PREPARATION OF LEVOFLOXACIN AND FORMS THEREOF

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ABSTRACT

Levofoxacin was prepared by reacting (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with N-methyl piperazine in a polar solvent or in a neat mixture to form levofoxacin. Further processing of the levofloxacin produced novel levofloxacin forms, including a hemihydrate and Forms A, B, C, F, G and H.
PREPARATION OF LEVOFLOXACIN AND FORMS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority of provisional application Ser. Nos. 60/326,958, filed Oct. 3, 2001, 60/334,316, filed Nov. 29, 2001 and 60/354,939, filed Feb. 11, 2002, and non-provisional application serial no. [attorney docket 1662/58004], filed concurrently herewith. The entire content of each of these applications is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to processes for preparing levofloxacin and novel forms thereof.

BACKGROUND OF THE INVENTION

[0003] Levofloxacin is a broad spectrum synthetic antibiotic. Levofloxacin is the S-enantiomer of the racemate, ofloxacin, a fluoroquinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the S-enantiomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves the inhibition of DNA gyrase (bacterial topoisomerase II), an enzyme required for DNA replication, transcription repair and recombination. Levofloxacin is available as LEVAQUIN® which may be orally administered or administered intravenously.

[0004] Levofloxacin is a chiral fluorinated carboxyquinolone. Its chemical name is (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (CAS Registry No. 100986-85-4). The chemical structure of levofloxacin is shown as Formula I.

[0005] U.S. Pat. No. 4,382,892 is directed toward pyrido[1,2,3-de]-1,4-benzoxazine derivatives and methods of preparing them.

[0006] U.S. Pat. No. 5,053,407 is directed toward optically active pyridobenzoxazine derivatives, processes for preparing the same, and intermediates useful for preparing such derivatives.

[0007] U.S. Pat. No. 5,051,505 is directed toward processes for preparing piperazinyl quinolone derivatives. The process comprises reacting diazaoquinolones with piperazine derivatives and tetraalkyl ammonium halides in the presence of a polar solvent such as acetonitrile, dimethylformamide, pyridine, sulfolane and dimethyl sulfoxide.

[0008] U.S. Pat. No. 5,155,223 is directed toward the preparation of quinolinecarboxylic acids.

[0009] U.S. Pat. No. 5,545,737 discloses selectively producing a levofloxacin hemihydrate or monohydrate by controlling the water content of an aqueous solvent in which levofloxacin is dissolved during a crystallization.

[0010] Levofloxacin Forms

[0011] Three polymorphic forms (anhydrous a, b, g) and two pseudopolymorphic forms (hemihydrate and monohydrate) of levofloxacin are mentioned in the literature. Hemihydrate and monohydrate forms are mentioned in EP 0444 678 B1 and in U.S. Pat. No. 5,545,737. These two patents are directed toward processes for the preparation of hemihydrate form free of monohydrate and for the preparation of monohydrate free of hemihydrate.

[0012] The article titled "Effect of dehydration on the formation of Levofloxacin Pseudopolymorphs," Chem. Pharm. Bull. 43(4) 649-653 (1995), examines the physical properties of the hydrates forms of levofloxacin. According to the article, heating the hemihydrate form resulted in a removal of the hydrated water to give anhydrous form g.

[0013] Further heating resulted in the formation of anhydrous form b, and then the formation of anhydrous form a. Heating of the monohydrate form resulted in a removal of the hydrated water to give anhydrous form a. Form g and form a adsorbed water vapor rapidly under ordinary relative humidity conditions and transformed into the hemihydrate and monohydrate, respectively.

[0014] The present invention relates to the solid state physical properties of levofloxacin. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talse, starch or tribasic calcium phosphate.

[0015] Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medications. The solid state Form of a compound may also affect its behavior on compaction and its storage stability.

[0016] These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic Form of a substance. The polymorphic Form may give rise to thermal behavior different from that of the amorphous material or another polymorphic Form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and can be used to distinguish some polymorphic forms from others. A particular polymorphic Form may also give rise to distinct spectroscopic
properties that may be detectable by powder X-ray crystallography, solid state C-NMR spectrometry and infrared spectrometry.

SUMMARY OF THE INVENTION

[0017] In one embodiment the present invention provides a process for the preparation of levofloxacin comprising reacting (S)-(-)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4-benzoxazine-6-carboxylic acid (“Compound I”) with N-methyl piperazine to form levofloxacin, and recovering the levofloxacin. Compound I may react with N-methyl piperazine either in a polar solvent or as a neat mixture.

[0018] In another embodiment of the invention, novel crystal forms A, B, C, F, G, and H, and methods for their preparation are described. In one embodiment, a method for preparing a levofloxacin form comprises maintaining levofloxacin at an elevated temperature, adding a polar solvent; and recovering a levofloxacin form. Preferably, this method further comprises cooling and maintaining the levofloxacin-solvent mixture at a below ambient temperature.

BRIEF DESCRIPTION OF THE FIGURES

[0019] FIG. 1 is an XRD diffractograms of novel levofloxacin crystal form A.
[0020] FIG. 2 is an XRD diffractograms of novel levofloxacin crystal form B.
[0021] FIG. 3 is an XRD diffractograms of novel levofloxacin crystal form C.
[0022] FIG. 4 is an XRD diffractograms of novel levofloxacin crystal form F.
[0023] FIG. 5 is an XRD diffractograms of novel levofloxacin crystal form G.
[0024] FIG. 6 is an XRD diffractograms of novel levofloxacin crystal form H.
[0025] FIG. 7 is a DTG thermogram of novel levofloxacin crystal form A.
[0026] FIG. 8 is a DTG thermogram of novel levofloxacin crystal form C.
[0027] FIG. 9 is a DTG thermogram of novel levofloxacin crystal form G.
[0028] FIG. 10 is a DTG thermogram of novel levofloxacin crystal form H.

