Title: AN IMPROVED PROCESS FOR THE PREPARATION OF SOLIFENACIN AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

Abstract: The present invention relates to an improved process for the preparation of solifenacin compound of formula (1) and its succinate salt compound of formula (Ia), comprising the condensation of (R)-3-quinuclidinol with (S)-ethyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate in presence of a suitable hydroxide base in a suitable solvent.
An Improved Process for the Preparation of Solifenacin and Its Pharmaceutically Acceptable Salts Thereof

Related Application:

This application claims the benefit of priority of our Indian patent application number 1161/CHE/2008 filed on May 12, 2008, which is incorporated herein by reference.

Field of the Invention:

The present invention relates to an improved process for the preparation of solifenacin and its pharmaceutically acceptable salts thereof, especially succinate. Solifenacin succinate is chemically known as (lS)-3,4-dihydro-l-phenyl-2(lH)-isoquinoline-carboxylic acid (3R)-l-azabicyclo-[2.2.2]oct-3-yl ester succinate, which is represented by formula-1 and its succinate salt is represented by formula-Ia.

Formula-1

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{O}
\end{array}
\]

Formula-Ia

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{OH}
\end{array}
\]

Solifenacin succinate is a urinary antispasmodic, acting as a selective antagonist to the M(3)-receptor. It is used for the treatment of symptoms of overactive bladder, such as urinary urgency and increased urinary frequency, as may occur in patients with overactive bladder syndrome (OAB), as reviewed in Chilman-Blair, Kim et al., Drugs of Today, 40(4):343-353(2004). It's reported as a white to pale yellowish crystalline powder and is freely soluble at room temperature in water, glacial acetic acid, DMSO, and methanol.

Solifenacin succinate was approved by US FDA for once daily treatment of OAB for the dosage strength of 5 mg and 10 mg tablets and marketed under the trade name of VESICARE®.
Background of the Invention:

US Patent No. 6,017,927 discloses solifenacin and its pharmaceutically acceptable salts, and a process for the preparation of solifenacin and its salts. European patent No. 1714965 describes compositions containing solifenacin succinate with less impurities and a process for its preparation. European patent No. 1726304 describes solifenacin or its salts having high purity. Processes for the preparation of solifenacin have also been described in *Drugs of the Future*, 24(8) 871-874, (1999) and *Journal of Medicinal Chemistry*, 2005, 48, 6597-6606.

There are two principal ways for synthesizing solifenacin disclosed in the art. The overall synthesis as reported by Mealy, N., et al. in *Drugs of the Future*, 24(8) 871-874, (1999) is depicted in the following scheme-1.

Scheme-1:
US Patent No. 6,017,927 discloses another process for the preparation of solifenacin wherein 3-quinuclidinyl chloro formate monohydrochloride is admixed with (IS)-l-phenyl-1,2,3,4-tetrahydroisoquinoline to obtain solifenacin as illustrated in the following scheme-2.

Scheme-2:

![Scheme-2](image)

The methods described in the art involves the usage of sodium hydride for the condensation of (R)-3-quinuclidinyl fragment with (IS)-l-phenyl-1,2,3,4-tetrahydroisoquinoline fragment. Also in one process the separation of isomeric impurities is carried out in the final stages; hence there is a greater probability for the isomeric impurities being present in the final product.

The present synthesis of solifenacin involves the condensation of stereo specific starting materials i.e. (R)-3-quinuclidinol fragment with (IS)-l-phenyl-1,2,3,4-tetrahydroisoquinoline fragment, which prevents the formation of byproducts. The use of inorganic hydroxide bases like sodium hydroxide, potassium hydroxide and the like control the side reactions thereby increasing the purity and yield of the final product.

The process of the present invention has advantages of using simple base with improved yield and increased productivity. The process is also industrially scalable, economic and eco-friendly.

**Brief Description of the Invention:**

The present invention relates to an improved process for the preparation of solifenacin and its pharmaceutically acceptable salts thereof.

