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(54) Title: PROCESS FOR GARENOXACIN MESYLATE

(57) Abstract: The present invention provides garenoxacin mesylate crystalline form characterized by an X-ray powder diffraction pattern with peaks at about 13.77, 20.54, 21.50, 21.77, 22.12 and 23.90 ± 0.2 °θ.

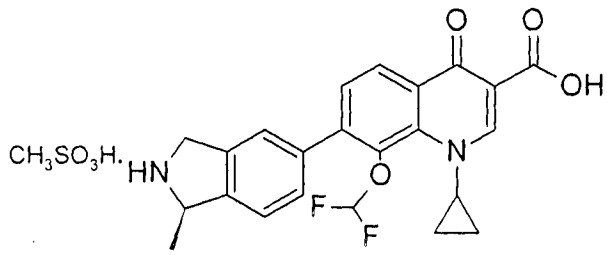
PROCESS FOR GARENOXACIN MESYLATE

FIELD OF THE INVENTION

The present invention relates to a novel crystalline form of garenoxacin mesylate and a novel process for the preparation of garenoxacin mesylate.

BACKGROUND OF THE INVENTION:

Garenoxacin is a quinolone antibiotic approved as mesylate salt. Garenoxacin mesylate, chemically known as 1 - Cyclopropyl - 8 - (difluoromethoxy) - 7 - [1(R) - methyl - 2,3 - dihydro - 1H - isoindol - 5 - yl] - 4 - oxo - 1,4 - dihydroquinoline - 3 - carboxylic acid monomethanesulfonate, represented by Formula **1**:



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United States Patent No. 6,025,370 describes a group of quinolone carboxylic acid derivatives which exhibit strong antibacterial activity, which includes garenoxacin.

United States Patent No. 6,337,399 (US'399) discloses garenoxacin mesylate and its preparation.

The present invention provides a novel crystalline form of garenoxacin mesylate.

The present invention provides a novel process for preparation of garenoxacin mesylate, which involves use of triarylphosphine with palladium catalyst. The process known in prior art requires use of substantial amount of palladium catalyst, making the process expensive. In the present invention, external addition of triarylphosphine leads to reduction in the amount of palladium catalyst required for the reaction, making the process economical. The amount of palladium catalyst in the present invention is half the amount used in the US'399 process, thus leading to cost reduction.

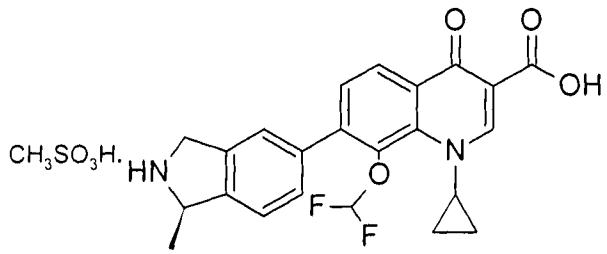
The present invention also provides a process for the preparation of the garenoxacin mesylate comprising preparation of mesylate salt in a non-hydroxylic solvent. The garenoxacin mesylate, so obtained, is substantially free of impurities like alkyl and aryl mesylates, known to be genotoxic compounds, which form if the mesylate salt is prepared in the presence of hydroxylic solvents.

The present invention also provides a process for the purification of garenoxacin mesylate compound of Formula **1.**

SUMMARY OF THE INVENTION

The present invention provides a novel garenoxacin mesylate crystalline form characterized by an X-ray powder diffraction pattern with peaks at about 13.77, 20.54, 21.50, 21.77, 22.12 and 23.90 ± 0.2 °θ.

The present invention provides a process for the preparation of garenoxacin mesylate compound of Formula **1**



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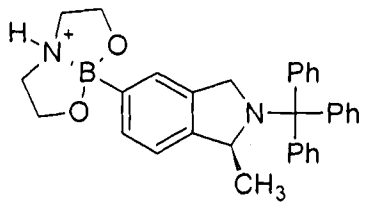
comprising:

I. reacting a compound of Formula **2,** with a compound of Formula **3** wherein R is selected from the group consisting of alkyl and -alkylaryl and X is a halogen in the presence of a catalytic amount of a palladium catalyst and triarylphosphine to obtain a compound of Formula **4;**



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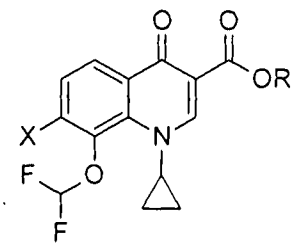

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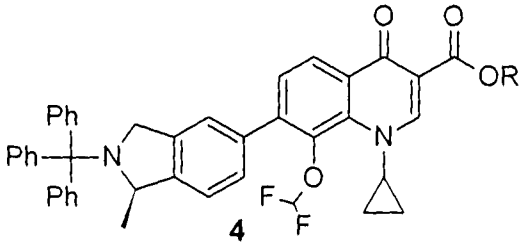

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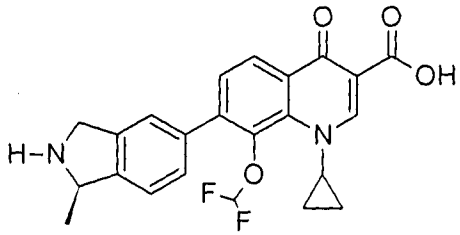
II. converting the compound of Formula **4** to garenoxacin compound of Formula **6** or its salt; and



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III. treating the compound of Formula **6** or its salt, with methanesulfonic acid in non- hydroxylic solvent to obtain a compound of Formula **1.**

The present invention provides a process for the preparation of garenoxacin mesylate compound of Formula **1** comprising reacting a garenoxacin compound of Formula **6** or its salt, with methanesulfonic acid in the presence of non-hydroxylic solvents.

The present invention provides a process for the purification of garenoxacin mesylate compound of Formula **1**, the process comprising

I. treating the compound of Formula **1** with a mixture of a halogenated hydrocarbon and an alcohol;
II. concentrating the reaction mixture; and
III. recrystallization of the product obtained in II from an ester solvent.

BRIEF DESCRIPTION OF THE ACCOMPANYING FIGURES

Fig. 1: X-ray powder diffraction pattern of novel polymorphic form of garenoxacin mesylate.

DETAILED DESCRIPTION OF THE INVENTION

As used herein "alkyl" refers to an aliphatic hydrocarbon group with C1 to C5 carbon atoms, for example methyl, ethyl, isopropyl and the like.

As used herein, "-alkylaryl" refers to groups wherein the aryl portion of the group is attached to the parent molecule via the alkyl group. – alkylaryl groups include benzyl, phenylethyl and the like.

It is well known in the art that polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. A single compound may have a variety of polymorphic forms where each form may have different and distinct physical properties, such as different solubility profiles, different melting point temperatures and/or different x-ray diffraction peaks. Owing to a possibility of variation in solubility profiles of various polymorphs of the same compound, identification of pharmaceutical polymorphs is essential for providing pharmaceuticals with predicable solubility profiles. It is desirable to investigate all solid state forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as, infrared spectrometry.