DETAILED DESCRIPTION OF THE INVENTION

[0029] One embodiment of the present invention provides a process for preparing levofloxacin. In some embodiments, yields from about 70% to about 85%, or more, of purified levofloxacin are achieved. As used herein, “crude” and “purified” are relative terms meaning less pure or more pure, respectively. Greater yields are obtainable by the present invention, vis-a-vis prior art processes, due at least in part to the use of highly concentrated mixtures.

[0030] Unless indicated otherwise, the terms “levofloxacin” and “levofloxacin form” include the salts, hydrates, solvates and physiologically functional derivatives of levofloxacin. The term also includes all polymorphous forms of levofloxacin to the extent that they are not considered to be salts, hydrates, solvates or physiologically functional derivatives of levofloxacin.

[0031] One embodiment of the present invention provides a process for preparing levofloxacin comprising reacting (S)-(-)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4-benzoxazine-6-carboxylic acid (“Compound I”) with N-methyl piperazine in a polar solvent, preferably at an elevated temperature, to form levofloxacin. The elevated temperature is preferably about 70-120°C. The levofloxacin can then be precipitated and recovered using techniques well known in the art. As used herein, the term “precipitated” includes the formation of a solid in a solution or an increase in the amount of solid in a slurry. The preparation of Compound I is described, for example, in U.S. Pat. No. 4,382,892, which is incorporated herein by reference.

[0032] A suitable polar solvent is any that is capable of dissolving levofloxacin. Preferably, the polar solvent is dimethylsulfoxide (DMSO), an alcohol (preferably isobutanol), a ketone, propylene-glycol-monomethyl-ether (PGME) or dimethyl acetamide (DMA). As used herein, the term “polar solvent” is intended as a relative term to mean relatively more polar than another solvent.

[0033] In one embodiment, the volume of solvent is from about 14 ml to about 4 ml per gram of Compound I. In this embodiment, the solvent is preferably selected from the group consisting of isobutanol and PGME. In an alternative embodiment, the volume of solvent is less than about 3 ml per gram of the compound of Compound I. In this latter embodiment, the solvent is preferably selected from the group consisting of DMSO and DMA. Advantageously, short reaction times are needed to obtain high yields with DMSO.

[0034] If DMSO is used as the solvent, the preferred volume of solvent is up to about 3 ml solvent/g compound, more preferably about 0.5 to about 3 ml solvent/g compound, but more could be used. If PGME is used as the solvent, the preferred volume of solvent is about 4 to about 14 ml solvent/g compound, but more could be used.

[0035] Optionally, the process of the invention may further comprise adding an anti-solvent to the solvent after the reaction step to increase yield. As used herein, the term “anti-solvent” means a liquid in which levofloxacin is poorly soluble such that the addition of an anti-solvent to a solvent reduces the solubility of a levofloxacin. Preferably, the anti-solvent is one or more of the following: n-heptane, hexane, isopropyl alcohol, isopropyl alcohol in water (about 5% isopropyl alcohol or greater), butanol, acetonitrile, methyl ethyl ketone, or DMSO/water. When the solvent is propylene glycol monomethyl ether or isobutanol, the preferred anti-solvent is heptane or hexane. When the solvent is DMSO, the preferred anti-solvent is isopropanol.

[0036] In another embodiment, Compound I reacts with N-methyl piperazine as a neat mixture. In this embodiment, Compound I is preferably dissolved in a suspension of the N-methyl piperazine.

[0037] In one embodiment, the N-methyl piperazine is in molar excess over Compound I. Preferably, the molar excess...
is from about 2 to about 4 times. More preferably, the molar excess is from about 2 to about 2.5 times.

[0038] The preferred duration of the reaction step will depend on balancing the desire for the reaction to go to completion, which in turn depends on the reaction conditions, particularly the choice of solvent and the temperature, while maximizing efficiency and/or minimizing side reactions and/or degradation. For example, the reaction step is typically performed for a time period from about 1 h to about 24 h when a solvent is used. When the reaction is performed as a neat mixture, the time period for the reaction may be less than 1 h.

[0039] The reaction step may be performed at a temperature as high as about 110°C to about 120°C or higher. When the reaction is performed as a neat mixture, the reaction step is preferably performed at about the reflux temperature.

[0040] Preparation of Levofoxacin Forms

[0041] In another embodiment of the invention, a method for preparing a levofoxacin form comprises maintaining levofoxacin at a first elevated temperature, preferably in a first solvent; adding a polar solvent; and recovering a levofoxacin form. Preferably, this method further comprises cooling and maintaining the levofoxacin solvent mixture at a below-ambient temperature.

[0042] The first solvent is a polar solvent capable of dissolving levofoxacin and preferably having a relatively high boiling point. Examples include PGME, DMA and DMSO. The levofoxacin may be heated to a first elevated temperature. However, it is preferable that the levofoxacin is first synthesized, such as by reacting Compound I with N-methyl piperazine, described above, and the reaction mixture is then brought directly to the second elevated temperature that is suitable for adding the polar solvent. The first elevated temperature depends on the particular solvent, but is generally in the range of about 70°C to about 120°C, preferably about 80°C to about 85°C. The second elevated temperature depends on the particular polar solvent, but is generally in the range of about 60°C to about 80°C, preferably about 75°C to about 79°C.

[0043] The polar solvent is added to the levofoxacin, preferably slowly, at the second elevated temperature. The polar solvent is preferably added over about 2 h. Optionally, the mixture is maintained, preferably with stirring or other agitation, for an additional period of time.

[0044] Recovering the levofoxacin typically includes cooling the mixture to precipitate the levofoxacin followed by filtration.