The first aspect of the present invention is to provide an improved process for the preparation of solifenacin and its pharmaceutically acceptable salts, especially succinate salt compound of formula- Ia, which comprises of reacting (R)-3-quinuclidinol compound
of formula-2 with (S)-ethyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate compound of formula-3 in presence of an inorganic base in a suitable solvent to provide solifenacin compound of formula-1, which on in-situ treatment with succinic acid provides solifenacin succinate compound of formula-Ia.

The second aspect of the present invention is to provide a process for the recovery of (R)-3-quinuclidinol from mother liquors obtained from the preparation of solifenacin or its pharmaceutically acceptable salts.

**Advantages of the Present Invention:**

- Avoids the usage of strong bases such as sodium hydride and involves the usage of simple bases like alkali metal hydroxide, which prevents side reactions and helps to control the formation of byproducts.
- Present invention involves the usage of optically pure intermediates and thereby avoids the resolution in the final stages, which leads to improvement in the yield and purity of the final products.
- Easy to scale up to industrial level.

**Brief Description of the Drawings:**

- **Figure-1:** Illustrates the powder X-ray diffraction pattern of crystalline solifenacin succinate
- **Figure-2:** Illustrates the IR spectrum of crystalline solifenacin succinate
- **Figure-3:** Illustrates the DSC of crystalline solifenacin succinate

**Detailed Description of the Invention:**

The present invention related to an improved process for the preparation of Solifenacin and its pharmaceutically acceptable salts, especially succinate compound of formula-Ia. Solifenacin succinate represented by the following structural formula-Ia.
Accordingly the first aspect of the present invention provides an improved process for the preparation of solifenacin and its pharmaceutically acceptable salts thereof, especially succinate compound of formula-Ia, which comprises of reacting (R)-3-quinuclidinol compound of formula-2

![Formula-2]

with (S)-ethyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate compound of formula-3

![Formula-3]

in presence of an inorganic base selected from a group which includes but is not limited to hydroxides of alkali and alkaline earth metals such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like and bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate and the like, preferably sodium hydroxide in a suitable solvent selected from aromatic hydrocarbon solvents such as benzene, toluene, xylene, chlorobenzene and the like; or halogenated solvents such as dichloromethane, chloroform, ethylene dichloride and the like; and their mixtures thereof; preferably toluene, to provide solifenacin, which on in-situ treatment with succinic acid in acetone to provide solifenacin succinate compound of formula-Ia.
The obtained solifenacin succinate was further purified in a suitable solvent selected from methanol, ethanol, isopropyl alcohol, acetone, ethyl acetate and mixtures thereof to provide pure solifenacin succinate.

In the processes reported in the prior art for the preparation of solifenacin, the condensation reaction is carried out using strong base like sodium hydride or metal alkoxides, which are difficult to handle, pyrophoric and not utilizable in a large scale process. Apart from that when the same process has been practiced in the laboratory, these reagents led to side reactions, leading to the formation of byproducts, hence decreasing the purity of the final product. The use of sodium hydroxide or potassium hydroxide minimized the side reactions as well as the formation of byproducts. This provided an added advantage that the purity of the product increased, minimizing the workup procedure and making it easier for scale up to an industrial level.

The present invention represented by the following scheme-3:

Scheme-3:
The pure crystalline solifenacin succinate compound of formula-1a obtained as per the present invention is characterized by its powder X-ray diffractogram, IR spectrum and DSC thermogram substantially as shown in Figure-1, Figure-2 and Figure-3 respectively.

