Title: PREPARATION OF DARIFENACIN AND ITS SALTS

Abstract: Provided are various processes and compounds related to darifenacin and/or its salts. For example, there is provided a process for preparing a free base of darifenacin: Formula, or the salt thereof, the process including reacting 3-(S)-(cyanodiphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl] pyrroldine of the Formula (IV), or a salt thereof: Formula (IV) with a base effective to convert the nitrile group of the compound of the Formula (IV) to the amide group of the darifenacin in an organic solvent, the reaction being carried out in the organic solvent, with a proviso that the solvent is not 2-methylbutan-2-ol, and with further proviso that the reaction produces less than about 0.5 % of the compound of the Formula (Ic): Formula (Ic) in the reaction mass, as measured by HPLC. Various embodiments and variants are provided.
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PREPARATION OF DARIFENACIN AND ITS SALTS

TECHNICAL FIELD

The present patent application relates to processes for the preparation of darifenacin and its salts. It also relates to substantially pure darifenacin hydrobromide and a process for its preparation.

INTRODUCTION

Darifenacin hydrobromide is described chemically as (S)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)-ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide and is represented structurally by Formula I.

\[
\begin{align*}
\text{Ph} & \\
\text{NH}_2 & \\
\text{Ph} & \\
\text{HBr} & \\
\end{align*}
\]

Darifenacin is useful as a potent muscarinic receptor antagonist and is marketed as its hydrobromide salt under the brand name ENABLEX as extended release tablets containing 7.5 or 15 mg darifenacin as its hydrobromide salt.

US Patent No. 5,096,890 discloses darifenacin, its derivatives, salts and processes for preparing them. The patent discloses several routes for preparing darifenacin as described below.

Route A involves a reaction of 3-(S)-(1-(carbamoyl-1,1-diphenylmethyl)pyrrolidone (Formula XIII) with 5-(2-bromoethyl)-2,3-dihydrobenzofuran (Formula XIV) in the presence of potassium carbonate to give a free base of darifenacin (Formula V), which is in-turn converted to its hydrobromide salt using aqueous hydrobromic acid in acetone.
Route B involves hydrolysis of 3-[(S)-cyanodiphenylmethyl]-1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl] pyrrolidine (Formula IV) using concentrated aqueous mineral acid to give the free base of darifenacin.

Route D involves reduction of (S)-2-[(1-[2-(benzofuran-5-yl)-ethyl]-3-pyrrolidinyl)-2,2-diphenylacetamide (Formula Vb) using palladium carbon in the presence of acetic acid.

Route E involves a reduction of 3-[(S)-(1-carbamoyl-1,1-diphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl)-2-oxoethyl]pyrrolidone using palladium carbon to give the free base of darifenacin (Formula V).
US Patent No. 6,930,188 (Example 5), and PCT Application Publication No. WO2007/076157 (Example 6) exemplify hydrolysis of the compound of Formula IVa in the presence of potassium hydroxide using 2-methyl-2-butanol as the solvent to give free base of darifenacin (Formula V), which is subsequently converted to its hydrobromide salt, as depicted below:

Various other processes for the preparation of darifenacin and its salts have also been described in PCT Application Publication Nos. WO2007/076158 and WO2007/076159.

There still exists a need to provide a commercially viable process for the preparation of darifenacin and its salts.

SUMMARY

In one aspect, there is provided a process for preparing a free base of darifenacin:

or the salt thereof, the process including reacting 3-[(S)-(cyanodiphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl) ethyl] pyrrolidine of the Formula IV, or a salt thereof:

(00010077.1)
with a base effective to convert the nitrile group of the compound of the Formula (IV) to the amide group of the darifenacin in an organic solvent, the reaction being carried out in the organic solvent, with a proviso that the solvent is not 2-methylbutan-2-ol, and with further proviso that the reaction produces less than about 0.5 % of the compound of the Formula Ic:

in the reaction mass, as measured by HPLC. Various embodiments and variants are provided.

In another aspect, there is provided a process for preparing a free base of darifenacin:

or the salt thereof, the process including:

a) condensing 3-(S)-(++)-1-cyano-1,1-diphenylmethyl)-pyrrolidine of the Formula II:

or its acid addition salt, with 5-haloethyl-2,3-dihydrobenzofuran of the Formula III:

(III), wherein X is Cl, Br, or I,
in the presence of an organic base to afford 3-(S)-(cyanodiphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl) ethyl] pyrrolidine of the Formula IV:

(IV); and

b) converting the compound of the Formula (IV) to darifenacin or its acid addition salt;

wherein the condensing step is carried out in the absence of an external solvent. Various embodiments and variants are provided.

In another aspect, there is provided a process for the preparation of 5-haloethyl-2,3-dihydrobenzofuran of the Formula III:

(III)

the process including:

a) reacting 2,3-dihydrobenzofuran of the Formula XI

(XI)

with haloacetyl halide to give 5-haloacetyl-2,3-dihydrobenzofuran of the Formula XII:

(XII)

wherein X is Cl, Br, or I, and

b) reacting 5-haloacetyl-2,3-dihydrobenzofuran of the Formula XII with a reducing agent to provide the compound of the Formula III. Various embodiments and variants are provided.

In yet another aspect, there is provided a pharmaceutical intermediate that includes:
a) a major portion containing 5-haloethyl-2,3-dihydrobenzofuran of the
Formula III:

\[ \text{(III)} \]

wherein X is Cl, Br, or I, and

b) a minor portion containing one or more compounds of the Formula
IIIa, IIIb, or IIIc:

\[ \text{(IIIa)} \]  
\[ \text{(IIIb)} \]  
\[ \text{(IIIc)} \]

wherein the minor portion contains less than about 2% of one or more compounds
of the Formula IIIa, IIIb, and/or IIIc, as measured by area % in HPLC with respect
to the total area % of all compound peaks in the HPLC chromatogram of the
intermediate. Various embodiments and variants are provided.

In yet another aspect, there is provided a process for the preparation of
darifenacin hydrobromide, the process including:

a) providing a solution of free base of darifenacin in an organic solvent to
form a reaction medium substantially free from moisture;

b) adding the source of hydrobromic acid to obtain a solution of darifenacin
hydrobromide, the source of hydrobromic acid being added in a non-aqueous

20 carrier; and

c) recovering the darifenacin hydrobromide as a solid;

wherein the reaction medium is maintained substantially free from moisture during
the providing step and the adding step. Various embodiments and variants are
provided.

In yet another aspect, there is provided a solid active ingredient for use in
pharmaceutical compositions that includes:

a) a major portion that includes darifenacin hydrobromide; and

b) a minor portion that includes one or more of the impurities of the
Formula Ia, Ib, Ic, Id, Ie, If, and/or Ig:
wherein the major portion is representing 95% or more of the solid active ingredient, and the minor portion contains less than about 1% of one or more impurities of the Formula la, lb, lc, ld, lf, and/or lg, as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of the solid active ingredient. Various embodiments and variants are provided.

In yet another aspect, there is provided a process for purifying darifenacin hydrobromide, the process including:

a) providing a solution of darifenacin hydrobromide in a C1-C3 alcoholic solvent;

b) cooling the solution; and

c) isolating the separated solid, which is the purified darifenacin hydrobromide. Various embodiments and variants are provided.

In yet another aspect, there is provided a process for preparing darifenacin hydrobromide substantially free from residual organic solvents, the process including:

a) providing a solution of darifenacin hydrobromide in an alcoholic or a chlorinated solvent;

b) removing the solvent from the solution obtained in step a);

c) adding an anti-solvent to the residue obtained; and

d) isolating the solid.

Various embodiments and variants are provided.

In yet another aspect, there are provided compounds that are an amorphous form of darifenacin and an amorphous form of darifenacin hydrobromide.

In yet another aspect, there is provided a process for preparing an amorphous solid of darifenacin or its hydrobromide salt, the process including:

a) providing a solution of darifenacin or its hydrobromide salt in a volatile organic solvent; and

b) removing the solvent to obtain the amorphous solid.
BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1: XRPD pattern for a sample of crystalline darifenacin hydrobromide (prepared as per Example 17).

Fig. 2: XRPD pattern for a sample of amorphous darifenacin (prepared as per Example 18).

Fig. 3: XRPD pattern for a sample of amorphous darifenacin hydrobromide (prepared as per Example 19).

DETAILED DESCRIPTION

To describe the application, certain terms are defined herein as follows. The term "compound" is used to denote a molecule of unique, identifiable chemical structure. A "composition" may contain one compound or a mixture of compounds. A "pharmaceutical composition" is any composition useful or potentially useful in producing physiological response in a subject to whom such pharmaceutical composition is administered. The term "pharmaceutically acceptable" with respect to excipients is used to denote non-toxic substances generally suitable for use in human or animal pharmaceutical products.

The term "external solvent" means a dissolving substance ("a solvent") intentionally added to a reaction mass to provide a dissolution medium for the reaction without participating in the reaction from the chemical standpoint. The term "organic solvent" means a solvent the molecules of which contain at least atoms of carbons and hydrogen. The "organic solvent" may contain other atoms such as oxygen and nitrogen as well. The term "non-aqueous" with regards to solvent or carrier is used to denote a medium that does not contain water other than residual moisture. The term "anti-solvent" is used to denote a liquid substance that functions by reducing the solubility of a solute in the primary solvent without affecting the solute from the chemical standpoint. Typically, the solute (e.g., a compound) is dissolved in a solvent and then anti-solvent is added to cause precipitation of purified solute.

The term "organic base" means a base the molecule of which contains at least atoms of carbons and hydrogen. The "organic base" may contain other atoms such as oxygen and nitrogen as well.
The term "active ingredient" is used to denote a substance, usually a powder, which forms the physiologically active portion of pharmaceutical products. Active pharmaceutical ingredients (API) are usually commercial products sold to formulatogs of final pharmaceutical products. The term "pharmaceutical intermediate" is used to denote a compound that is useful as an intermediate in preparation of APIs, or a composition, which contains a major portion of such compound.

The term "purifying" with respect to a mixture is used with respect to the ingredient of interest to denote a process for increasing the content of the ingredient of interest in the mixture.

The term "substantially free of moisture" denotes a reaction medium with total moisture content of the reaction medium does not exceed about 5%.

The term "substantially free" with regards to residual organic solvents denotes substances in which the weight content of total residual organic solvent(s) is less than 1% by weight.

