Title: NOVEL PROCESS FOR THE PREPARATION OF MOXIFLOXACIN HYDROCHLORIDE AND A NOVEL POLYMORPH OF MOXIFLOXACIN

Abstract: The present invention relates to a novel process for the preparation of moxifloxacin hydrochloride compound of formula-1 through novel quinoline carboxamide intermediate compounds of general formula-2. The present invention provides the process for the preparation of novel quinoline carboxamide intermediate compounds of general formula-2. The present invention also relates to a novel process for the preparation of anhydrous form of moxifloxacin hydrochloride and a novel crystalline form of moxifloxacin.
Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, GB, GR, HU, IE, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— without international search report and to be republished upon receipt of that report
Related Applications:

This application claims the benefit of priority of our Indian patent application number 2111/CHE/2006 filed on Nov. 14th 2006 and also of our Provisional Patent application number 1345/CHE/2007 filed on June 25th 2007.

5 Field of the Invention:

The present invention relates to a novel process for the preparation of moxifloxacin hydrochloride through novel intermediate compound of general formula-2. Moxifloxacin hydrochloride is chemically known as l-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinoline carboxylic acid hydrochloride compound represented by formula-1.

![Formula-1](image1)

The present invention also relates to novel quinoline carboxamide intermediate compounds of general formula-2 and process for their preparation, which are useful as intermediates in the preparation of important antibacterial compound moxifloxacin hydrochloride compound of formula-1.

![Formula-2](image2)
The present invention also relates to a novel process for the preparation of anhydrous form of moxifloxacin hydrochloride, also a novel crystalline form of moxifloxacin.

Moxifloxacin hydrochloride is a synthetic broad-spectrum antibacterial agent. The active moiety, moxifloxacin has been shown to be clinically active against most strains of microorganisms such as aerobic gram-positive microorganisms including staphylococcus aureus, streptococcus pneumonia (penicillin-susceptible strains) and streptococcus pyogenes, aerobic gram-negative microorganisms including haemophilus influenza hemophilus parainfluenzae, klebsiella pneumonia. Moxifloxacin is commercially available under the brand name of AVELOX® marketed by Bayer pharms.

Background of the Invention:

Moxifloxacin and its pharmacologically acceptable salts are disclosed in European patents EP 350733, EP 550903 and EP 657,448. The disclosed process for the preparation of moxifloxacin hydrochloride comprises of condensing l-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid or its esters with (S,S)2,8-diazobicyclo[4.3.0]nonane, in presence of a base at high temperature followed by conversion into hydrochloride salt. This process not only produces desired moxifloxacin hydrochloride but also its positional isomer namely l-cyclopropyl-7-fluoro-1,4-dihydro-8-methoxy-6-(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridine-6-yl]-4-oxo-quinolinecarboxylic acid as a major impurity which is difficult to separate. The purification of moxifloxacin to remove this isomer results in lower yields thereby increasing the product cost.

The International publication WO 2005/012285 discloses an improved process for the preparation of moxifloxacin hydrochloride incorporated herein by reference. The disclosed process involves the preparation of moxifloxacin hydrochloride from the ethyl 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinolme carboxylate through a novel intermediate (4aS-cis)-1-cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinolinecarboxylicacid-0³,0⁴)bis(acyloxy-0)-borate.
US patent application 6897315 discloses a process for the preparation of 8-methoxy-3-quinoline carboxylic acid especially moxifloxacin incorporated herein by reference. The disclosed process involves the preparation of moxifloxacin from 8-halo moxifloxacin derivative using methanol and potassium tertiary butoxide. US patent 5639886 discloses one-pot process for the preparation of 3-quinoline carboxylic acid derivatives including moxifloxacin.


US Pat.No.5,849,752 discloses specific crystalline forms of anhydrous moxifloxacin mono hydrochloride and monohydrated moxifloxacin mono hydrochloride. Anhydrous moxifloxacin mono hydrochloride disclosed in US Pat. No.5,849,752 has been designated as "Form-I" and the hydrated form as "Form-II" in US Pat. No.7,230,006. It also discloses a novel crystalline Form-III of anhydrous moxifloxacin mono hydrochloride. US patent US 5,480,879 discloses the melting range of moxifloxacin in example part as 203-208°C and does not speaks about polymorphism of moxifloxacin. Experiment executed as per the procedure given in example Z19 of US 5,480,879 and resulted in acetonitrile solvated form of moxifloxacin with low purity and the obtained solvated form can not used for formulations.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like moxifloxacin, may give rise to a variety of crystalline forms having distinct crystal structures and physical properties like melting point, x-ray diffraction pattern, infrared absorption fingerprint, and solid state NMR spectrum. One crystalline form may give rise to thermal behaviors different from that of another crystalline form. Thermal behavior can be measured in the laboratory by such techniques as capillary melting point, thermo gravimetric analysis ("TGA"), and differential scanning calorimetry ("DSC"), which have been used to distinguish polymorphic forms.

The difference in the physical properties of different crystalline forms results from the orientation and intermolecular interactions of adjacent molecules or complexes.
in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula yet having distinct advantageous physical properties compared to other crystalline forms of the same compound or complex.

One of the important physical properties of pharmaceutical compounds is their solubility in aqueous solution, particularly their solubility in the gastric juices of a patient. For example, where absorption through the gastrointestinal stomach or intestine to dissolve slowly so that it does not accumulate in a deleterious environment. Different crystalline forms or polymorphs of the same pharmaceutical compounds can and reportedly do have different aqueous solubilities.

The present invention provides novel crystalline polymorphic form of moxifloxacin, which is of high purity free flow solid and it can be directly used for the formulation as an active pharmaceutical ingredient

Moxifloxacin hydrochloride is an important broad spectrum antibacterial drug which can be used to treat various types of infections, it would be beneficial to have an efficient, high yielding and cost effective process for the preparation of moxifloxacin hydrochloride.

**Brief Description of the Invention:**

The present invention provides a novel process for the preparation of moxifloxacin hydrochloride compound of formula-1 through a novel amide intermediate compound.

