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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF DARIFENACIN HYDROBROMIDE

(57) Abstract: The present invention relates to an improved process for the preparation of Darifenacin hydrobromide of Formula (I), (i) condensing 3-(S)-(±)-[2-(3,3-dimethyl-2,2-diphenylacetic acid)-phenyl]pyrrolidine (III), or its salt with a compound of Formula XIII in the presence of a base in a solvent, wherein X represents Cl, Br, C₂₋₄ alkyl sulfonate or C₆₋₁₀ aryl sulfonate; to produce (S)-2-[2-(2,3-dimethyl-2,2-diphenyl-5-yethyl)phenyl]-2,2-diphenylacetamide (Darifenacin) (la), (ix) treating (S)-2-[2-(2,3-dimethyl-2,2-diphenyl-5-yethyl)phenyl]-2,2-diphenylacetamide (Darifenacin) (la) with an acid in a solvent and water mixture, (x) isolating pure (S)-2-[2-(2,3-dimethyl-2,2-diphenyl-5-yethyl)phenyl]-2,2-diphenylacetamide (Darifenacin) (la), (x) treating pure Darifenacin (la) with HBr to produce Darifenacin hydrobromide (I).
AN IMPROVED PROCESS FOR THE PREPARATION OF DARIFENACIN HYDROBROMIDE

FIELD OF INVENTION:

The present invention relates to an improved process for the preparation of Darifenacin hydrobromide of Formula (I).

![Formula (I)](attachment)

BACKGROUND OF THE INVENTION

Darifenacin (la) is chemically known as (S)-2-[^l-^[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide and is approved as hydrobromide salt.

Darifenacin is a potent muscarinic M3 receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of the urinary bladder, gastrointestinal smooth muscle, saliva production, and iris sphincter function. Darifenacin has greater affinity for the M3 receptor than for the other known muscarinic receptors. Darifenacin hydrobromide is commercially available under the brand name Enablex® in the US. It has been approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

US 5,096,890 disclosed Darifenacin and its pharmaceutically acceptable salts. US '890 discloses several processes for preparing Darifenacin.
According to the process disclosed in US '890, Darifenacin (la) may be prepared by condensing 5-(2-bromoethyl)-2,3-dihydrobenzofuran (II) with 3-\((S)-(-)-(l\)-carbamoyl-1,1-diphenylmethyl)pyrrolidine (III) in the presence of K\(_2\)C\(_3\)O\(_3\) in acetonitrile.

**The process is as shown in Scheme-I below:**

US '890 also discloses a variant process for the preparation of Darifenacin (la) by condensing 5-(2-bromoethyl)-2,3-benzofuran (IV) with 3-\((S)-(-)-(l\)-carbamoyl-1,1-diphenylmethyl)pyrrolidine (III) in the presence of K\(_2\)C\(_3\)O\(_3\) in acetonitrile to produce (S)-2-[l-[2-(2,3-benzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (V), which is further hydrogenated in the presence of Pd/C in acetic acid to produce Darifenacin crude, followed by purification using column chromatography.

**The process is as shown in Scheme-II below:**

US '890 also discloses an another variant process for the preparation of Darifenacin hydrobromide (I) by condensing 5-chloroacetyl-2,3-dihydrobenzofuran (VI) with 3-
(S)-(−)-(1-carbamoyl-1,1-diphenylmethyl)pyrrolidine (III) in the presence of K\textsubscript{2}CO\textsubscript{3} in an industrial methylated spirit to produce (S)-2-[l-[2-(2,3-benzofuran-5-yl)-2-oxoethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide hydrochloride (VII), which is further hydrogenated in the presence of Pd/C in acetic acid to produce Darifenacin crude, followed by purification using column chromatography to produce pure Darifenacin (la), which is converted to Darifenacin hydrobromide (I) using aqueous hydrobromic acid in acetone.

The process is as shown in Scheme-III below:

The disadvantage with the above processes is the use of column chromatography in the purification of Darifenacin (la). Employing column chromatography technique is tedious and laborious and also involves use of large quantities of solvents, and hence is not suitable for industrial scale operations.