[0045] For the preparation of levofoxacin hemihydrate, the polar solvent comprises water, preferably a mixture of isopropanol and water, preferably about 3% to about 4% (v/v) water. In this embodiment, the first elevated temperature is preferably about 80°C and the second elevated temperature is preferably about 75°C. Preferably, the polar solvent is added dropwise over about 2 h. Following the adding step, the levofoxacin-polar-solvent mixture is slowly cooled to a below-ambient temperature, preferably in the range of about 0°C to about 20°C, more preferably about 5°C. Preferably, the cooling step occurs over about 1 to about 10 hours, more preferably about 4 hours. Preferably, the below-ambient temperature is maintained for an additional about 2 hours.

[0046] For the preparation of Form C, the polar solvent preferably comprises isopropanol. In this embodiment, the first elevated temperature is preferably about 85°C and the second elevated temperature is preferably about 79°C. Preferably, the polar solvent is added dropwise over about 2 hours followed by an additional about 2 hours at this temperature.

[0047] For the preparation of Form A, the polar solvent preferably comprises isopropanol. In this embodiment, the first elevated temperature is preferably about 80°C and the second elevated temperature is preferably about 75°C. Following the adding step, the levofoxacin-polar-solvent mixture is slowly cooled to a below-ambient temperature, preferably in the range of about 0°C to about 20°C, more preferably about 5°C. Preferably, the cooling step occurs over about 1 to about 10 hours, more preferably about 4 hours. Preferably, the below-ambient temperature is maintained for an additional about 2 hours.

[0048] For the preparation of Forms G and B, the polar solvent preferably comprises isopropanol. In this embodiment, the first elevated temperature is preferably about 80°C and the second elevated temperature is preferably about 75°C. Following the adding step, the levofoxacin-polar-solvent mixture is slowly cooled to a below-ambient temperature, preferably in the range of about 0°C to about 20°C, more preferably about 5°C. Preferably, the cooling step occurs over about 1 to about 10 hours, more preferably about 4 hours. Preferably, the below-ambient temperature is maintained for an additional about 2 hours.

[0049] For the preparation of Form H, the polar solvent comprises a mixture of isopropanol and water, more preferably about 0.3% to about 0.4% (v/v) water. In this embodiment, the first elevated temperature is preferably about 80°C and the second elevated temperature is preferably about 75°C. Preferably, the polar solvent is added dropwise over about 1 hour. Following the adding step, the levofoxacin-polar-solvent mixture is preferably maintained at the second elevated temperature for about 2 hours. The mixture is then slowly cooled to a below-ambient temperature, preferably in the range of about 0°C to about 20°C, more preferably about 5°C. Preferably, the cooling step occurs over about 1 to about 10 hours, more preferably about 4 hours. Preferably, the below-ambient temperature is maintained for an additional about 12 hours.

[0050] In another embodiment of the invention, a method for preparing a levofoxacin form comprises maintaining a first mixture of levofoxacin and a polar solvent at a first elevated temperature for about 4 hours or more, preferably at least 4.5 hours, cooling the first mixture to a second
elevated temperature, adding additional polar solvent to the cooled first mixture to form a second mixture, maintaining the second mixture at a third elevated temperature until complete dissolution of the levofloxacin, optionally adding additional polar solvent to the second mixture during the maintaining step, cooling the second mixture to form a levofloxacin form, and recovering the levofloxacin form.

[0051] For the preparation of Form F, the polar solvent comprises isobutyl alcohol. In this embodiment, the first and third elevated temperatures are preferably reflux and the second elevated temperature is preferably about 80°C. Preferably, the minimum amount of the polar solvent that is sufficient to completely dissolve the levofloxacin is added to the second mixture. The second mixture is slowly cooled to a below-ambient temperature, preferably in the range of about −5°C to about 20°C, more preferably about 5°C. Preferably, the cooling step occurs over about 1 hour to about 10 hours, more preferably about 1.5 hours.

[0052] Another embodiment of the invention is a pharmaceutical composition comprising a therapeutically effective amount of Forms A, B, C, F, G, H, or combinations thereof, and, optionally, a pharmaceutically acceptable carrier.

[0053] Another embodiment of the invention is a method for preparing a levofloxacin hemihydrate comprising storing one or more forms selected from the group consisting of Forms A, B, C, F, G, and H for an amount of time sufficient for the one or more forms to convert to a levofloxacin hemihydrate by the absorption of atmospheric water. For example, Forms A, B, C, F, G and H were converted to hemihydrate after 7-29 days of storing in a closed bottle at RT. The conversion to hemihydrate was faster (about 24 h) when keeping in the sample in an open bottle.

[0054] Another embodiment of the invention is a method for preparing a levofloxacin form. (S)-(-)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid is reacted with N-methyl piperazine at an elevated temperature to form levofloxacin. The levofloxacin is then precipitated and maintained at a first elevated temperature in a first solvent. A polar solvent is added to precipitate the levofloxacin Form C, Form A, Form G, Form B, Form H, Form F, or the hemihydrate form, which can then be recovered by known means, such as filtration.