![Formula-1](attachment:image)

The first aspect of the present invention provides a novel process for the preparation of moxifloxacin hydrochloride compound of formula-1 which comprises of the following steps:
a) reacting the quinoline carboxamide compound of general formula-2 with nonane compound of general formula-3 in presence of a suitable base in a suitable organic solvent to obtain the condensed amide compound of general formula-4,
b) reacting the condensed amide compound of general formula-4 with a suitable alkali or alkaline metal hydroxides, alkali metal carbonates in suitable polar solvent to obtain moxifloxacin compound of formula-5,
c) reacting the moxifloxacin compound of formula-5 with hydrochloric acid in a suitable aqueous alcoholic solvent to obtain moxifloxacin hydrochloride compound of formula-1.

The second aspect of the present invention provides a novel process for the preparation of moxifloxacin hydrochloride compound of formula-1 through quinoline nitrile intermediate compound of formula-6, which comprises of the following steps:
  a) reacting the nitrile compound of formula-6 with nonane compound of general formula-3 in presence of a suitable base in a suitable organic solvent to obtain the condensed compound of general formula-7,
  b) reacting the condensed compound of general formula-7 with a suitable alkali or alkaline metal carbonates, hydrogen carbonates or hydroxides in suitable polar solvent to obtain moxifloxacin compound of formula-5,
  c) reacting the moxifloxacin compound of formula-5 with hydrochloric acid in a suitable aqueous alcoholic solvent to obtain moxifloxacin hydrochloride compound of formula-1.

The third aspect of the present invention provides a novel process for the preparation of quinoline nitrile intermediate compound of formula-6, which comprises of the following steps:
  a) reacting the 2,4,5-trifluoro-3-methoxy benzoic acid of formula-8 with thionyl chloride followed by reaction with 2-cyano ethyl acetate to obtain compound of formula-9,
  b) decarboxylation of the compound of formula-9 with a suitable aqueous acid or alkali or alkaline base in a suitable solvent to obtain compound of formula-10,
c) reacting the compound of formula-10 with triethylorthoformate in presence of acetic anhydride followed by treating with cyclopropyl amine in presence of an alkali or alkaline base to obtain nitrile compound of formula-6.

The fourth aspect of the present invention provides a novel process for the preparation of beta keto amide intermediate compound of formula-13, which comprises of the following steps:

a) reacting the 2,4,5-trifluoro-3-methoxy benzoic acid of formula-8 with thionyl chloride followed by reaction with diethyl malonate to obtain compound of formula-11,

b) decarboxylation of the compound of formula-11 with a suitable aqueous acid or alkali or alkaline base in a suitable solvent to obtain compound of formula-12,

c) reacting the compound of formula-12 with an amine compound to obtain beta keto amide compound of general formula-13.

The fifth aspect of the present invention provides moxifloxacin hydrochloride monohydrate with particles having oval shape and porous texture as illustrated in photographs of microscopic moxifloxacin hydrochloride monohydrate in figure-4. These particles are more suitable for the preparation of various medicament forms. It also provides a process for its preparation.

The sixth aspect of the present invention provides a novel process for the preparation of anhydrous form of moxifloxacin hydrochloride compound of formula-1, which comprises of the following steps:

a) suspending moxifloxacin hydrochloride in a suitable alcohol solvent and heating the solution,

b) optionally adding chloro solvent and stirring the reaction mixture for complete dissolution,

c) cooling the reaction mixture,

d) stirring the reaction mixture at low temperature for some time,

e) separating the precipitated solid by filtration under inert atmosphere and washing with methanol,
The seventh aspect of the present invention provides novel crystalline form of moxifloxacin, herein defined as Form-I and process for preparing it, which comprises of the following steps:

a) suspending the moxifloxacin HCl or/and its hydrates in a suitable polar solvent,
b) adjusting the pH of the reaction mixture to basic,
c) extracting with suitable water immiscible solvent,
d) distilling off the solvent under reduced pressure,
e) cooling the reaction mixture temperature to low temperature,
f) adding a suitable keto solvent,
g) isolating the product by filtration and optionally washing it with water,
h) drying the material to get the crystalline Form-I of moxifloxacin.

Or

a) 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid on reaction with [S,S]-2,8-diazabicyclo [4,3,0] nonane in an organic solvent in presence of a base followed by adjusting the pH of the reaction mixture with hydrochloric acid,
b) extracting the reaction mixture with chloro or/and ester solvents,
c) isolating the product by using keto solvents to afford Form-I of moxifloxacin.

Moxifloxacin hydrochloride used in step a) of the above process can be prepared by conventional methods known in the art.

Brief Description of the Drawings:

Figure-1: Illustrates the powder X-ray diffraction pattern of crystalline Form-I of moxifloxacin.

Figure-2: Illustrates the IR spectrum of crystalline Form-I of moxifloxacin.

Figure-3: Illustrates the DSC of crystalline Form-I of moxifloxacin.

Figure-4: Illustrates the photographs of microscopic moxifloxacin hydrochloride monohydrate.
Detailed Description of the Invention:

Accordingly the present invention provides a novel process for the preparation of moxifloxacin hydrochloride compound of formula-1 through novel amide intermediate compound of general formula-3. Moxifloxacin hydrochloride compound of formula-1 is chemically known as l-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinoline carboxylic acid hydrochloride.

![Formula-1](image)

In accordance with the present invention, the first aspect of the present invention provides a novel process for the preparation of moxifloxacin hydrochloride compound of formula-1, which comprises of the following steps:

a) reacting the quinoline carboxamide compound of general formula-2

![Formula-2](image)

wherein R and R_i are hydrogen or selected from C_i to C_5 linear or branched chain alkyl group,

with nonane compound of general formula-3

![Formula-3](image)
wherein $R_2$ is Hydrogen, trityl, silyl group like TMS (trimethyl silyl) / TBDMS (tertiary butyl dimethyl silyl) or -COOR$_3$ wherein R$_3$ is phenyl or ethy or butyl analogs.

in presence of a suitable base like 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO) in a suitable organic solvent like acetonitrile, dimethyl formamide preferably acetonitrile to obtain the condensed compound of general formula-4,

$$
\text{Formula-4}
$$

b) reacting the condensed compound of general formula-4 with a suitable alkali or alkaline metal carbonates, hydrogen carbonates, hydroxides like sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, preferably sodium hydroxide in a suitable solvents like ethylene glycol and/or polar solvent like water or mixtures thereof to obtain moxifloxacin compound of formula-5,

$$
\text{Formula-5}
$$

c) reacting the moxifloxacin compound of formula-5 with hydrochloric acid in a suitable aqueous alcoholic solvent like methanol, ethanol and isopropanol preferably aqueous methanol to obtain moxifloxacin hydrochloride compound of formula-1.