The present invention provides a novel crystalline form of garenoxacin mesylate characterized by an X-ray powder diffraction pattern with peaks at about 13.77, 20.54, 21.50, 21.77, 22.12 and 23.90 ± 0.2 °θ. The novel crystalline form is further characterized by an X-ray powder diffraction pattern with peaks at about 10.86, 14.26, 18.99, 20.91, 23.41, 25.59, and 27.42 ± 0.2 °θ.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate characterized by an X-ray powder diffraction pattern with peaks at about 8.0, 8.40, 8.90, 10.33, 10.71, 10.86, 13.02, 13.40, 13.77, 14.26, 14.85, 15.06, 16.00, 16.28, 16.87, 17.35, 17.57, 17.60, 17.89, 18.24, 18.72, 18.99, 19.78, 20.54, 20.91, 21.35, 21.50, 21.77, 22.12, 22.48, 23.41, 23.90, 24.11, 24.46, 24.92, 25.59, 26.18, 26.39, 26.87, 27.42, 27.61, 27.88, 28.83, 29.22, 29.97, 30.07, 30.42, 31.26, 32.06, 32.73, 33.82, 34.60, 35.47, 35.90, 36.54, 37.88 ± 0.2 °θ.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate, which is anhydrous.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate having a water content of not more than about 1% as measured by Karl Fischer method.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate characterized by peaks at about 10.86, 13.77, 14.26, 18.99, 20.54, 20.91, 21.50, 21.77, 22.12, 23.41, 23.90, 25.59, 27.42 ± 0.2 °θ and having a water content of not more than about 1% as measured by Karl Fischer method.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate having a water content of about 0.38 % as measured by Karl Fischer method.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate free of hydroxylic solvents.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate characterized by peaks at about 10.86, 13.77, 14.26, 18.99, 20.54, 20.91, 21.50, 21.77, 22.12, 23.41, 23.90, 25.59, 27.42 ± 0.2 °θ and free of hydroxylic solvents.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate free of methanol.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate free of ethanol.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate free of isopropyl alcohol.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate free of alkyl mesylates.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate characterized by peaks at about 10.86, 13.77, 14.26, 18.99, 20.54, 20.91, 21.50, 21.77, 22.12, 23.41, 23.90, 25.59, 27.42 ± 0.2 °θ and free of alkyl mesylates.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate, which is free of methyl mesylate.

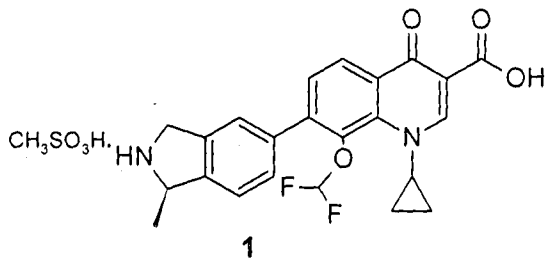
In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate, which is free of ethyl mesylate.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate, which is free of isopropyl mesylate.

In one embodiment, the present invention provides a novel crystalline form of garenoxacin mesylate characterized by peaks at about 10.86, 13.77, 14.26, 18.99, 20.54, 20.91, 21.50, 21.77, 22.12, 23.41, 23.90, 25.59, 27.42 ± 0.2 °θ, with water content of not more than about 1% as measured by Karl Fischer method and free of hydroxylic solvents and alkyl mesylates.

The novel crystalline form of garenoxacin mesylate of the present invention was characterized by X-ray powder diffraction, which was performed on a Philips X'pert PRO Diffractometer using Cu Kα radiation (Cu Kα1=1.54060Å). The X-ray source is operated at 45 kV and 40mA. Spectra are recorded at start angle from 2° to 50° 2θ, a step size 0.0170° with a time per step of 50 seconds.

In one embodiment, the present invention provides a process for the preparation of garenoxacin mesylate compound of Formula **1**,



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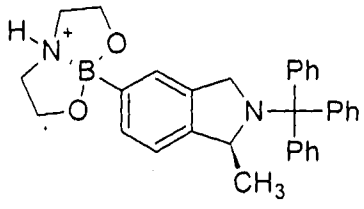
the process comprising:

I. reacting a compound of Formula **2**, with a compound of Formula **3** wherein R is selected from the group consisting of alkyl and -alkylaryl and X is a halogen in the presence of a catalytic amount of a palladium catalyst and triarylphosphine to obtain a compound of Formula **4**;



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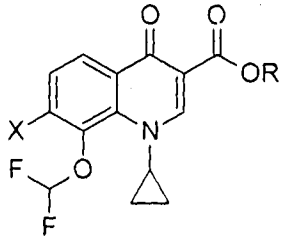

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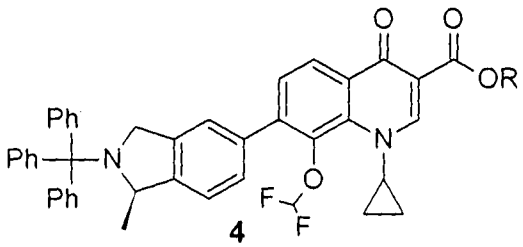

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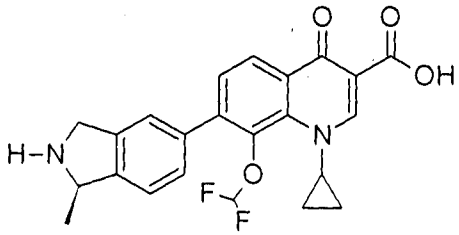
II. converting the compound of Formula **4** to garenoxacin compound of Formula **6** or its salt; and



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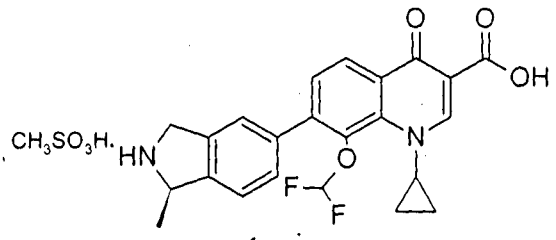
III. treating the compound of Formula **6** or its salt, with methanesulfonic acid in non-hydroxylic solvent to obtain compound of Formula **1**.

In one embodiment, the present invention provides a process for the preparation of garenoxacin mesylate compound of Formula **1**,



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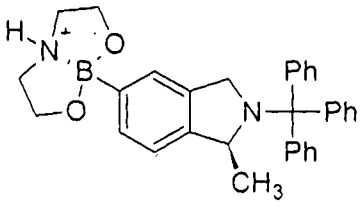
the process comprising:

I. reacting a compound of Formula **2**, with a compound of Formula **3** wherein R is selected from the group consisting of alkyl and -alkylaryl and X is a halogen, in the presence of 0.005 to about 0.020 moles of palladium catalyst per mole of compound of Formula **2** and triarylphosphine to obtain a compound of Formula **4**;



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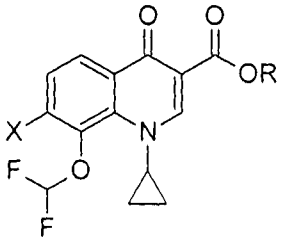

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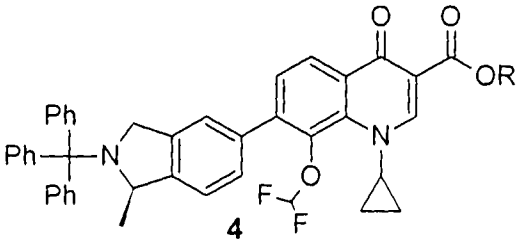

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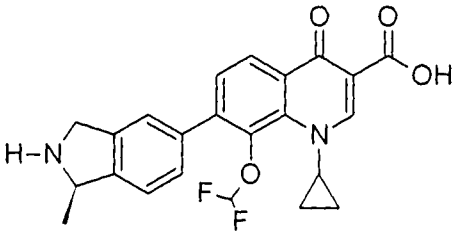
II. converting the compound of Formula **4** to garenoxacin compound of Formula **6** or its salt; and



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III. treating the compound of Formula **6** or its salt with methanesulfonic acid in non-hydroxylic solvent to obtain compound of Formula **1**.

In one embodiment, the present invention provides that in the compound of Formula **3**, R is an alkyl group and X is a halogen. Preferably R is ethyl and X is bromine.