US 6,930,188 discloses a process for the preparation of Darifenacin hydrobromide (I), by condensing 2-(2,3-dihydrobenzofuran-5-yl)acetic acid (VIII) with (S)-2,2-diphenyl-2-(3-pyrrolidinyl)acetonitrile hydrobromide (IX) in the presence of carbonyldiimidazole in ethyl acetate to produce (S)-3-(cyanodiphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl)acetyl]pyrrolidine (X), which is further reduced in the

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presence of sodium borohydride and boron trifluoride tetrahydrofuran complex to produce (S)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenyl acetonitrile (XI), followed by treating with HBr to produce (S)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenyl acetonitrile hydrobromide (XII). Compound (XII) is treated with potassium hydroxide at 50 to 60°C to produce Darifenacin (la), followed by treating with ion-exchange resin to produce Darifenacin toluene solvate (lb), which is further converted to Darifenacin hydrobromide (I) using 48% hydrobromic acid in 2-butanone.

The process is as shown in Scheme-IV below:
It has now been found that, during the condensation of 5-(2-bromoethyl)-2,3-benzofuran (IV) with 3-(S)-(-)-(l-carbamoyl-1,1-diphenylmethyl)pyrrolidine (III) to produce (S)-2-[l-[2-(2,3-benzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (V), 3-(S)-(-)-(l-carbamoyl-1,1-diphenylmethyl)pyrrolidine (III) remained unreacted to about 8 to 10% in the reaction mass. It is difficult to separate the compound (III) through crystallization from Darifenacin hydrobromide (I), which typically require two to three crystallizations to achieve desired Darifenacin hydrobromide (I) purity. The second and third crystallization adds time to the manufacturing process and thus negatively impacts product throughput. Additionally, a second and third crystallization reduces yield as some Darifenacin hydrobromide (I) remains uncrystallized and is not recovered from the liquid phase.

Hence, there is a need to develop a purification process, which removes the unreacted intermediate compound 3-(S)-(-)-(l-carbamoyl-1,1-diphenylmethyl)pyrrolidine (III) from the reaction mass, which in turn provides Darifenacin hydrobromide of high purity with improved yield.

Further, it has been found that Darifenacin produced by the condensation of 5-(2-bromoethyl)-2,3-dihydrobenzofuran (II) with 3-(S)-(-)-(1-carbamoyl-1,1-diphenylmethyOpyrrolidine (III) contains dimmer impurity (XII).

Hence, there is a need to develop process, which reduces the unwanted Darifenacin dimer (XII), which is influenced by controlling the quantity of compound (XIII).
OBJECTIVE OF INVENTION

The main objective of the present invention is to provide a simple and effective process for the preparation of highly pure \((S)-2-[(1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide\) hydrobromide (Darifenacin hydrobromide) of Formula (I) with high purity and good yield on a commercial scale.

SUMMARY OF THE INVENTION

The present application provides an improved process for the preparation of highly pure \((S)-2-[(1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide\) hydrobromide (Darifenacin hydrobromide) of Formula (I), which comprises:

(i) condensing \(3-(S)-(-)-(1\text{-carbamoyl-1,1-diphenylmethyl})pyrrolidine\) (III), or its salt,
with a compound of Formula XIII in the presence of a base in a solvent,

\[ \text{Formula (XIII)} \]

wherein X represents Cl, Br, C1.3 alkyl sulfonate or C6-i0 aryl sulfonate; to produce (S)-2-[l-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (Ia),

(ii) treating (S)-2-[l-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (Ia) with an acid in a solvent and water mixture,

(iii) separating the layers,

(iv) extracting with a solvent,

(v) treating the organic layer with a base in water,

(vi) separating the layers,

(vii) isolating pure (S)-2-[l-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (Ia),

(viii) treating Darifenacin (Ia) with HBr to produce Darifenacin hydrobromide (I).

