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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 November 2010 (11.11.2010)

PCT

(10) International Publication Number
WO 2010/128517 A1

(51) **International Patent Classification**:
C07B 57/00 (2006.01)

(21) **International Application Number**:
PCT/IN2009/000378

(22) **International Filing Date**:
3 July 2009 (03.07.2009)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
1062/CHE/2009 7 May 2009 (07.05.2009) 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, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, 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:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2010/128517 A1

(54) **Title**: IMPROVED PROCESS FOR THE PREPARATION OF *D-THREO*-RITALINIC ACID HYDROCHLORIDE BY RESOLUTION OF *DL-THREO*-RITALINIC ACID USING CHIRAL CARBOXYLIC ACID

(57) **Abstract**: The invention disclosed in this application relates to an improved process for the manufacture of *d-threo*-ritalinic acid hydrochloride and *l-threo*-ritalinic acid hydrochloride in an optically pure form by the resolution of *dl-threo*-ritalinic acid using a chiral carboxylic acid The *d-threo*-ritalinic acid hydrochloride prepared by the process of the present invention on esterification gives *d-threo*-methylphenidate, a very well known CNS stimulant.

IMPROVED PROCESS FOR THE PREPARATION OF *d-threo*-RITALINIC ACID HYDROCHLORIDE BY RESOLUTION OF *dl-threo*-RITALINIC ACID USING CHIRAL CARBOXYLIC ACID

The following specification describes the nature of the invention and the manner in which it is to be performed:

- **Field of the invention**

The objective of the present invention relates to improved process for the manufacture of a *d-threo*-ritalinic acid hydrochloride and *l-threo*-ritalinic acid hydrochloride in an optically pure form by the resolution of *dl-threo*-ritalinic acid using a chiral carboxylic acid.

- **Background of invention**

Methylphenidate available in the market to treat Attention Deficient Hyperactivity Disorder (ADHD) is *dl-threo* mixture. It is a controlled substance. Methylphenidate contains two chiral carbon atoms and so exists in four enantiomeric forms. Of all the forms, the studies of its *threo*-diastereomer revealed that *d-threo* isomer has been found to be more active and also showed significant metabolic difference than *l-threo* enantiomer.

To date, there have been several methods disclosed in the literature for preparing *d-threo* enantiomer of methylphenidate. For example, the process reported first by Patrick et.al. [*The Journal of Pharmacology and Experimental Therapeutics*, 241, 152-158 (1987)], describes the use of expensive resolving agent, 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate in the resolution of *dl-threo*-methylphenidate. More efficient resolutions, using a O,O-Diaroyltartaric acid or menthoxy-acetic acid or dibenzoyl-D-tartaric acid are disclosed in WO9727176, GB97/00643, US 6100401, US 6121453, US 6162919 and US 6242464. Resolution of *threo*-methylphenidate may also be achieved by enzymatic hydrolysis methods proposed by Prashad (1998) [US7247730] and in WO98/25902.

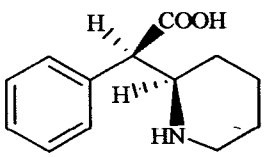
U.S.2957880 discloses the resolution of *erythro*-phenylpiperidyl acetamide using tartaric acid. This, however, must be followed by amide hydrolysis and equilibration at the benzylic centre, to give the *threo* isomer of the ritalinic acid.

In addition, U.S.2002/0019535 describes the manufacture of *threo*-ritalinic acid by resolution of *threo*-ritalinic acid hydrochloride using chiral base *(S)-(-)*-1-phenethylamine affording the product in 77% *ee*.

It would be desirable to find

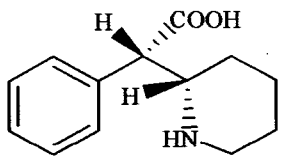
1) a satisfactory substrate for resolution that did not involve handling of the active drug and
2) a more practical and efficient process to produce compound with high optical purity. Ritalinic acid in *threo* form might be a target. *threo*-Ritalinic acid contains a carboxylic group and a tertiary amino function in the moiety, due to which either chiral carboxylic acid or chiral organic base can be used for resolution. The *d-threo*–enantiomer of ritalinic acid thus obtained can be converted to *d-threo*-methylphenidate hydrochloride by reaction with methanol and hydrochloric acid.