The first aspect of the present invention is represented by the following scheme-1
SCHEME-I:

Formula-2

\[
\begin{align*}
\text{Formula-3} & \xrightarrow{\text{R, R}_1} \text{Formula-4} \\
\text{Formula-1} & \xrightarrow{\text{HCl}} \text{Formula-5}
\end{align*}
\]

wherein \( R \) and \( R_1 \) are hydrogens or selected from \( C_1 \) to \( C_5 \) linear or branched chain alkyl group, wherein \( R_2 \) is Hydrogen, trityl, silyl group like TMS (trimethyl silyl) / TBDMS (tertiary butyl dimethyl silyl) or -COOR, wherein \( R_3 \) is phenyl or ethy or butyl analogs.

The second aspect of the present invention provides a novel process for the preparation of moxifloxacin hydrochloride compound of formula-1, which comprises of the following steps:

a) reacting the nitrile compound of formula-6 with nonane compound of general formula-3 in presence of a suitable base in a suitable organic solvent to obtain the condensed compound of general formula-7,

b) reacting the condensed compound of general formula-7 with a suitable alkali or alkaline metal carbonates, hydrogen carbonates, hydroxides like sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, preferably sodium hydroxide in a suitable solvent like ethylene glycol and/or polar solvent like water or mixtures thereof to obtain moxifloxacin compound of formula-5,

c) reacting the moxifloxacin compound of formula-5 with hydrochloric acid in a suitable aqueous alcoholic solvent to obtain moxifloxacin hydrochloride compound of formula-1.
The second aspect of the present invention is represented by the following scheme-2:

SCHEME-2:

![Chemical structures](image)

wherein $R_2$ is Hydrogen, trityl, silyl group like TMS (trimethyl silyl) / TBDMS (tertiary butyl dimethyl silyl) or $-\text{COOR}_3$ wherein $R_3$ is phenyl or ethyl or butyl analogs.

N-protected compound of general formula-4 and formula-7 can be deprotected by the conventional methods.

The third aspect of the present invention provides a novel process for the preparation of quinoline nitrile intermediate compound of formula-6, which comprises of the following steps:

1. a) reacting the 2,4,5-trifluoro-3-methoxy benzoic acid of formula-8 with thionyl chloride followed by reaction with 2-cyano ethyl acetate to obtain compound of formula-9,
2. b) decarboxylation of the compound of formula-9 with a suitable aqueous acid or alkali or alkaline base in a suitable solvent to obtain compound of formula-10,
3. c) reacting the compound of formula-10 with triethylorthoformate in presence of acetic anhydride followed by treating with cyclopropyl amine in presence of an alkali or alkaline base to obtain nitrile compound of formula-6.
The third aspect of the present invention is represented by the following scheme-3:

**SCHEME-3:**

![Chemical Structures](image)

The fourth aspect of the present invention provides a novel process for the preparation of beta keto amide intermediate compound of formula-13, which comprises of the following steps:

a) reacting the 2,4,5-trifluoro-3-methoxy benzoic acid of formula-8 with thionyl chloride followed by reaction with diethylmalonate to obtain compound of formula-11,

b) decarboxylation of the compound of formula-11 with a suitable aqueous acid or alkali or alkaline base in a suitable solvent to obtain compound of formula-12,

c) reacting the compound of formula-12 with an amine compound to obtain beta keto amide compound of general formula-13.

The fourth aspect of the present invention is represented by the following scheme-4
In Scheme-4:

\[
\begin{align*}
\text{Formula-8} & \xrightarrow{\text{diethylmalonate} \ \text{SOCl}_2} \text{Formula-11} \\
\text{Formula-13} & \xrightarrow{\text{RR}_1\text{NH}} \text{Formula-12}
\end{align*}
\]

wherein \(R\) and \(R_1\) are hydrogens or selected from \(C_1\) to \(C_5\) linear or branched chain alkyl group.

The quinoline carboxamide compound of formula-2 can be prepared by the following conventional methods as illustrated in Scheme-5:

In Scheme-5:

\[
\begin{align*}
\text{Formula-6} & \xrightarrow{\text{H}^+} \text{Formula-14} \\
\text{Formula-15} & \xrightarrow{\text{DCC/HOBT/RR}_1\text{NH} \ \text{or} \ \text{SOCl}_2/RR}_1\text{NH}} \text{Formula-2} \\
\end{align*}
\]

wherein \(R\) and \(R_1\) are hydrogens or selected from \(C_1\) to \(C_5\) linear or branched chain alkyl group.
US Patent No. 5,849,752 disclosed moxifloxacin hydrochloride monohydrate with crystals in the form of needles and prisms. The crystals in the form of prisms are more suitable for preparation of pharmaceutical formulations, when compared to crystals in the form of needles.

The fifth aspect of the present invention provides moxifloxacin hydrochloride monohydrate with particles having oval shape and porous texture as illustrated in photographs of microscopic moxifloxacin hydrochloride monohydrate in figure-4. These particles are also imparted with excellent trickling and free flowing properties, hence suitable for the preparation of various medicament forms or pharmaceutical formulations.

The present invention also provides a process for the preparation moxifloxacin hydrochloride monohydrate with particles having oval shape, which comprises of the following steps:

a) suspending moxifloxacin hydrochloride in a solution of aqueous alcohol,
   b) heating the above reaction mixture to higher temperature,
   c) filtering the reaction mixture in hot condition and cooling the filtrate,
   d) adjusting the pH of the filtrate to make it acidic by addition of hydrochloric acid,
   e) further cooling the reaction mixture to lower temperatures to obtain a solid,
   f) dissolving or dispersing or slurrying or washing the solid obtained with with a mixture of water and water miscible solvent containing above 30% of water, or with water alone to obtain moxifloxacin hydrochloride monohydrate having oval shaped particles.

The water miscible solvent is selected from a group of solvents such as alcohols like methanol, ethanol or ketones like acetone or nitriles like acetonitrile etc., and the like.