The palladium catalyst may be selected from the group consisting of palladium-activated carbon, palladium carbon, palladium chloride, palladium acetate, tetrakis(triphenyl-phosphine)palladium(0), bis(triphenylphosphine)-palladium(II) chloride and 1,1'-bis(diphenylphosphino)-ferrocenepalladium(II) chloride. Preferably, the palladium catalyst used is bis(triphenylphosphine)-palladium(II) chloride.

Catalytic amount, in this invention, refers to the number of moles of the catalyst required per mole of the compound of Formula **2** which may range from about 0.005 moles to about 0.020, preferably from about 0.008 moles to about 0.015 moles. Preferably catalytic amount refers to less than 0.015 moles of the palladium catalyst per mole of compound of Formula **2**.

The triarylphosphine is selected from the group consisting of triphenylphosphine, trichlorotriphenylphosphine, p-trichlorophenylphosphine and p-trimethoxytriphenylphosphine. Preferably, the triarylphosphine is triphenylphosphine. The addition of the triarylphosphine leads to reduction in the amount of palladium catalyst required for the reaction, thus considerably reducing the reaction cost.

The solvent used in I of the process immediately described above, may be selected from the group consisting of hydrocarbons, ethers, halogenated hydrocarbons, nitriles, ketones, esters, amides and sulfoxides.

Hydrocarbons may be aliphatic and aromatic hydrocarbons selected from the group consisting of n-hexane, cyclohexane, toluene, xylene and the like.

Ethers may be acyclic and cyclic ethers selected from the group the group consisting of isopropyl ether, diethyl ether, tetrahydrofuran, tetrahydropyran and the like.

Halogenated hydrocarbons may be selected from the group consisting of methylene chloride, chloroform, dichloroethane and the like.

Nitriles may be selected from the group consisting of acetonitrile and the like.

Ketones may be selected from the group consisting of acetone, methylethyl ketone and the like.

Esters may be selected from the group consisting of ethyl acetate, butyl acetate and the like.

Amides may be selected from the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide and the like.

Sulfoxides may be selected from the group consisting of dimethylsulfoxide and the like.

The solvents may be used singly or as mixture of two or more solvents.

In one embodiment, in I of the present reaction immediately described above, comprises adding compound of Formula **2**, compound of Formula **3**, palladium catalyst and triphenylphosphine in ethyl acetate.

The reaction of compound of Formula **2** with compound of Formula **3** may be performed in the presence of a base, which may be organic or inorganic. Preferably, an inorganic base.

The organic bases may be selected from the group consisting of diisopropylamine, triethylamine, tributylamine, 1,8-diazabicylco[5.4.0]-undecane and the like.

The inorganic bases may be selected from the group consisting of alkali metal and alkaline metal carbonates, alkali and alkaline metal hydroxides, alkoxides and the like.

The reaction involves heating of the reaction mass to about 65–85 °C, preferably about 75-80 °C, over about 5–8 hours. Preferably about 6 hours.

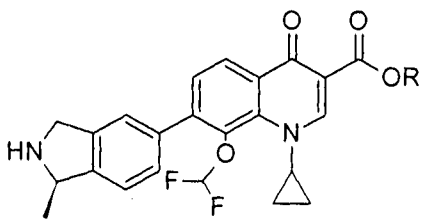
In one embodiment, the present invention provides that the compound of Formula **2** is reacted with a compound of Formula **3**, wherein R is ethyl and X is bromine, in the presence of bis(triphenylphosphine)-palladium(II) chloride, triphenylphosphine and potassium carbonate in ethyl acetate.

The amount of palladium catalyst may be about 0.010 – 0.015 moles per mole of compound of Formula **2**.

The compound of Formula **4** may be recrystallized from an alcohol, preferably absolute ethanol. Preferably, the process involves partial distillation of ethyl acetate containing the product followed by addition of absolute ethanol. The distillation is continued which leads to precipitation of the product. The product may be isolated by methods known in the art like filtration and drying.

In II, of the process immediately described above, the compound of Formula **4** is converted to the compound of Formula **6** or its salt.

In one embodiment, the reaction in II involves detritylation of a compound of Formula **4** to prepare a compound of Formula **5,** followed by deesterification of the compound of Formula **5** to prepare compound of Formula **6** or its salt.



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In one embodiment, the compound of Formula **5** may be prepared in situ.

Detritylation may be performed using an acid.

The acid may be selected from the group consisting of mineral acids, organic carboxylic acids and sulfonic acids.

The mineral acids may be selected from the group consisting of hydrochloric acid, nitric acid, sulphuric acid, hydrobromic acid and the like.

The organic carboxylic acids may be selected from the group consisting of formic acid, oxalic acid, acetic acid, tartaric acid, lactic acid, trichloroacetic acid, trifluoroacetic acid and the like.

The sulfonic acids may be selected from the group consisting of methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, mesitylenesulfonic acid, naphthalene sulfonic acid and the like.

Preferably, the acid use for detritylation is aqueous hydrochloric acid.

Deesterification of compound of Formula **5** may be performed by acidic or alkaline hydrolysis methods known in the art.

For acidic hydrolysis, the acids may include, but are not limited to, hydrochloric acid, sulphuric acid, nitric acid and the like.

For alkaline hydrolysis, the bases may include, but not limited to, sodium hydroxide, potassium hydroxides, calcium hydroxide and the like.

Preferably, the hydrolysis is done using ethanolic sodium hydroxide.

The salt of compound of Formula **6** may be an inorganic salt or organic salt.

The organic salt of compound of Formula **6** may be a salt of an organic acid such as formic acid, oxalic acid, acetic acid, tartaric acid, lactic acid, citric acid, trichloroacetic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like; or nitrogen containing salts of organic bases such as methylamine, diethylamine, trimethylamine, triethylamine, propylamine, isopropylamine, isobutylamine, tributylamine, tert-butylamine, dicyclohexylamine, dibenzylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine and the like.

The inorganic salt of compound of Formula **6** may be a salt of an inorganic acid such as hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid and the like; or

salts containing alkali and alkaline earth metals such as sodium, potassium, calcium, magnesium and the like.

Preferably, the salt of compound of Formula **6** is hydrochloric acid salt.

In one embodiment, the present invention provides the process comprising the conversion of compound of Formula **4** to compound of Formula **6** or its salt in a halogenated solvent, preferably methylene chloride.

III of the present process, immediately described above, involves treating the compound of Formula **6** or its salt with methanesulfonic acid in non-hydroxylic solvent to obtain a compound of Formula **1.**

In one embodiment, in III of the present process, immediately described above, the non-hydroxylic solvent used may be selected from the group consisting of hydrocarbons, ethers, halogenated hydrocarbons, nitriles, ketones and esters.

Hydrocarbons may be aliphatic and aromatic hydrocarbons selected from the group consisting of n-hexane, cyclohexane, toluene, xylene and the like.

Ethers may be acyclic and cyclic ethers selected from the group the group consisting of isopropyl ether, diethyl ether, tetrahydrofuran, tetrahydropyran and the like.

Halogenated hydrocarbons may be selected from the group consisting of methylene chloride, chloroform, dichloroethane and the like.

Nitriles may be selected from the group consisting of acetonitrile and the like.

Ketones may be selected from the group consisting of acetone, methylethyl ketone and the like.

Esters may be selected from the group consisting of ethyl acetate, butyl acetate and the like.

In one embodiment, the non-hydroxylic solvent may be a cyclic ether, preferably tetrahydrofuran.

In one embodiment, in III of the present process, hydrochloric acid salt of compound of Formula **6** may be treated with methanesulfonic acid in tetrahydrofuran.