[0055] Physical Characterization of Levofloxacin Forms

<table>
<thead>
<tr>
<th>Crystal Form</th>
<th>XRD characteristic peaks (2θ)</th>
<th>Additional XRD peaks (2θ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5.5, 11.3, 12.6, 18.8</td>
<td>2.9, 8.1, 10.8, 15.9, 16.1, 20.7, 21.5, 21.9, 23.2, 25.7, 29.4, 29.7</td>
</tr>
<tr>
<td>C</td>
<td>12.2, 17.6, 18.0, 21.7, 22.4, 23.4</td>
<td>7.8, 10.8, 15.6, 17.2, 20.0, 20.6, 23.9, 24.5, 27.5, 27.8</td>
</tr>
<tr>
<td>F</td>
<td>11.9, 17.8, 18.4</td>
<td>5.3, 6.0, 6.7, 9.7, 10.6, 13.2, 13.4, 13.7, 15.5, 15.9, 19.4, 20.1, 25.3, 26.4, 26.8</td>
</tr>
<tr>
<td>G</td>
<td>5.3, 6.7, 13.1, 13.4, 26.4, 26.7</td>
<td>2.8, 9.9, 16.1, 18.7, 19.6, 20.1, 21.5, 25.6, 33.1, 33.8, 34.5, 35.0</td>
</tr>
<tr>
<td>H</td>
<td>4.9, 5.2, 5.5, 18.7</td>
<td>2.8, 6.7, 8.1, 10.7, 13.4, 16.1, 18.7, 20.1, 20.7, 21.4, 29.6, 35.1</td>
</tr>
</tbody>
</table>

[0056] DTG thermograms were performed on Shimadzu DTG-50, Heating rate: 10°C/min. The melting point was determined by an endothermic peak in the DTA curve to be about 225-230°C. For all the discussed crystal forms, the main differences in the DTA and TGA curves were observed in the temperature range of up to 160°C.

Thermal Analysis of Levofloxacin Forms

[0057] Levofloxacin novel form A is characterized by an endothermic peak at about 100°C. A weight loss step of about 18-22% is observed in this temperature range due to the removal of solvent from the crystals. See FIG. 7.

[0058] Levofloxacin novel form C is characterized by high content of DMSO (30-50%) and water content of about 3.5% by KF. See FIG. 8.

[0059] Levofloxacin novel form G is characterized by two endothermic peaks at about 82°C and about 103°C. A weight loss step 3-6% is observed in this temperature range. This weight loss value is in coincident with the DMSO content in the sample. See FIG. 9.

[0060] Levofloxacin novel form H is characterized by an endothermic peak at about 122°C. A weight loss step of about 8% is observed in the range of 60 to 150°C. This weight loss percent is equal to the expected value corresponds to Levofloxacin:IPA solvate in the ratio of 1:0.5, which is 7.7%. See FIG. 10.

[0061] The function and advantages of these and other embodiments of the present invention will be more fully understood from the examples below. The following examples are intended to illustrate the benefits of the present invention, but do not exemplify the full scope of the invention.

EXAMPLES

[0062] Example 1

Synthesis of Levofloxacin in DMSO

[0063] 5 g (17.8 mmole) of (S)-(-)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid was put in suspension in 2.5 mL of DMSO and 4.2 mL (37.9 mmole) of N-methyl piperazine. The reaction mixture was heated to 120°C and the suspension became soluble. After 2.5 h the reaction was completed. The mixture was then cooled to 70°C and isopropanol (25 mL) was then added at this temperature. The reaction mixture was slurried for 1 h at ambient temperature, filtered, and dried overnight to obtain 5.86 g (91.3%) of levofloxacin.

Example 2

Synthesis of Levofloxacin in PGME

[0064] 3 g (10.67 mmole) of (S)-(-)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid was put in suspension in 30 mL of PGME and 4.75 mL (43 mmole) of N-methyl piperazine. The reaction mixture was heated to reflux for 23 hours until completion of the reaction. During that time, the reaction mixture became soluble. The mixture was then cooled to 50°C and n-Heptane (10 mL) was added at this temperature. The reaction mixture was then cooled to 0°C and the
precipitation occurred around 65°C. The reaction was left at 0°C for 3 hours, filtered under vacuum and dried overnight to obtain 2.98 g (77.3%) of levofloxacin.

Example 3

Synthesis of Levofloxacin in Isobutanol

[0065] 3 g (10.67 mmole) of (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrilo[1,2,3-de]1,4]benzoxazine-6-carboxylic acid was put in suspension in 21 mL of isobutanol and 4.75 mL (43 mmole) of N-methylpyperazine. The reaction mixture was heated to reflux for 6 hours, filtered under vacuum and dried overnight to obtain 2.83 g (77.3%) of levofloxacin.

Example 4

Synthesis of Levofloxacin (Neat)

[0066] 5 g (17.99 mmole) of (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrilo[1,2,3-de]1,4]benzoxazine-6-carboxylic acid was put in suspension in 6.8 mL (0.06 mole) of N-methylpyperazine. The reaction mixture was heated to reflux for 40 minutes until completion of the reaction. The mixture was then cooled to 80°C, filtered under vacuum, washed with 7 mL isobutanol and 10 mL n-heptane, and dried overnight to yield 4.9 g (76%) levofloxacin.

Example 5

Synthesis of Levofloxacin in DMA

[0067] 10 g (35.6 mmole) of (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrilo[1,2,3-de]1,4]benzoxazine-6-carboxylic acid was put in suspension in 5 mL of DMA (dimethyl acetamide) and 8.3 mL (75 mmole) of N-methylpyperazine. The reaction mixture was heated to 110°C until the complete conversion of the starting material, about 1.5 h. The reaction mixture was then cooled to 60°C and 60 mL of isopropyl alcohol was added. The reaction mixture was then filtered for 3 hours at ambient temperature and dried overnight to obtain 11.48 g (89.3%) of levofloxacin.

Example 6

Synthesis of Hemihydrate

[0068] In 1 liter reactor equipped with a mechanical stirrer, a condenser and a thermometer, heated at 80°C, was charged 87.5 g (0.31 mole) of (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrilo[1,2,3-de]1,4]benzoxazine-6-carboxylic acid, 61.3 mL DMSO and 86.3 mL (0.77 mole) of N-methylpyperazine. The slurry was stirred at a rate of 250 rpm under nitrogen atmosphere at 80°C until completion of the reaction. Then the slurry was cooled to 75°C and a mixture of isopropanol (675 mL) and water (25 mL) was added dropwise at this temperature during 2 hours. The slurry was then cooled to 5°C, maintained at this temperature for 2 hours and diluted under vacuum at this temperature. The solid was then washed with 175 mL of isopropanol (2 rinses) and dried under vacuum to obtain levofloxacin hemihydrate.