While not intended to limit the claims in any way, Scheme-1 may be useful to illustrate the process for making a free base of darifenacin according to an aspect(s) of the invention.

![Scheme-1](image)

**Scheme-1**

In the step a), the secondary amine of the formula (II) is reacted with the compound of the formula (III) that contains a leaving group X in the presence of an
organic base to afford the compound of the formula (IV). Preferably, the reaction is conducted without an external solvent, with the organic base itself acting as the dissolution medium for the reaction.

Organic bases which are particularly useful for the reaction of step a) include, but are not limited to salts of primary, secondary, and tertiary amines such as triethylamine, methyl amine, tertiary butyl amine, dicyclohexylamine, and substituted amines including naturally occurring substituted amines. The preferred organic base is triethylamine.

An acid addition salt of 3-(S)-(+)-(1-cyano-1,1-diphenylmethyl)-pyrrolidine may be used as the starting material instead of the free amine. Acid addition salts of organic or inorganic acids capable of forming a salt with the amine of the compound of the Formula II are suitable. Preferably, the acid addition salt of the compound of the formula (II) is first treated with the base and then reacted with 5-haloethyl-2,3-dihydrobenzofuran of the Formula III.

Temperatures for conducting the reaction range from about 25 to about 200 °C, or from about 50 to about 150 °C.

3-(S)-(cyanodiphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl) ethyl] pyrrolidine of the Formula IV may be obtained and/or isolated as a free base or as acid addition salt by reacting the free base with the corresponding acid.

In the step b), the compound of the formula (IV) is treated with an external base to convert the nitrile group of the compound of the formula (IV) to the amide of the free base of darifenacin. As set forth above in the background, the conversion of the nitrile intermediate to the amide with a base was disclosed, for example, in the U.S. Patent No. 6,930,188. However, the inventors of the present patent application have discovered that the reaction condition used therein result in the formation of significant amount of the impurity of the Formula Ic in the reaction medium as determined by HPLC.
Attempts to prepare darifenacin hydrobromide with desired purity levels starting from free base of darifenacin containing significant levels of the impurity of the Formula Ic were unsuccessful. For example, free base samples containing more than 0.5% of the impurity of the formula (Ic) by HPLC, when progressed to darifenacin hydrobromide in the normal course of the process, lead to darifenacin hydrobromide containing the impurity of the Formula Ic at levels which are not in accordance with the pharmaceutically acceptable standards. Surprisingly, the free base samples containing less than 0.5% of the impurity gave a pure final product, without direct correlation below about 0.5% of the impurity in the starting free base.

The results of these experiments are set forth in Table 1:

<table>
<thead>
<tr>
<th>Expt. No.</th>
<th>% of impurity of Formula Ic in Darifenacin</th>
<th>% of impurity of Formula Ic in Darifenacin hydrobromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.15</td>
<td>1.16</td>
</tr>
<tr>
<td>2.</td>
<td>0.87</td>
<td>0.81</td>
</tr>
<tr>
<td>3.</td>
<td>0.6</td>
<td>0.57</td>
</tr>
<tr>
<td>4.</td>
<td>0.41</td>
<td>0.03</td>
</tr>
<tr>
<td>5.</td>
<td>0.091</td>
<td>Less than 0.003</td>
</tr>
<tr>
<td>5.</td>
<td>0.13</td>
<td>0.0081</td>
</tr>
</tbody>
</table>

Hence, the inventors have discovered the need for maintaining the impurity of the formula (Ic) below 0.5% upon completion of the reaction that converts the nitrile group of the compound of the formula (IV) into the amide group of the free base of darifenacin. To this end, the inventors have found that this conversion reaction is best carried out in a solvent other than 2-methyl-2-butanol under controlled reaction conditions. The inventors have also discovered that if the content of the impurity of Formula Ic does not exceed 0.5% in the reaction medium after the free base is prepared, the subsequent conversion of the free base to darifenacin hydrobromide results in the final product containing less than 0.15% of the impurity of Formula Ic.

The conversion reaction of the step b) is carried out in the presence of a base. Bases which are useful for the reaction of step b) include, but are not limited to alkali metal hydrides such as lithium hydride, sodium hydride; alkali metal
hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide; carbonates of alkali metals such as sodium carbonate, and potassium carbonate; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate; ammonia; and mixtures thereof. The preferred base is potassium hydroxide.

Solvents which are useful for conducting the reaction of the step b) include, but are not limited to alcohols such as ethanol, n-propanol, isopropanol, 2-butanol, isobutanol; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform; hydrocarbon solvents such as toluene, xylene, n-heptane, n-hexane, cyclohexane, methylcyclohexane, and mixtures thereof. The preferred solvent is 2-butanol.

Suitably, the concentration of the base in the reaction medium may range from about 0.1 g/ml, to about 0.3 g/ml.

Suitably, the reaction is maintained for durations which result in the conversion of at least about 80%, or at least about 85% of the starting material of Formula IV to the corresponding product of Formula V.

Temperatures for conducting the reaction range from about 50 °C to about 150 °C, or from about 50 °C to about 120 °C.

In an embodiment, the reaction is conducted using potassium hydroxide as base, and 2-butanol as solvent. The reaction is conducted at a temperature of about 100 °C for a period of about 50 hours to achieve the desired results.

At each stage (i.e., 3-(S)-(cyanodiphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl) ethyl] pyrrolidine of Formula IV in step a) and darifenacin of Formula V in step b)), the compounds may be isolated, or progressed further downstream without isolation. When the compounds are isolated, the preferred isolation temperatures are lower than about 50 °C, or lower than about 40 °C. It has been discovered that the lower temperatures act to minimize or prevent the formation of the corresponding oxidized impurities of Formula IVb, and Formula Vb, respectively.
Use of higher temperatures for longer periods of time during isolation of the compounds of the Formula IV or the Formula V results in enhancement of the content of the impurities of Formula IVb, or Formula Vb, respectively, in the product, which eventually appears as the oxidized impurity of darifenacin hydrobromide in the final product.

The preparation of 3-(S)-(+)-(1-cyano-1,1-diphenylmethyl)-pyrrolidine of the Formula II or its acid addition salt may be accomplished, for example, as follow:

a) decarboxylation of (2S, 4R)-(−)-4-hydroxy-2-pyrrolidinecarboxylic acid of Formula VI to give 3-(R)-(−)-hydroxypyrrolidine and subsequent conversion to hydrochloride of Formula VII.

b) tosylation of 3-(R)-(−)-hydroxypyrrolidine hydrochloride of Formula VII using a suitable tosylating agent in the presence of an inorganic base to afford 1-tosyl-3-(R)-(−) hydroxypyrrolidine of Formula VIII.

c) reaction of 1-tosyl-3-(R)-(−)hydroxypyrrolidine of Formula VIII with a tosylating agent in the presence of diisopropylazodicarboxylate and triphenylphosphine, to afford 1-tosyl-3-(S)-(−) tosyoxyypyrrolidine of Formula IX.
d) reaction of 1-tosyl-3-(S)-(−)-tosyloxypyrrolidine of Formula IX with diphenyl acetonitrile to afford 3-(S)- (+)-(1-cyano-1,1-diphenylmethyl)-1-tosyloxypyrrolidine of Formula X; and

![Chemical Structure IX]

e) deprotection of the compound 3-(S)-(−)-(1-cyano-1,1-diphenylmethyl)-1-tosyloxypyrrolidine of Formula X using an acid to afford 3-(S)-(−)-(1-cyano-1,1-diphenylmethyl)-pyrrolidine of Formula II or its acid addition salt.

![Chemical Structure X]

The above process is illustrated in Scheme-2:

![Scheme 2 Diagram]

**Scheme-2**

Solvents which are useful for conducting the reaction at each stage include, but are not limited to: ketones such as acetone, methyl isobutyl ketone, and cyclohexanone; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol, tertiary-butyl alcohol, cyclohexan-1-ol, ethylene glycol; chlorinated solvents such as dichloromethane, chloroform, carbon tetrachloride; hydrocarbon
solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane; and mixtures thereof.

Bases which are useful in steps b) and d) include inorganic bases such as alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide; carbonates of alkali metals such as sodium carbonate, potassium carbonate; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate.

Suitably, diisopropylazodicarboxylate (DIAD) in combination with triphenylphosphine is used for inversion of configuration in step c) instead of diethylazodicarboxylate (DEAD) used on the prior art, which is difficult to handle on large scale.

Suitably, the product 3-(S)-(+-)(1-cyano-1,1-diphenylmethyl)-pyrrolidine of Formula II can be converted to its acid addition salt by reacting with an acid in an aqueous or a non-aqueous solution.

The acid for preparing the salt may be hydrobromic acid in the form of a non-aqueous solution in acetic acid to form the corresponding hydrobromide salt of the compound of Formula II.

The preparation of 5-haloethyl-2,3-dihydrobenzofuran of the Formula III may be accomplished, for example, as follows:

a) reaction of 2,3-dihydrobenzofuran of Formula XI with haloacetyl halide to give 5-haloacetyl-2,3-dihydrobenzofuran of Formula XII;

\[ \text{(XI)} \]

\[ \text{(XII)} \]

b) reaction of 5-haloacetyl-2,3-dihydrobenzofuran of Formula XII with a reducing agent to afford 5-haloethyl-2,3-dihydrobenzofuran of Formula III;

\[ \text{(III)} \]
5-haloethyl-2,3-dihydrobenzofuran of the Formula III may be purified by recrystallization or slurrying from a suitable solvent.

The above process is illustrated in Scheme-3:

Scheme-3

Solvents which are useful in step a) include, but are not limited to halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, or mixtures thereof.

Reducing agents which are useful in step b) include, but are not limited to triethyl silane and trifluoroacetic acid, sodium bis(2-methoxyethoxy) aluminum hydride (Vitride), lithium aluminium hydride, sodium borohydride/acetic acid, diisobutyl aluminium hydride (DIBAL H), silanes, boranes, metal hydrides like sodium borohydride, lithium aluminium hydride, formates, hypophosphorous acid salts.

Optionally, 5-haloacetyl-2,3-dihydrobenzofuran of Formula XII and 5-haloethyl-2,3-dihydrobenzofuran of Formula III obtained can be further purified by recrystallization or slurry in a suitable solvent.