In one embodiment, a base may be required during conversion of salt of compound of Formula **6** to garenoxacin mesylate compound of Formula **1.** The base may be an organic or inorganic base.

The organic base may be selected from the group consisting of methylamine, diethylamine, trimethylamine, triethylamine, propylmaine, isopropylamine, isobutylmaine, tributylamine, tert-utylamine, dicyclohexylamine, dibenzylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine and the like.

The inorganic base may be selected from the group consisting of alkali and alkaline metal hydroxides and carbonates such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate and the like; alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like.

If required, the garenoxacin mesylate compound of Formula **1** may be recrystallized from ethyl acetate. Preferably, the process involves dissolution of the product in ethyl acetate at reflux temperature, preferably at about 70-80 °C, followed by cooling preferably to about 50-60°C followed by filtration. The process may be repeated, if required. The compound of Formula **1** may be isolated by techniques known in the art, like filtration and drying.

Optionally, if required, the recrystallization step may be repeated.

In one embodiment, the present invention provides a process for the preparation of garenoxacin mesylate compound of Formula **1**, the process comprising reacting a garenoxacin compound of Formula **6** or its salt, with methanesulfonic acid in the presence of a non-hydroxylic solvent.

The non-hydroxylic solvents may be those described earlier.

The salts of compound of Formula **6** may be those described earlier.

In one embodiment, the non-hydroxylic solvent may be acyclic ether, preferably tetrahydrofuran.

In one embodiment, in the present process, immediately described above, for the preparation of garenoxacin mesylate compound of Formula **1,** hydrochloric acid salt of compound of Formula **6** may be treated with methanesulfonic acid in tetrahydrofuran.

In one embodiment, a base may be required during conversion of salt of compound of Formula **6** to garenoxacin mesylate compound of Formula **1.** The base may be an organic or inorganic base such as those discussed earlier.

In one embodiment, the present invention provides a process for the purification of garenoxacin mesylate compound of Formula **1**, the process comprising

I. treating the compound of Formula **1** with a mixture of halogenated hydrocarbon and an alcohol;
II. concentrating the reaction mixture; and
III. recrystallization of the product obtained in II from an ester solvent.

In one embodiment, in I of the present process, immediately described above, the halogenated hydrocarbon may be methylene chloride and the alcohol may be selected from C1-C5 alcohols, preferably methanol.

In one embodiment, in I of the present process, immediately described above, the ratio of the halogenated hydrocarbon to alcohol may be from 10:2 to 8:2, preferably 8:2.

In one embodiment, in I of the present process, immediately described above, the ratio of methylene chloride to methanol may be from 10:2 to 8:2, preferably 8:2.

In one embodiment, in III of the present process, immediately described above, the ester solvent may be ethyl acetate.

In one embodiment, in I of the present process, immediately described above, the process comprises adding garenoxacin mesylate to methylene chloride followed by adding of methanol to the mixture, heating the mixture and cooling it. The mixture may be heated to a temperature of about 35-45 °C, preferably about 35-40°C. The mixture may be heated from about 30 min to 90 min, preferably about 60 min. The reaction mass may be cooled to about 30-40°C, preferably about 30-35°C. The mixture may be cooled from about 10 min to 60 min, preferably about 30 min.

In one embodiment, in II of the present process, immediately described above, the process comprises removal of the solvent by distillation, adding methanol, and distillation of solvent from the mass. Removal of the solvent from the mass obtained in I may be performed by distillation at about 45-55°C, preferably about 50-55°C. The time required may be about 1.5 to 2.5 h, preferably about 2 h. After adding methanol, the mixture may be heated to a temperature of about 55-70°C, preferably about 60-65°C. Thereafter after adding methanol, distillation may be performed at about 50-60°C, preferably at about 50-55°C. The distillation may not involve complete removal of solvent. Distillation may be done for about 1.5 to 2.5 h, preferably for about 2 h.

In a specific embodiment, in III of the present process of purification, immediately described above, the process comprises adding ethyl acetate to the mass obtained in II, distilling the solvent and cooling the mass obtained. The ethyl acetate may be added at about 50-60°C, preferably at about 50-55°C, and the temperature of the mixture may be raised to about 60-80°C, preferably to about 65-75°C. Distillation of the solvent may be performed at about 60-80°C, preferably at about 65-75°C, over a period of about 30- 90 min, preferably about 60 min. Product may be filtered at about 50-60 °C, preferably at about 55-60°C.

The wet cake obtained may further undergo addition of ethyl acetate, followed by distillation of ethyl acetate and cooling. Wet cake as obtained above may be added to ethyl acetate and the mixture refluxed at about 70-80°C for about 1-2 h preferably about 1 h. Ethyl acetate may be distilled out at about 70-80°C for about 1.5-3 h ,.preferably about 2.5 h. The reaction mass may be cooled to about 50-60°C. The product may be recovered by any method

known in the art, such as filtration, drying and the like. Herein, the product may be filtered at about 50-60°C and dried. If required, the process of recrystallization from ethyl acetate may be repeated to obtain the required moisture content.

Optionally, if required, the purification step may be repeated as previously described above.

In one embodiment, the present invention provides garenoxacin mesylate compound of Formula **1** having a purity of more than about 99.5% as measured by high performance liquid chromatography (HPLC).

In one embodiment, the present invention provides the purification of garenoxacin mesylate compound of Formula **1**, comprising the process described above.

Garenoxacin mesylate of a defined particle size may be produced by recrystallization from various solvents. It is well accepted that particle size plays an important role in the solubility properties of an active pharmaceutical ingredient (API). Particle size reduction leads to increase in surface area of the solid phase that is in contact with the liquid phase, thus leading to increased solubility. Rate of dissolution of a poorly soluble drug may limit its rate of absorption, thus affecting its bioavailability. In such cases, particle size reduction may enhance the absorption thus improving the bioavailability. Further, particle size can also affect how freely crystals or a powdered form of a drug will flow past each other, which in turn, has consequences in the production process of pharmaceutical products containing the drug. In view of all these it is desirable to have a defined particle size for an API.

The various techniques employed to attain a defined particle size are well known in the art. These methods include pH adjustment, cooling, evaporation of solvent, addition of antisolvent to a solution or by co-precipitation to obtain a precipitate with a defined particle size. Particle size of garenoxacin mesylate may be further adjusted by employing known methods of particle size reduction like milling or micronizing and sorting the milled product according to particle size.

In one embodiment, the present invention provides garenoxacin mesylate having d_{90} less than about 30 μ.

In one embodiment, the present invention provides garenoxacin mesylate having d_{90} of about 24 μ.

In one embodiment, the present invention provides garenoxacin mesylate having d_{50} less than about 20 μ.

In one embodiment, the present invention provides garenoxacin mesylate having d_{50} of about 11 μ.

In one embodiment, the present invention provides garenoxacin mesylate having d_{10} less than about 10 μ.

In one embodiment, the present invention provides garenoxacin mesylate having d_{10} of about 5 μ.

In one embodiment, the present invention provides garenoxacin mesylate having d_{90} less than about 30 μ, d_{50} less than about 20 μ and d_{10} less than about 10 μ.

In one embodiment, the present invention provides a process of particle size reduction of garenoxacin mesylate, the process comprising micronizing the garenoxacin mesylate API under inert gas, preferably nitrogen atmosphere.

It is well accepted that the use of hydroxylic solvents for the preparation of mesylate salt leads to the likelihood of forming undesirable genotoxic by-products, such as alkyl or aryl mesylates . In one embodiment, the present invention provides garenoxacin mesylate compound of Formula **1**, which is free of any alkyl or aryl mesylate.

In one embodiment, the present invention provides a garenoxacin mesylate compound of Formula **1**, free of alkyl mesylate.

