



(86) Date de dépôt PCT/PCT Filing Date: 2005/07/18
(87) Date publication PCT/PCT Publication Date: 2006/01/26
(45) Date de délivrance/Issue Date: 2012/10/16
(85) Entrée phase nationale/National Entry: 2007/01/05
(86) N° demande PCT/PCT Application No.: KR 2005/002294
(87) N° publication PCT/PCT Publication No.: 2006/009374
(30) Priorité/Priority: 2004/07/21 (KR10-2004-0056637)

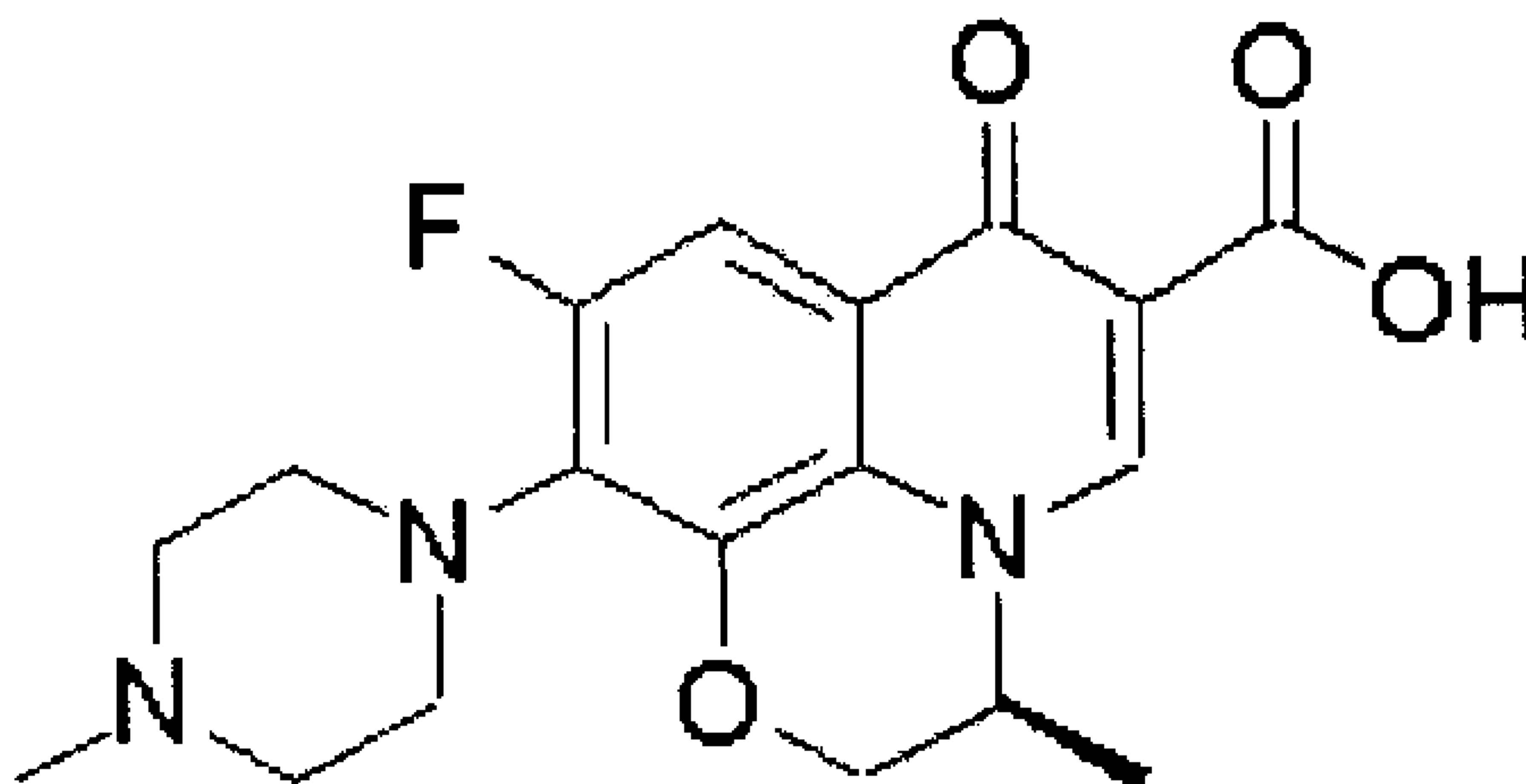
(51) Cl.Int./Int.Cl. *C07D 498/06* (2006.01)