In another embodiment, the present invention also relates to a process for the preparation of Darifenacin hydrobromide (I), wherein 3-(S)-(−)-(1-carbamoyl-1,1-diphenylmethyl)pyrroolidine (III), and compound (XIII) are used in a molar ratio of 1:0.8 to 1:0.95.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to a process for the preparation of pure (S)-2-[l-2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide hydrobromide (Darifenacin hydrobromide) of Formula (I).
The process comprises, condensing the compound (XIII) is with 3-(S)-(−)-(1-carbamoyl-1,1-diphenylmethyl)pyrrolidine (III) in the presence of suitable base in a solvent to produce (S)-2-[1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (la). The suitable base used in the reaction is selected from an inorganic base such as alkali carbonate, more preferably, K₂CO₃, Na₂C₅O₃, Cs₂C₅O₃, NaHCO₃ or KHCO₃. The most preferred base is K₂CO₃. The solvent is an organic solvent selected from acetonitrile, toluene, methyl isobutyl ketone (MIBK), and acetone, more preferably acetonitrile or mixture thereof. The reaction may be performed at a temperature ranging from about 25°C to about reflux temperature of the solvent or mixture of solvents used for the reaction. The reaction time is about 2 to about 10 hours, more preferably about 2 to about 4 hours. After completion of the reaction, salts obtained in the reaction were filtered off and the solvent was evaporated to obtain a residue.

3-(S)-(−)-(1-Carbamoyl-1,1-diphenylmethyl)pyrrolidine (III), and compound (XIII) are used in a molar ratio of 1:0.8 to 1:0.95, preferably in a molar ratio of 1:0.9.

The residue containing (S)-2-[1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (la) in a solvent selected from dichloromethane, toluene, methyl isobutyl ketone (MIBK) and water is treated with an acid selected from hydrochloric acid, hydrobromic acid, sulfuric acid, methane sulfonic acid, /?-toluene sulfonic acid to a pH of about 1.0 to 2.0, followed by separating the layers and the aqueous layer is extracted with a solvent selected from dichloromethane, toluene, methyl isobutyl ketone (MIBK) or mixture thereof. Water is added to the combined organic layer, followed by treating with base, which is selected from K₂CO₃, Na₂C₅O₃, Cs₂C₅O₃, NaHCO₃ or KHCO₃ to a pH of about 9.0 to 9.5 and separated the layers and removal of the solvent to produce pure (S)-2-[1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (la).

(S)-2-[1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (la) produced by the above process is treated with
HBr in a solvent to produce Darifenacin hydrobromide (I). The solvent used in the process is selected from ketones such as acetone, methyl isobutyl ketone (MIBK), esters such as methyl acetate, ethyl acetate, propyl acetate, butyl acetate, alcohols such as ethanol, isopropanol, n-butanol or mixture thereof.

The process further comprises dissolving Darifenacin hydrobromide in a solvent, which is selected from acetic acid, acetone, water or mixtures thereof and precipitating pure Darifenacin hydrobromide (I) by cooling the solution to about 0-30°C, preferably 0-25°C and isolating pure Darifenacin hydrobromide (I).

It has been observed that preparation of Darifenacin hydrobromide (I) produced by the process having 3-(S)-(−)-(1-carbamoyl-1,1-diphenylmethyl)pyrrolidine (III) less than 0.05% by HPLC and Darifenacin dimer (XII), less than 0.15% by HPLC without further purification. Further, the process of the present invention does not involve tedious and laborious column chromatography for the purification of Darifenacin free base (Ia) and the resulting finished product has high chemical and optical purity according to high performance liquid chromatography (HPLC).

In another embodiment, the present invention provides a process for the preparation of compound (XIII).

The process comprises, reacting 2-(2,3-dihydrobenzofuran-5-yl)ethanol (XIV) with a reagent containing the leaving group.