In one embodiment, the present invention provides a garenoxacin mesylate compound of Formula **1**, free of methyl mesylate.

In one embodiment, the present invention provides a garenoxacin mesylate compound of Formula **1**, wherein methyl mesylate is present to an extent of less than 0.1ppm.

In one embodiment, the present invention provides a garenoxacin mesylate compound of Formula **1**, free of ethyl mesylate.

In one embodiment, the present invention provides a garenoxacin mesylate compound of Formula **1**, wherein ethyl mesylate is present to an extent of less than 0.1ppm.

In one embodiment, the present invention provides a garenoxacin mesylate compound of Formula **1**, free of isopropyl mesylate.

In one embodiment, the present invention provides garenoxacin mesylate compound of Formula **1**, free of hydroxylic solvents.

In one embodiment, the present invention provides garenoxacin mesylate compound of Formula **1**, free of methanol.

In one embodiment, the present invention provides garenoxacin mesylate compound of Formula **1**, free of ethanol.

In one embodiment, the present invention provides garenoxacin mesylate compound of Formula **1**, free of isopropyl alcohol.

In one embodiment, the present invention provides a garenoxacin mesylate compound of Formula **1** with water content of not more than about 1% as measured by Karl Fischer method.

In one embodiment, the present invention provides a garenoxacin mesylate compound of Formula **1** with water content of about 0.38 % as measured by Karl Fischer method.

In one embodiment, the present invention provides garenoxacin mesylate compound of Formula **1**, having water content of not more than about 1% as measured by Karl Fischer method, and free of hydroxylic solvents and alkyl mesylates.

In one embodiment, the present invention provides a purification process for methyl 2,4-dibromo-3-hydroxybenzoate, the process comprising the procedure as in Example 1, the process leading to reduction in levels of monobromo and tribromo derivatives, that subsequently means better purity levels of the target product.

In one embodiment, the present invention provides a purification process for ethyl 7-bromo-1-cyclopropyl-8-(difluoromethoxy)-4-oxo-1,4- dihydroquinoline-3-carboxylate, the process comprising the procedure as in Example 4, the process leading to improved purity levels of about 99.4 %, as measured by high performance liquid chromatography (HPLC).

In one embodiment, the present invention provides a composition comprising the novel crystalline form of garenoxacin mesylate and a pharmaceutically acceptable carrier.

The composition of the present invention may be used to prepare formulations like tablets or capsules, preferably tablets.

The formulation may be prepared by a method known to a formulator skilled in the art, preferably by dry granulation.

HPLC analysis in the present invention was done by using the following conditions:

Column: C_8 Hypersil BDS, 250 X 4.6mm, 5µ

Column temperature: 25°C

Mobile Phase A: Buffer

Buffer : 0.01M Potassium dihydrogen phosphate in water. Add 0.1% Triethylamine in it and adjust pH to 4.5 with diluted o-phosphoric acid (10% in water).

Mobile Phase B: Acetonitrile.

Time(min.)	% Mobile phase A	% Mobile phase B
0.0	80	20
40	55	45
50	20	80
55	20	80
60	80	20
70	80	20

Diluent : Buffer: Acetonitrile (80 : 20, v/v)

Flow Rate: 1.0mL/minute

Detection: UV 279nm and 260nm

Injection Volume: 20µL

Water determination, in the present invention, was done by Karl Fischer method using Karl Fischer titrator employing the following process:

The titration vessel was filled with the 15-20 ml of methanol. Parameters were changed to 'KFT' mode. About 30.0 mg of water was added and the weight was entered and the start button was pressed. Burette reading was noted from the display after completion of the titration. K.F. Factor was calculated using the formula:

K.F. Factor = (weight of water in mg / Burette reading)

The instrument was then changed to 'KF mode'. About 500mg of the test sample was transferred into the titration vessel and the sample weight was entered. After completion of titration burette reading was noted from the display

Water content of the test sample was calculated using the following equation:

$$\text{Water Content (\%)} = \frac{\text{Burette reading} \times \text{K.F. Factor}}{\text{Weight of sample in mg}} \times 100$$

Analysis for genotoxic impurities

Chromatographic Parameters:

Instrument : Gas chromatography- Mass spectrometry (GC-MS)

Column : Rtx-1701, 30m x 0.53mmID, 1.0µm

Column Temp. : 40°C (hold for 5 minutes) to 240°C @ 20°C/minute (hold at 240°C for 15 minutes)

Injector : 220°C

Carrier gas : Helium

Linear velocity : 30 cm/sec

Split Ratio : (2:1)

Injection Volume : 1 µl

Diluent : Methylene chloride (MDC)

SIM Mode : Mesityl oxide

Mass Dwell

55 50

83 100

98 50

Methyl mesylate

Mass Dwell

65 50

79 50

80 100

Ethyl mesylate

Mass Dwell

79 100

97 50

109 50

Preparation of Standard Stock Solution:

Take 76µl of Mesityl oxide, 46µl of methyl mesylate and 50µl of ethyl mesylate into a 100ml of volumetric flask, containing 50-60 ml of methylene chloride and mix. Dilute up to the mark with methylene chloride and mix.

Preparation of Standard solution:

Take 2.0ml of Standard stock solution in a 50ml volumetric flask and dilute up to the mark with methylene chloride. Further dilute 2.0mL of this solution to 50mL with methylene chloride and mix.

Preparation of Sample Solution:

Weigh 500mg of sample; add 2ml of methylene chloride into it and mix. Filter this solution through 0.45µ PTFE filter and Fill this solution into a liquid injection vial.

Procedure:

Separately inject the equal volumes (1µl) of the blank (Methylene chloride), standard solution(six injections), blank and the sample solution (duplicate) into the system, record the

chromatogram of SIM mode, measure the peak responses and calculate the amount of residualsolvent present in sample.

System suitability:

The relative standard deviation (RSD) for each solvent peak response (area) must be less than15% from replicate injections of standard solution.

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the features and advantages.

EXAMPLES

Example 1: Preparation of methyl- 2,4-dibromo-3-hydroxybenzoate:

Tert-butylamine was added in methylene chloride and stirred. The resultant solution was cooled. Bromine was added to the reaction mass. The reaction mass was stirred for about 1h. A solution of 3-hydroxybenzoic acid methyl ester in methylene chloride was added to the reaction mass. Water was added and pH of reaction mass was adjusted to <2 using aqueous hydrochloric acid. Layers were separated. The aqueous layer was extracted with methylene chloride and the organic layer was separated. The combined organic layers were concentrated and the product was recrystallized by treatment with cyclohexane and isopropyl ether.

Example 2: Preparation of 2,4-dibromo-3-(difluoromethoxy)benzoic acid

The compound obtained in example 1 was added to N,N-dimethylformamide. Potassium carbonate was added to the solution and the mass was stirred. The reaction mass was heated to about 80-85°C. Chlorodifluoromethane gas was purged into the reaction mass. After the completion of the reaction, the reaction mass was cooled and water was added to it at about 15-25°C in about 40±5 min. The slurry mass obtained was filtered and washed with water. The wet cake obtained was suspended in a mixture of about 10% w/v aqueous sodium hydroxide solution and ethanol and stirred. Water and toluene were added and the reaction mass was stirred. The layers were separated. The aqueous layer was washed with toluene. The pH of aqueous layer was adjusted to less than 2 with aqueous hydrochloric acid. The slurry mass was cooled to about 10-15°C and stirred for about 1 h. The product was filtered, washed with water and dried.