(72) Inventeurs/Inventors:
LEE, TAI-AU, KR;
KHOO, JA-HEOUK, KR;
SONG, SEONG-HO, KR

(73) Propriétaire/Owner:
YUHAN CORPORATION, KR

(74) Agent: RIDOUT & MAYBEE LLP

(54) Titre : PROCEDE POUR LA PREPARATION DE LEVOFLOXACINE OU DE SON HYDRATE
(54) Title: PROCESS FOR PREPARING LEVOFLOXACIN OR ITS HYDRATE



(I)

(57) Abrégé/Abstract:

The present invention provides a process of preparing levofloxacin hemihydrate or monohydrate without impurities, i.e. Impurities B, C, D, E, and F. The process comprises (a) adding crude levofloxacin to a novel mixed solvent, (b) refluxing the mixture obtained in (a) to form a solution, and (c) recovering levofloxacin hemihydrate or monohydrate from the solution obtained in (b).



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 January 2006 (26.01.2006)

PCT

(10) International Publication Number
WO 2006/009374 A1

(51) International Patent Classification⁷: **C07D 498/06**

(21) International Application Number:
PCT/KR2005/002294

(22) International Filing Date: 18 July 2005 (18.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2004-0056637 21 July 2004 (21.07.2004) KR

(71) Applicant (for all designated States except US): **YUHAN CORPORATION** [KR/KR]; 49-6 Taebang-dong, Tongjak-gu, Seoul 156-754 (KR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LEE, Tai-Au** [KR/KR]; 1-606 SinHyundai Apt., 65 Hoegi-dong, Dongdaemun-gu, Seoul 130-792 (KR). **KHOO, Ja-Heouk** [KR/KR]; 512-1004 Kaya Apt., Suri-dong, Kunpo-city, Kyungki-do 435-044 (KR). **SONG, Seong-Ho** [KR/KR]; 9/1, 321-1 Oksu2-dong, Seongdong-gu, Seoul 133-840 (KR).

(74) Agent: **Y.P.LEE, MOCK & PARTNERS**; The Cheonghwa Bldg., 1571-18 Seocho-dong, Seocho-gu, Seoul 137-874 (KR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING LEVOFLOXACIN OR ITS HYDRATE

(57) Abstract: The present invention provides a process of preparing levofloxacin hemihydrate or monohydrate without impurities, i.e. Impurities B, C, D, E, and F. The process comprises (a) adding crude levofloxacin to a novel mixed solvent, (b) refluxing the mixture obtained in (a) to form a solution, and (c) recovering levofloxacin hemihydrate or monohydrate from the solution obtained in (b).