![Formula (XIV)](image)

The reagent containing the leaving group used in the above reaction is selected from phosphorous halide, thionyl halide, aliphatic sulfonyl halide and aromatic sulfonyl halide. More preferably, the phosphorous halide is phosphorous tribromide, triphenylphosphine dibromide, tri-n-butylphosphine dibromide, triphenylphosphite dibromide, triphenylphosphine-N-bromosuccinimide, triphenylphosphine carbon tetrabromide the thionyl halide is either thionyl bromide or thionyl chloride, while
the preferred aliphatic sulfonyl halide is methanesulfonyl chloride and the preferred aromatic sulfonyl halide is benzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride or p-toluenesulfonyl chloride.

The suitable inert organic solvents for the above reaction include but are not limited to halogenated solvents, such as dichloromethane, ethylene dichloride, and chloroform; ether, toluene like. The reaction may be performed at a temperature ranging from 0°C to about 35°C based on the solvent or mixture of solvents used for the reaction.

The reaction is carried out in presence or absence of a base. When the leaving group is sulfanyl chloride, the reaction is earned out in presence of a base. Preferably, the organic base is an amine, more preferably, triethylamine, diisopropylethylamine, and pyridine. The sufficient period of time necessary for obtaining compound (XIII) will depend on the parameters of the reaction. Preferably, maintaining the reaction mixture for about 1 to about 8 hours. More preferably, the reaction mixture is maintained for about 1 hour to about 2 hours.

The compound (XIII) obtained by the above process can be isolated by precipitation of compound from the reaction mixture or by removing the solvent from the reaction mixture.

The following examples illustrate the nature of the invention and are provided for illustrative purposes only and should not be construed to limit the scope of the invention.

**EXAMPLE - 1**

**Stage-1:**

**PREPARATION OF 5-(2-TOSYLOXYETHYL)-2,3-DIHYDROBENZOFURAN**

2-(2,3-Dihydrobenzofuran-5yl)ethanol (65 g, 0.39 mol) was dissolved in dichloromethane (650 ml) at 20-25°C under nitrogen atmosphere. The solution was cooled to 0-5°C and p-toluenesulfonyl chloride (79.27 g, 0.41 mol) was added in one
lot. Triethylamine (60.04 g, 0.59 mol) was added slowly at 0-10°C, stirred for ~ 15 h at 20-25°C and the reaction was monitored by HPLC. Water was added and stirred for 10 min at 20-25°C. Layers were separated and the aqueous layer was extracted with dichloromethane (130 ml). The organic layer was combined and washed with water (2 x 130 ml) at 20-25°C at pH 12 - 12.5. Finally the organic layer was washed with saturated brine solution (130ml) and concentrated to complete dryness under reduced pressure at 35-45°C. The product was crystallized from ethyl acetate and n-hexanes mixture.

Yield: 96.5 g

Chromatographic purity (By HPLC): 97.85%

Stage-2:
PREPARATION OF DARIFENACIN HYDROBROMIDE

3-(S)-(−)-(1-Carbamoyl-1,1-diphenylmethyl)pyrrolidine L-(+)-tartrate (10 g, 0.02 mol), anhydrous potassium carbonate (22.50 g, 0.16 mol) and 5-(2-tosyloxyethyl)-2,3-dihydrobenzofuran (7 g, 0.02 mol) were suspended in anhydrous acetonitrile (100 ml) under nitrogen atmosphere at 25 ± 2°C. The reaction suspension was heated to 70 ± 2 °C and stirred for 4 h. Reaction progress was monitored by HPLC. The reaction mass was cooled to 30 ± 2°C, the salts were filtered and washed with acetonitrile (10 ml). The filtrate was concentrated under reduced pressure at 50 ± 2°C. The residue was dissolved in dichloromethane (50 ml), water (50 ml) was added and the pH was adjusted to 2 ± 0.1 with 24% w/w aqueous hydrobromic acid at 25-30°C. The layers were separated and the aqueous layer was extracted with aqueous dichloromethane (20 ml). Water (50 ml) was added to the combined dichloromethane layer and pH was adjusted to 9 ± 0.1 with 25% w/w aqueous potassium carbonate solution at 25 ± 2°C. The layers were separated and concentrated under reduced pressure at 35-40°C. The residue was dissolved in acetone (50 ml), cooled to 5-10°C and the pH was adjusted to acidic with 48% w/w aqueous hydrobromic acid at 5-10°C. The residue was stirred for 2 h at 20-25°C,
cooled to 0-5°C and stirred for 1 h at 0-5°C. The product was filtered, washed with chilled acetone (10 ml) and dried at 50-55°C. 
Yield: 9.4 g
Chromatographic purity (By HPLC): 98.2%.
5-(2-Tosyloxyethyl)-2,3-dihydrobenzofuran : Nil
Darifenacin dimer impurity: 0.96%.