Moxifloxacin hydrochloride used in step a) may be moxifloxacin hydrochloride Form-Y obtained in the present invention and also disclosed in our earlier patent WO 2007 / 010555 A2 or any other monohydrate or anhydrous crystalline forms of moxifloxacin hydrochloride disclosed in the prior art.
The sixth aspect of the present invention provides a novel process for the preparation of anhydrous crystalline Form-I of moxifloxacin hydrochloride of formula-I which comprises of the following steps:

a) suspending moxifloxacin hydrochloride in a suitable alcohol solvent like methanol and heating the solution to 45-50°C,

b) optionally adding chloro solvent like methylene chloride and stirring the reaction mixture at 50°C for 15-50 minutes for complete dissolution, optionally concentrating the solvent partially,

c) cooling the reaction mixture to 0-30°C, preferably 0-15°C, more preferably 0-5°C,

d) stirring the reaction mixture at 0-5°C for 1-2 hours, preferably 60-90 minutes,

e) separating the precipitated solid by filtration under inert atmosphere and washing with methanol,

f) drying the solid at 100°-150°C, preferably at 110-120°C till the moisture content reaches below 0.5%.

Moxifloxacin hydrochloride used in step a) may be moxifloxacin hydrochloride Form-Y obtained in the present invention and also disclosed in our earlier patent WO 2007/10555 or any anhydrous crystalline forms of moxifloxacin hydrochloride other than form-I disclosed in prior art, like Form-III of anhydrous moxifloxacin mono hydrochloride disclosed in US 7,230,006.

The seventh aspect of the present invention provides a novel crystalline Form-I of moxifloxacin, which is characterized by its PXRD pattern as illustrated in Figure-1, IR spectrum as illustrated in Figure-2, and DSC as illustrated in Figure-3.

Moxifloxacin Form-I in accordance with the present invention is characterized by X-ray powder diffraction peaks at about 9.7, 10.2, 11.7, 18.4 and 23.3 ± 0.2 degrees two-theta.

Moxifloxacin Form-I in accordance with the present invention is characterized by Infrared spectrum peaks at about 3329.4, 1728.4, 1621.0, 1437.1, 1341.9, 881.9 and 804.9cm⁻¹.

Moxifloxacin Form-I in accordance with the present invention is characterized by endotherm at about 211°C by differential scanning calorimetry ("DSC").
The present invention also provides a method of preparing crystalline Form-I of moxifloxacin comprising of the following steps:

a) suspending the moxifloxacin hydrochloride and/or its hydrates in a suitable polar solvent like water,

b) adjusting the pH of the reaction mixture to basic with aqueous sodium hydroxide or aqueous ammonia solution at 10-40°C, preferably at 20-30°C and most preferably at 25-30°C,

c) extracting the reaction mixture with suitable chloro and/or ester solvents like methylene chloride, chloroform or ethyl acetate preferably methylene chloride,

d) concentrating the mass by distillation of the solvent completely preferably under reduced pressure at below 60°C,

e) cooling the reaction mixture to 5-35°C, preferably at 25-35°C,

f) treating the obtained reaction mixture with a suitable organic solvents like keto solvents such as acetone,

g) isolating the product by filtration and optionally washing it with water,

h) drying the material to afford Form-I of moxifloxacin.

(Or)

a) 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid on reaction with [S,S]-2,8-diazabicyclo [4,3,0] nonane in an organic solvent selected from acetonitrile, toluene, dimethyl formamide, dimethyl acetamide in presence of a base like 1,8-Diazabicyclo(5,4,0)undec-7-ene followed by adjusting the pH of the reaction mixture to 5-6 with hydrochloric acid,

b) extracting the reaction mixture with chloro solvents like methylene chloride, chloroform or ester solvents like ethyl acetate,

c) isolating the product by using keto solvents like acetone, methyl ethyl ketone, methyl isobutyl ketone, filtering it and followed by optionally washing it with water to afford Form-I of Moxifloxacin.

Crystalline moxifloxacin as provided by the present invention can in turn be prepared from salts of moxifloxacin such as moxifloxacin hydrochloride or any other suitable salt or directly from the reactions which are schematically represented in scheme-6:
In US Pat. No. 5,849,752 it has been disclosed that anhydrous moxifloxacin hydrochloride is hygroscopic and absorbs water from the atmosphere. Hence special measures were necessary for packing and storing anhydrous moxifloxacin hydrochloride. The process for packaging and storage used herein increased the stability of the anhydrous moxifloxacin hydrochloride and increased its shelf life.

A process for packaging and storage of anhydrous moxifloxacin hydrochloride comprises of the following steps:

a) placing moxifloxacin hydrochloride in a clear low-density polyethylene bag under nitrogen atmosphere and tying with a thread,

b) placing the primary container containing moxifloxacin hydrochloride inside a second low-density black colored polyethylene bag and sealing it,

c) placing the second polyethylene bag inside a triple laminated bag along with silica gel bag and then sealing it, or
c) optionally vacuum sealing the second polythene bag in step b) and the triple laminated bag in step d) after flushing them with nitrogen,
d) placing the sealed triple laminated bag inside a closed high density polyethylene (HDPE) container.

The preferred embodiments of the present invention is represented as follows

```
Formula-2a
```

```
Formula-2b
```

```
Formula-3a
```

```
Formula-3b
```

```
Formula-3c
```

```
Formula-3d
```

```
Formula-4a
```

```
Formula-4b
```

```
Formula-4c
```

```
Formula-4d
```

```
Formula-4e
```

```
Formula-4f
```

Quinoline carboxamide compound of formula-2 is a novel compound which is used in the preparation of moxifloxacin hydrochloride compound of formula-1 of the present invention.

5 Particle Size Determination
A Malvern laser diffraction instrument was used to characterize the particle size distribution of crystalline anhydrous moxifloxacin hydrochloride.
Instrument: The Malvern Mastersizer S, Ver. 2.15
Technique used: Wet method

10 Optical parameters: i) Particle RI: 1.5295, 0.1000
ii) Dispersant RI : 1.3300
Analysis model: Fraunhofer / General purpose
Dispersion medium: Paraffin oil.

15 Determination of bulk density and tapped density:
Bulk density and tapped density were determined as per the methods given in US Pharmacopeia.