The second aspect of the present invention provides a process for the recovery of (R)-3-quinuclidinol compound of formula-2 from the mother liquors obtained from the preparation of solifenacin and its pharmaceutically acceptable salts, which comprises of the following steps,

a) Treating the mother liquor with suitable base such as alkali metal hydroxides like sodium hydroxide, potassium hydroxide preferably sodium hydroxide,

b) stirring the reaction mixture for 0-60 min at room temperature,

c) filtering the obtained solid,

d) suspending the obtained solid in a suitable hydrocarbon solvent selected from toluene\(^{x}\) xylene, cyclohexane, heptane and hexane or mixtures thereof,

e) stirring the suspension for 5-60 min at 0-35\(^{0}\)C,

f) recovering the (R)-3-quinuclidinol compound of formula-2 by filtration, washing with a suitable solvent followed by drying.

The starting materials like (R)-3-quinuclidinol compound of formula-2 and (S)-ethyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate compound of formula-3 used in the present invention is prepared by the processes outlined in the following schemes 4, 4a & 5 or by the conventional methods.

Scheme-4:

![Chemical Reaction Diagram]
Scheme-4a:

As mentioned in scheme-4, the organic amine used is selected from triethylamine, isopropyl amine, diisopropyl amine preferably triethylamine; chloro solvent used is selected from methylene chloride or chloroform and base used is selected from alkali metal hydroxides like sodium hydroxide, potassium hydroxide; alkali metal carbonates like sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate; alkoxide bases like sodium tertiary butoxide and potassium tertiary butoxide; and hydrocarbon solvent used is selected from toluene, xylene, cyclohexane, heptane and hexane and the alcohol is selected from methanol, ethanol, isopropanol and butanol or mixtures thereof.

Scheme-5:

As mentioned in scheme-5, the inorganic base used is selected from alkali metal hydroxide like sodium hydroxide, potassium hydroxide; alkali metal carbonates like sodium carbonate, potassium carbonate, sodium bicarbonate and potassium bicarbonate; and the solvent used is selected from hydrocarbon solvents like toluene, xylene, heptane, hexane and cyclohexane; chloro solvents like methylene chloride or chloroform; and the organic base used is selected from triethylamine, isopropyl amine and diisopropyl amine.
**HPLC Analysis of Related Substances:**

Apparatus: A liquid chromatogram is equipped with UV-Detector.

Column: Symmetry shield RP 18, 250 X 4.6 mm, 5 µm

Flow rate: 1.0 ml/min

Wave length: 210 nm

Temperature: 27°C

Load: 1 µl

Run time: 65 min

Diluents: Buffer for diluent: acetonitrile in the ratio 70:30 v/v

(Buffer for diluent preparation: Dissolve 1.36 gram (0.01 m) of KH₂PO₄ in 1000 ml of water, to this add 1 ml of triethyl amine).

Sample concentration: 1 mg/ml

Elution: gradient

Mobile phase-A: Buffer

Mobil phase B: acetonitrile: water (800:200) v/v

Buffer preparation: 0.01 M of KH₂PO₄ in water, pH=3.5 with H₃PO₄.

**Isomer Content by chiral HPLC**

Apparatus: A liquid chromatograph is equipped with variable Wavelength UV detector

Column: Chiralpak AD-H, 250 X 4.6 mm, 5 micron

Flow rate: 1.0 ml/min

Wavelength: 220 nm

Temperature: 17°C

Load: 20 µl

Elution: isocratic

Run time: 60 minutes

Diluent: ethanol

Mobile phase: A mixture of 870 volumes of n-hexane, 130 volumes of 2-propanol and 1 volume of diethyl aniline

Sample concentration: 10 mg/ml
Analysis of particle size distribution of Solifenacin succinate:

A Malvern laser diffraction instrument was used to characterize the particle size distribution of solifenacin succinate.