Solvents which can be used for recrystallization or slurry include, but are not limited to ethers such as diethyl ether, diisopropyl ether, methyl tertiary-butyl ether, petroleum ether; alcohols such as methanol, ethanol, isopropyl alcohol, n-butanol; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone; nitriles such as acetonitrile, propionitrile, or mixtures thereof, or their mixtures with water in various proportions.

As described above, 5-haloethyl-2,3-dihydrobenzofuran of the Formula III is the key intermediate in the synthesis, e.g., of darifenacin. Separately
contemplated is a pharmaceutical intermediate that contains a major portion of 5-haloethyl-2,3-dihydrobenzofuran and minor portion of certain impurity compounds. The major portion represents more than about 95% of the intermediate, more preferably, more than about 97%. The minor portion represents less than about 5% of the intermediate, and preferably, includes less than about 2%, more preferably, less than about 1% of 2-chloro-1- (2,3-dihydro-benzofuran-7-yl)-ethanone of Formula IIIa, 2-chloro-1-[3-(2-chloro-ethyl)-4-hydroxy-phenyl]-ethanone of Formula IIIb, and/or 2-chloro-1-[3-(2-chloro-ethyl)-2-hydroxy-phenyl]-ethanone of Formula IIIc as characterized by a high performance liquid chromatography ("HPLC") chromatogram obtained from a mixture containing the desired compound and one or more of the impurities. Separately contemplated are variants in which all and/or each of the described impurities are present the amount greater than 0.01%. The percentages refers to the area-% of the peaks representing the impurities ion the chromatogram of the intermediate as a whole.

The High Performance Liquid Chromatography (HPLC) method used for the analysis utilizes a C-8 column (250x4.6x5 μm) or equivalent. Additional method parameters are as shown in Table 2:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow</td>
<td>1.0 ml/min</td>
</tr>
<tr>
<td>Elution</td>
<td>Gradient</td>
</tr>
<tr>
<td>Wavelength</td>
<td>210 mn</td>
</tr>
<tr>
<td>Injection volume</td>
<td>10 μl</td>
</tr>
<tr>
<td>Oven temperature</td>
<td>Ambient</td>
</tr>
<tr>
<td>Mobile phase preparation</td>
<td>Buffer: Dissolve 3.4 g of KH₂PO₄ in 1000 ml of milliliq water, add 1 ml triethyl amine and adjust 3.5 with ortho phosphoric acid Mobile Phase A: buffer: acetonitrile</td>
</tr>
<tr>
<td></td>
<td>(80:20)(v/v)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Mobile phase B: Water: acetonitrile (20:80)</td>
<td>(v/v)</td>
</tr>
<tr>
<td>Run time</td>
<td>70 min</td>
</tr>
<tr>
<td>Diluent</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>Sample concentration</td>
<td>1 mg/ml</td>
</tr>
<tr>
<td>Mobile phase preparation</td>
<td></td>
</tr>
<tr>
<td>Buffer: dissolve 3.4 g of KH₂PO₄ in 1000 ml of milliq water add 1 ml triethyl amine and adjust pH to 3.5 with ortho phosphoric acid</td>
<td></td>
</tr>
<tr>
<td>Mobile phase A; Buffer: acetonitrile (80:20)v/v</td>
<td></td>
</tr>
<tr>
<td>Mobile phase B; Water:acetonitrile (20:80) v/v</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gradient program</th>
<th>Time</th>
<th>%A</th>
<th>%B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.01</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>75</td>
<td>25</td>
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<td></td>
<td>30</td>
<td>20</td>
<td>80</td>
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<td></td>
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</tr>
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</tr>
<tr>
<td></td>
<td>70</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

As set forth above, also provided is a process for making a hydrobromide salt of darifenacin that includes the steps of:

a) providing a solution of free base of darifenacin in an organic solvent to form a reaction medium substantially free from moisture;

b) adding the source of hydrobromic acid to obtain a solution of darifenacin hydrobromide, the source of hydrobromic acid being added in a non-aqueous carrier; and

c) recovering the darifenacin hydrobromide as a solid;

The particular feature of this process is that the reaction medium is maintained substantially free from moisture during the providing step and the adding step.

In the step a), a solution of the free base in a solvent is provided while taking care to keep the reaction medium as moisture free as possible. Solvents...
which are useful for preparing the solution of darifenacin include, but are not limited to C₂–C₆ ketone solvents such as acetone, ethyl methyl ketone, and diethyl ketone; C₁-C₄ alcohols; chlorinated solvents, such as C₁-C₆ straight chain, branched, or aromatic chlorohydrocarbons including dichloromethane, ethylene dichloride, chloroform, carbon tetrachloride, chlorobenzene, dichlorobenzene, or mixtures thereof. The preferred solvents are acetone and methanol.

Step b) involves adding a source of hydrobromic acid to form the hydrobromide salt in solution while maintaining the reaction medium substantially free from moisture. Suitable sources of hydrobromic acid include but are not limited to ammonium bromide, hydrobromic acid gas, salts containing hydrobromic acid, or the gas purged in organic solvents like acetic acid are for the purpose.

After the addition of the source for hydrobromic acid, the reaction mass may be maintained further at temperatures lower than the reaction temperatures such as for example below about 10° C to about 25° C, for a period of time as required for a more complete isolation of the product.

In yet another embodiment, the present invention provides substantially pure darifenacin hydrobromide. In yet another embodiment, the present invention provides substantially pure darifenacin.

By “substantially pure darifenacin” it is meant that darifenacin or any of the pharmaceutically acceptable salts of darifenacin prepared in accordance with the present invention contains less than about 0.5%, or less than about 0.1% of one or more of the corresponding impurities like the desnitride impurity, the acid impurity, the compound of Formula IV, and the impurities having the Formulas Ic, Id, Ie, If, and Ig as characterized by HPLC obtained from a mixture comprising the desired compound and one or more of the said impurities. It is also free of the impurities at RRT (Relative retention time) 1.37 having a mass number 500, and at RRT 1.77 having a mass number 570 as determined by HPLC. The percentage here refers to the area-% of the peaks representing the said impurities.

As used herein “desnitride impurity” refers to 3-benzhydryl-1-[2-(2,3-dihydrobenzofuran-5-yl)-ethyl]-pyrrolidine represented by Formula Ia;
“acid impurity” refers to \{1-[2-(2,3-dihydro-benzofuran-5-yl)-ethyl]-pyrrolidin-3-yl\}-diphenyl-acetic acid, represented by Formula Ib;

“compound of Formula Ic” refers to 2-{1-[2-(4-hydroxy-3-vinyl-phenyl)-ethyl]-pyrrolidin-3-yl}-2,2-diphenyl-acetamide;

“compound of Formula Id” refers to (R)-2-{1-[2-(3-dihydrobenzofuran-5-yl)-ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide;

“compound of Formula Ie” refers to 2-{1-[2-(2,3-dihydro-benzofuran-6-yl)-ethyl]-pyrrolidin-3-yl}-2,2-diphenyl-acetamide;
“compound of Formula If” refers to 2-{1-[2-(2,3-dihydro-benzofuran-5-yl)-2-ethyl]-pyrrolidin-3-yl}-2,2-diphenyl-acetamide;

(If)

“compound of Formula Ig” refers to 2-{1-[2-(2,3-dihydro-benzofuran-5-yl)-2-hydroxy-ethyl]-pyrrolidin-3-yl}-2,2-diphenyl-acetamide

(Ig)

The pharmaceutically acceptable salts of darifenacin refer to salts prepared form pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

Salts derived from inorganic acids include hydrochloride, hydrobromide, hydroiodide. Salts derived from organic non-toxic acids include tartarate, oxalate, maleate, acetate.

The desnitriile impurity, the acid impurity, and impurities of Formula Ic and Ie were analyzed by the High Performance Liquid Chromatography (HPLC) method using a C-18 column, 250 x 4.6 mm ID, 5 µ particle size or equivalent. The other parameters are as shown in Table 3

Table 3:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow rate</td>
<td>1.0 ml/min</td>
</tr>
<tr>
<td>Wavelength</td>
<td>210 nm</td>
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<tr>
<td>Injection load</td>
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<tr>
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<td>Ambient</td>
</tr>
<tr>
<td>Elution</td>
<td>Isocratic</td>
</tr>
<tr>
<td>Diluent</td>
<td>Mobile Phase B</td>
</tr>
</tbody>
</table>

{00010077.1}
Sample preparation

Take 10 mg of test sample into a 10 ml volumetric flask, dissolve and dilute up to the mark with diluent.

Mobile phase preparation

Buffer: dissolve 3.48 g of K₂HPO₄ and 2.44 g of 1-decane sulphonylic acid sodium salt anhydrous 1000 ml of milliQ water and pH adjusted to 7 with diluted H₃PO₄.

Mobile Phase A: Buffer: Acetonitrile (7:3) (v/v)
Mobile Phase B: Buffer: Acetonitrile (3:7) (v/v)

Gradient program

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>% B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
</tr>
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<td>20</td>
</tr>
<tr>
<td>70</td>
<td>20</td>
</tr>
</tbody>
</table>

The impurity of Formula If was analyzed by the High Performance Liquid Chromatography (HPLC) method using a C-18 column, 250 x 4.6 mm ID, 5 μ particle size or equivalent. Remaining parameters are as shown in Table 4.

Table 4:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow rate</td>
<td>1.0 ml/min</td>
</tr>
<tr>
<td>Wavelength</td>
<td>210 nm</td>
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<tr>
<td>Injection load</td>
<td>10 μl</td>
</tr>
<tr>
<td>Temperature</td>
<td>Ambient</td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>Elution</td>
<td>Isocratic</td>
</tr>
<tr>
<td>Diluent</td>
<td>Acetonitrile : Buffer (1:1)</td>
</tr>
<tr>
<td>Sample preparation</td>
<td>Take 10 mg of test sample into a 10 ml volumetric flask, dissolve and dilute up to the mark with diluent.</td>
</tr>
<tr>
<td>Mobile phase preparation</td>
<td>Buffer: dissolve 3.4 g of K₂HPO₄ and 3.4 g of tetra-n-butyl ammonium hydrogen sulfate in 1000 ml of milliQ water and add 2 ml of triethylamine pH adjusted to 7 with diluted KOH. Mobile Phase A: Buffer: Acetonitrile (800:200) (v/v) Mobile Phase B: Acetonitrile: Water (800:200) (v/v)</td>
</tr>
<tr>
<td>Gradient program</td>
<td></td>
</tr>
<tr>
<td>0.01</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
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<td>65</td>
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</tr>
<tr>
<td>75</td>
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<table>
<thead>
<tr>
<th>IMPURITY NAME</th>
<th>RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula If</td>
<td>1.7</td>
</tr>
</tbody>
</table>

The isomeric impurity of Formula 1d was analyzed by the Chiral High Performance Liquid Chromatography (HPLC) method using a Chiral Cel-OD, 250 x 4.6 mm ID x 5 μm. Remaining parameters are as shown in Table 5.