Morphology: Method of analysis.

20 Samples were mounted on aluminium stubs using double adhesive tape, coated with gold using HUS-5GB vacuum evaporation and observed in Hitachi S-3000 N SEM, at an acceleration Voltage of 10KV.

25 FI-IR spectrum of moxifloxacin was recorded on Thermo model Nicolet-380 as KBr pellet.

The thermal analysis of moxifloxacin 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.

5 Examples:
Example-1:
**Preparation of (S,S)-2-benzyl-8-trityl-2,8-diazabicyclo (4.3.0) nonane:**

A mixture of (S,S)-2-benzyl-2,8-diazabicyclo-(4.3.0) nonane 50 grams, dichloromethane 300 ml and triethylamine 28 ml was stirred at 25-35°C. Trityl chloride 71 grams was added to the reaction mixture. The reaction mixture was stirred at 25-35°C for 5 hrs. The organic layer was washed with 5% sodium bicarbonate solution followed by water. The organic layer was distilled off completely to provide the title compound as a residue.

Yield: 96 grams

Example-2:
**Preparation of (S,S)-8-trityl-2,8-diazabicyclo (4.3.0) nonane:**

A mixture of (S,S)-2-benzyl-8-trityl-2,8-diazabicyclo (4.3.0) nonane 130 grams, 2-butanol 1600 ml and 5% Pd/C was taken in an autoclave and heated to 45-50°C at 4.0-4.5 Kg/cm² of hydrogen pressure. The reaction mixture was stirred at this condition for 45-50 hrs. The reaction mixture was cooled to 25-30°C and filtered through hyflow bed. The solvent was distilled off completely to provide the title compound as a residue.

Yield: 95 grams

Example-3:
**Preparation of condensed compound of formula-4a:**

A mixture of 20 grams of 1-cyclopropyl-N,N-diethyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide, 11.8 grams of (S,S)2,8-diazabicyclo (4.3.0) nonane, 100 ml of acetonitrile and 2 grams of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was heated to 80°C. The reaction mixture was stirred for 35 hours at 80°C. The reaction mixture was cooled to 32°C and stirred for 45 minutes at 32°C. The solvent was distilled
off under reduced pressure. Water (100 ml) was added to the obtained residue. The reaction mixture was cooled to 25-35°C. The reaction mixture was extracted with ethyl acetate. The solvent was distilled off to get the title compound as a residue.  
Yield: 12 grams.

Example-4:
Preparation of condensed compound of formula-4b:

A mixture of 5 grams of 1-cyclopropyl-N,N-diethyl-6J-difluoro-M-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide, 2.9 grams of (S,S)-8-phenyloxy carbonyl-2,8-diazabicyclo[4.3.0]nonane, 25 ml of acetonitrile and 0.5 grams of diazabicyclo[5.4.0]undec-7-ene (DBU) was heated to 80°C. The reaction mixture was stirred for 35 hours at 75-80°C. The reaction mixture was cooled to 25-35°C. The reaction mixture was stirred for 45 minutes at 25-35°C. The solvent was distilled off under reduced pressure. Water (100 ml) was added to the obtained residue. The reaction mixture was cooled to 25-35°C. The reaction mixture was extracted with ethyl acetate. The solvent was distilled off to get the title compound as a residue.  
Yield: 1 gram.

Example-5:
Preparation of condensed compound of formula-4c:

A mixture of 5 grams of 1-cyclopropyl-N,N-diethyl-βJ-difluoro-l^-dihydro-S-methoxy-4-oxoquinoline-3-carboxamide, 2.9 grams of (S,S)-8-tertiary butyloxycarbonyl-2,8-diazabicyclo[4.3.0]nonane, 25 ml of acetonitrile and 0.5 grams of diazabicyclo[5.4.0]undec-7-ene (DBU) was heated to 80°C. The reaction mixture was stirred for 35 hours at 75-80°C. The reaction mixture was cooled to 25-35°C and stirred for 45 minutes at 25-35°C. The solvent was distilled off under reduced pressure. Water (100 ml) was added to the obtained residue. The reaction mixture was cooled to 25-35°C. The reaction mixture was extracted with ethyl acetate. The solvent was distilled off to get the title compound as a residue.  
Yield: 1 gram.
Example-6:

**Preparation of condensed compound of formula-4d:**

A mixture of 20 grams of 1-cyclopropyl-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxamide, 2.9 grams of (S,S)-2,8-diazabicyclo (4.3.0) nonane, 100 ml of acetonitrile and 2 grams of diazabicyclo[5.4.0]undec-7-ene (DBU) was heated to 75-80°C. The reaction mixture was stirred for 35 hours at 75-80°C. The reaction mixture was cooled to 25-35°C. The reaction mixture was stirred for 45 minutes at 25-35°C. The solid obtained was filtered and washed with acetonitrile. The material was dried at 40-45°C to get the title compound.

Yield: 12 grams; M.R: 210-212°C.

Example-7:

**Preparation of condensed compound of formula-4e:**

A mixture of (S,S)-8-trityl-2,8-diazabicyclo (4.3.0) nonane (42 grams), 1-cyclopropyl-N,N-diethyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxamide (10 grams), potassium carbonate (7.9 grams) and dimethyl formamide (80 ml) was heated to 110-120°C and stirred for 20 hours at 110-120°C. The reaction mixture was cooled to 80°C. The solvent was distilled off under reduced pressure. Water (100 ml) was added to the obtained residue. The reaction mixture was cooled to 25-35°C. The reaction mixture was extracted with ethyl acetate. The solvent was distilled off to obtain the title compound as a residue.

Yield: 14.5 grams

Example-8:

**Preparation of moxifloxacin from 4d:**

A mixture of 165 ml of water, 35 grams of sodium hydroxide, 150 ml of ethylene glycol and 12 grams of condensed compound of formula-4d was heated to 115°C. The reaction mixture was stirred for 15 hours at 115°C. The reaction mixture was cooled to 5°C. The pH of the reaction mixture was adjusted to 5.5 using hydrochloric acid and stirred for 30 minutes at 5°C. The obtained solid was filtered and washed with water. The solid was dried at 45°C to get the title compound.