WO 2006/009374 A1

Description

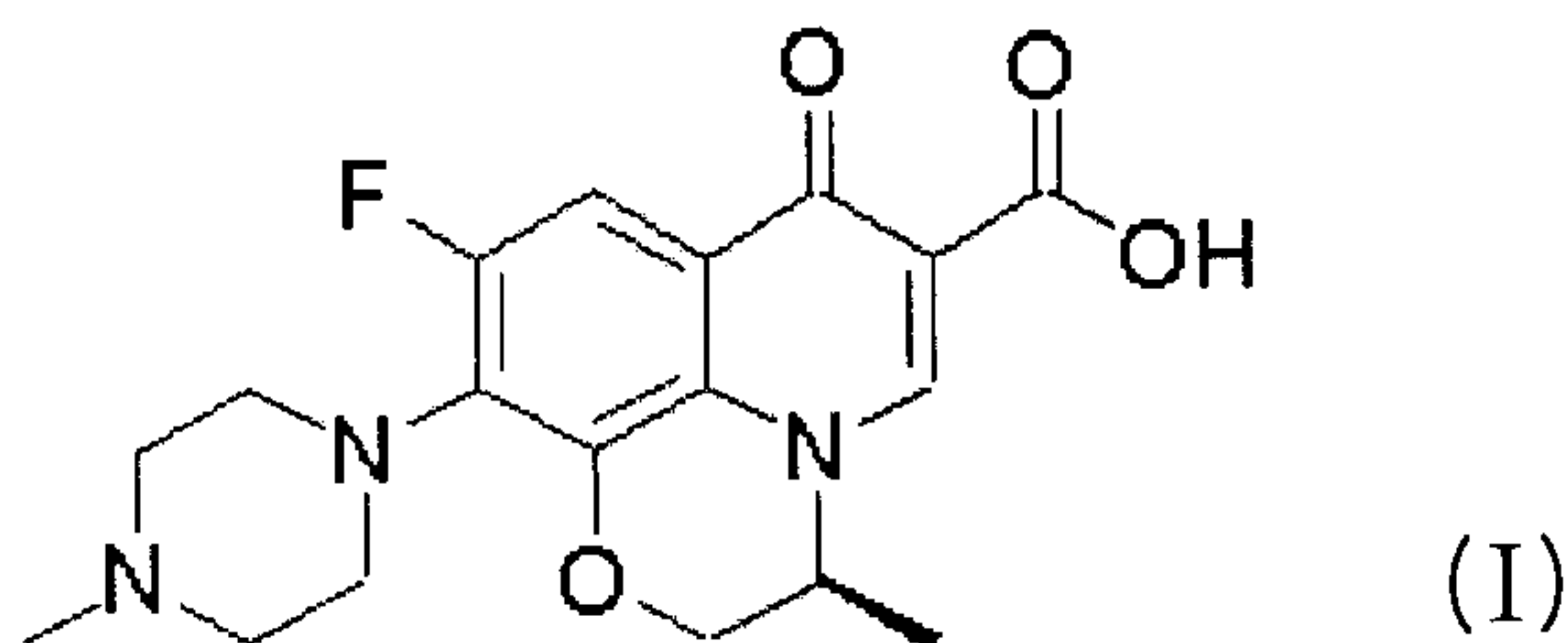
PROCESS FOR PREPARING LEVOFLOXACIN OR ITS HYDRATE

Technical Field

- [1] The present invention relates to a process of preparing high purity levofloxacin or its hydrate, e.g., hemihydrate or monohydrate.

Background Art

- [2] Levofloxacin, whose 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, is known as a useful anti-bacterial agent, and is represented by the following formula (I).



- [3] Levofloxacin may be used in its hydrate forms, such as a hemihydrate form or a monohydrate form. Known methods of preparing levofloxacin are disclosed in US Patent Nos. 5,053,407, 4,777,253, 4,382,892, 5,237,060 and 6,316,618.
- [4] In these methods, column chromatography is performed in order to obtain a purified levofloxacin or one of its hydrates from synthesized crude levofloxacin, which makes it difficult to apply the methods to industrial-scale mass production.
- [5] US Patent No. 5,545,737 discloses a process of selectively producing levofloxacin hemihydrate or monohydrate by controlling the water content of an aqueous solvent in which levofloxacin is dissolved during crystallization. However, one disadvantage of the process disclosed in US Patent No. 5,545,737 is an unsatisfactory yield. For example, a 45 - 65 % yield is typical.
- [6] In addition, the above methods have a disadvantage in that it is difficult to remove impurities, such as decarboxy-levofloxacin (Impurity B), desfluoro-levofloxacin (Impurity C), anti-levofloxacin (Impurity D), desmethyl-levofloxacin (Impurity E), and N-oxide levofloxacin (Impurity F), which may be produced during the process for preparing levofloxacin.
- [7] To solve these problems, US Publication Nos. 2003/0130507 and 2003/0144511 disclose processes for purifying crude levofloxacin by using a polar solvent such as n-butanol or acetonitrile; or a mixed solvent containing water and a polar solvent, such as