Table 5:

| Wavelength | 230 nm |

{00010077.1}
<table>
<thead>
<tr>
<th>Flow Rate</th>
<th>1.0 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection load</td>
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<td>Temperature</td>
<td>Ambient</td>
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<tr>
<td>Run time</td>
<td>45 minutes</td>
</tr>
<tr>
<td>Diluent</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Sample Preparation</td>
<td>20 mg/10 ml in diluent.</td>
</tr>
</tbody>
</table>

Separately contemplated is an active pharmaceutical ingredient that contains

a) a major portion that includes 95% or more of darifenacin hydrobromide;

and

b) a minor portion that includes one or more of the impurities of the Formula Ia, Ib, Ic, Id, Ie, If, and/or Ig, wherein the minor portion contains less than about 1% of one or more impurities of the Formula Ia, Ib, Ic, Id, If, and/or Ig, as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of the solid active pharmaceutical ingredient.

The major portion represents more than about 95% of the active pharmaceutical ingredient, more preferably, more than about 97%. The minor portion represents less than about 5% of the intermediate, and preferably, represents less than about 1%, as characterized by a high performance liquid chromatography ("HPLC") chromatogram. Separately contemplated are variants in which all and/or each of the described impurities of the minor portion are present the amount greater than 0.01%.

As set forth above, also provided is a process for purifying darifenacin hydrobromide that includes the steps of:

a) providing a solution of darifenacin hydrobromide in a C1-C3 alcoholic solvent;

b) cooling the solution; and

c) isolating the separated solid, which is the purified darifenacin hydrobromide.

Step a) involves providing a solution of darifenacin hydrobromide in a C1 to C3 alcoholic solvent. Darifenacin hydrobromide for the purpose of purification
may be one prepared according to the processes described in the prior art, or using a process similar to the one described above. The solution of darifenacin hydrobromide may be obtained by dissolving the darifenacin hydrobromide in a suitable solvent, or such a solution may be obtained directly from a reaction in which darifenacin hydrobromide is formed. When the solution is prepared by dissolving darifenacin hydrobromide in a suitable solvent, any form of darifenacin hydrobromide such as any crystalline or amorphous form including any salts, solvates and hydrates may be utilized for preparing the solution.

Suitable alcoholic solvents which may be used for dissolving darifenacin hydrobromide include but are not limited to methanol, ethanol, isopropyl alcohol, n-propanol. The dissolution temperatures range from about 20 to 120 °C depending on the solvent used for dissolution. Any other temperature is also acceptable as long as the stability of darifenacin hydrobromide is not compromised and a clear solution is obtained. The quantity of solvent used for dissolution depends on the solvent and the dissolution temperature adopted. The concentration of darifenacin hydrobromide in the solution may generally range from about 0.1 to about 10 g/ml in the solvent.

The solution is optionally treated with activated charcoal, or similar adsorbing agents like silica gel, and others to enhance the color of the compound followed by filtration through a medium such as through a flux calcined diatomaceous earth (Hyflow) bed to remove the carbon. The carbon treatment can be given either at the temperatures of the preparation of the mixture or after cooling the solution to lower temperatures.

Step b) involves cooling the solution.

For isolation to occur, the reaction mass may be maintained further at temperatures lower than the concentration temperatures such as for example below about 10° C to about 25° C, for a period of time as required for a more complete isolation of the product. The exact cooling temperature and time required for complete isolation can be readily determined by a person skilled in the art and will also depend on parameters such as concentration and temperature of the solution or slurry. Optionally isolation may be enhanced by methods such as cooling, partial removal of the solvent from the mixture, by adding an anti-solvent to the reaction mixture or a combination thereof.
Step c) involves recovering the separated solid.

The method by which the solid material is recovered from the final mixture, with or without cooling below the operating temperature by any of techniques such as filtration by gravity, or by suction, centrifugation. The crystals so isolated will carry a small proportion of occluded mother liquor containing a higher percentage of impurities. If desired the crystals can be washed on the filter with a solvent to wash out the mother liquor.

The above described process may be adapted to form the basis of a continuous crystallization process. The purity of the product obtained in step c) is periodically to ascertain the percentage of the impurities. If required the purification process is repeated till impurity levels attained are nil or less than about 0.15 area % by HPLC.

The wet cake obtained in step c) may be further dried. Drying is suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer. The drying is carried out at temperatures of about 25°C to about 70°C for any desired time periods from about 1 to 20 hours.

Darifenacin hydrobromide having a reduced level of impurities typically also contains residual solvents. For purposes of the present description, any residual solvents in purified darifenacin hydrobromide are also considered as impurities.

Residual solvents can be quantified by application of known chromatographic techniques.

In yet another embodiment, there is provided darifenacin hydrobromide substantially free from residual organic solvents. In yet another embodiment, there is provided darifenacin hydrobromide substantially free of residual organic solvents.

Darifenacin hydrobromide obtained using the process described herein contains less than about 5000 ppm, or less than about 3000 ppm, or less than about 1000 ppm of individual residual organic solvents. In particular, it has less than about 1000 ppm, or less than about 600 ppm of the solvents selected from methanol, acetone, n-propanol, ethyl acetate, 2-butanol, cyclohexane, and acetic acid.

Also provided is a process for preparing darifenacin hydrobromide substantially free from residual organic solvent that includes the steps of:
a) providing a solution of darifenacin hydrobromide in an alcoholic or a chlorinated solvent;
b) removing the solvent from the solution obtained in step a);
c) adding an anti-solvent to the residue obtained; and
d) isolating the solid.

Alcoholic or chlorinated solvents which are used include, but are not limited to alcoholic solvents like methanol, ethanol, isopropyl alcohol; chlorinated solvents such as dichloromethane, chloroform, carbon tetrachloride.

Removal of the solvent in step b) may be carried out suitably using techniques such as evaporation, atmospheric distillation, distillation under vacuum. Distillation of the solvent may be conducted under vacuum, such as below about 100 mm Hg to below about 600 mm Hg, at temperatures such as below about 70 °C.

Anti-solvents which are useful include, but are not limited to water, hydrocarbons such as n-hexane, n-heptane, cyclohexane, toluene, xylene, or mixtures thereof.

The mass may be maintained further at temperatures of the range of about 10 °C to about 50 °C, for a period of time as required for a more complete isolation of the product. The exact cooling temperature and time required for complete precipitation is readily determined by a person skilled in the art.

The wet solid obtained may be dried. Drying is carried out at reduced pressures, at temperatures of below about 80 °C. The drying is carried out for any desired or required time periods, times about 1 to 20 hours being suitable.

Substantially pure darifenacin hydrobromide prepared according to the process described herein is characterized by its XRPD pattern substantially in accordance with the pattern of Fig. 1. It is also characterized by an XRPD pattern having significant peaks at about 8.1, 9.0, 11.4, 16.9, 18.1, 18.7, 20.1, 20.2, 22.0, and 25.8, ± 0.2 degrees 2θ.

Darifenacin hydrobromide prepared according to the process described herein has particle size of less than about 100 μm or less than about 50 μm. The D_{10}, D_{50} and D_{90} values are useful ways for indicating a particle size distribution. D_{90} refers to the value for the particle size for which at least 90 volume percent of
the particles have a size smaller than the value. Likewise $D_{50}$ and $D_{10}$ refer to the values for the particle size for which 50 volume percent, and 10 volume percent, of the particles have a size smaller than the value. Methods for determining $D_{10}$, $D_{50}$ and $D_{90}$ include laser diffraction, such as using Malvern Instruments Ltd. (of Malvern, Worcestershire, United Kingdom) equipment.

In an embodiment, darifenacin hydrobromide prepared according to the process described herein has $D_{10}$ less than about 10 $\mu$m or less than about 5 $\mu$m, $D_{50}$ less than about 50 $\mu$m or less than about 40 $\mu$m, and $D_{90}$ less than about 200 $\mu$m or less than about 100 $\mu$m. There is no specific lower limit for any of the $D$
values.

Also provided is an amorphous form of darifenacin and its hydrobromide salt, and amorphous premix of darifenacin and its hydrobromide salt with pharmaceutically acceptable excipients and a process for their preparation.

Amorphous darifenacin and its hydrobromide salt and amorphous premix of darifenacin and its hydrobromide salt in combination with a pharmaceutically acceptable carrier are characterized by their XRPD pattern. All XRPD data reported herein were obtained using Cu Kα radiation, having the wavelength 1.541 Å and were obtained using a Bruker Axe D8 Advance Powder X-ray Diffractometer.

Amorphous forms of darifenacin and its hydrobromide salt are characterized by their XRPD patterns showing no peaks substantially in accordance with Fig. 2 and Fig. 3, respectively.

The amorphous solid of darifenacin or its hydrobromide salt may be prepared by a process that includes the steps of:

a) providing a solution of darifenacin or its hydrobromide salt in a volatile organic solvent; and

b) removing said solvent.

Step a) involves providing a solution of darifenacin or its hydrobromide salt either alone or in combination with a pharmaceutically acceptable carrier in a suitable solvent. The solution of darifenacin or its hydrobromide salt may be obtained by dissolving them in a suitable solvent, or such a solution may be obtained directly from a reaction in which they are formed. When the solution is
prepared by dissolving darifenacin or its hydrobromide salt in a suitable solvent, any polymorphic form such as any crystalline form including any salts, solvates and hydrates may be utilized for preparing the solution.

When the solution is prepared along with a pharmaceutically acceptable carrier, the order of charging the different materials is not critical for the product obtained. A specific order may be preferred with respect to the equipment actually used and will be easily determined by a person skilled in the art.

