-tartrate with a base.

DETAILED DESCRIPTION OF THE INVENTION:

Unless specified 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. Although any methods and material 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. To describe the invention, certain terms are defined herein specified as follows:

Unless stated to the contrary, any of the words 'having', 'including', 'includes', 'comprising' and 'comprises' mean 'including without limitations' 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 are given for the purpose illustration rather than limitation of the invention as set forth the appended claims.

The inventors have surprisingly found that simultaneous use of (D)-(-) and L-(+)-tartaric acids in the resolution of medetomidine provides dexmedetomidine in high yield which is at least double than that obtained by using known resolution methods.

Accordingly, the present invention provides a process for preparation of dexmedetomidine comprising:

step (i): reacting medetomidine with D-(-)-tartaric acid in presence of solvent;

step (ii): filtering the resulting solution;

step (iii): neutralizing the filtrate with a base;

step (iv): reacting the resulting product with L-(+)-tartaric acid to provide dexmedetomidine L-(+)-tartrate; and

step (v): reacting dexmedetomidine L-(+)-tartrate with a base.

The step (i) of the present invention is advantageously carried out by reacting medetomidine with D-(-)-tartaric acid in presence of at least one solvent. The solvent for the step (i) is selected from polar solvents. The solvent is preferably an alcohol. The most preferred solvent for the step (i) is ethanol. The step (i) is carried out at 30 - 100°C, more preferably at 50 - 80°C.

The step (ii) of filtration is followed by concentration and neutralization of the filtrate.

Neutralization of the filtrate in the step (iii) is carried out by using a base selected from organic or inorganic bases. The preferred base for neutralization is an inorganic base selected from alkali metal carbonates and alkali metal bicarbonates. The most preferred

base for the step of neutralization is sodium bicarbonate. The step (iii) is carried out at 0 - 50°C, more preferably at 15 - 35°C.

The resulting product of the step (iii) is reacted with L-(+)-tartaric acid in the step (iv) to provide dexmedetomidine L-(+)-tartrate. Advantageously the step (iv) is carried out in presence of a solvent. The solvent for the step (iv) is selected from at least one polar solvent. The preferred solvent for the step (iv) is alcohol. The most preferred solvent for the step (iv) is ethanol. The step (iv) is carried out at 30 - 100°C, more preferably 50 - 80°C.

In the step (v) dexmedetomidine L-(+)-tartrate is reacted with a base to provide dexmedetomidine. The base for step (v) is selected from inorganic base or organic base. The preferred base for the step (v) is at least one inorganic base. The most preferred base for the step (v) is sodium bicarbonate. Advantageously the step (v) is carried out in presence of a solvent selected from at least one polar solvent. The preferred solvent for the step (v) is at least one alcohol. The most preferred solvent for the step (v) is ethanol. The step (v) is carried out at 0 - 50°C, more preferably 15 - 35°C.

The process further comprises recrystallizing dexmedetomidine L-(+)-tartrate from at least one solvent; or neutralizing dexmedetomidine L-(+)-tartrate with a base and reacting the resulting product with L-(+)-tartaric acid.

The solvent for recrystallizing dexmedetomidine L-(+)-tartrate is selected from polar solvents. Preferred solvent for recrystallization is alcohol containing 1 to 5 carbon atoms. The most preferred solvent for recrystallization of dexmedetomidine L-(+)-tartrate is ethanol.

The base used for neutralizing dexmedetomidine L-(+)-tartrate is selected from an organic base or an inorganic base. Preferably neutralization of dexmedetomidine L-(+)-tartrate is carried out in presence of an inorganic base selected from alkali metal carbonates or alkali metal bicarbonates. The most preferred base for neutralization of dexmedetomidine L-(+)-tartrate is sodium bicarbonate.

The process of the invention provides dexmedetomidine in 47% yield and with enantiomeric excess of at least 99%. The yield of dexmedetomidine obtained by using the novel process is 2.2 times higher than that obtained by using resolution methods reported in the prior art.

All the steps of the process can be carried out in a single solvent and in a single base which are inexpensive; the process is thus highly economical.

Dexmedetomidine is further converted into its hydrochloride salt by methods known in the art.

The pure Dexmedetomidine hydrochloride obtained by the process of the invention may be formulated into a dosage form by combining with one or more pharmaceutically acceptable excipients using known techniques. Further, the dosage form may be immediate release or extended release.

Further details of the process of the present invention will be apparent from the examples presented below. Examples presented are purely illustrative and are not limited to the particular embodiments illustrated herein but include the permutations, which are obvious as set forth in the description.

EXAMPLE:

A 1000 ml four neck round bottom flask was charged with medetomidine (52 gm), ethanol (125 ml), D-(-)-tartaric acid (20 gm) and water (20 ml). The flask was heated at 60°C for 0.5 hour and the reaction mixture was concentrated to obtain thick oil. The flask was charged with ethanol (125 ml) and water (12.5 ml) under heating. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated, neutralized with 5% sodium bicarbonate, extracted with dichloromethane, dried and concentrated to obtain oil. The oil was dissolved in ethanol (150 ml), treated with L-(+)-tartaric acid (35 gm) and water (20 ml), and heated at 60°C for 2 hours. The reaction mixture was cooled to room temperature to obtain a solid, which was collected by

filtration and dried to obtain dexmedetomidine L-(+)-tartrate (35.6 gni, $[\alpha]_D^{25=}$ 49.16 (c = 1 in methanol)).