Example 7

Synthesis of Form C

[0069] Preparation

[0070] A 1 liter reactor equipped with mechanical stirrer, condenser and thermometer, was heated to 85°C, charged with (S)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrilo[1,2,3-de]1,4]benzoxazine-6-carboxylic acid (87.5 g), DMSO (61.3 mL) and N-methylpyperazine (86.3 mL). The slurry was stirred at a rate of 250 rpm under nitrogen atmosphere. The heating was continued for 4.5 hours until completion of the reaction (monitoring by HPLC). Then the slurry mixture was cooled to 70°C and isopropanol (700 mL) was added dropwise at this temperature during 2 hours and stirred at this temperature for an additional 2 hours. At the end of the addition, a sample was filtered under vacuum and washed with isopropanol.

Example 8

Synthesis of Form A

[0071] Preparation

[0072] A 1 liter reactor equipped with mechanical stirrer, condenser and thermometer, was heated to 80°C, charged with (S)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrilo[1,2,3-de]1,4]benzoxazine-6-carboxylic acid (87.5 g), DMSO (61.3 mL) and N-methylpyperazine (86.3 mL). The slurry was stirred at a rate of 250 rpm under air atmosphere. The heating was continued for 4.5 hours until completion of the reaction (monitoring by HPLC). Then the slurry mixture was cooled to 75°C, and isopropanol (700 mL) was added dropwise at this temperature during 2 hours. A sample was taken for XRD analysis. The mixture was maintained with stirring for 2 hours at this temperature. Then the reaction mixture was cooled during 4 hours until 5°C and maintained with the stirring for 2 hours at this temperature. At the end, the reaction mixture was filtered under vacuum and washed with isopropanol (175 mL) to obtain 171 g of wet material (106.8 g dry material, 92.7%).

Example 9

Synthesis of Form G and Form B

[0073] Preparation

[0074] A 1 liter reactor equipped with mechanical stirrer, condenser and thermometer, was heated to 80°C, charged with (S)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrilo[1,2,3-de]1,4]benzoxazine-6-carboxylic acid (87.5 g), DMSO (61.3 mL) and N-methylpyperazine (86.3 mL). The slurry was stirred at a rate of 250 rpm under nitrogen atmosphere. The heating was continued for 4.5 hours until completion of the reaction. Then the slurry mixture was cooled to 75°C and isopropanol (700 mL) was added dropwise at this temperature during 2 hours.
At the end of the addition the stirring was maintained for 2 hours at 75°C, then cooled during 4 hours until 5°C and maintained with stirring for 11 hours at this temperature. The slurry was filtrated under vacuum and washed with isopropanol (175 ml) to obtain 149 g of wet material.

The wet material was divided in two portions for drying. The first portion was dried under vacuum with stirring at 40°C for 21 hours and the second fraction was dried under vacuum with stirring at 60°C for 21 hours. Levofloxacin Form G was resulted after drying at 40°C for 3 or 6 hours, and after drying at 60°C for 3 hours. Levofloxacin Form B was resulted after drying at 40°C for 21 hours, and after drying at 60°C for 6, 9 and 21 hours.

Example 10

Synthesis of Form H

A 1 liter reactor equipped with mechanical stirrer, condenser and thermometer, was heated to 80°C, charged with (S)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (87.5 g), DMSO (61.3 ml) and N-methylpyperazine (86.3 ml). The slurry was stirred at a rate of 250 rpm under nitrogen atmosphere. The heating was continued for 4.5 hours until completion of the reaction (monitoring by HPLC). Then the slurred mixture was cooled to 75°C and isopropanol (697.5 ml) mixed with H2O (2.5 ml) was added dropwise at this temperature during 1 hour. At the end of the addition the stirring was maintained for 2 hours and then cooled during 4 hours until 5°C. The stirring was maintained for 12 hours at this temperature. The reaction mixture was then filtrated under vacuum and washed with isopropanol (175 ml) to obtain 150 g of wet material.

Example 11

Synthesis of Form F

4.0 g of Levofloxacin was put in a flask equipped with a condenser. Isobutyl alcohol (8 ml) was added and the mixture was heated to reflux temperature. After 15 minutes, the mixture was cooled to 80°C and 4 ml of isobutyl alcohol was added. The mixture was then heated again to reflux temperature. Isobutyl alcohol (6 ml) was added until complete dissolution. The solution became clear and the mixture was cooled to 0°C in 1.5 hour. The precipitate was then filtrated under vacuum, washed with isobutyl alcohol (4 ml) and dried under vacuum at 60°C.

Example 12

Time-Induced Conversion of Forms

A 1 liter reactor equipped with mechanical stirrer, condenser and thermometer, was charged with (S)-9,10, difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (87.5 g), DMSO (61.3 ml), N-methylpyperazine (86.3 ml) and H2O (0.44 ml). The slurry was then heated to 80°C and stirred at a rate of 250 rpm under nitrogen atmosphere. The heating was continued for 4.5 hours until completion of the reaction. Then the slurred mixture was cooled to 75°C and isopropanol (700 ml) was added dropwise at this temperature over 2 hours.

The mixture was then maintained with stirring for 2 hours at 75°C. The mixture was then cooled over 4 hours until 5°C, at which temperature the mixture was maintained with the stirring for 9 hours. The slurry was filtrated under vacuum and washed with isopropanol (175 ml) to obtain 147 g of wet polymorph H.

The wet material was exposed to the air at RT covered with paper (for protection). After 3, 6, 9 hours the polymorph of the wet samples was Form G. After 24 hours the wet sample was the hemihydrate polymorph.