Solvents which are useful for dissolving darifenacin or its hydrobromide salt either alone or along with a pharmaceutically acceptable carrier include but are not limited to: alcohols such as methanol, ethanol, isopropyl alcohol, n-propanol; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate; ethers such as diethyl ether, dimethyl ether, diisopropyl ether; hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane; nitriles such as acetonitrile, propionitrile; or mixtures thereof or their combinations with water in various proportions.

The pharmaceutically acceptable carriers that are useful for the preparation of amorphous combinations of darifenacin and its hydrobromide salt include but are not limited to pharmaceutical hydrophilic carriers such as polyvinyl pyrrolidone (homopolymers or copolymers of N-vinyl pyrrolidone), gums, cellulose derivatives (including hydroxypropyl methylcellulose, hydroxypropyl cellulose and others), cyclodextrins, gelatins, hyromellose phthalate, sugars, polyhydric alcohols, polyethylene glycol, polyethylene oxides, polyoxyethylene derivatives, polyvinyl alcohol, propylene glycol derivatives. The use of mixtures of more than one of the pharmaceutical carriers to provide desired release profiles or for the enhancement of stability is within the scope of this invention. Also, all viscosity grades, molecular weights, commercially available products, their copolymers, mixtures are all within the scope of this invention without limitation.

The solution may optionally be treated with materials such as carbon or similar adsorbing agents like silica gel, or sodium sulfate for clarification.

Step b) involves removing the solvent.

Removal of the solvent may be carried out suitably using evaporation, atmospheric distillation, or distillation under vacuum.
Distillation of the solvent may be conducted under a vacuum, such as below about 100 mm Hg to below about 600 mm Hg, at elevated temperatures such as about 20° C to about 70° C.

Techniques which are useful for distillation include, distillation using a rotational evaporator device such as a Buchi Rotovap, spray drying, agitated thin film drying ("ATFD").

The amorphous material obtained from step b) is be collected from the equipment using techniques such as by scraping, or by shaking the container.

The solid product may be dried. The drying is carried out at reduced pressures, such as below about 200 mm Hg or below about 50 mm Hg, at temperatures such as about 35° C to about 70° C. The drying is carried out for any desired time period that achieves the desired result, such as times about 1 to 20 hours. Drying may also be carried out for shorter or longer periods of time depending on the product specifications.

Also provided are a pharmaceutical composition that includes substantially pure darifenacin or its pharmaceutically acceptable salts and with one or more pharmaceutically acceptable carriers, excipients or diluents.

Darifenacin or its pharmaceutical acceptable salts are formulated as solid compositions for oral administration in the form of capsules, tablets, pills, powders or granules. In these compositions, the active product is mixed with one or more pharmaceutically acceptable excipients. The drug substance is formulated as liquid compositions for oral administration including for example solutions, suspensions, syrups, elixirs and emulsions, containing solvents or vehicles such as water, sorbitol, glycerine, propylene glycol or liquid paraffin, may be used.

Compositions for parenteral administration include suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions may contain adjuvants, especially wetting, emulsifying and dispersing agents.

Sterilization may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilizing agents in the composition, by irradiation or by heating. The compositions may be prepared in the form of sterile compositions, which can
be dissolved at the time of use in sterile water or any other sterile injectable medium.

Pharmaceutically acceptable carriers that include but are not limited to diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar; binders such as acacia, guar gum, tragacanth, gelatin, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, pregelatinized starch; disintegrants such as starch, sodium starch glycolate, pregelatinized starch, crospovidone, croscarmellose sodium, colloidal silicon dioxide; lubricants such as stearic acid, magnesium stearate, zinc stearate; glidants such as colloidal silicon dioxide; solubility or wetting enhancers such as anionic or cationic or neutral surfactants, complex forming agents such as various grades of cyclodextrins, resins; release rate controlling agents such as hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose, ethyl cellulose, methyl cellulose, various grades of methyl methacrylates, waxes. Pharmaceutically acceptable excipients include but not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants.

Certain specific aspects and embodiments of this invention are described in further detail by the examples below, which are provided only for the purpose of illustration and are not intended to limit the scope of the invention in any manner.

EXAMPLE 1: PREPARATION OF 3-(R)-(−)-HYDROXYPYRROLIDINE HYDROCHLORIDE (FORMULA VII):

Cyclohexanol (80 liters) were taken into a reactor and heated to about 155 °C. Water was removed azeotropically till the MC of the solvent is not more than 0.2%W/W. The solvent was then cooled to about 45 °C, and (2S, 4R)-(−)-4-hydroxy-2-pyrrolidinocarboxylic acid (15 kg) was added to it and stirred for about 10 minutes. Methyl isobutyl ketone (4.275 liters) was added to the reaction mass and the reaction mass was heated to about 154 °C. The reaction mass was maintain at the same temperature for about 5 hours. Reaction completion was checked using thin layer chromatography. After the reaction is completed, the reaction mass was cooled to about 0 °C under nitrogen atmosphere, and pH of the reaction mass was adjusted to 1.0- 2.0 using EA-HCl (41 liters) at the same
temperature. After pH adjustment is complete, the temperature was raised to about 25°C and maintained for about 2-3 hours. The isolated solid was filtered and washed with ethyl acetate (30 liters) in two equal lots under nitrogen atmosphere, and finally washed with isopropyl alcohol (15 liters). The wet solid was dried under suction for about 1 to 2 hours, followed by drying at about 55°C under reduced pressure for about 5 hours to yield 10.7 kg of the title compound. (% yield: 76%).

Purity By HPLC: 98.5%

EXAMPLE 2: PREPARATION OF 1-TOSYL-3-(R)-(−)-HYDROXYPYRROLIDINE (FORMULA VIII):

Para toluene sulfonyl chloride (17.17 kg) and dichloromethane (112 liters) were taken into a reactor and sodium carbonate (14.3 kg) was added to it at 25 – 35°C. DAN-1 (11.15 kg) was added to the above reaction mass and the reaction mass was heated to about 38°C and maintained for about 3 hours. Reaction completion was checked using thin layer chromatography. After the reaction was completed, the reaction mass was cooled to about 35°C. The unwanted solids were filtered and the filtered bed was washed with dichloromethane (44.5 liters). The filtrate was washed with water (56 liters) followed by washing with 10% NaCl solution (56 liters). About 80% of the solvent was distilled off from the filtrate below about 45°C to get a residue to which 22.3 liters of toluene was added. The reaction mixture was again distilled off at about 45°C under reduced pressure to distill off dichloromethane completely. The reaction mass was then cooled to about 25°C, and maintained for about 2 hours. The separated solid was filtered and the filtered solid was washed with Toluene (11.2 liters). The wet compound was dried at about 65°C for about 5 hours to yield 19.0 kg of the title compound (% yield: 87%).

Purity By HPLC: 99.9%

EXAMPLE 3: PREPARATION OF 1-TOSYL-3-(S)-(−)-TOSYLOXYPYRROLIDINE (FORMULA IX):

Charge DAN-2 (19.0 kg), and toluene (190 liters) were taken into a reactor and stirred at about 25°C for 10 minutes. Triphenylphosphine (29.45 kg), and methyl-4-toluene sulfonate (20.9 kg) were added to the above reaction mass at the same temperature and then the reaction mass was cooled to about 0 to 5°C.
Di-isopropyl azodicarboxylate (26.03 kg) was added to the reaction mass and the temperature was slowly raised to about 55°C. The reaction mass was maintained at about 55 °C for about 5 hours. Reaction completion was checked using thin layer chromatography. After the reaction was completed, the solvent was distilled off below 60 °C under reduced pressure. Isopropanol (190 liters) was added to the residue obtained and cooled to about 30 °C. The reaction mass was maintained at about 30 °C for about 2 hours. The separated solid was filtered and washed with isopropanol (190 liters). The wet solid was dried at about 65 °C for about 7 hours to yield 22 kg of the title compound (% yield: 71)

Purity By HPLC: 99.48%.

EXAMPLE 4: ALTERNATE PREPARATION OF 1-TOSYL-3-(S)-(−)
TOSYLOXYPYRROLIDINE (FORMULA IX):

1-tosyl-3-(R)-(−)-hydroxypropylidine (20 g) and cyclohexane (100 ml) were taken into a clean and dry round bottom flask. Dicyclohexyldicarbodiimide (17.5 g) and cupric iodide (0.4 g) were added at a temperature of about 25 to 35 °C.

The resultant reaction mixture was heated to about 75 to 85 °C and stirred for about 10 to 12 hours. The reaction mass was cooled to about 25 to 35 °C followed by distillation of solvent completely under reduced pressure to obtain the crude material. The crude material was dissolved in dichloromethane (100 ml) and washed with aqueous ammonia (3x100 ml). The solvent was distilled completely and cyclohexane (150 ml) was added to the residue. Methyl-4-tosylate (18.5 g) was then added and the reaction mass was heated to about 75 to 85 °C. The reaction mass heated to about 75 to 85°C for about 25 to 30 hours. The supernatant liquid was decanted and the crude material obtained was dissolved in dichloromethane (100 ml). The organic layer was washed with 5% of hydrochloric acid solution. Solvent was distilled completely at about below 60°C under reduced pressure. Isopropyl alcohol (100 ml) was added to the crude and stirred at a temperature of about 25 to 35 °C for about 2 to 2 hours 30 minutes. The solid separated was filtered and the solid was washed with 40 ml of isopropyl alcohol followed by drying the solid obtained at about 60 °C to 70 °C to afford 10 g of the title compound.

EXAMPLE 5: PREPARATION OF 3-(S)-(−)-(1-CYANO-1,1-DIPHENYL METHYL)-1-TOSYLOXYPYRROLIDINE (FORMULA X):
Toluene (220 liters), NaOH flakes (4.4 kg), tetrabutyl ammonium bromide (1.32 kg) were taken into a reactor and stirred for about 10 minutes. Diphenyl acetonitrile (11.66 kg) was added to it at 25 to 35 °C followed by the addition of DAN-3 (22 kg) at the same temperature. The reaction mass was then heated to about 60°C and maintained for about 4 to 6 hours. Reaction completion was checked using thin layer chromatography. After the reaction was completed, water (110 liters) was added to the reaction mass and heated to about 65 °C. The reaction mass was maintained at the same temperature for about 30 minutes and then the aqueous layer was separated. The reaction mass was then again washed with another 110 liters of water at the same temperature and then cooled to about 30 °C. The organic layer was then distilled off at about 65 °C under reduced pressure to distill off about 50 % of the solvent. The remaining residue was cooled to about 40 °C and methanol (44 liters) was added to it. Methanol was distilled off completely at about 65 °C under reduced pressure and to the residue another 66 liters of methanol was added. The mixture was cooled to about 30 °C and maintained for about 2 hours. The separated solid was filtered and the filtered solid was washed with methanol (44 liters). The wet solid was dried at 70 to 75 °C for about 5 hours to yield 19.9 kg of the title compound (% yield: 86%).