Yield: 8 grams; M.R: 203-205°C
Example-9:
Preparation of moxifloxacin from 4b:
Moxifloxacin can be prepared from 4b (3 grams), by a method which is analogous to the method illustrated in Example-8
Yield: 0.85 grams; M.R: 203-205°C

Example-10:
Preparation of moxifloxacin from 4c:
Moxifloxacin can be prepared from 4c (3 grams), by a method which is analogous to the method illustrated in Example-8
Yield: 1.0 grams; M.R: 203-205°C

Example-11:
Preparation of moxifloxacin from 4a:
Moxifloxacin can be prepared from 4a (10 grams), by a method which is analogous to the method illustrated in Example-8
Yield: 7.5 grams; M.R: 203-205°C

Example-12:
Preparation of moxifloxacin from 4e:
The condensed compound of formula-4e (14.5 grams) was dissolved in ethyl acetate 100ml. Aqueous hydrochloric acid (5 ml in 20 ml of water) was added to the above reaction mixture. The reaction mixture was stirred at 25-30°C for 30-45 min. 20ml of water was added to the reaction mixture. The two layers were separated. The aqueous layer was washed twice with ethyl acetate. The pH of the aqueous layer was adjusted to 10.8 using sodium hydroxide solution. The reaction mixture was extracted with methylene chloride. The solvent distilled off to get a residue. The residue was suspended in 165 ml of water, 35 grams of sodium hydroxide; 150 ml of ethylene glycol was heated to 115°C. The reaction mixture was stirred for 15 hours at 115°C. The reaction mixture was cooled to 5°C. The pH of the reaction mixture was adjusted to 5.5 using hydrochloric
acid and stirred for 30 minutes at 5°C. The obtained solid was filtered and washed with water and dried at 45°C to get the title compound.
Yield: 4.5 grams; M.R: 203-205°C

Example-13:

Preparation of moxifloxacin hydrochloride compound of formula-1:

A mixture of 8 grams of moxifloxacin, 16 ml of water and 64 ml of methanol was heated to reflux temperature of 70°C. The reaction mixture was filtered to remove undissolved material. Filtrate was cooled to 35°C. The pH of the filtrate was adjusted to 1.6 using hydrochloric acid. The reaction mixture was cooled to 15°C. The reaction mixture was stirred for 45 minutes at 15°C. The solid obtained was filtered and washed with methanol and dried at 40-45°C to get crystalline Form-Y of moxifloxacin hydrochloride monohydrate.
Yield: 5.5 grams

Example-14:

Preparation of moxifloxacin hydrochloride monohydrate:

A mixture of 25 grams of moxifloxacin, 16 ml of water and 64 ml of methanol was heated to reflux temperature of 70°C. The reaction mixture was filtered to remove undissolved material. Filtrate was cooled to 35°C. The pH of the filtrate was adjusted to 1.6 using hydrochloric acid. The reaction mixture was cooled to 15°C. The reaction mixture was stirred for 45 minutes at 15°C. The obtained solid was taken into a mixture of 22 ml of water and 0.5 ml of hydrochloric acid and stirred 30 min at 5°C. The compound was filtered and washed with water, dried at 40-45°C to get moxifloxacin hydrochloride monohydrate particles having oval shape.
Yield: 20 grams

Example-15:

Preparation of anhydrous crystalline Form-I of moxifloxacin hydrochloride:

Moxifloxacin hydrochloride (Form-Y, 10 grams) suspended in 50 ml of methanol and the reaction mixture was heated to 45-50°C. 18 ml of dichloromethane was added
slowly to the reaction mixture. The reaction mixture was stirred at 45-50°C for 15-20 minutes. The reaction mixture was cooled slowly to around 0-5°C and stirred for 1-1.5 hours. The precipitated solid was filtered under nitrogen atmosphere and washed with 5 ml of methanol. The solid obtained was dried at 110-120°C till the moisture content reached below 0.5%.

Yield: 8.0 grams.

Bulk density: 0.28 g/ml; Tapped density: 0.52 g/ml
Particle size distribution: \( D(v,0.1) : 1.6 \mu m \); \( D(v,0.5) : 5.5 \mu m \); \( D(v,0.9) : 25.0 \mu m \)

Example-16:

**Preparation of anhydrous crystalline Form-I of moxifloxacin hydrochloride:**

Moxifloxacin hydrochloride (Form-Y, 10 grams) suspended in 50 ml of methanol and the reaction mixture was heated to 45-50°C. 18 ml of dichloromethane was added slowly to the reaction mixture. The reaction mixture was stirred at 45-50°C for 15-20 minutes. The solvent was distilled off partially. The reaction mixture was cooled slowly to around 0-5°C and stirred for 1-1.5 hours. The precipitated solid was filtered under nitrogen atmosphere and washed with 5 ml of methanol. The solid obtained was dried at 110-120°C till the moisture content reached below 0.5%.

Yield: 7.5 grams.

Bulk density: 0.30 g/ml; Tapped density: 0.60 g/ml
Particle size distribution: \( D(v,0.1) : 1.7 \mu m \); \( D(v,0.5) : 6.0 \mu m \); \( D(v,0.9) : 20.1 \mu m \)

Example-17:

**Preparation of anhydrous crystalline Form-I of moxifloxacin hydrochloride:**

Moxifloxacin hydrochloride (Form-Y, 20 grams) suspended in 190 ml of methanol and the reaction mixture was heated to reflux. The reaction mixture was stirred for complete dissolution. The reaction mixture was allowed to cool to 25-35°C, further cooled to 15-20°C and stirred for 60 minutes. Filtered the precipitated solid under nitrogen atmosphere and washed solid with 5 ml of methanol. The solid obtained was dried at 110-120°C till the moisture content reached below 0.5%.

Yield: 16.5 grams.
Bulk density: 0.28 g/m; Tapped density: 0.49 g/ml
Particle size distribution: $D(v,0.1) = 2.2 \mu m$; $D(v,0.5) = 7.0 \mu m$; $D(v,0.9) = 24.7 \mu m$

**Example-18:**

**Preparation of Form-I of moxifloxacin**

Moxifloxacin hydrochloride (120 grams) was suspended in 600 ml of water. The pH of the reaction mixture was adjusted to 7.9 with aqueous sodium hydroxide solution. The reaction mixture was stirred for 10 minutes at 25-30°C. The reaction mixture was extracted with methylene chloride. The solvent completely was distilled off under reduced pressure at below 60°C. 100 ml of acetone was added and the reaction mixture was stirred for 30 minutes at 25-30°C. The solid obtained was filtered and washed with acetone and dried at 60°C.