Example 13

Conversion of Form H in a Slurry

A 1 liter reactor equipped with mechanical stirrer, condenser and thermometer, was heated to 80°C, charged with (S)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (87.5 g), DMSO (61.3 ml) and N-methylpyperazine (86.3 ml). The slurry was stirred at a rate of 250 rpm under nitrogen atmosphere. The heating was continued for 4.5 hours until completion of the reaction (monitoring by HPLC). Then the slurred mixture was cooled to 75°C and isopropanol (697.5 ml) mixed with H2O (2.5 ml) was added dropwise at this temperature over 1 hour.

The mixture was then maintained with stirring for 2 hours. The mixtures was then cooled over 4 hours until 5°C, at which temperature it was maintained for 12 hours. The reaction mixture was then filtrated under vacuum and washed with isopropanol (175 ml) to obtain 150 g of wet polymorph H.

A first portion of the wet material was stirred in 5 v of acetonitrile at 75°C for 2 h, then filtrated under vacuum. The polymorphism of the wet sample was Hemihydrate. A second portion of the wet material was exposed to the air at RT covered with paper (for protection).

After a few hours the polymorph of the wet samples was Hemihydrate.

Example 14

Conversion of Form G in a Slurry

A 1 liter reactor equipped with mechanical stirrer, condenser and thermometer, was charged with (S)-9,10, difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (87.5 g), DMSO (61.3 ml) and N-methylpyperazine (86.3 ml) at ambient temperature. The slurry was then heated to 80°C and stirred at a rate of 250 rpm under nitrogen atmosphere. The heating was continued for 4 hours until completion of the reaction. Then the slurred mixture was cooled to 75°C and isopropanol (679 ml) mixed with H2O (21 ml) was added dropwise at this temperature over 2 hours.

The mixtures was then maintained with stirring for 2 hours at 75°C. The mixture was then cooled over 4 hours until 5°C, at which temperature it was maintained with the stirring for 10 hours. The slurry was filtrated under vacuum and washed with isopropanol (175 ml) to obtain 166.5 g of wet polymorph G.
The wet material (162 g) was mixed with acetonitrile (486 ml). The slurry was stirred at 27°C for 1 hour at a rate of 250 rpm. The slurry was then filtered under vacuum and washed with acetonitrile (162 ml). The wet sample was the hemihydrate polymorph. The solid was dried in a vacuum oven at 40°C for 6 hours. The dry levofloxacin crude was the hemihydrate polymorph.

Example 15

Dry

A 1 liter reactor equipped with mechanical stirrer, condenser and thermometer, was charged with (S)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4-benzoazin-6-carboxylic acid (87.5 g), DMSO (61.3 ml) and N-methylpiperazine (86.3 ml) at ambient temperature. The slurry was then heated to 80°C and stirred at a rate of 250 rpm under nitrogen atmosphere. The heating was continued for 4.5 hours until completion of the reaction. Then the slurry mixture was cooled to 75°C and isopropanol (700 ml) was added at once. At the end of the addition, the mixture was stirred at a rate of 300 rpm. The reaction mixture was cooled over 2 hours until 7°C. The stirring was continued for 2 hours at this temperature and at a rate of 350 rpm. The reaction mixture was then filtered under vacuum and washed with isopropanol (175 ml).

The wet material (162 g) was mixed with isopropanol (180 ml). The slurry was stirred at 40°C for 1 hour at a rate of 250 rpm. The slurry was then filtered under vacuum and washed with isopropanol (60 ml). The polymorph of the wet sample was H.

The solid was dried in a vacuum oven at 60°C for 14 hours to obtain 106 g (92%) of dry levofloxacin Form B.

Example 16

Dry

A 1 liter reactor equipped with mechanical stirrer, condenser and thermometer, was charged with (S)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4-benzoazin-6-carboxylic acid (87.5 g), DMSO (61.3 ml) and N-methylpiperazine (86.3 ml) at ambient temperature. The slurry was then heated to 80°C and stirred at a rate of 250 rpm under nitrogen atmosphere. The heating continued for 4.5 hours until completion of the reaction. Then the slurry mixture was cooled to 75°C and isopropanol (700 ml) was added at once. At the end of the addition, the mixture was stirred at a rate of 300 rpm. The reaction mixture was cooled over 2 hours until 7°C. The stirring was maintained for 2 hours at this temperature and at a rate of 350 rpm. The reaction mixture was then filtered under vacuum and washed with isopropanol (175 ml).

The wet material (162 g) was mixed with isopropanol (180 ml). The slurry was stirred at 40°C for 1 hour at a rate of 250 rpm. The slurry was then filtered under vacuum and washed with isopropanol (60 ml). The polymorph of the wet sample was G.

The solid was dried in a vacuum oven at 60°C for 14 hours to obtain 106 g (92%) of dry levofloxacin Form B.

Example 17

Preparation of Hemihydrate using n-BuOH

1 g of levofloxacin crude was put in suspension in 7 ml of n-BuOH. The mixture was heated to reflux temperature until complete dissolution of the material. Then the solution was cooled to RT over a period of 2.5 hours. The precipitate was filtered under vacuum, washed with n-BuOH and dried at 60°C in a vacuum oven to give 810 mg (81%) of purified levofloxacin hemihydrate.

Example 18

Preparation of Hemihydrate Using ACN

1.5 g of levofloxacin crude was put in suspension in 10.5 ml of ACN. The mixture was heated to reflux temperature until complete dissolution of the material. Then the solution was cooled to 60°C over a period of 20 minutes. The precipitate was filtered under vacuum, washed with ACN (1.5 ml) and dried at 30°C in a vacuum oven to give 1.15 g (77%) of purified levofloxacin (hemihydrate/mono-hydrate mixture). The purified levofloxacin contained approximately half the amount of desmethyl levofloxacin as that in the crude sample.