The present invention provides an improved process for preparing *d*-and *l-threo* isomers of ritalinic acid of formula I & II,



d-threo-Ritalinic acid

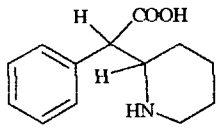
(Formula I)



l-threo-Ritalinic acid

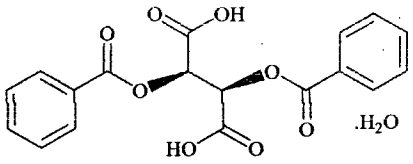
(Formula II)

and its salt by resolution of *dl-threo*-ritalinic acid of the formula III using chiral carboxylic acid of the formula IV as the resolving agent .



dl-threo-Ritalinic acid

(Formula III)

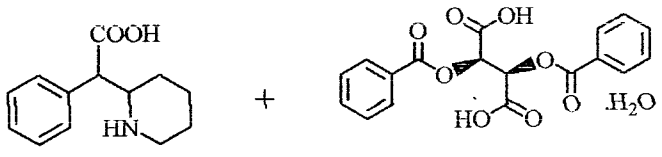


(+)-Dibenzoyl-D-tartaric acid monohydrate

(Formula IV)

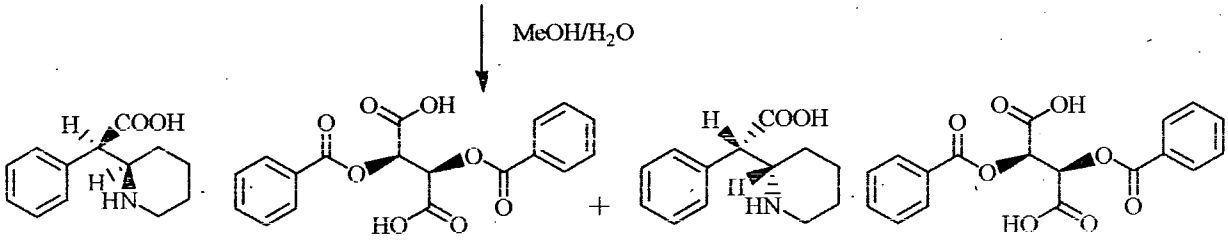
The method of the present invention is quite preferable and economical for the preparation of *d-threo*-ritalinic acid as an industrial procedure and gives *d-threo*-ritalinic acid hydrochloride with high optical purity.

More particularly, the process involves the resolution of *dl-threo*-ritalinic acid with (+)-dibenzoyl-D-tartaric acid to yield the desired tartrate salt of *d-threo*-isomer of ritalinic acid in the first step and the breaking of salt in the second step to obtain the hydrochloride form of the *d-threo*-isomer with high optical purity, while the *l-threo*-isomer and the dibenzoyltartaric acid are recovered from the mother liquors as shown below:



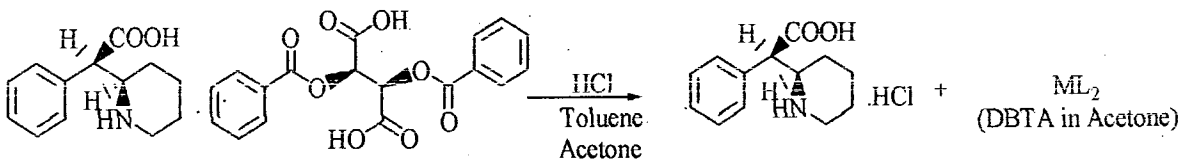
dl-threo-Ritalinic acid

(+)-Dibenzoyl-D-tartaric acid monohydrate



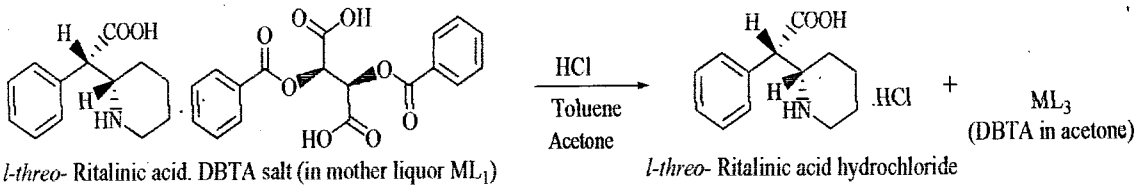
d-threo- Ritalinic acid. DBTA salt crude

l-threo- Ritalinic acid. DBTA salt (in mother liquor ML_1)