Example 3: Preparation of ethyl 3-(cyclopropylamino)-2-[2,4-dibromo-3-(difluoromethoxy)-benzoyl]acrylate

20 gm of the compound prepared in Example 2 was suspended in methylene chloride (100 ml). This was followed by the addition of imidazole (4.3 gm) and triethylamine (20 gm) under stirring. The reaction mass was cooled to about 15-20°C. Thionyl chloride (8.9 gm) was added to the reaction mass and the reaction mass was stirred. Anhydrous magnesium chloride (6.2 gm) was added to the reaction mass. Triethylamine, monoethyl malonate potassium salt and dimethylformamide were added and the reaction mixture was heated to about 40-45°C and stirred. The reaction mass was cooled and water was added. The pH of the reaction mass was adjusted to about < 2 using aqueous hydrochloric acid. The layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with aqueous sodium bicarbonate solution. The organic layer was concentrated. Acetic anhydride and

N,N-Dimethylformamide dimethyl acetal (13.5 gm) were added to the reaction mass under stirring. Water was added and the ensuing layers were yet again separated. The organic layer was concentrated and residue obtained was recrystallized from isopropyl alcohol. To an isopropyl alcohol solution cyclopropylamine was added and the reaction mass was stirred. The slurry obtained was cooled to about 15-20°C and stirred for about 1h. The product was filtered and dried.

Example 4: Preparation of ethyl 7-bromo-1-cyclopropyl-8-(difluoromethoxy)-4-oxo-1,4-dihydroquinoline-3-carboxylate (compound of Formula 3)

14 gm of the compound prepared in Example 3 was added in 70 ml N,N dimethylformamide and stirred. 5 gm potassium carbonate was added and the reaction mass was heated to about 90-95°C and stirred for about 7 h. Reaction mass was cooled to about 25-30°C and water was added. The product obtained was filtered, washed with water and dried. The product obtained was recrystallized from acetone.

Example 5: Preparation of (1R)-1-phenylethyl-2,2-dimethylpropanamide

To (1R)-1-phenylethylamine was added to aqueous sodium hydroxide solution. Pivaloyl chloride (3.02 kg) was added and the reaction mass was stirred. The product was filtered and the wet cake obtained was washed with water and purified by stirring with water to obtain the title compound.

Example 6: Preparation of 2-[(1R)-1-[(2,2-dimethyl-1-oxopropyl)amino]ethyl] benzoic acid methyl ester

The compound prepared in Example 5 was added to tetrahydrofuran (THF) under nitrogen atmosphere and the mixture was stirred. The reaction mass cooled to about -40 to -35 °C. n-butyl lithium was added to the reaction mass. Carbon dioxide gas was purged. Water was added to the reaction mass. Ethyl acetate was added at about 20-25°C under stirring. The layers were separated. Ethyl acetate was added to the aqueous layer. The layers were separated. Ethyl acetate was added to the aqueous layer at about 20-25°C and pH was adjusted to about 2-3 by adding hydrochloric acid solution. Layers were separated. The combined organic layers were concentrated under reduced pressure. Methanol was added to the residue at about 40-45°C and the contents were stirred. Methanolic solution was cooled to about 10-15°C. Thionyl chloride was added to the reaction mass. The temperature of the reaction mass was raised to about 60-65°C. The reaction mass was cooled and concentrated under reduced pressure. The reaction mass was cooled and water was added to the reaction mass to obtain the product.

Example 7: Preparation of 5-bromo-2-[(1R)-1-[(2,2-dimethyl-1-oxopropyl)amino]ethyl]benzoic acid methyl ester

A solution of the compound prepared in Example 6 in methylene chloride was added to sulphuric acid at about -10 to -5°C under stirring. Sodium *N*-bromoisocyanurate was added and the reaction mass was slowly added in a mixture of ice flakes and methylene chloride. The layers were separated. The aqueous layer was extracted with methylene chloride. 10% w/w aqueous sodium metabisulphite solution was added to the combined organic layers at about 20-25°C and the contents were stirred. The layers were separated. The organic layer was washed with aq. sodium bicarbonate. The layers were separated. The organic layer was concentrated and cyclohexane was added to the residue mass. The temperature of contents was raised to reflux at about 80-85°C. The solution was cooled and stirred to obtain the product.

Example 8: Preparation of (1R)-5-bromo-2-(2,2-dimethyl-1-oxopropyl)-2,3-dihydro-1-methyl-1*H*isoindole.

To the compound prepared in Example 7 was added to ethanol under stirring. The temperature was raised to about 35-40°C. Calcium chloride anhydrous was added followed by sodium borohydride. Water was added and contents were stirred at about 25-30°C. The pH was adjusted to about 2-4 by adding aqueous hydrochloric acid. Toluene was added. The layers were separated. Aqueous layer was extracted with toluene. The combined organic layers were concentrated. The contents were cooled to about 25-30°C and thionyl chloride was added. Then water was added. The layers were separated. Aqueous sodium bicarbonate solution was added to the organic layer. The layers were separated. The organic layer was concentrated at about 60-65 °C under reduced pressure. The contents were cooled to about 25-30°C and toluene was added. Sodium tert. butoxide was added to the mass under nitrogen atmosphere and the reaction mass was stirred for about 2 h. Water was added to the reaction mass. The pH of the mass was adjusted to about 5-6. The layers were separated. The organic layer was concentrated at about 50-55°C. The residue was cooled and hexane was added and stirring was continued for about 1 h. The product obtained was filtered and washed with hexane. The material was dried under vacuum.

Example 9: Preparation of (1R)-5-bromo-2, 3-dihydro-1-methyl-2-triphenylmethyl -1*H*-isoindole.

230 gm of the compound prepared in Example 8 was added to a mixture of aqueous hydrochloric acid (1150 ml) and ethanol (1150 ml). The temperature was raised to reflux at about 85-90°C and

stirring was continued at about the reflux temperature for about 12 h. The reaction mass was concentrated at about 60-65°C and cooled to about 25-30°C. To the residue mass water was added followed by toluene. The layers were separated. Methylene chloride was added to the aqueous layer. The pH was adjusted to about 8-10 by adding aqueous sodium hydroxide solution. The aqueous layer was extracted with methylene chloride. The combined organic layers were concentrated at about 40-45°C. The contents were cooled to about 0-10°C. Triethyl amine was added to the reaction mass at about 0-10°C followed by trityl chloride followed by addition of water. The product was isolated by extraction with methylene chloride followed by treatment with isopropyl alcohol.

Example 10: Preparation of 2-[(1R)]-2,3-dihydro-1-methyl-2-(triphenylmethyl)-1*H*isoindol-5-yl]-1,3,6,2-dioxazaborocane (compound of Formula 2)

50 gm of the compound prepared in example 9 was added to tetrahydrofuran (500 ml) under nitrogen under stirring. The solution was cooled to about -70 to -65°C. 9.1 gm of n-butyl lithium (1.6 M solution in n- hexane) was added to the reaction mass followed by addition of triisopropyl borate (25.85 gm) and stirred. The temperature of the reaction mass was raised to about 10-15°C. Water and ethyl acetate were added to the reaction mass at about 10-15°C. The temperature of reaction mass was raised to about 25-30°C. The layers were separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined and the solvent was distilled out. To the residue tetrahydrofuran and n-hexane were added followed by addition of diethanolamine(12.87 gm) and stirring was continued for about 2 h. The product obtained was filtered and washed with n-hexane. The wet cake obtained was recrystallized from ethyl acetate. The product was dried at about 50-55°C.