Purity by HPLC: 99.6%.

EXAMPLE 6: PREPARATION OF 3-(S)-(+-)(1-CYANO-1,1-DIPHENYLMETHYL)PYRROLIDINE (FORMULA II):

3-(S)-(+-)(1-cyano-1,1-diphenylmethyl)-1-tosyloxypyrrolidine (16 kg) and 33% HBr in glacial acetic acid (68.2 kg) were taken into a reactor and stirred at 25 to 35 °C for about 20 min. The mixture was then heated to 70 to 75 °C and maintained at the same temperature for about 6 hours. Reaction completion was checked using thin layer chromatography. After the reaction was completed, the reaction mixture was cooled to 25 to 35 °C and water (48 liters) was added to it, followed by addition of toluene (48 liters). The reaction mixture was stirred for about 15 minutes, and the organic layer was separated. The aqueous layer was extracted into toluene (96 liters) in two equal lots. The aqueous layer was then cooled to 0 to 5 °C, toluene (48 liters) was added to it and pH of the aqueous layer was adjusted to about 13 using caustic lye (48 liters). After the desired pH is
reached, the temperature of the mixture is raised to 30 to 35 °C and stirred for about 30 minutes. The toluene layer was separated and the aqueous layer was extracted into another 48 liters of toluene. The combined organic layer was washed with water (96 liters) in two equal lots. The organic layer was then distilled off at a temperature of below 75 °C under reduced pressure to get a residue. The residue obtained was co-distilled with ethyl acetate (32 liters) and then another 27 liters of ethyl acetate was added to the residue obtained. The mixture was stirred at 35 °C for about 30 minutes and a solution of 33 % HBr in acetic acid (10 liters) was added to it. The reaction mixture was stirred at about 35 °C for about 45 minutes. The separated solid was filtered and washed with ethyl acetate (16 liters). The wet compound was dried at 60 to 65 °C for about 4 hours to yield 10 kg of the title compound. Purity by HPLC: 98.7%.

**EXAMPLE 7: PREPARATION OF 3-(S)-(+)-(1-CARBAMYOL-1,1-DIPHENYL METHYL)-PYRROLIDINE L (+) –TARTRATE (FORMULA XIII):**

3-(S)-(+)1-cyano-1,1-diphenylmethyl)-pyrrolidine (39.5 g) and 95% sulphuric acid (97 ml) were taken into a clean and dry round bottom flask followed by heating to about 80 °C for about 10 hours. The reaction mass was cooled to about 10 to 15 °C and the pH was adjusted to about 10 by adding caustic lye (150 ml). The resultant reaction solution was extracted using dichloromethane (315 ml) followed by separation of organic and aqueous layers. The organic layer was washed with water (315 ml) followed by separation of organic and aqueous layers. The solvent from the organic layer was distilled below 60 °C completely under reduced pressure. L (+) tartaric acid (11.6 g) and ethanol (210 ml) were taken into a clean and dry round bottom flask. The crude material obtained above was dissolved in ethanol (116 ml) and added to the above material over a period of about 45 minutes. The reaction mass was stirred for about an hour. The solid that was separated was filtered and the solid was washed with 42 ml of ethanol. The solid obtained was dried at about 60 °C to afford 24.3 g of the title compound.

**EXAMPLE 8: PREPARATION OF 3-(S)-(−)-(1-CARBAMOYL-1,1-DIPHENYL METHYL)-PYRROLIDINE (FORMULA XIII):**

3-(S)-(+)-(1-carbomoyl-1,1-diphenylmethyl)-pyrrolidine l (+) tartrate (22 g) and water (440 ml) were taken into a clean and dry round bottom flask.
Dichloromethane (220 ml) was added and the pH of the reaction suspension adjusted to 12 using 10% aqueous sodium hydroxide solution (50 ml) followed by separation of organic and aqueous layers. The resultant reaction mass was extracted with dichloromethane (2x 220 ml) followed by separation of organic and aqueous layers. Both the organic layers were combined and washed with water (220 ml) followed by separation of organic and aqueous layers. The organic layer was dried over anhydrous sodium sulfate followed by separation of organic layer. The solvent was distilled completely at about 35-40 °C under reduced pressure to afford 23 g of the title compound.

**EXAMPLE 9: PREPARATION OF 5-CHLOROACETYL-2,3-DIHYDRO BENZOFURAN (FORMULA XII):**

Dichloromethane (8 liters) was taken into a reactor and cooled to -5 to 5 °C. Chlороacetil chloride (15.5 kg) was added to it at the same temperature and stirred for about 10 minutes. 2,3-dihydrobenzofuran (15 kg) was then added to the reaction mixture at the same temperature followed by addition of aluminium chloride (16.8 kg) in 4 equal lots slowly at a temperature of about -5 to 5 °C. The reaction mass was stirred at the same temperature for about 10 minutes. The temperature was gradually raised to about 25 °C and maintained at 0 to 5 °C for about 2 hours, at 10 to 15 °C for 1 hour and at 25 °C for about 5 hours. Reaction completion was checked using thin layer chromatography. After the reaction was completed, dichloromethane (150 liters) was added to it and stirred for about 15 minutes. The reaction mixture was then added to a reactor containing water (450 liters) precooled to 5 to 10 °C. The reaction mixture was stirred for about 1 hour and the organic layer was separated. The aqueous layer was then extracted into dichloromethane (100 liters), and the combined organic layer was washed with 5% aqueous sodium bicarbonate solution (150 liters) followed by washing with water (200 liters). 70 to 80 % of the solvent was distilled off from the organic layer atmospherically below 45 °C followed by complete distillation of the solvent under reduced pressure. Methanol (90 liters) was added to the residue obtained and heated to 55 to 60 °C to get a clear dissolution. The solution was then cooled to 25 to 35 °C and maintained for about 5 hours. The separated solid was filtered and the filtered solid was washed with methanol (15 liters). The wet compound

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was dried at about 40 °C under reduced pressure to yield 19.3 kg of the title compound (% Yield: 63%).

Purity By HPLC: 98.1%.

**EXAMPLE 10: PREPARATION OF 5-CHLOROETHYL-2, 3-DIHYDROBENZOFURAN (FORMULA III):**

5-chloroacetyl -2,3-dihydro benzofuran (10 kg) and trifluoroacetic acid (25 liters) were taken into a reactor and cooled to 0 to 5 °C. Triethylsilane (14.8 kg) was then added to the above reaction mixture at the same temperature slowly. The temperature of the reaction mixture was then raised to 25 to 35 °C and maintained for about 10 hours. Reaction completion was checked using thin layer chromatography. After the reaction was completed, water (50 liters) was added to it, followed by the addition of petroleum ether (50 liters). The reaction mass was stirred for about 20 minutes, and the organic layer was separated. The organic layer was washed with 5% sodium bicarbonate solution (50 liters) in two equal lots followed by washing with water (25 liters). The organic layer was treated with a mixture of silica gel (10 kg) and carbon (1 kg) at 25 to 35 °C and filtered. The filtered bed was washed with petroleum ether (60 liters) in 3 equal lots. The combined filtrate was distilled off completely below 45 °C under reduced pressure and 20 liters of petroleum ether was added to the residue and cooled to 0 to 5 °C. The mixture was maintained at 0 to 5 °C for about 1 hour and the separated solid was filtered and washed with chilled petroleum ether (5 liters). The wet compound was dried at about 40 °C for 12 hours to yield 6.28 kg of the title compound (% Yield 68%)

Purity by HPLC: 97.2%.

**EXAMPLE 11: PREPARATION OF 3-(S)-(1-CARBAMOYL-1,1-DIPHENYL METHYL)-1-[2-(2,3-DIHYDROBENZOFURAN-5-YL)-2-OXOETHYL]-PYRROLIDINE HYDROCHLORIDE (FORMULA XV):**

5-chloroacetyl-2,3-dihydrobenzofuran (15.5 g) and ethanol (200 ml) were taken into a clean and dry round bottom flask under nitrogen atmosphere.

Potassium carbonate (19.8 g) was added followed by addition of 3-(S)-(1-carbomoyl-1,1-diphenylmethyl-pyrrolidine (20 g). The resultant reaction mass was stirred for about 16 to 18 hours. The solvent was distilled completely at about 50 °C under reduced pressure followed by addition of water (200 ml). The reaction
solution was extracted into dichloromethane (3 x 200 ml) followed by separation of organic and aqueous layers. The total organic layer was washed with water (200 ml) followed by separation of organic and aqueous layers. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled completely at about 35-40 °C under reduced pressure. The resultant solid was dissolved in ethyl acetate (400 ml) followed by adjusting the pH to 2 using a solution of 11 ml of hydrochloric acid in isopropyl alcohol. The solid separated was filtered and washed with ethyl acetate (100 ml) followed by drying at about 50 °C to afford 29.1 g of the title compound.

**EXAMPLE 12: ALTERNATE PROCESS FOR THE PREPARATION OF 3-(S)-(-)-(1-CARBAMOYL-1,1-DIPHENYL METHYL)-1-[2-(2,3-DIHYDROBENZOFURAN-5-YL)-ETHYL]-PYRROLIDINE (FORMULA XV):**

3-(S)-(-)-(1-carbamoyl-1,1-diphenylmethyl-pyrrolidine (14 g) and 5-chloroethyl-2,3-dihydrobenzofuran (9.2 g) were taken into a clean and dry round bottom flask. To the reaction mixture was added sodium carbonate (10.6 g), tetra butyl ammonium bromide (TBAB) (3.2 g), sodium iodide (0.8 g) and cyclohexane (140 ml) under stirring. The reaction mixture was heated to about 75 to 80 °C for about 38 to 40 hours followed by allowing the reaction mass to reach 25-35 °C. The supernatant solvent was decanted and dichloromethane (70 ml) and water (140 ml) were added to the reaction mass and stirred for about 10 minutes. Organic and aqueous layers separated and the aqueous layer was extracted with dichloromethane (2x70 ml). The total organic layer was washed with water (3 x 70 ml) followed by separation of organic and aqueous layers. The organic layer was dried over anhydrous sodium sulphate. The solvent was distilled completely at about 35-40 °C under reduced pressure. The crude material obtained was purified with the aid of column chromatography and eluted with ethyl acetate. The fractions were distilled completely about 45 °C under reduced pressure to afford 7.3 g of the title compound.