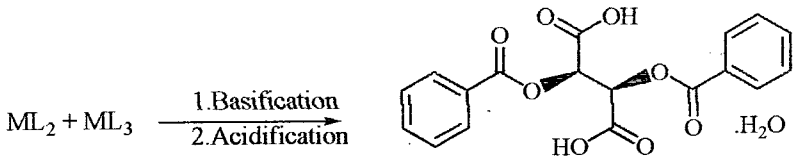
d-threo- Ritalinic acid. DBTA salt

d-threo- Ritalinic acid hydrochloride



l-threo- Ritalinic acid. DBTA salt (in mother liquor ML_1)

l-threo- Ritalinic acid hydrochloride



(+)-Dibenzoyl-D-tartaric acid monohydrate

- **Objectives of the invention**

The main objective of the present invention is to provide an improved process for the resolution of *dl-threo*-ritalinic acid

Another objective of the present invention is to provide an improved process for the preparation of *d-threo*-ritalinic acid hydrochloride and *l-threo*-ritalinic acid hydrochloride by resolving the *dl-threo*-ritalinic acid using chiral carboxylic acid as the resolving agent.

Another objective of the present invention is to provide an improved process for the preparation of *d-threo*-ritalinic acid hydrochloride by resolving the *dl-threo*-ritalinic acid involving the use of stoichiometric quantity of the resolving agent.

Still another objective of the present invention is to provide an improved process for the preparation of *d-threo*-ritalinic acid hydrochloride by resolving the *dl-threo*-ritalinic acid with reduced process steps for isolating *d-threo*-ritalinic acid in high optical purity of > 99%.

Yet another objective of the present invention is to provide an improved process for the preparation of *d-threo*-ritalinic acid hydrochloride by resolving the *dl-threo*-ritalinic acid involving the recovery of derivative of tartaric acid from the mother liquors with highest yield.

As a result, the present invention provides a simple but efficient, economical, less time consuming and less tedious method for producing *d-threo*-ritalinic acid hydrochloride.

- **Detailed description of the invention**

Accordingly, the present invention provides an improved process for the preparation of *d-threo*-ritalinic acid hydrochloride and *l-threo*-ritalinic acid hydrochloride by resolution of *dl–threo*-ritalinic acid using chiral carboxylic acid which comprises of

(i) dissolving *dl–threo*-ritalinic acid in a solvent, water mixture (60:40) and adding a solution of an ester of tartaric acid in a solvent to the dissolved *dl-threo*-ritalinic acid solution at a temperature in the range from −10 °C to 100 °C for a period ranging from 5 min to 5 h.

(ii) heating the mass to reflux for a period ranging from 15 min to 24 h and filtering it through the hyflo bed and cooling the filtrate to a temperature in the range of −10 °C to 40 °C to obtain a slurry containing solid mass of *d-threo*-ritalinic acid–tartaric acid ester salt.

(iii) maintaining the resulting slurry for a period ranging from 30 min to 24 h and filtering to obtain *d-threo*-ritalinic acid–tartaric acid ester salt.

(iv) adding to the mother liquor, concentrated or dilute hydrochloric acid, solvent and concentrating the mother liquor under vacuum by maintaining temperature 40 °C to 100° C.

(v) adding organic solvent to the concentrated mother liquor.

(vi) cooling the mass to a temperature in the range of −15 °C to 40 °C and filtering to get *l-threo*-ritalinic acid hydrochloride and the mother liquor containing the resolving agent.

(vii) adding organic solvent and water along with organic or inorganic acids to the *d-threo*-ritalinic acid–tartaric acid ester salt obtained in step (iii) and removing the water present in the acid using the known methods.

(viii) adding an organic solvent to the concentrated mass obtained in step (vii) under stirring at a temperature range of -10 °C to 25 °C and filtering, to get the *d-threo*-ritalinic acid hydrochloride and the mother liquor containing the resolving agent.

(ix) concentrating the mother liquors obtained in step (vi) and (viii) basifying and acidifying by conventional methods and filtering the resolving agent.

The *dl- threo*-ritalinic acid used in step (i) may be prepared through multi-step process in which 2-chloropyridine and benzyl cyanide initially are coupled to form α-pyrid-2-yl-phenylacetonitrile. The resulting α-pyridyl-2-ylphenylacetonitrile then is hydrated in the presence of acid to yield α-pyrid-2-ylphenylacetamide which in turn is catalytically hydrogenated to yield α-piperid-2-ylphenylacetamide and then is hydrolysed and epimerized to *dl-threo*-ritalinic acid. The solvent used in the step (i) along with water may be selected from organic solvents. The solvent used to dissolve ester of tartaric acid may be selected from organic solvents. Conventional esters of tartaric acid used may include dibenzoyltartaric acid and ditoluoyltartaric acid, the preferred one being (+)-dibenzoyltartaric acid of 0.2 to 1.6 eq to that of ritalinic acid, preferably, 1.06 eq in a solvent, preferably methanol adding at a temperature ranging preferably below 50 °C, for a period preferably ranging from 5 min to 5 h. Heating the mass in step (ii) at reflux temperature preferably in 1 h to 2 h and filtering the mass through hyflo bed. The filtrate is cooled to a temperature preferably 20 °C to 25 °C.