Yield: 86 grams.

Water content: 2.30% w/v

Chloride content: Not Detected

**Example-19:**

**Preparation of Form-I of moxifloxacin**

Moxifloxacin hydrochloride (120 grams) was suspended in 600 ml of water. The pH of the reaction mixture was adjusted to 7.9 with aqueous sodium hydroxide solution. The reaction mixture was stirred for 10 minutes at 25-30°C. The reaction mixture was extracted with methylene chloride. The solvent completely was distilled off under reduced pressure at below 60°C. 100 ml of acetone was added and the reaction mixture was stirred for 30 minutes at 25-30°C. The solid obtained was filtered and washed with acetone. The obtained wet solid taken in 1200 ml of cyclohexane. The reaction mixture was heated to reflux and partially distilled off the solvent to remove the traces of acetone. The reaction mixture stirred at azeotropic reflux for 12-14 hours. The traces of water were removed at reflux temperature. The reaction mixture was cooled to 25-30°C under nitrogen atmosphere. The reaction mixture was stirred at 25-30°C under nitrogen atmosphere for 30 minutes. The precipitated solid was filtered, washed with isopropyl alcohol and dried at 90-100°C.
Example-20:

Preparation of Form-I of moxifloxacin

A mixture of l-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-l,4-dihydro-3-quinoline carboxylic acid (100 grams), [S,S]-2,8-diazabicyclo [4,3,0] nonane (52 grams), 1,8-Diazabicyclo(5,4,0)undec-7-ene (10 grams) and acetonitrile (300 ml) was heated to 85°C. The reaction mixture was stirred for 12 hours at 85°C. The solvent was distilled off completely under reduced pressure at below 70°C. The reaction mixture cooled to 60°C and water was added. The pH of the reaction mixture was adjusted to 5.8 with hydrochloric acid. The reaction mixture was extracted with methylene chloride. The solvent was distilled off completely under reduced pressure. Acetone (300 ml) was added to the obtained residue. The reaction mixture was stirred for 30 minutes at 25-30°C. The obtained solid was filtered, washed with acetone and dried at 60°C. The obtained solid was recrystallized by using acetone as a solvent.

Yield: 100 grams.
Water content: 2.2%
Chloride content: 130 ppm.
We Claim:

1. A novel process for the preparation of moxifloxacin hydrochloride compound of formula-1, which comprises of the following steps:
   
a) reacting the quinoline carboxamide compound of general formula-2

\[
\text{Formula-2}
\]

wherein R and R₁ are hydrogens or selected from C₁ to C₅ linear or branched chain alkyl group, with nonane compound of general formula-3,

\[
\text{Formula-3}
\]
dimethyl wherein R₂ is Hydrogen, trityl, silyl group like TMS (trimethyl silyl) / TBDMS (tertiary butyl silyl) or -COOR₃ wherein R₃ is phenyl or ethyl or butyl analogs, in presence of a suitable base like 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,4-diazabicyclo[2,2,2]octane(DABCO) in a suitable organic solvent like acetonitrile, dimethylformamide preferably acetonitrile to obtain the condensed compound of general formula-4,

\[
\text{Formula-4}
\]

wherein R and R₁ are hydrogen or selected from C₁ to C₅ linear or branched chain alkyl group, and
. $R_2$ is Hydrogen, trityl, silyl group like TMS (trimethyl silyl) / TBDMS (tertiary butyl dimethyl silyl) or -$COOR_3$ wherein $R_3$ is phenyl or ethy or butyl analogs.

b) reacting the condensed compound of general formula-4 with a suitable alkali or alkaline metal carbonates, hydrogen carbonates, hydroxides like sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide preferably sodium hydroxide in a suitable solvents like ethylene glycol and/or polar solvent like water or mixtures thereof to obtain moxifloxacin compound of formula-5,

![Formula-5](image)


c) reacting the moxifloxacin compound of formula-5 with hydrochloric acid in a suitable aqueous alcoholic solvent like methanol, ethanol and isopropanol preferably aqueous methanol to obtain moxifloxacin hydrochloride compound of formula-1.


![Formula-4](image)

Wherein $R$ and $R_1$ are hydrogen or selected from $C_1$ to $C_5$ linear or branched chain alkyl group, and $R_2$ is Hydrogen, trityl, silyl group like TMS (trimethyl silyl) / TBDMS (tertiary butyl dimethyl silyl) or -$COOR_3$ wherein $R_3$ is phenyl or ethy or butyl analogs.
3. The compound according to claim 2 is the compound of formula 4a.

[Diagram of compound 4a]

4. The compound according to claim 2 is the compound of formula 4b.

[Diagram of compound 4b]

5. The compound according to claim 2 is the compound of formula 4c.

[Diagram of compound 4c]

6. The compound according to claim 2 is the compound of formula 4d.

[Diagram of compound 4d]

7. The compound according to claim 2 is the compound of formula 4e.

\[
\text{Formula-2}
\]

Wherein \( R \) and \( R_1 \) are hydrogen or selected from \( C_1 \) to \( C_5 \) linear or branched chain alkyl group

9. The compound according to claim 8 is a compound of formula 2a.

\[
\text{Formula-2a}
\]

10. The compound according to claim 8 is a compound of formula 2b.

\[
\text{Formula-2b}
\]
11. A nonane compound of general formula-3

\[
\begin{array}{c}
\text{R}_2 \\
\text{N} \\
\text{H} \\
\text{H} \\
\text{N} \\
\text{H}
\end{array}
\]

Formula-3

wherein R₂ is Hydrogen, trityl, silyl group like TMS (trimethyl silyl) / TBDMS (tertiary butyl dimethyl silyl) or -COOR₃ wherein R₃ is phenyl or ethyl or butyl analogs.