Example 11: Preparation of 1-cyclopropyl-8-(difluoromethoxy)-7-(1R)-2,3-dihydro-1-methyl-2-(triphenylmethyl)-1*H*-isoindol-5-yl]-1,4-dihydro-4-oxo-3-quinoline carboxylic acid ethyl ester (compound of Formula 4)

20 g of the compound prepared in example 10, 18.16 g of the compound prepared in example 4, 0.34g of bis(triphenylphosphine) palladium (II) dichloride and 0.54 g of triphenylphosphine were added in 300 ml of ethyl acetate at about 25-30°C. The reaction mass was heated to about 50°C. Aqueous potassium carbonate solution was added in reaction mass at about 50°C and the contents were stirred. The temperature of the reaction mass was raised to about 75-80°C and stirring was continued for about 12 h. The reaction mass was cooled to about 20-25°C and the contents were stirred for 3 h. The solid obtained was filtered through hyflo bed and washed with ethyl acetate.

The organic layer was washed with water. Activated carbon was added to the organic layer at about 20-25°C. The contents were filtered at about 20-25°C through hyflo bed and washed with ethyl acetate. The organic layer was concentrated at about 50-55°C. Absolute ethanol was added to the residue at about 50-55°C and distillation of the solvent was continued at about 50-55°C. The residue was cooled to about 25-30°C and the contents were stirred for about 2h. The product was filtered, washed with absolute ethanol at about 25-30°C and dried.

Example 12: Preparation of 1-cyclopropyl-8-(difluoromethoxy)-7-(1R)-2,3-dihydro-1-methyl-2-1*H*isoindol-5-yl]-1,4-dihydro-4-oxo-3-quinoline carboxylic acid hydrochloride (hydrochloric acid salt of compound of Formula 6)

910 g of the compound prepared in Example 11 was added in methylene chloride (about 3.7 lit) at about 25-30°C and the contents were stirred. Aqueous hydrochloric acid was added to the reaction mass. The layers were separated. The methylene chloride layer was extracted with aqueous hydrochloric acid. The aqueous layers were combined and activated charcoal was added at about 25-30°C. The contents were filtered and the residue was washed with aqueous hydrochloric acid. The reaction mass was cooled to about 15°C and the pH of the mass was adjusted to more than 12 with aqueous sodium hydroxide solution. Temperature of the reaction mass was raised to about 25-30°C and ethanol (about 2.5 lit) was added and stirring of the reaction mass was continued for about 5 h. Water was added to the reaction mass at about 25-30°C and stirring was continued for about 30 min. The pH of the reaction mass was adjusted to about 3 using aqueous hydrochloric acid. The product was filtered, washed with water and stirred in water. The product obtained was filtered and dried at about 55-60°C until the moisture content of the material is NMT about 6% w/w.

Example 13: Preparation of 1-cyclopropyl-8-(difluoromethoxy)-7-[(1R)-2,3-dihydro-1-methyl-1*H*isoindol-5-yl]-1,4-dihydro-4-oxo-3-quinolinecarboxylicacid methanesulfonate (compound of Formula 1)

15 g of the compound prepared in example 12 was added to tetrahydrofuran (15 ml) under nitrogen atmosphere at about 20-25°C and the contents were stirred for about 10 min. A solution of methanesulphonic acid (about 8.8 g) in tetrahydrofuran (about 15 ml) at about 25-30°C was added to the reaction mass at about 20-25°C and stirring was continued for 30 min. Tetrahydrofuran (108 ml) was added to the reaction mass at about 20-25°C and stirring was continued for about 3h. The product was filtered at about 20-25°C. The wet cake was washed with tetrahydrofuran. The wet cake was added in ethyl acetate at about 25-30°C under nitrogen

atmosphere and the contents were stirred for about 10 min. The temperature of the slurry mass was raised to reflux temperature at about 75-80°C and stirring was continued at about the reflux temperature for about 1 h. The slurry mass was cooled to about 50-60°C. The product was filtered, washed with ethyl acetate and dried under vacuum. **Moisture content of the material is NMT 1.5% w/w.**

Example 14: Purification of 1-cyclopropyl-8-(difluoromethoxy)-7-[(1R)-2,3-dihydro-1-methyl-1*H*isoindol-5-yl]-1, 4-dihydro-4-oxo-3-quionolinecarboxylic acid methanesulfonate. (compound of Formula 1)

16 g of the compound prepared in example 13 was added to methylene chloride (128 ml). Methanol (32 ml) was added and the contents were stirred at about 25-30°C. The temperature of reaction mass was raised to about 35-40°C followed by addition of activated charcoal and stirring was continued for about 60 min. The reaction mass was cooled to about 30-35°C, filtered and the residue was washed with a mixture of methylene chloride and methanol (8:2 mixture) at about 25-30°C. The solvent was distilled out, methanol was added and the reaction mass was heated to about 60-65°C and stirring was continued for about 10 min. Solvent was distilled under reduced pressure at about 50-55°C. Ethyl acetate was added to reaction mass and temperature was raised to about 65-75°C. The solvent was distilled under atmospheric pressure at about 65-75°C. The reaction mass was cooled to about 55-60°C. The product was filtered at about 55-60°C and the wet cake was washed with ethyl acetate. The product was further recrystallized from ethyl acetate. The wet material was dried under vacuum.

Moisture content NMT: 1.0% w/w. The genotoxic impurities methyl mesylate, ethyl mesylate and mesityl oxide were not detected. (detection limit of 0.04ppm)

Example 15: Preparation of potassium salt of monoethylmalonate.

Diethyl malonate was added in abs. ethanol. Ethanolic potassium hydroxide was added to the solution. The reaction mass was heated to reflux and stirring was continued for about 30 min. The solution obtained was cooled. Product was filtered washed with isopropyl ether. The product was dried under vacuum.

Example 16: Preparation of sodium N-bromoisocyanurate

Sodium hydroxide was dissolved in water and the solution was cooled to about 5-10°C. Cyanuric acid was added to the aqueous sodium hydroxide solution stirred. The contents were cooled to about 0-10°C. Bromine was added to the reaction mass and the stirring of the reaction mass was

continued for about 20 min. The temperature of the reaction mass was raised to about 25-30°C and stirring was continued at the same temperature for about 4h. The solid was filtered, the wet cake was washed with water and stirred with water. The product was filtered and dried.

Example 17:

Garenoxacin mesylate tablets have the following composition:

Ingredients	**mg/Tab**
Blending/Compaction	
Garenoxacin Mesylate Anhydrous eq. to Garenoxacin 200 mg	245.08
Lactose anhydrous (DCL 21)	50 - 100
Microcrystalline cellulose (Avicel pH 112)	20 - 60
Cros carmelose sodium (Ac-di-sol)	20 - 60
Talc	4- 12
Magnesium stearate	4- 12
Colloidal silicon dioxide (Aerosil 200)	4- 12
Lubrication	
Talc	4- 12
Magnesium stearate	4- 12
Colloidal silicon dioxide (Aerosil 200)	4- 12
Total weight	**400**
Opadry	Upto 3%
Isopropyl Alcohol	q.s.
Methylene Chloride	q.s.

The above tablet may be prepared by carrying out the following process:

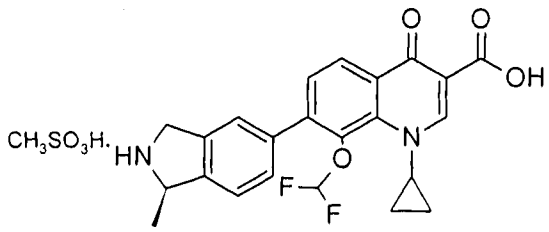
Garenoxacin mesylate, lactose anhydrous (DCL 21), Cros carmelose sodium (Ac-di-sol) and colloidal silicon dioxide (aerosol 200) were mixed in a blender. Talc and magnesium stearate were added. The blend was roll compacted and sized and lubricated with talc, magnesium stearate and aerosolized. This final mixture was then compressed into tablets. The tablets were coated with opadry coating solution.