Dexmedetomidine L-(+)-tartrate was neutralized with 7.5% sodium bicarbonate, extracted with dichloromethane, dried and concentrated to obtain a solid (20.5 gm). Ethanol (230 ml), water (15 ml) and L-(+)-tartaric acid (23 gm) were added to the solid, heated at 60°C for one hour, cooled the reaction mixture overnight and filtered to obtain dexmedetomidine L-(+)-tartrate (29 gm, $[\alpha]_D^{25=}$ 55.98 (c = 1 in methanol), 95.68% e.e.). Dexmedetomidine L-(+)-tartrate was purified by crystallization from ethanol to obtain pure product (23.3 gm, $[a]_D^{25}$ = 58.34 (c = 1 in methanol), 99.12% e.e.).

The purified dexmedetomidine L-(+)-tartrate was neutralized with sodium bicarbonate, extracted with dichloromethane, dried and concentrated to obtain dexmedetomidine (12.16 gm, $[a]_D^{25}$= 63.94 (c = 1 in methanol), 99.54% e.e.).

WE CLAIM,

1. A process for preparation of dexmedetomidine comprising reacting medetomidine with D-(-)-tartaric acid in presence of a solvent; filtering the resulting solution; neutralizing the filtrate with a base; reacting the resulting product with L-(+)-tartaric acid to provide dexmedetomidine L-(+)-tartrate; and reacting dexmedetomidine L-(+)-tartrate with a base.

2. The process as claimed in claim 1, comprising neutralizing dexmedetomidine L-(+)-tartrate with a base and reacting the resulting product with L-(+)-tartaric acid.

3. The process as claimed in claim 1, comprising recrystallizing dexmedetomidine L-(+)-tartrate from at least one solvent.

4. The process as claimed in claim 1, wherein the solvent is polar solvent selected from C1 to C5 alcohols.

5. The process as claimed in claim 1 and 4, wherein the solvent is ethanol.

6. The process as claimed in claim 3, wherein the solvent for recrystallization is selected from alcohols containing 1 to 5 carbon atoms.

7. The process as claimed in claim 3 and 6, wherein the solvent for recrystallization is ethanol.

8. The process as claimed in claim 1, wherein the base for neutralization of the filtrate is selected from an organic base or an inorganic base.

9. The process as claimed in claim 1 and 8, wherein the base for neutralization of the filtrate is an inorganic base selected from alkali metal carbonates or alkali metal bicarbonates.

10. The process as claimed in claim 1, 8 and 9, wherein the base is sodium bicarbonate.

11. The process as claimed in claim 1 and 2, wherein dexmedetomidine L-(+)-tartrate is reacted with the base selected from an organic base or an inorganic base.

12. The process as claimed in claim 1, 2 and 11, wherein dexmedetomidine L-(+)-tartrate is reacted with the base selected from alkali metal carbonates or alkali metal bicarbonates.

13. The process as claimed in claim 1, 2, 11 and 12, wherein dexmedetomidine L-(+)-tartrate is reacted with sodium bicarbonate.

14. The process as claimed in claim 1 to 13, wherein the process provides dexmedetomidine with at least 99 % enantiomeric excess.

INTERNATIONAL SEARCH REPORT

International application No
PCT/ I N2012/0000 13

A. CLASSIFICATION OF SUBJECT MATTER
I NV. C97D233/58 B0 1D9/02 C07B57/OO
ADD .

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D B01D C07B

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-I nternal , CHEM ABS Data , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CORDI A A ET AL: "EFFI CI ENT SYNTH ESI S OF (S) - 4 (5) -Äl - (2, 3 - DI METHY LPH ENYL) ETHY LÜI MI D AZO LE TARTRATE, THE POTENT ALPHA2 ADRENOCEPTOR AGON I ST DEXMEDETOMI DI NE", SYNTH ETI C COMMUN I CATI ONS, TAY LOR & FRANC I S GROU P, PHI LAD ELPH I A, PA, vol . 26, no. 8, 1 January 1996 (1996-01 -01) , page s 1585 - 1593 , XP0090 14489 , I SSN: 0039-79 11, DOI: 10 . 1080/003979 19608003527 cited in the appl i cati on page 1588 , l i ne 1 - l i ne 7 l ast paragraph ; page 1586 ----- -/--	1- 14

X I Further documents are listed in the continuation of Box C.

X See patent family annex.

* Special categories of cited documents :

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 2012	18/06/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2O12/00OO13

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 910 214 A (KARJALAINEN ARTO J [FI] ET AL) 20 March 1990 (1990-03-20) cited in the application column 6, line 12 - line 13 -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent Tamlly members

International application No
PCT/ IN2012/000013

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