Instrument model : Malvern Mastersizer 2000

Dispersant name : light liquid paraffin

Instrument parameters:

i) Material RI: 1.600

ii) Dispersant RI : 1.468

iii) Analysis model : general purpose

iv) Sensitivity : Normal

XRD analysis of solifenacin succinate was carried out using SIEMENS/D-5000 X-Ray diffractometer using Cu, Ka radiation of wavelength 1.54 Å and continuous scan speed of 0.045°/min. FT-IR spectrum of solifenacin succinate was recorded on Thermo model Nicolet-380 as KBr pellet. The thermal analysis of solifenacin succinate was carried out on Waters DSC Q-10 model differential scanning calorimeter.
The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

Examples:

Reference example-1:

Preparation of \((lS)-3,4\text{-dihydro-1-phenyl-2(1H)-isoquinolinecarboxylic acid-}(3R)\)-l-azabicyclo-[2.2.2]oct-3-yl ester succinate(solifenacin succinate):

A mixture of 20 grams of (R)-3-quinuclidinol and 15 grams of (lS)-ethyl-l-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate in 150 ml of toluene was refluxed azeotropically for 2 hrs using dean stark apparatus to remove water from the solvent. The reaction mixture was cooled under atmosphere of nitrogen to 25°C, 0.36 grams of sodium hydride was added to it and further refluxed for 18 hrs. The reaction mixture was cooled to 25°C and quenched with saturated sodium chloride solution. The aqueous and organic layers were separated. The organic layer was extracted with 20% hydrochloric acid solution. The extracted solution was neutralized with saturated sodium carbonate solution and then extracted it with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. The ethyl acetate layer was treated with activated carbon, stirred for 15 min and filtered through hyflow bed. The solvent was distilled off under reduced pressure to provide a residue. The residue was dissolved in 100 ml of acetone and 5.5 grams of succinic acid was added to it. The reaction mixture was heated to 55°C and stirred for 15 min, it was further cooled to 25°C and stirred for 45 min. The reaction mixture was finally cooled to 0-5°C and stirred for 1 hr. The solid precipitated was filtered, washed with acetone and dried at 50°C to provide the title compound.

Yield: 17 grams.
Reference example-2:

**Preparation of (lS)-3,4-dihydro-l-phenyl-2(lH)-isoquinolinecarboxylic acid-(3R)-l-azabicyclo-[2.2.2]oct-3-yl ester succinate (solifenacin succinate):**

A mixture of 20 grams of (R)-3-quinuclidinol and 15 grams of (lS)-ethyl-l-phenyl-l,2,3,4-tetrahydro-2-isoquinoline carboxylate in 150 ml of toluene was refluxed azeotropically for 2hrs using dean stark apparatus to remove water from the solvent. The reaction mixture was cooled under atmosphere of nitrogen to 25°C; 2.87 grams sodium methoxide was added to it and further refluxed for 18 hrs. The reaction mixture was cooled to 25°C and quenched with saturated sodium chloride solution. The aqueous and organic layers were separated. The organic layer was extracted with 20% hydrochloric acid solution. The extracted solution was neutralized with saturated sodium carbonate solution and then extracted it with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. The ethyl acetate layer was treated with activated carbon, stirred for 15 min and filtered through hyflow bed. The solvent was distilled off under reduced pressure to provide a residue. The residue was dissolved in 100 ml of acetone and 5.5 grams of succinic acid was added to it. The reaction mixture was heated to 55°C and stirred for 15 min; it was further cooled to 25°C and stirred for 45 min. The reaction mixture was finally cooled to 0-5°C and stirred for 1 hr. The solid precipitated was filtered, washed with acetone and dried at 50°C to provide the title compound.

Yield: 16.5 grams.

Example-1:

**Preparation of (lS)-3,4-dihydro-l-phenyl-2(lH)-isoquinolinecarboxylic acid (3R)-l-azabicyclo-[2.2.2]oct-3-yl ester succinate (solifenacin succinate):**