n-butanol & water, dimethyl sulfoxide & water, and acetonitrile & water. However, the processes disclosed in US Publication Nos. 2003/0130507 and 2003/0144511 require the adding of an antioxidant, such as ascorbic acid or sodium metabisulfite, in order to prevent the formation of N-oxide levofloxacin (Impurity F), which is a drawback since the antioxidant remains as an impurity in the final product, i.e., levofloxacin or its hydrate. Further, the processes have another problem in that desmethyl-levofloxacin (Impurity E) cannot be completely removed, thus remaining in the final product.

- [8] Thus, there is a need for a novel process of purifying levofloxacin to completely remove known impurities, such as Impurities B, C, D, E, and F.

Disclosure of Invention

Technical Problem

- [9] The present invention provides a process of preparing high purity levofloxacin hemihydrate or monohydrate without using additional agents, e.g., antioxidants. The present invention employs a novel mixed solvent system, which is allowed to completely remove any known impurities, i.e. Impurities B, C, D, E, and F.

Technical Solution

- [10] According to an aspect of the present invention, there is provided a process of preparing levofloxacin hemihydrate or monohydrate, the process comprising: (a) adding crude levofloxacin to a mixed solvent (A) containing water and an organic solvent selected from the group consisting of methyl acetate, ethyl acetate, and isobutyl methyl ketone or a mixed solvent (B) containing water and two organic solvents selected from the group consisting of t-butanol, isopropyl acetate, methyl acetate, ethyl acetate, and isobutyl methyl ketone, (b) refluxing the mixture obtained in the adding the crude levofloxacin to the mixed solvent (A) or (B) to form a solution, and (c) recovering levofloxacin hemihydrate or monohydrate from the solution.

Best Mode

- [11] A process of preparing levofloxacin hemihydrate or monohydrate without impurities according to an embodiment of the present invention includes purifying crude levofloxacin through re-crystallization using a novel mixed solvent.
- [12] As used herein, "crude levofloxacin" refers to levofloxacin before purification and may be prepared by known methods in the art, e.g., processes as disclosed in US Patent No. 6,316,618. The impurities include decarboxy-levofloxacin (Impurity B), desfluoro-levofloxacin (Impurity C), anti-levofloxacin (Impurity D), desmethyl-levofloxacin (Impurity E), and N-oxide levofloxacin (Impurity F).
- [13] The process of preparing levofloxacin hemihydrate or monohydrate includes (a) adding crude levofloxacin to a mixed solvent, (b) refluxing the mixture obtained in the step (a) to form a solution, and (c) recovering levofloxacin hemihydrate or

monohydrate from the solution obtained in the step (b).

[14] In the step (a), the mixed solvent may be a two- or three- component system. A mixed solvent (A) of a two-component system includes water and an organic solvent selected from the group consisting of methyl acetate, ethyl acetate, and isobutyl methyl ketone. Further, a mixed solvent (B) of a three-component system includes water and two organic solvents selected from the group consisting of t-butanol, isopropyl acetate, methyl acetate, ethyl acetate, and isobutyl methyl ketone.

[15] The water content in the mixed solvent (A) or (B) may be about 1.5 ~ 6.0 % (v/v), for example, about 3.0 % (v/v). If the amount of water in a mixed solvent is greater than 6.0 % (v/v), the yield may be decreased.

[16] Among the mixed solvents, a mixture of t-butanol, ethyl acetate, and water may be used. The volume ratio of t-butanol, ethyl acetate and water in the mixture may be 32.3 : 64.7 : 3.

[17] The refluxing may be performed using a conventional method, e.g., at about 50°C ~ 115°C, to produce solution of levofloxacin. Further, the recovering of levofloxacin hemihydrate or monohydrate may be performed using a conventional crystallization method, e.g., cooling, filtering under reduced pressure, and/or distilling under reduced pressure.