The resulting mass of step (iii) is maintained under stirring preferably for 13 h before filtering the *d- threo*-ritalinic acid–tartaric acid ester salt.

The mother liquor of step (iii) is concentrated under vacuum at a temperature preferably 70 °C to 80 °C after the addition of concentrated or dilute hydrochloric acid along with solvent preferably toluene. The solvent used in step (v) may be selected from water, aliphatic ketones or alcohols, the preferred one being acetone.

The mass obtained is cooled in step (vi) to a temperature in the range –15 °C to 40 °C, preferably 10 °C before filtering the *l-threo*-ritalinic acid hydrochloride.

In step (vii), the solvents like aliphatic ketones or aromatic ketones or alcohols or aromatic/aliphatic hydrocarbons preferably toluene are added to *d-threo*-ritalinic acid–

tartaric acid ester salt along with organic or inorganic acids, preferably hydrochloric acid and heated to evaporate the solvent.

In step (viii), solvents like aliphatic ketones or aromatic ketone or alcohols preferably acetone is added under stirring for preferably 15 min to 30 min at a temperature range of −10 °C to 25 °C preferably 5 °C to 10 °C while filtering the *d-threo*-ritalinic acid salt. The mother liquors of steps (vi) and (viii) are concentrated together, diluted with water and basified. The ester of tartaric acid formed was filtered after acidification.

The details of the invention are given in the examples given below which are provided solely to illustrate the invention and therefore should not be construed to limit the scope of the invention.

Example 1

dl-threo-Ritalinic acid	: 100 g
(+)-Dibenzoyl-D-tartaric acid	: 182 g
Methanol	: 2.3 L
Water	: 1.8 L
Acetone	: 175 mL
HCl	: 65 mL
Toluene	: 450 mL

dl-threo-Ritalinic acid (100 g, 0.456 mole) was dissolved in methanol-water mixture (1.8 L and 1.6 L) at room temperature and stirred for 15 min.

(+)-Dibenzoyl-D-tartaric acid (182 g, 0.483 moles) was dissolved in 300 mL of methanol and was added at a temperature below 50 °C in 30 min. The resulting mass was heated to reflux temperature 78 °C to 85 °C and maintained for 1 h to 2 h. The mass was filtered through hyflo bed and washed with 200 mL of water-methanol mixture (1:1). The filtrate was cooled to 20 °C to 25 °C and maintained for 13 h. The precipitated material out was

filtered and washed with 200 mL of chilled water-methanol mixture (1:1) to obtain 132 g *d-threo*-ritalinic acid–dibenzoyl tartaric cid salt.

The mother liquor obtained was treated with 35 mL of conc. hydrochloric acid, 225 mL of toluene and concentrated under vacuum by maintaining a temperature of 70 °C to 80 °C. On addition of 100 mL of acetone to the residue and on cooling to 10 °C followed by filtration 45 g of *l-threo*-ritalinic acid hydrochloride was isolated.

Purity by HPLC	: 99.78%
Chiral purity	: 99.05%
Yield	: 90%
mp	: 236 °C - 240 °C
$[\alpha]_D$	: − 88.5° (c = 2% in methanol)

To 132 g of *d-threo*-ritalinic acid–dibenzoyl tartaric acid salt, toluene 225 mL, 100 mL water and 30 mL of 35% hydrochloric acid were added and concentrated under vacuum by maintaining temperature of 60 °C to 65 °C. On addition of 75 mL of acetone to the residue and on cooling to 5 °C to 10 °C followed by filtration, 46 g of *d-threo*-ritalinic acid hydrochloride was obtained.

Purity by HPLC	: 99.92%
Chiral purity	: 99.95%
Yield	: 92%
mp	: 238 °C − 240 °C
$[\alpha]_D$	: + 89.08° (c = 2% in methanol)

Respective mother liquors obtained from the *d-threo*-ritalinic acid hydrochloride and the *l-threo*-ritalinic acid hydrochloride were concentrated, basified and acidified to recover (+)-dibenzoyl-D-tartaric acid in 90% yield showing optical rotation of −113° and melting point 88 °C-93 °C.