A mixture of 20 grams of (R)-3-quinuclidinol and 15 grams of (lS)-ethyl-l-phenyl-l,2,3,4-tetrahydro-2-isoquinoline carboxylate in 150 ml of toluene was refluxed azeotropically for 2 hrs using dean stark apparatus to remove water from the solvent. The reaction mixture was cooled under atmosphere of nitrogen to 25°C, 2.56 grams of sodium hydroxide was added to it and further refluxed for 18 hrs. The reaction mixture was cooled to 25°C and quenched with saturated sodium chloride solution. The aqueous and
organic layers were separated. The organic layer was extracted with 20% hydrochloric acid solution. The extracted solution was neutralized with saturated sodium carbonate solution and then extracted it with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. The ethyl acetate layer was treated with activated carbon, stirred for 15 min and filtered through hyflow bed. The solvent was distilled off under reduced pressure to provide a residue. The residue was dissolved in water and treated with sodium hydroxide solution. The pH was neutralized with 25°C to 25°C and stirred for 45 min. The reaction mixture was finally cooled to 0-5°C and stirred for 1 hr. The solid precipitated was filtered, washed with acetone and dried at 50°C to provide the title compound. The PXRD of the obtained solifenacin succinate is similar to the PXRD shown in figure-1.

Yield: 16.9 grams.
Purity by HPLC 99.51%; Isomer content by chiral HPLC 99.42%, other isomer 0.57%.

Example-2:
Preparation of (lS)-3,4-dihydro-l-phenyl-2(IH)-isoquinolinecarboxylic acid (3R)-l-azabicyclo-[2.2.2]oct-3-yl ester succinate (solifenacin succinate):

A mixture of 13.2 grams of (R)-3-quinuclidinol and 10 grams of (lS)-ethyl-l-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate in 100 ml of toluene was refluxed azeotropically for 2 hrs using dean stark apparatus to remove water from the solvent. The reaction mixture was cooled under atmosphere of nitrogen to 25°C, 4 grams of potassium hydroxide was added to it and further refluxed for 18 hrs. The reaction mixture was cooled to 25°C and quenched with saturated sodium chloride solution. The aqueous and organic layers were separated. The organic layer was extracted with 20% hydrochloric acid solution. The extracted solution was neutralized with saturated sodium carbonate solution and then extracted it with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. The ethyl acetate layer was treated with activated carbon, stirred for 15 min and filtered through hyflow bed. The solvent was distilled off under reduced pressure to provide a residue. The residue was dissolved in
100 ml of acetone and 5.5 grams of succinic acid was added to it. The reaction mixture was heated to 55°C and stirred for 15 min, it was further cooled to 25°C and stirred for 45 min. The reaction mixture was finally cooled to 0-5°C and stirred for 1 hour. The solid precipitated was filtered, washed with acetone and dried at 50°C to provide the title compound.

Yield: 12 grams.

**Example-3:**

**Preparation of (1S)-3,4-dihydro-l-phenyl-2(lH)-isoquinolinecarboxylic acid (3R)-l-azabicyclo-[2.2.2]oct-3-yl ester (solifenacin):**

A mixture of 13.2 grams of (R)-3-quinuclidinol and 10 grams of (1S)-ethyl-l-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate in 100 ml of toluene was refluxed azeotropically for 2 hrs using dean stark apparatus to remove water from the solvent. The reaction mixture was cooled under atmosphere of nitrogen to 25°C, 4.0 grams of potassium hydroxide was added to it and further refluxed for 18 hrs. The reaction mixture was cooled to 25°C and quenched with saturated sodium chloride solution. The aqueous and organic layers were separated. The organic layer was extracted with 20% hydrochloric acid solution. The extracted solution was neutralized with saturated sodium carbonate solution and then extracted it with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. Distilled of the solvent to obtain the title compound as a solid.

Yield: 11.5 grams.

MR: 82-89°C

**Example-4:**

**Purification of (1S)-3,4-dihydro-l-phenyl-2(lH)-isoquinolinecarboxylic acid (3R)-l-azabicyclo-[2.2.2]oct-3-yl ester succinate (solifenacin succinate):**

A mixture of 47 grams of solifenacin succinate, 40ml of methanol and 200 ml of ethyl acetate was heated to reflux to get a clear solution. The reaction mixture was filtered through a hyflow bed and cooled to 25°C and stirred for 2 hrs. The solid
precipitated was filtered, washed with ethyl acetate and dried at 50°C to provide crystalline solifenacin succinate.