EXAMPLE - 2
Stage-1:
PREPARATION OF 5-(2-BROMOETHYL)-2,3-DIHYROBENZOFURAN

2-(2,3-Dihydrobenzofuran-5-yl)ethanol (10 g, 0.06 mol) was dissolved in acetonitrile (60 ml) at 25 ± 2°C under nitrogen atmosphere and triphenylphosphine dibromide (27.02 g, 0.06 mol) was added in one lot at 25 ± 2°C. The reaction mass was heated to 76-78°C and stirred for 2 h. Reaction progress was monitored by TLC [Ethyl acetate: n-Hexanes; 2:8 v/v], Acetonitrile was completely distilled off under reduced pressure at 76-78°C. The residue was cooled and the product was extracted with n-hexanes (4 x 30 ml) at 25 ± 2°C. The solution was filtered and diluted with ethyl acetate (50 ml) and washed with 5% w/w aqueous sodium bicarbonate solution (2 x 50 ml) at 25 ± 2°C. The organic layer was concentrated under reduced pressure at 40-50°C.
Yield: 7 g

Stage-2
PREPARATION OF DARIFENACIN HYDROBROMIDE

3-(S)-(-)-(l-Carbamoyl-l,l-diphenylmethyl)pyrrolidine L-(+)-tartrate (5 g, 0.01 mol), anhydrous potassium carbonate (11.25 g, 0.08 mol) and 5-(2-bromoethyl)-2,3-dihydrobenzofuran (2.5 g, 0.01 mol) were suspended in anhydrous acetonitrile (50 ml) under nitrogen atmosphere at 25 ± 2°C. The reaction suspension was heated to 70 ± 2 °C and stirred for 4 h. Reaction progress was monitored by HPLC. The reaction mass was cooled to 30 ± 2°C, salts were filtered and washed with
acetonitrile (5 ml). The filtrate was concentrated under reduced pressure at 50 ± 2 °C. The residue was dissolved in dichloromethane (25 ml), water (25 ml) was added and the pH was adjusted to 2 ± 0.1 with 24% w/w aqueous hydrobromic acid at 25-30°C. The layers were separated and the aqueous layer was extracted with dichloromethane (10 ml). Water (25 ml) was added to the combined dichloromethane layer and pH was adjusted to 9 ± 0.1 with 25% w/w aqueous potassium carbonate solution at 25 ± 2°C. The layers were separated and the organic layer was concentrated under reduced pressure at 35-40°C. The residue was dissolved in acetone (25 ml), cooled to 5-10°C and the pH was adjusted to acidic with 48% w/w aqueous hydrobromic acid at 5-10°C. The residue was stirred for 2 h at 20-25°C, cooled to Q-5°C and stirred for 1 h at 0-5°C. The product was filtered, washed with chilled acetone (5 ml) and dried at 50-55°C.

Yield: 4.5 g
Chromatographic purity (By HPLC): 99.24%
5-(2-bromoethyl)-2,3-dihydrobenzofuran: Nil
Darifenacin dimer impurity: 0.39%.