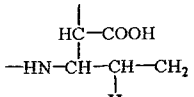
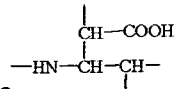
Spectroscopic interpretation

The structure of the product, *d-threo*-ritalinic acid hydrochloride was confirmed with the help of the following spectroscopic data.

a) IR (cm^{-1}) (KBr)

O-H str. of bonded COOH group at 3150-2710, $\overset{+}{H}N$-H str. at 2567, 2509, C = O str. of COOH group at 1709, benzenoid bands at 1585, 1456, C-N str. at 1396, C – O str. at 1182, C-H out of plane bending of mono-substituted benzene ring at 729,704.

b) ^{1}H NMR (DMSO-d_6, 300 MHz) (δ_H)

1.24-1.66 (6H, m, -NH-C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$ of piperidyl ring), 2.96 (1H, s, Ha of ), 3.29 (1H, d, Hb of ) [where Ha and Hb are diastereotopic protons], 3.73 (1H, s, -CH-C<u>H</u>-NH-), 4.08 (1H, d, Ph-C<u>H</u>-COOH), 7.27-7.43 (5H, m, aromatic protons), 8.67 (1H, bs, N<u>H</u> proton), 9.73 (1H, bs, COO<u>H</u> proton).

c) ^{13}C NMR (DMSO-d_6, 300 MHz) (δ_C)

21.29 (-NH-CH$_2$-CH$_2$-<u>C</u>H$_2$), 21.44 (-NH-CH-<u>C</u>H$_2$), 25.50 (-NH-CH$_2$-<u>C</u>H$_2$), 44.56 (-NH-<u>C</u>H$_2$-), 53.21 (Ph-CH-<u>C</u>H-NH), 56.69 (Ph-<u>C</u>H-COOH), 127.85 – 134.89 (aromatic protons), 172.38 (CH-<u>C</u>OOH).

d) Mass spectrum (EI)

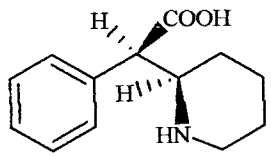
$[M]^{+\cdot}$ at m/z 220(<1), $[M^{+\cdot} - CO_2]$ at m/z 175(2), $[M^{+\cdot} - C_5H_9N]$ at m/z 136(2),  at m/ z 84(100), tropylium cation at m/z 91(11), [m/z 84 – (CH_2N)] at m/z 56(21).

- **Advantages of the invention**

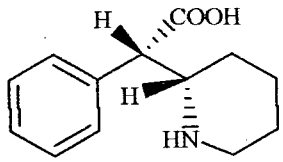
1. The process uses resolving agent which is easily available
2. The resolving agent used can be recovered almost quantitatively.
3. Resolution process is simple as it requires lesser number of steps and the *d-threo*-ritalinic acid is obtained in >99 % optical purity in >90%of theoretical yield (first crop).
4. The process is very economical and useful for commercial production as the variable cost is very low.

We Claim

1. An improved process for the preparation of *d-threo*-Ritalinic acid & *l-threo*-Ritalinic acid of the formula I& II and their salts

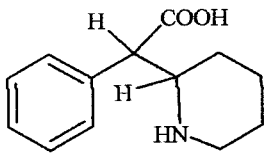


d-threo-Ritalinic acid
(Formula I)

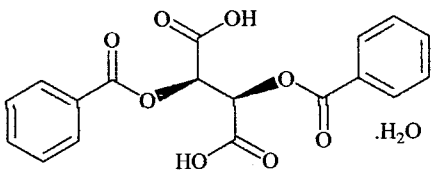


l-threo-Ritalinic acid
(Formula II)

by resolution of dl-threo-ritalinic acid of formula III using ester of tartaric acid of formula IV which comprises of



dl-threo-Ritalinic acid
(Formula III)



(+)-Dibenzoyl-D-tartaric acid monohydrate
(Formula IV)

(i) dissolving *dl-threo*-ritalinic acid in a solvent, water mixture (60:40) and adding a solution of an ester of tartaric acid dissolved in an organic solvent to the solution

at a temperature in the range from −10 °C to 100 °C for a period ranging from 5 min to 5 h.