Example 19

Preparation of Hemihydrate Using DMSO/Water

1 g of levofloxacin crude was put in suspension in 1.5 ml of DMSO. The mixture was heated to 108°C until complete dissolution of the material. Then H2O (7.5 ml) was added over 10 minutes and the mixture was cooled to RT. The precipitate was filtered under vacuum, washed with 1 ml of a mixture DMSO:H2O 1:1.5 and dried at 60°C in an air-flow oven to give 840 mg (84%) of purified levofloxacin hemihydrate.

Example 20

Preparation of Hemihydrate Using MEK

1.5 g of levofloxacin crude was put in suspension in 15 ml of MEK. The mixture was heated to reflux temperature until complete dissolution of the material. Then the solution was cooled to 5°C over a period of 3 hours. The precipitate was filtered under vacuum, washed with 1.5 ml of MEK and dried at 30°C in a vacuum oven to give 840 mg (84%) of purified levofloxacin hemihydrate.

1. A method for preparing levofloxacin comprising:
   reacting (S)-(+) 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4-benzoazin-6-carboxylic acid with N-methyl piperazine at an elevated temperature to form levofloxacin;
   precipitating the levofloxacin; and
   recovering the levofloxacin.

2. The method of claim 1, wherein the yield is about 75% or greater.

3. The method of claim 1, wherein the yield is about 85% or greater.

4. The method of claim 1, wherein the reacting step occurs in a polar solvent.

5. The method of claim 4, wherein the polar solvent is selected from the group consisting of dimethylsulfoxide (DMSO), isobutanol, propylene-glycol-monomethyl-ether (PGME), dimethyl acetamide (DMA), and mixtures thereof.

6. The method of claim 4, wherein the volume of the solvent ranges from about 14 ml to about 4 ml per gram of
(S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4]benzoazin-6-carboxylic acid.

7. The method of claim 5, wherein the solvent is selected from the group consisting of isobutanol and PGME.

8. The method of claim 4, wherein the volume of solvent is less than about 3 ml per gram of (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4]benzoazin-6-carboxylic acid.

9. The method of claim 8, wherein the solvent is selected from the group consisting of DMSO and DMA.

10. The method of claim 1, wherein N-methyl piperazine is in molar excess over (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4]benzoazin-6-carboxylic acid.

11. The method of claim 10, wherein the molar excess is from about 2 to about 4 times.

12. The method of claim 10, wherein the molar excess is from about 2 to about 2.5 times.

13. The method of claim 4, further comprising adding an anti-solvent to the mixture after the reacting step.

14. The method of claim 13, wherein the anti-solvent is selected from the group consisting of n-heptane, hexane, isopropyl alcohol, isopropyl alcohol in water, butanol, acetonitrile, methyl ethyl ketone, and DMSO/water.

15. The method of claim 1, wherein the reacting step occurs in a neat mixture.

16. The method of claim 15, wherein the reacting step is performed at reflux.

17. The method of claim 15, wherein (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4]benzoazin-6-carboxylic acid is dissolved in a suspension of N-methyl piperazine.

18. A method for preparing a levofloxacin form comprising:

- maintaining levofloxacin at a first elevated temperature in a first solvent; adding a polar solvent to precipitate the levofloxacin form; and
- recovering a levofloxacin form selected from the group consisting of Form C, Form A, Form G, Form B, Form H and Form F.

19. The method of claim 18, wherein the amount of the polar solvent is less than about 8 volumes polar solvent/g starting material; and

- wherein the polar solvent comprises isopropanol and water.

20. The method of claim 19, wherein the recovering step comprises

- cooling the second mixture to about 0°C. to about 20°C.; and
- maintaining the second mixture at 0°C. to about 20°C. for at least about 2 hours.

21. (canceled)

22. The method of claim 18,

- wherein a slurry is formed prior to the adding step; and
- wherein the polar solvent is isopropanol.

23. Levofloxacin Form C made by the process of claim 22.

24. The method of claim 18, further comprising

- cooling the levofloxacin-solvent mixture to 0°C. to about 20°C. over a period of at least about 0.5 h;
- maintaining the levofloxacin-solvent mixture at 0°C. to about 20°C. for a period of at least about 2 h;
- wherein the elevated temperature is about 75°C.; and
- wherein the polar solvent is isopropanol.

25. Levofloxacin Form A made by the process of claim 24.

26. The method of claim 18, further comprising

- cooling the levofloxacin-solvent mixture to 0°C. to about 20°C. over a period of at least about 0.5 h;
- maintaining the levofloxacin-solvent mixture at 0°C. to about 20°C. over a period of at least about 2 h;
- wherein the recovering step comprises drying the levofloxacin for about 3 to about 6 hours at about 40°C. and for about 3 hours at about 60°C.;
- wherein the elevated temperature is about 75°C.; and
- wherein the polar solvent is isopropanol.

27. Levofloxacin Form G made by the process of claim 26.

28. The method of claim 18, further comprising

- cooling the levofloxacin-solvent mixture to 0°C. to about 20°C. over a period of at least about 0.5 h;
- maintaining the levofloxacin-solvent mixture at 0°C. to about 20°C. for a period of at least about 2 h;
- wherein the recovering step comprises drying the levofloxacin for about 20 hours at about 40°C. and for at least about 6 hours at about 60°C.;
- wherein the elevated temperature is about 75°C.; and
- wherein the polar solvent is isopropanol.

29. Levofloxacin Form B made by the process of claim 28.

30. The method of claim 18, further comprising

- cooling the levofloxacin-solvent mixture to 0°C. to about 20°C. over a period of at least about 0.5 h;
- maintaining the levofloxacin-solvent mixture at 0°C. to about 20°C. for a period of at least about 2 h;
- wherein the elevated temperature is about 75°C.; and
- wherein the polar solvent is isopropanol containing about 0.3% to about 0.4% by volume water.