Yield: 34 grams.

Particle size distribution: D (0.1):22.21 µm; D (0.5):49.41 µm; D (0.9):94.71 µm; D (mean): 54.28 µm.

Example-5:

**Purification of (lS)-3,4-dihydro-l-phenyl-2(lH)-isoquinolinecarboxylic acid (3R)-l-azabicyclo-[2.2.2]oct-3-yl ester succinate (solifenacin succinate):**

A mixture of 10 grams of solifenacin succinate, 10 ml of ethanol and 40 ml of ethyl acetate was heated to reflux to get a clear solution. The reaction mixture was filtered through a hyflow bed and cooled to 25°C and stirred for 2 hrs. The solid precipitated was filtered, washed with ethyl acetate and dried at 50°C to provide crystalline solifenacin succinate. The PXRD of the obtained solifenacin succinate is shown in figure-1.

Yield: 7.3 grams.

Purity by HPLC 99.94%; Isomer content by chiral HPLC 99.95%, other isomer 0.05%.

Particle size distribution: D (0.1):16.037 µm; D (0.5):41.80 µm; D (0.9):103.01 µm; D (mean): 53.50 µm.

Example-6:

**Preparation of (IS)-3,4-dihydro-l-phenyl-2(lH)-isoquinolinecarboxylic acid (3R)-l-azabicyclo-[2.2.2]oct-3-yl ester succinate (solifenacin succinate):**

67.4 grams of ethylchloroformate was slowly added to a mixture of 100 grams of (S)-l-phenyl-1,2,3,4-tetrahydroisoquinoline, 92.31 grams of potassium carbonate in 1 litre of toluene at 25-35°C and stirred for 2 hours. The reaction mixture was quenched with water and the layers were separated. The aqueous layer was extracted with toluene and the combined organic layer was dried wit sodium sulphate. 121.5 grams of (R)-quinuclidinol and 38.16 grams of sodium hydroxide powder were added to the dried organic layer at 25-35°C. The reaction mixture was heated to reflux through azotropic distillation mode and stirred for 24 hours at azeotropic refluxion. After completion of the reaction, the reaction mixture was cooled to 25-35°C then quenched with quenched with
water. The layers were separated and the organic layer washed with water followed by 20% hydrochloric acid. The pH of the aqueous layer was basified with saturated sodium carbonate solution. The reaction mixture extracted with toluene. The combined organic layer washed with water and then distilled off completely under reduced pressure at below 60°C. 500 ml of acetone was added to the above residue and subjected to carbonate treatment. The reaction mixture filtered through hyflow and washed with acetone. 56.28 grams of succinic acid was added to the filtrate at 25-35°C and heated to make a clear solution. The reaction mixture was cooled to 25-35°C then to 0-5°C and stirred for 60 minutes at 0-5°C. The reaction mixture was filtered and washed with chilled acetone. The PXRD of obtained solid is similar to the PXRD shown in figure-1.

Purity by HPLC: 97.50 %

265 ml of acetone was added to the above obtained wet solid and heated to reflux temperature and stirred for 30 minutes. The reaction mixture was cooled to 0-5°C and stirred for 60 minutes. The solid obtained is filtered, washed with acetone and then dried to get the title compound. The PXRD of the obtained solifenacin succinate is similar to the PXRD shown in figure-1.

Yield: 150 grams
Purity by HPLC: 99.45 %

Example-7:

Process for the recovery of (R)-3-quinuclidinol:

7.6 grams of sodium hydroxide was added to 20 ml of mother liquor obtained from the example-6 and stirred for 60 minutes at 25-35°C. Filtered the obtained solid then 20 ml of toluene was added to the solid and stirred for 30 minutes at 25-35°C. Filtered the solid, washed with toluene and then dried to get (R)-3-quinuclidinol.