12. A nonane compound of formula-3 according to claim 11 is a compound of formula-3d.

\[
\begin{array}{c}
\text{CPh}_3 \\
\text{N} \\
\text{H} \\
\text{H} \\
\text{N} \\
\text{H}
\end{array}
\]

Formula-3d

13. Moxifloxacin hydrochloride monohydrate with particles having oval shape and porous texture as illustrated in photographs of microscopic moxifloxacin hydrochloride monohydrate in figure-4.

14. A process for preparation of moxifloxacin hydrochloride monohydrate of claim 13 comprising of:
   a) suspending moxifloxacin hydrochloride in a solution of aqueous alcohol,
   b) heating the above reaction mixture to higher temperature,
   c) filtering the reaction mixture in hot condition and cooling the filtrate,
   d) adjusting the pH of the filtrate to make it acidic by addition of hydrochloric acid,
   e) further cooling the reaction mixture to lower temperatures.
   f) dissolving or dispersing or slurrying or washing the solid obtained with a mixture of water and water miscible solvent containing above 30% of water, or with water
alone to obtain moxifloxacin hydrochloride monohydrate having oval shaped particles.

15. The process according to claim 14 wherein the mixture of water and water miscible solvent used in step f) is aqueous methanol which has 70 % of water.

16. The process according to claim 14 wherein in step f) water alone is used to obtain moxifloxacin hydrochloride monohydrate having oval shaped particles.

17. A novel process for the preparation of anhydrous crystalline form-I of moxifloxacin hydrochloride of formula-1 which comprises of:
   a) suspending moxifloxacin hydrochloride in a suitable alcohol solvent and heating the solution to 45-50°C,
   b) optionally adding chloro solvent and stirring the reaction mixture at 50°C for 15-50 minutes for complete dissolution, optionally concentrating the solvent partially,
   c) cooling the reaction mixture,
   d) stirring the reaction mixture for 1-2 hours,
   e) separating the precipitated solid by filtration under inert atmosphere and washing with methanol,
   f) drying the solid at higher temperature till the moisture content reaches below 0.5%.

18. The process according to claim 17 wherein the alcoholic solvent used in step a) is methanol.

19. The process according to claim 17 wherein the chloro solvent used in step b) is dichloromethane.

20. The process according to claim 17 wherein, in step c) the reaction mixture is cooled to 0-20°C.

21. The process according to claim 17 wherein, in step f) the solid is dried at 110-120°C.
22. Moxifloxacin hydrochloride has a mean particle size in the range of 5-25 microns and D (v. 0.9) in the range of 10-40 microns.

23. Moxifloxacin hydrochloride having bulk density in the range of 0.2-0.4 gm/ml.

24. Moxifloxacin hydrochloride having tapped density in the range of 0.50-0.70 gm/ml.

25. A crystalline form-I of moxifloxacin compound of the following structure

![Chemical Structure]

26. The crystalline form-I of moxifloxacin according to claim 25, is characterized by X-ray powder diffraction pattern having peaks at about 9.7, 10.2, 11.7, 18.4 and 23.3 ±0.2 degrees two-theta.

27. The crystalline form-I of moxifloxacin according to claim 25, is characterized by IR spectrum having peaks at about 3329.4, 1728.4, 1621.0, 1437.1, 1341.9, 881.9 and 804.9 cm⁻¹.

28. The crystalline form-I of moxifloxacin according to claim 25, having an X-ray powder diffraction pattern substantially as shown in figure-1.

29. The crystalline form-I of moxifloxacin according to claim 25, having an Infrared absorption spectrum substantially as shown in Figure-2.

30. The crystalline form-I of moxifloxacin according to claim 25, having DSC substantially as shown in Figure-3.

31. The crystalline form-I of moxifloxacin according to claim 25, is having water content in the range of 0.05-3.0 %.
32. The process for the preparation of Crystalline Form-I of moxifloxacin, which comprises of the following:
   a) suspending the moxifloxacin hydrochloride or/and its hydrates in a suitable polar solvent,
   b) adjusting the pH of the reaction mixture to 7-8 with aqueous sodium hydroxide or aqueous ammonia solution at 10-40°C preferably at 20-30°C and most preferably at 25-30°C,
   c) extracting the reaction mixture with suitable chloro or ester solvents like methylene chloride, chloroform or ethyl acetate,
   d) distilling the solvent completely, preferably under reduced pressure at below 60°C,
   e) cooling the reaction mixture to 5-35°C, preferably at 25-35°C,
   f) treating the crude with a suitable organic solvent like keto solvent,
   g) isolating the product by filtration and optionally washing it with water,
   h) drying the material to afford crystalline form-I of moxifloxacin.

33. The process according to claim 32 wherein in step a) the polar solvent used is water.

34. The process according to claim 32 wherein in step c) the solvent used for extraction of reaction mixture is methylene chloride.

35. The process according to claim 32 wherein in step f) the keto solvent used is acetone.

36. A process for the preparation of crystalline form-I of moxifloxacin, which comprises of the following:
   a) 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydro-3-quinoline carboxylic acid on reaction with [S,S]-2,8-diazabicyclo [4,3,0] nonane in acetonitrile in presence of 1,8-Diazabicyclo(5,4,0)undec-7-ene followed by adjusting the pH of the reaction mixture to 5-6 with hydrochloric acid,
   b) extracting the reaction mixture with chloro solvents like methylene chloride, chloroform or ester solvents like ethyl acetate, preferably methylene chloride,
a) isolating the product by using keto solvents like acetone, methyl ethyl ketone, methyl isobutyl ketone, preferably acetone, filtering it and followed by optionally washing it with water to afford Form-I of moxifloxacin.

37. Crystalline form-I of moxifloxacin according to above claims 24-35 having Chloride content less than about 500 ppm.

38. A process of packaging and storage for anhydrous moxifloxacin hydrochloride form-I comprising of:
   a) placing moxifloxacin hydrochloride in a clear low-density polyethylene bag under nitrogen atmosphere and tying with a thread,
   b) placing the primary container containing moxifloxacin hydrochloride inside a second low-density black colored polyethylene bag and sealing it.
   c) placing the second polyethylene bag inside a triple laminated bag along with silica gel bag and then sealing it, or
   e) optionally vacuum sealing the second polythene bag in step b) and the triple laminated bag in step d) after flushing them with nitrogen,
   d) placing the sealed triple laminated bag inside a closed high density polyethylene (HDPE) container.
Figure 2