EXAMPLE - 3
PURIFICATION OF DARIFENACIN HYDROBROMIDE

Darifenacin hydrobromide (10 g) was suspended in acetic acid (15 g) at 25 ± 2°C and heated to 65-70°C. Activated carbon (0.25 g) was added and stir-ed for 15 min at 65-70°C. Carbon was filtered off through hyflo and washed with hot acetic acid (5 g). Water (200 ml) was added to the filtrate slowly at 50-55°C, cooled to 45°C and Darifenacin hydrobromide seed (0.05 g) was added. The resulting solution was cooled to 20-25°C and stir-ed for 1 h and further cooled to 0-5°C and stirred for 1 h. The solid was filtered and washed with cold water (10 ml). The product was dried at 50-55°C.

Yield: 7.6 g
Chromatographic purity (By HPLC): 99.52%
5-(2-bromoethyl)-2,3-dihydrobenzofuran: Nil
5-(2-Tosyloxyethyl)-2,3-dihydrobenzofuran: Nil
Darifenacin dimer impurity: 0.20%.

**EXAMPLE - 4**

**PURIFICATION OF DARIFENACIN HYDROBROMIDE**

Darifenacin hydrobromide (15 g) was suspended in a mixture of acetic acid (25 g) and water (25 ml) at 25 ± 2°C and heated to 65-70°C. Activated carbon (0.75 g) was added and stirred for 15 min at 65-70°C. Carbon was filtered off through hyflo and washed with a mixture of acetic acid and DM water (10 g). Water (120 ml) was added to the filtrate slowly at 50-55°C, cooled to 45°C and Darifenacin hydrobromide seed (0.05 g) was added. The resulting solution was cooled to 20-25°C and stirred for 1 h and further cooled to 0-5°C and stirred for 1 h. The solid was filtered and washed with cold water (30 ml). The product was dried at 50-55°C.

Yield: 11.9 g

Chromatographic purity (By HPLC): 99.71%

5-(2-bromoethyl)-2,3-dihydrobenzofuran: Nil
5-(2-Tosyloxyethyl)-2,3-dihydrobenzofuran: Nil
Darifenacin dimer impurity: 0.20%.

**EXAMPLE - 5**

**PURIFICATION OF DARIFENACIN HYDROBROMIDE**

Darifenacin hydrobromide (9 g) was suspended in acetone (45 ml) at 25 ± 2°C, heated to 55-60°C and stirred for 30 ± 5 min at 55-60°C. The resulting solution was cooled to 20-25°C and stirred for 30 ± 5 min, which is further cooled to 0-5°C and stirred for 1 h. The solid was filtered and washed with chilled acetone (9 ml). The product was dried at 50-55°C.

Yield: 8.8 g

Chromatographic purity (By HPLC): 99.87%

5-(2-bromoethyl)-2,3-dihydrobenzofuran: Nil
5-(2-Tosyloxyethyl)-2,3-dihydrobenzofuran: Nil
Darifenacin dimer impurity: 0.08%.
EXAMPLE - 6
PURIFICATION OF DARIFENACIN HYDROBROMIDE

Darifenacin hydrobromide (9 g) was suspended in a mixture of acetone (45 ml) and DM water (1.77 ml) at 25 ± 2°C, heated to 55-60°C and stirred for 30 ± 5 min at 55-60°C. The resulting solution was cooled to 20-25°C and stirred for 30 ± 5 min, which was further cooled to 0-5°C and stirred for 1 h. The product was filtered and washed with chilled acetone (9 ml). The product was dried at 50-55°C.

Yield: 8.4 g
Chromatographic purity (By HPLC): 99.88%

EXAMPLE - 7
PURIFICATION OF DARIFENACIN HYDROBROMIDE

Darifenacin hydrobromide (10 g) was suspended in a mixture of acetone (50 ml) and DM water (3.95 ml) at 25 ± 2°C, heated to 55-58°C and stirred for 30 ± 5 min. The resulting solution was cooled to 20-25°C and stirred for 30 ± 5 min, which was further cooled to 0-5°C and stirred for 1 hour. The product was filtered and washed with chilled acetone (10 ml, 0-5°C). The product was dried at 50-55°C.