**EXAMPLE 13: PREPARATION OF DARIFENACIN HYDROBROMIDE (FORMULA I):**

3-(S)-(+)-(1-cyano-1,1-diphenylmethyl)-pyrrolidine (25 g), ethyl acetate (125 ml) and water (125 ml) were taken into a round bottom flask and stirred for about 10 minutes. Caustic lye (25 ml) was added to it slowly at 25 to 35 °C and stirred
for about 15 minutes. The organic layer was separated and the aqueous layer was extracted into ethyl acetate (50 ml). The combined ethyl acetate layer was washed with 10% sodium chloride solution (125 ml) and the ethyl acetate layer was distilled off completely to get a residue. To the residue obtained 5-chloroethyl-2,3-dihydrobenzofuran (14.4 g), and triethylamine (12 ml) were added and heated to about 95 °C. The reaction mass was maintained at the same temperature for about 15 hours. Reaction completion was checked using thin layer chromatography. After the reaction was completed, ethyl acetate (125 ml) was added to the reaction mass at 40 to 45 °C, followed by addition of water (125 ml).

The organic layer was separated and the aqueous layer was extracted into ethyl acetate (75 ml). The combined ethyl acetate layer was washed with 10% sodium chloride solution (125 ml) and then distilled at about 45 °C to get a residue. To the residue obtained acetone (122 ml) was added and stirred at about 30 °C for 1 hour. To the above solution aqueous hydrobromic acid (12.8 g) was added and stirred for another 1 hour. The separated solid was filtered and washed with acetone (61 ml). The wet solid was dried at 60-65 °C for about 4 hours to yield 24.6 g of the title compound (% yield: 70 %).

Purity By HPLC: 98.78%.

**EXAMPLE 14: PREPARATION OF DARIFENACIN HYDROBROMIDE (FORMULA I):**

3-(S)-(1-cyano-1, 1-diphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl)-ethyl]-pyrrolidine hydrobromide (20 g) was added to a solution of potassium hydroxide (57.2 g) in 2-butanol (300 ml). The mixture was allowed to reflux at 105 to 110 °C for about 50 hours. Reaction completion was checked using thin layer chromatography. After the reaction is completed, water (100 ml) was added to the reaction mass and the organic layer was separated. The organic layer was washed with water (200 ml) in two equal lots followed by washing with 20 % sodium chloride solution (100 ml). The organic layer was then distilled off completely at 60 to 65 °C, and the residue obtained was co-distilled with acetone (40 ml). To the residue obtained, acetone (72 ml) was added followed by addition of hydrogen bromide in acetic acid (14.8 g). The mixture was stirred for about 1 hour and the separated solid was filtered. The wet solid was taken into another round bottom flask and n-propanol (162 ml) was added to it. The mixture was
heated to 90 to 95 °C and maintained for about 10 minutes. Then it was cooled to
25 to 35 °C and maintained for about 1 hour. The separated solid was filtered and
washed with n-propanol (27 ml). The process was repeated twice with the wet
compound using n-propanol (135 ml) and the separated solid was filtered and
washed with 27 ml of n-propanol. The final wet solid was dried at 65 °C for about 5
hours to yield 7.6 g of the title compound.

The dry compound was again taken into another round bottom flask and
ethyl acetate (56 ml), and water (56 ml) were added to it and stirred at 25 to 35 °C
for about 10 minutes. A solution of caustic lye (7 ml) in water (7 ml) was then
added to the above mixture and stirred for about 20 minutes. The organic layer
was separated and the aqueous layer was extracted into ethyl acetate (27 ml).
The combined organic layer was washed with 10 % sodium chloride solution (35
ml) and then distilled off completely to get a residue. To the residue obtained
acetone (24 ml) and a solution of hydrogen bromide in acetic acid (5.9 g) was
added and stirred for about 1 hour. The separated solid was filtered and washed
with acetone (12 ml). The wet solid was dried at 65 °C for about 5 hours to yield
5.7 g of the title compound (% yield: 27.5%).

Purity By HPLC: 99.59%.

EXAMPLE 15: PREPARATION OF DARIFENACIN HYDROBROMIDE

(FORMULA I):

Darifenacin (1 g) and acetone (5 ml) were taken into a round bottom flask
followed by stirring for about 5-10 minutes. 48% aqueous hydrogen bromide (0.4
g) was added over about 15 to 20 minutes followed by stirring for about 1 to 2
hours. Separated solid was filtered and washed with acetone (5 ml). The solid
obtained was dried at about 60-70 °C to afford 0.4 g of the title compound.
Purity by HPLC: 98.01%.

EXAMPLE 16: PREPARATION OF DARIFENACIN HYDROBROMIDE USING
AMMONIUM BROMIDE (FORMULA I)

3-(S)-(−)-(1-carbamoyl-1,1-diphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-
yl)-ethyl]-pyrrolidine (1 g) and methanol (20 ml) were taken into a clean and dry
round 4 neck bottom flask followed by stirring for about 10 minutes. The resultant
reaction solution was cooled to about 15 °C followed by addition of ammonium
bromide (0.5 g). The reaction mixture was stirred for about 1.5 hours followed by

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addition of charcoal carbon (0.2 g). The resultant suspension was stirred for about 5 minutes then filtered through a celite bed and the bed was washed with 4 ml of methanol. The filtrate was distilled completely at about 65 °C under reduced pressure to afford 2.1 g of a crude form of the title compound. To the crude solid obtained, dichloromethane (50 ml) was added followed by stirring for about 20 minutes. The mixture was filtered and the solid was washed with dichloromethane (50 ml). The filtrate was distilled completely at about 42 °C under reduced pressure to afford 1.8 g of residue. To the residue acetone (10 ml) was added followed by stirring at about 26 °C for about 20 minutes. The mixture was filtered and the solid was washed with acetone (4 ml) followed by drying the solid at about 75 °C for about 12 hours to afford 0.7 g of the title compound in pure form. Purity by HPLC: 99.2%.

SOR: [α]D25 = +43.93° (C= 1 in methylene chloride)

EXAMPLE 17: PURIFICATION OF DARIFENACIN HYDROBROMIDE (FORMULA I):

Darifenacin hydrobromide (3.75 kg), and methanol (30 liters) were taken into a reactor and heated to 45 to 50 °C. The reaction mass was maintained at 45 to 50 °C for about 30 minutes to get a clear solution and then carbon (0.19 kg) was added to it and stirred at the same temperature for another 10 minutes. The reaction mixture was then filtered over a celite bed and the bed was washed with methanol (7.5 liters). The filtrate was taken into another reactor and heated to 60 to 65 °C. About 50 to 60% of the total volume of methanol was distilled off from the filtrate and cyclohexane (37.5 liters) was added to it and then allowed to cool to 25 to 35 °C. Another 11.25 liters of cyclohexane was added to the above reaction mass and maintained at 25 to 35 °C for about 30 minutes. The separated solid was filtered and washed with cyclohexane (7.0 liters). The wet solid was dried at 70 °C under reduced pressure for about 12 hours to yield 3.12 kg of the title compound (% yield: 83.2%). Purity By HPLC: 99.8%.

All other individual impurities: Less than 0.1%.

Residual Organic Solvents: Methanol: 288 ppm,
Cyclohexane: 252 ppm,
Particle Size Distribution: D10: 4.8 μm, D50: 17.1 μm, D90: 47.3 μm
EXAMPLE 18: PREPARATION OF AMORPHOUS DARIFENACIN (FORMULA V):

27 g of 3-(S)-(1-carbamoyl-1,1-diphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl)-2-oxoethyl]-pyrrolidine hydrochloride of Formula III and 30 g of 5% palladium carbon in 270 ml of acetic acid were charged into a clean and dry autoclave followed by heating to about 80 to 90 °C for about 7 to 8 hours maintaining anhydrous hydrogen gas pressure of about 3 to 4 kgs/cm². After the completion of the reaction, the reaction mass was filtered on celite and the celite was washed with methanol. The solvent was distilled completely about 65 °C under vacuum. To the crude obtained 270 ml of water was charged and the pH was adjusted to 10 using 55 ml of 5N sodium hydroxide solution. The resultant reaction mass was extracted with 3 x 270 ml of dichloromethane followed by separation of organic and aqueous layers. Total organic layer was washed with 2 x 270 ml of water followed by separation of organic and aqueous layers. The organic layer was distilled completely at about 35-40 °C under vacuum. The crude oil material obtained was purified with the aid of column chromatography using the ethyl acetate and methanol in the ration of 9:1 as eluents. The collected fractions were distilled under vacuum to afford 12.8 g of the title compound.

EXAMPLE 19: PREPARATION OF DARIFENACIN HYDROBROMIDE AMORPHOUS FORM (FORMULA I).

Darifenacin hydrobromide (0.5 g) and methanol (25 ml) were taken into a round bottom flask followed by stirring at about 26 °C for about 10 minutes. To the resultant homogenous solution charcoal carbon (0.05 g) was added followed by stirring for about 15 minutes. The resultant reaction suspension was filtered through a celite bed and the bed was washed with methanol (5 ml). The filtrate was distilled completely at about 55 °C under reduced pressure to afford 0.4 g of the title compound having an XRPD pattern substantially in accordance with Fig. 3.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as defined by the appended claims.
What is claimed is:
1. A process for preparing a free base of darifenacin:

![Chemical Structure]

or the salt thereof, said process comprising reacting 3-(S)-(cyanodiphenylmethyl)-
1-[2-(2,3-dihydrobenzofuran-5-yl) ethyl] pyrrolidine of the Formula IV, or a salt
thereof:

![Chemical Structure (IV)]

with a base effective to convert the nitrile group of the compound of the Formula
(IV) to the amide group of the darifenacin in an organic solvent, the reaction being
carried out in said organic solvent, with a proviso that said solvent is not 2-methyl-
butan-2-ol, and with further proviso that said reaction produces less than about
0.5 % of the compound of the Formula Ic:

![Chemical Structure (Ic)]

in the reaction mass, as measured by HPLC.