Claims:

1. Garenoxacin mesylate crystalline form characterized by an X-ray powder diffraction pattern with peaks at about 13.77, 20.54, 21.50, 21.77, 22.12 and 23.90 ± 0.2 °θ.

2. Garenoxacin mesylate as claimed in claim1, further characterized by an X-ray powder diffraction pattern with peaks at about 10.86, 14.26, 18.99, 20.91, 23.41, 25.59, and 27.42 ± 0.2 °θ.

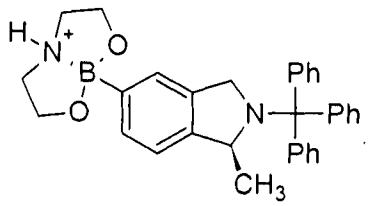
3. A process for the preparation of garenoxacin mesylate compound of Formula **1**



1

comprising:

I. reacting a compound of Formula **2**, with a compound of Formula **3** wherein R is selected from the group consisting of alkyl and -alkylaryl and X is a halogen in the presence of a catalytic amount of a palladium catalyst and triarylphosphine to obtain a compound of Formula **4**;



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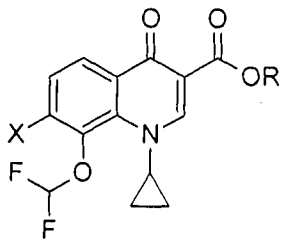

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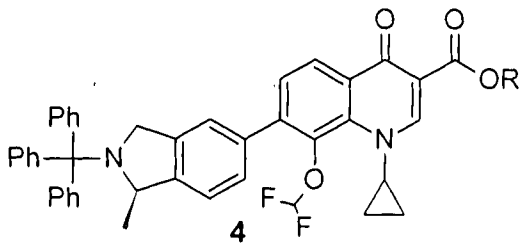

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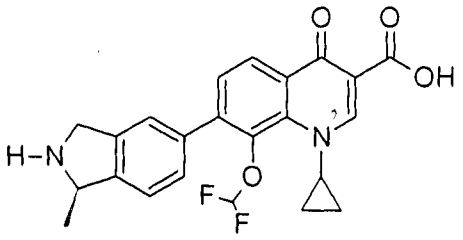
II. converting the compound of Formula **4** to garenoxacin compound of Formula **6** or its salt; and



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III. treating the compound of Formula **6** or its salt, with methanesulfonic acid in non-hydroxylic solvent to obtain compound of Formula **1.**

4. The process as claimed in claim 1 wherein in I, R is an alkyl group and X is Br in the compound of Formula **3**.

5. The process as claimed in claim 1, wherein the palladium catalyst is selected from the group consisting of palladium-activated carbon, palladium carbon, palladium chloride, palladium acetate, tetrakis(triphenyl-phosphine)palladium(0), bis(triphenylphosphine)-palladium(II) chloride, and 1,1'-bis(diphenylphosphino)-ferrocenepalladium(II) chloride.

6. The process as claimed in claim 1wherein in I, the molar ratio of compound of Formula **2** to palladium catalyst is about 1:0.008 to 1: 0.015.

7. The process as claimed in claim 1wherein the non-hydroxylic solvent in III is selected from the group consisting of hydrocarbons, ethers, halogenated hydrocarbons, nitriles, ketones and esters.

8. A process for the preparation of garenoxacin mesylate compound of Formula **1**, the process comprising reacting a garenoxacin compound of Formula **6** or its salt, with methanesulfonic acid in the presence of non-hydroxylic solvents.

9. The process as claimed in claim 8 wherein non-hydroxylic solvent is selected from the group consisting of hydrocarbons, ethers, halogenated hydrocarbons, nitriles, ketones and esters.

10. The process as claimed in claim 8 wherein non-hydroxylic solvent is a cyclic ether.

11. A process for the purification of garenoxacin mesylate compound of Formula **1** comprising

I. treating the compound of Formula **1** with a mixture of halogenated hydrocarbon and an alcohol;

II. concentrating the reaction mixture; and

III. recrystallization of the product obtained in II from an ester solvent.

12. The process as claimed in claim 11, wherein the halogenated hydrocarbon used in I is methylene chloride.

13. The process as claimed in claim 11wherein the alcohol used in I is methanol.
14. The process as claimed in claim 11 wherein the ester solvent used in III is ethyl acetate
15. Garenoxacin mesylate having more than about 99.5% purity, as measured by high performance liquid chromatography.
16. Garenoxacin mesylate having d_{90} less than 30 μ.
17. Garenoxacin mesylate free of alkyl mesylate.
18. Garenoxacin mesylate free of hydroxylic solvents.
19. A pharmaceutical composition comprising garenoxacin mesylate crystalline form as defined in claim 1and a pharmaceutically acceptable carrier.

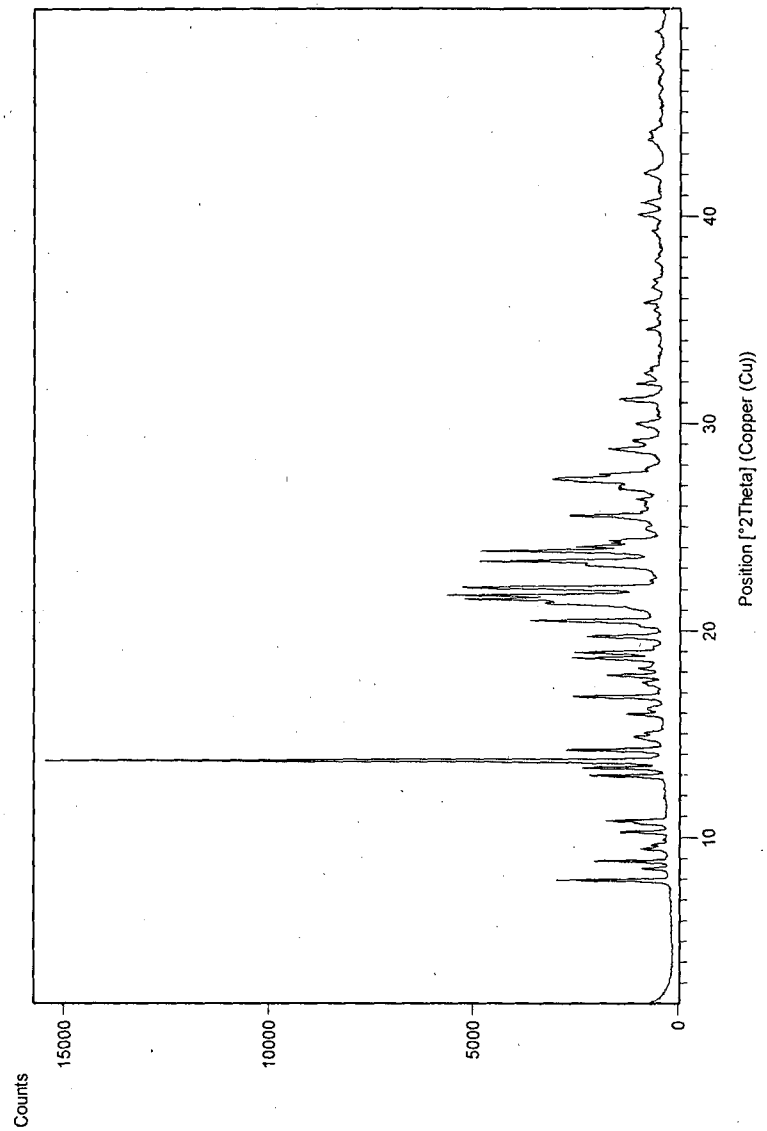

Fig. 1: X-ray powder diffraction pattern of novel polymorphic form of garenoxacin mesylate.