Yield: 8.30 g
Chromatographic Purity (By HPLC): 99.83%
Darifenacin dimmer: 0.10%

EXAMPLE - 8
PURIFICATION OF DARIFENACIN HYDROBROMIDE

Darifenacin hydrobromide (10 g) was suspended in a mixture of acetone (50 ml) and DM water (7.9 ml) at 25 ± 2°C, heated to 55-60°C and stirred for 30 ± 5 min. The resulting solution was cooled to 20-25°C and stirred for 30 ± 5 min, which was further cooled to 0-5°C and stirred for 1 hour. The product was filtered and washed with chilled acetone (10 ml, 0-5°C). The product was dried at 50-55°C.

Yield: 6.70 g
Chromatographic Purity (By HPLC): 99.94%
Darifenacin dimmer: Nil.
WE CLAIM

1. An improved process for the preparation of highly pure (S)-2-[l-[2-(2,3-
dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide
hydrobromide (Darifenacin hydrobromide) of Formula (I),

\[ \text{Formula (I)} \]

which comprises:

(i) condensing 3-(S)-(1-carbamoyl-1,1-diphenylmethyl)pyrrolidine
(III), or its salt,

\[ \text{Formula (III)} \]

with a compound of Formula (XIII) in the presence of a base in a solvent,

\[ \text{Formula (XIII)} \]

wherein \( X \) represents CI, Br, \( \text{C}_1 \) alkyl sulfonate or \( \text{C}_9-\text{to-10} \) aryl sulfonate;
to produce (S)-2-[l-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-
pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (la).
(ii) treating (S)-2-[l-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (Ia) with an acid in a solvent and water mixture,

(iii) separating the layers,

(iv) extracting with a solvent,

(v) treating the organic layer with a base in water,

(vi) separating the layers,

(vii) isolating pure (S)-2-[l-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (Darifenacin) (Ia),

(viii) treating Darifenacin (Ia) with HBr in a solvent to produce Darifenacin hydrobromide (I).

2. A process according to claim 1, wherein 3-(S)-(-)-(1-carbamoyl-1,1-diphenylmethyl)pyrrolidine (III), and compound (XIII) are used in a molar ratio of 1:0.8 to 1:0.95.

3. A process according to claim 1, wherein the base used in step (i) & step (v) is selected from an inorganic base such as alkali carbonate, more preferably, K₂CO₃, Na₂CO₃, Cs₂CO₃, NaHCO₃ or KHCO₃.

4. A process according to claim 1, wherein the solvent used in step (i) is an organic solvent selected from acetonitrile, toluene, methyl isobutyl ketone (MIBK), and acetone or mixture thereof.

5. A process according to claim 1, wherein the acid used in step (ii) is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, methane sulfonic acid, p-toluene sulfonic acid.

6. A process according to claim 1, wherein the solvent used in step (ii) & step (iv) is selected from dichloromethane, toluene, methyl isobutyl ketone (MIBK) or mixture thereof.
7. A process according to claim 1, wherein the solvent used in step (viii) is selected from ketones such as acetone, methyl isobutyl ketone (MIBK), esters such as methyl acetate, ethyl acetate, propyl acetate, butyl acetate, alcohols such as methanol, ethanol, isopropanol, n-butanol or mixture thereof.

8. A process according to claim 1, the process further comprises:
   (i) dissolving Darifenacin hydrobromide in a solvent, and
   (ii) precipitating pure Darifenacin hydrobromide (I) by cooling the solution, and
   (iii) isolating pure Darifenacin hydrobromide (I).

9. A process according to claim 8, wherein the solvent is selected from acetic acid, acetone, water or mixtures thereof.

10. A process according to claim 1, Darifenacin hydrobromide (I) having 3-(S)-(-)-(1-carbamoyl-1,l-diphenylmethyl)pyrrolidine (III) less than 0.05% by HPLC and Darifenacin dimer (XII), less than 0.15% by HPLC.
A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D405/06

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

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 practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search: 12 April 2011

Date of mailing of the international search report: 18/04/2011

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

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Menchaca, Roberto
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