31. Levofloxacin Form H made by the process of claim 30.

32. A method for preparing levofloxacin Form F comprising:

- maintaining a first mixture of levofloxacin and a polar solvent at a first elevated temperature for at least about 15 minutes;
- cooling the first mixture to less than about 80°C.;
- adding additional polar solvent to the cooled first mixture to form a second mixture;
- maintaining the second mixture at a second elevated temperature;
- adding additional polar solvent to the second mixture during the maintaining step;
- cooling the second mixture to form a levofloxacin form; and
- recovering levofloxacin Form F.
33. The method of claim 32, wherein the first elevated temperature is the reflux temperature; and wherein the polar solvent is isobutyl alcohol.

34. Levofloxacin Form F made by the process of claim 32.

35. A method for preparing a levofloxacin form comprising:

- reacting (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrano[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with N-methyl piperazine at an elevated temperature to form levofloxacin;
- adding a polar solvent to precipitate the levofloxacin form; and
- recovering a levofloxacin form selected from the group consisting of Form C, Form A, Form G, Form B, Form H and Form F.

36. (canceled)

37. Levofloxacin Form C.

38. The form of claim 37, wherein the Form C comprises about 30-50% by weight DMSO and about 3.5% by weight water.

39. The form of claim 37, wherein the Form C is characterized by peaks at 12.2, 17.6, 18.0, 21.7, 22.4, 23.4, each peak being ±0.3 deg. 20.

40. The form of claim 39, wherein the Form C is further characterized by peaks at 7.8, 10.8, 15.6, 17.2, 20.0, 20.6, 23.9, 24.5, 27.3, 27.8, each peak being ±0.3 deg. 20.

41. A pharmaceutical composition comprising a therapeutically effective amount of the form of claim 39 and a pharmaceutically acceptable carrier.

42. Levofloxacin Form A.

43. The form of claim 42, wherein the Form A is characterized by peaks at 5.5, 11.3, 12.6, 18.8, each peak being ±0.3 deg. 20.

44. The form of claim 43, wherein the Form C is further characterized by peaks at 2.9, 8.1, 10.8, 15.9, 16.1, 20.7, 21.5, 21.9, 23.2, 25.7, 29.4, 29.7, each peak being 0.3 deg. 20.

45. A pharmaceutical composition comprising a therapeutically effective amount of the form of claim 43 and a pharmaceutically acceptable carrier.

46. Levofloxacin Form G.

47. The form of claim 46, wherein the Form G is characterized by peaks at 5.3, 6.7, 13.1, 13.4, 26.4, 26.7, each peak being ±0.3 deg. 20.

48. The form of claim 47, wherein the Form G is further characterized by peaks at 2.8, 9.9, 16.1, 18.7, 19.6, 20.1, 21.5, 29.6, 33.1, 33.8, 34.5, 35.0, each peak being ±0.3 deg. 20.

49. A pharmaceutical composition comprising a therapeutically effective amount of the form of claim 47 and a pharmaceutically acceptable carrier.

50. Levofloxacin Form B.

51. The form of claim 50, wherein the Form B is characterized by peaks at 15.2, 15.8, 25.5, 25.8, each peak being ±0.3 deg. 20.

52. The form of claim 51, wherein the Form B is further characterized by peaks at 5.3, 6.0, 6.7, 9.7, 13.1, 19.4, 20.0, 26.3, 26.7, each peak being ±0.3 deg. 20.

53. A pharmaceutical composition comprising a therapeutically effective amount of the form of claim 51 and a pharmaceutically acceptable carrier.

54. Levofloxacin Form H.

55. The form of claim 54, wherein the Form H comprises a solvate such that the ratio of levofloxacin: solvate is about 2:1.

56. The form of claim 55, wherein the solvate is isopropanol.

57. The form of claim 54, wherein the Form H is characterized by peaks at 4.9, 5.2, 5.5, 18.7, each peak being ±0.3 deg. 20.

58. The form of claim 57, wherein the Form H is further characterized by peaks at 2.8, 6.7, 8.1, 10.7, 13.4, 16.1, 18.7, 20.1, 20.7, 21.4, 29.6, 35.1, each peak being ±0.3 deg. 20.

59. A pharmaceutical composition comprising a therapeutically effective amount of the form of claim 58 and a pharmaceutically acceptable carrier.

60. Levofloxacin Form F.

61. The form of claim 60, wherein the Form F is characterized by peaks at 11.9, 17.8, 18.4, each peak being ±0.3 deg. 20.

62. The form of claim 61, wherein the Form F is further characterized by peaks at 5.3, 6.0, 6.7, 9.7, 10.6, 13.2, 13.4, 13.7, 15.5, 15.9, 19.4, 20.1, 25.3, 26.4, 26.8, each peak being ±0.3 deg. 20.

63. A pharmaceutical composition comprising a therapeutically effective amount of the form of claim 61 and a pharmaceutically acceptable carrier.

64. (canceled)

65. A method for preparing a levofloxacin form comprising:

- reacting (S)-(−)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrano[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with N-methyl piperazine at an elevated temperature to form levofloxacin;
- precipitating the levofloxacin;
- maintaining the levofloxacin at a first elevated temperature in a first solvent;
- adding a polar solvent to precipitate the levofloxacin form; and
- recovering a levofloxacin form selected from the group consisting of Form C, Form A, Form G, Form B, Form H and Form F.

66. The method of claim 1, wherein the elevated temperature is from about 70-120° C.

67. The method of claim 14, wherein the polar solvent is PGME or isobutanol and the anti-solvent is heptane or hexane.

68. The method of claim 14, wherein the polar solvent is DMSO and the anti-solvent is isopropanol.

69-73. (canceled)

74. The method of claim 1, wherein the recovered levofloxacin is levofloxacin hemihydrate.

* * * *