Yield: 5.9 grams
S.O.R: - 33.58°C
We Claim:

1. An improved process for the preparation of solifenacin compound of formula-1,

![Formula-1](image)

which comprises of reacting (R)-3-quinuclidinol compound of formula-2

![Formula-2](image)

with (S)-ethyl-l-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate compound of formula-3

![Formula-3](image)

in presence of a suitable inorganic base in a suitable solvent to provide solifenacin, compound of formula-1.

2. An improved process for the preparation of solifenacin succinate compound of formula-Ia,

![Formula-Ia](image)

Which comprises of the following steps;

a) reacting the (R)-3-quinuclidinol compound of formula-2
with (S)-ethyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate compound of formula-3

in presence of a suitable inorganic base in a suitable solvent to provide solifenacin,
b) which on in-situ reaction with a succinic acid in a suitable solvent to provide solifenacin succinate compound of formula-1a,
c) purifying the solifenacin succinate compound of formula-1a in a suitable solvent to provide the pure solifenacin succinate.

3. The process according to any of the preceding claims, wherein the inorganic base used is selected from hydroxides of alkali and alkaline earth metals such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like and bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate and the like.

4. The process according to claim 1 and claim 2, wherein the inorganic base used is hydroxides of alkali and alkaline earth metals like lithium hydroxide, sodium hydroxide, potassium hydroxide.
5. The process according to claim 1 and claim 2, wherein the inorganic base used is carbonates and bicarbonate of alkali metals selected from sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and the like.

6. The process according to claim 1 and step a) of claim-2, wherein the suitable solvent is selected from a group consisting of aromatic hydrocarbon solvents like benzene, toluene, xylene, chlorobenzene and the like; halogenated solvents such as dichloromethane, chloroform, ethylene dichloride and the like; and their mixtures thereof.

7. The process according to step b) and c) of claim 2, wherein the suitable solvent used is selected from methanol, ethanol, ethyl acetate, isopropyl alcohol, acetone or mixtures thereof.

8. An improved process for the preparation of solifenacin compound of formula-1,

\[
\text{Formula-1}
\]

which comprises of reacting (R)-3-quinuclidinol compound of formula-2

\[
\text{Formula-2}
\]

with (S)-ethyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate compound of formula-3
in presence of sodium hydroxide in toluene to provide solifenacin compound of formula-1.

9. An improved process for the preparation of solifenacin succinate compound of formula-Ia,

Which comprises of the following steps;

a) Reacting the (R)-3-quinuclidinol, compound of formula-2

with (S)-ethyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinoline carboxylate compound of formula-3

in presence of sodium hydroxide in toluene to provide solifenacin,

b) which on in-situ reaction with succinic acid in acetone to provide solifenacin succinate compound of formula-Ia,
c) purifying the solifenacin succinate obtained from step-b) in a mixture of methanol and ethyl acetate to provide pure solifenacin succinate compound of formula-Ia.

10. The process according to claim 9, where in the solifenacin succinate prepared is having a mean particle size in the range of 30-80 µm and D (0.9) in the range of 70-130 µm.

11. A process for the recovery of (R)-3-quinuclidinol compound of formula-2 from the mother liquors obtained from the preparation of solifenacin and its pharmaceutically acceptable salts, which comprises of the following steps,
   a) Treating the mother liquor with suitable base such as alkali metal hydroxides like sodium hydroxide, potassium hydroxide preferably sodium hydroxide,
   b) stirring the reaction mixture for 0-60 min at room temperature,
   c) filtering the obtained solid,
   d) suspending the obtained solid in a suitable hydrocarbon solvent selected from toluene, xylene, cyclohexane, heptane and hexane or mixtures thereof,
   e) stirring the suspension for 5-60 min at 0-35°C,
   f) recovering the (R)-3-quinuclidinol compound of formula-2 by filtration, washing with a suitable solvent followed by drying.