(ii) heating the resulting mass to reflux for a period ranging from 15 min to 24 h and filtering it through the hyflo bed, cooling the filtrate to a temperature in the range of −10 °C to 40 °C to obtain a slurry containing solid mass of *d-threo*-ritalinic acid–tartaric acid ester salt.

(iii) maintaining the resulting slurry for a period ranging from 30 min to 24 h and filtering to obtain a mother liquor, separating *d-threo*-ritalinic acid–tartaric acid ester complex.

(iv) adding to the mother liquor, concentrated or dilute hydrochloric acid and concentrating the mother liquor under vacuum by maintaining the temperature 40 °C to 100 °C.

(v) adding organic solvent to the concentrated mother liquor.

(vi) cooling the mass to a temperature in the range of −15 °C to 40 °C and filtering to get *l-threo*-ritalinic acid hydrochloride and the mother liquor containing resolving agent .

(vii) adding an organic solvent along with organic or inorganic acids to the *d-threo*-ritalinic acid–tartaric acid ester salt obtained in step (iii) and removing water present in the acid using known methods.

(viii) adding an organic solvent to the concentrated mass obtained in step (vii) at a temperature range of −10 °C to 25 °C and filtering the *d-threo*-ritalinic acid hydrochloride and separating the mother liquor containing the resolving agent.

(ix) concentrating the mother liquors obtained in step (vi) and (viii), basifying and acidifying by conventional methods and filtering the resolving agent.

2. An improved process as claimed in claim1 wherein the *dl-threo*-ritalinic acid used is selected from derivatives of chiral tartaric acid and the solvent used is selected from organic solvents and water, preferred is methanol and water mixture (60:40). Ester of tartaric acid used is selected from dibenzoyltartaric acid and ditoluoyltartaric acid, preferably (+)-dibenzoyl-D-tartaric acid, the amount of ester used is 0.2 to 1.6 eq to that of the base used, preferably 1.06 eq. The organic

solvent used is methanol and the addition is carried at a temperature in the range of −10 °C to 100 °C preferably below 50 °C for a period ranging from 5 min to 5 h preferably 30 min.

3. The improved process as claimed in claims 1 to 2 wherein the mass is heated to reflux temperature of the solvent for a period ranging from 15 min to 24 h preferably 2 h and filtering it through the hyflo bed, the filtrate is cooled to a temperature in the range of −10 °C to 40 °C preferably 20 °C to 25 °C to obtain a slurry containing solid mass of *d-threo*-ritalinic acid–tartaric acid ester salt.

4. The improved process as claimed in claims 1 to 3 wherein the step (iii) slurry is maintained for a period ranging from a period 30 min to 24 h preferably 13 h to obtain a mother liquor, separating *d-threo*-ritalinic acid–tartaric acid ester salt.

5. The improved process as claimed in claims 1 to 4 wherein the concentrated hydrochloric acid is added along with toluene to the mother liquor and the mass is concentrated under vacuum at a temperature 70 °C to 80 °C, the organic solvent used in step (v) is acetone.

6. The improved process as claimed in claims 1 to 5 wherein the cooling in step (vi) is effected in the range −15 °C to 40 °C preferably 10 °C.

7. The improved process as claimed in claims 1 to 6 wherein the organic solvent added to the step (vii) is toluene and the acid is an organic or inorganic acid, preferably hydrochloric acid.

8. The improved process as claimed in claims 1 to 7 wherein the solvent used in step (viii) is selected from water, aliphatic ketones or alcohols, preferably acetone.

9. The improved process as claimed in claims 1 to 8 wherein the mother liquors are step (vi) and step (viii) are concentrated together, diluted with water and basified. The ester of tartaric acid formed is filtered after acidification.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 09/00378

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07B 57/00 (2009.01)
USPC - 514/317; 546/238; 562/402
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)
USPC: 514/317; 546/238; 562/402

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 210/198.1, 634 (text search) see search terms below.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,EPAB,JPAB), Google Scholar, DialogWEB

ritalinic acid, dl-threo-ritalinic acid, resolution, dibenzoyltartrate, ditoluoyltartrate, tartaric acid, $phenidate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/0019535 A1 (ZAVAREH et al.) 14 February 2002 (14.02.2002) para [0008], [0014]-[0015]	1-3
Y	US 6,242,464 B1 (HARRIS et al.) 05 June 2001 (05.06.2001) col 1, ln 44-53; col 2, ln 3 to col 3, ln 5.	1-3

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 December 2009 (08.12.2009)	17 DEC 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 09/00378

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-9
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.