2. The process of claim 1, wherein the concentration of said base in said
organic solvent is from about 0.1 g/ml to about 0.3 g/ml.

3. The process of claim 1, wherein said organic solvent has moisture content
of less than about 1%.

4. The process of claim 1, further comprising converting the free base of
darifenacin to its hydrobromide salt.

5. The process of claim 1, wherein said base is potassium hydroxide.

6. The process of claim 1, wherein said organic solvent is 2-butanol.
7. The process of claim 1, further comprising isolating said free base of darifenacin.
8. The process of claim 7, wherein said isolating step is carried out at a temperature equal to or less than about 50 °C.
9. The process of claim 1, further comprising providing the 3-(S)-(cyanodiphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl) ethyl] pyrrolidine of the Formula IV by condensing 3-(S)-(+)-(1-cyano-1,1-diphenylmethyl)-pyrrolidine of the Formula II:
   \[
   \text{(II),}
   \]
   or its acid addition salt, with 5-haloethyl-2,3-dihydrobenzofuran of the Formula III:
   \[
   \text{(III),}
   \]
   wherein X is Cl, Br, or I,
in the presence of an organic base.
10. The process of claim 9, wherein said condensing step is carried out in the absence of an external solvent.
11. The process of claim 9, wherein the organic base used is triethylamine.
12. The process of claim 9, further comprising isolating the compound of the Formula IV.
13. The process of claim 12, wherein said isolating step is carried out at temperatures lower than about 50 °C.
14. A process for preparing a free base of darifenacin:
   \[
   \text{or the salt thereof, said process comprising:}
   \]
   a) condensing 3-(S)-(+)-(1-cyano-1,1-diphenylmethyl)-pyrrolidine of the Formula II:
or its acid addition salt, with 5-haloethyl-2,3-dihydrobenzofuran of the Formula III:

(III), wherein X is Cl, Br, or I,

in the presence of an organic base to afford 3-(S)-(cyanodiphenylmethyl)-1-[2-(2,3-dihydrobenzofuran-5-yl) ethyl] pyrrolidine of the Formula IV:

(IV); and

b) converting the compound of the Formula (IV) to darifenacin or its acid addition salt;

wherein said condensing step is carried out in the absence of an external solvent.

15. The process of claim 14, wherein the organic base used is triethylamine.

16. The process of claim 14, further comprising isolating the compound of the Formula IV.

17. The process of claim 16, wherein said isolating step is carried out at temperatures lower than about 50 °C.

18. The process of claim 14, further comprising providing the 3-(S)-(+)-(1-cyano-1,1-diphenylmethyl)-pyrrolidine of the Formula II by the steps of:

i) providing 1-tosyl-3-(S)-(--)tosyloxy.pyrrolidine of the Formula IX:

(IX)

ii) reacting 1-tosyl-3-(S)-(--)tosyloxy.pyrrolidine of the Formula IX with diphenyl acetonitrile to afford 3-(S)-(++)-(1-cyano-1,1-diphenylmethyl)-1-tosyloxy.pyrrolidine of the Formula X:
(X)

iii) reacting the 3-(S)-(+)-(1-cyano-1,1-diphenylmethyl) of the Formula X with an external acid to provide the 3-(S)-(+)-(1-cyano-1,1-diphenylmethyl)-pyrrolidine of the Formula II.

19. The process of claim 18, further comprising providing 1-tosyl-3-(S)-(+)tosloyxypyrrolidine of the Formula IX by the steps of:

1) decarboxylating (2S, 4R)-(−)-4-hydroxy-2-pyrrolidinecarboxylic acid of the Formula VI:

![VI]

(VI)

to give 3-(R)-(−)-hydroxypyrrolidine;

2) converting 3-(R)-(−)-hydroxypyrrolidine to its hydrochloride of the Formula VII:

![VII]

(VII)

3) reacting 3-(R)-(−)-hydroxypyrrolidine hydrochloride of the Formula VII with a first tosylating reagent in the presence of an inorganic base to afford 1-tosyl-3-(R)-(−)-hydroxypyrrolidine of Formula VIII:

![VIII]

(VIII)

4) reacting 1-tosyl-3-(R)-(−)-hydroxypyrrolidine of the Formula VIII with a second tosylating agent in the presence of diisopropylazodicarboxylate and triphenylphosphine to afford the 1-tosyl-3-(S)-(−) tosloyxypyrrolidine of the Formula IX.

20. A process for the preparation of 5-haloethyl-2,3-dihydrobenzofuran of the Formula III:

![III]
said process comprising:

a) reacting 2,3-dihydrobenzofuran of the Formula XI

(XI)

5 with haloacetyl halide to give 5-haloacetyl-2,3-dihydrobenzofuran of the Formula XII:

(XII)

wherein X is Cl, Br, or I, and

b) reacting 5-haloacetyl-2,3-dihydrobenzofuran of the Formula XII with a reducing agent to provide the compound of the Formula III.

21. The process of claim 20, further comprising recrystallizing the compound of the Formula III from an ether solvent.

22. The process of claim 21, wherein the ether solvent is petroleum ether.

23. A pharmaceutical intermediate that comprises:

a) a major portion comprising 5-haloethyl-2,3-dihydrobenzofuran of the Formula III:

(XIII)

wherein X is Cl, Br, or I, and

b) a minor portion comprising one or more compounds of the Formula IIIa, IIIb, or IIIc:

(IIIa)

(IIIb)

(IIIc)
wherein said minor portion contains less than about 2% of one or more compounds of the Formula IIIa, IIIb, and/or IIIc, as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said intermediate.

24. The pharmaceutical intermediate of claim 23, wherein said minor portion includes more than about 0.01% of the compound of the formula IIIa, as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said solid intermediate.

25. The pharmaceutical intermediate of claim 23, wherein said minor portion includes the compound of the formula IIIb in the amount greater than about 0.01%, as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said solid intermediate.

26. The pharmaceutical intermediate of claim 23, wherein said minor portion includes the compound of the formula IIIc in the amount greater than about 0.01% as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said solid intermediate.

27. A process for the preparation of darifenacin hydrobromide, said process comprising:
   a) providing a solution of free base of darifenacin in an organic solvent to form a reaction medium substantially free from moisture;
   b) adding the source of hydrobromic acid to obtain a solution of darifenacin hydrobromide, said source of hydrobromic acid being added in a non-aqueous carrier; and
   c) recovering the darifenacin hydrobromide as a solid;

28. The process of claim 27, wherein said organic solvent is an alcoholic solvent.

29. The process of claim 28, wherein the alcoholic solvent is methanol.

30. The process of claim 27, wherein said organic solvent is acetone.

31. The process of claim 27, wherein said non-aqueous carrier is an organic carrier.

32. The process of claim 31, wherein the organic carrier is an organic acid.

33. The process of claim 32, wherein the organic carrier is acetic acid.
34. The process of claim 27, wherein said source of hydrobromic acid is ammonium bromide.
35. A solid active ingredient for use in pharmaceutical compositions comprising:
   a) a major portion that comprises darifenacin hydrobromide; and
   b) a minor portion that comprises one or more of the impurities of the Formula Ia, Ib, Ic, Id, Ie, If, and/or Ig:
(If)

wherein said major portion is representing 95% or more of said solid active ingredient, and said minor portion contains less than about 1% of one or more impurities of the Formula Ia, Ib, Ic, Id, If, and/or Ig, as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said solid active ingredient.

36. The solid active ingredient of claim 35, wherein said minor portion includes the compound of the formula Ia in the amount greater than about 0.01% as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said solid active ingredient.

37. The solid active ingredient of claim 35, wherein said minor portion contains the compound of the formula Ib in the amount greater than about 0.01% as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said solid active ingredient.

38. The solid active ingredient of claim 35, wherein said minor portion contains the compound of the formula Ic in the amount greater than about 0.01% as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said solid active ingredient.

39. The solid active ingredient of claim 35, wherein said minor portion contains the compound of the formula Id in the amount greater than about 0.01% as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said solid active ingredient.

40. The solid active ingredient of claim 35, wherein said minor portion contains the compound of the formula Ie in the amount greater than about 0.01% as measured by area % in HPLC with respect to the total area % of all compound peaks in the HPLC chromatogram of said solid active ingredient.

41. The solid active ingredient of claim 35, wherein said minor portion contains the compound of the formula If in the amount greater than about 0.01% as
measured by area % in HPLC with respect to the total area % of all compound
peaks in the HPLC chromatogram of said solid active ingredient.
42. The solid active ingredient of claim 35, wherein said minor portion contains
the compound of the formula I g in the amount greater than about 0.01% as
measured by area % in HPLC with respect to the total area % of all compound
peaks in the HPLC chromatogram of said solid active ingredient.
43. A process for purifying darifenacin hydrobromide, said process comprising:
a) providing a solution of darifenacin hydrobromide in a C1-C3 alcoholic
solvent;
b) cooling said solution; and
c) isolating the separated solid, which is the purified darifenacin
hydrobromide.
44. The process of claim 42, wherein said alcoholic solvent is n-propanol.
45. A pharmaceutical solid containing darifenacin hydrobromide having less
than about 2% of total residual organic solvent as determined by gas
chromatography.
46. The pharmaceutical solid of claim 43 having less than about 1% of the total
residual organic solvent.
47. A process for preparing darifenacin hydrobromide substantially free from
residual organic solvent, said process comprising:
d) providing a solution of darifenacin hydrobromide in an alcoholic or a
chlorinated solvent;
e) removing the solvent from the solution obtained in step a);
f) adding an anti-solvent to the residue obtained;
g) isolating the solid.
48. The process of claim 45, wherein the solvent used in step a) is methanol.
49. The process of claim 45, wherein the anti-solvent used is cyclohexane.
50. A compound, which is an amorphous form of darifenacin.
51. A compound, which an amorphous form of darifenacin hydrobromide.
52. A process for preparing an amorphous solid of darifenacin or its
hydrobromide salt, said process comprising:
a) providing a solution of darifenacin or its hydrobromide salt in a
volatile organic solvent; and
b) removing said solvent to obtain said amorphous solid.
53. The process of claim 50, further comprising drying said amorphous solid.

54. A compound, which an amorphous form of darifenacin hydrobromide produced by the process of claim 53.