[18] When the process of the present embodiment is performed, high purity ($\geq 99.8\%$) levofloxacin hemihydrate or monohydrate may be obtained. As confirmed in the following Examples, all known impurities, i.e., Impurities B, C, D, E, F, are completely removed by the process of the present embodiment.

[19] The hydrate forms of levofloxacin may be controlled by the mixed solvent used or the water content. The preferable hydrate form of levofloxacin is levofloxacin hemihydrate.

[20] The present invention will now be further illustrated and described by the following examples, which are not intended to limit the scope of the invention.

[21] **Example 1. Preparation of crude levofloxacin**

[22] 5.1 g (11.42 mmol) of (-) potassium N-(1-hydroxy-propyl-2(S)-yl)-6-fluoro-7-(N-methylpiperazinyl)-8-nitro-4-quinolone-3-carboxylate was dissolved in 34 ml of methanol. 1.07 g of potassium hydroxide was added to the solution, which was then refluxed for 2.5 hours. The resulting reaction mixture was evaporated under reduced pressure to remove the solvent. 5.7 ml of 3 M acetic acid solution was added to the reaction mixture to produce a pale yellow precipitate. 10 mL of tetrahydrofuran (THF) was added to the obtained precipitate while stirring. The resultant solid was filtered, washed with water/THF (1/1, v/v), and dried to produce 3.0 g of crude levofloxacin.

[23] M. P. 226.5 °C ~ 227.2 °C

[24] ^1H -NMR (D_2O , δ , ppm) 1.49 (d, 3H, $J=6.8\text{Hz}$), 2.93 (s, 3H), 3.38 (broad, 4H), 3.54 (m, 4H), 4.38-4.42 (dd, 1H, $J=11.2\text{Hz}$ & 2Hz), 4.51-4.54 (dd, 1H, $J=11.6\text{Hz}$ & 2Hz), 4.63 (m, 1H), 7.46 (d, 1H, $J=12.8\text{Hz}$), 8.38 (s, 1H)

[25] **Example 2. Purification with mixed solvent containing methyl acetate and water**

[26] 1.18 g of the crude levofloxacin prepared in Example 1 was added to 59 ml of a mixed solvent containing methyl acetate and water (97 : 3). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 2.4 ml of the mixed solvent containing methyl acetate and water (97 : 3). The resulting wet cake was dried under reduced pressure to provide 1.01 g of levofloxacin hemihydrate (yield: 85.6 %).

[27] **Example 3. Purification with mixed solvent containing isobutyl methyl ketone and water**

[28] 1.15 g of the crude levofloxacin prepared in Example 1 was added to 35.7 ml of a mixed solvent containing isobutyl methyl ketone and water (98.5 : 1.5). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 2.3 ml of the mixed solvent containing isobutyl methyl ketone and water (98.5 : 1.5). The resulting wet cake was dried under reduced pressure to provide 1.03 g of levofloxacin hemihydrate (yield: 89.6 %).

[29] **Example 4. Purification with mixed solvent containing ethyl acetate and water**

[30] 2.0 g of the crude levofloxacin prepared in Example 1 was added to 80 ml of a mixed solvent containing ethyl acetate and water (97 : 3). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 4 ml of the mixed solvent containing ethyl acetate and water (97 : 3). The resulting wet cake was dried under reduced pressure to provide 1.8 g of levofloxacin hemihydrate (yield: 90 %).

[31] **Example 5. Purification with mixed solvent containing ethyl acetate, methyl acetate, and water**

[32] 2.0 g of the crude levofloxacin prepared in Example 1 was added to 90 ml of a mixed solvent containing ethyl acetate, methyl acetate, and water (19.4 : 77.6 : 3). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 4.0 ml of the mixed solvent containing ethyl acetate, methyl acetate, and water (19.4 : 77.6 : 3). The resulting wet cake was dried under reduced pressure to provide 1.75 g of levofloxacin monohydrate (yield: 87.5 %).

[33] **Example 6. Purification with mixed solvent containing ethyl acetate, methyl acetate, and water**

[34] 2.0 g of the crude levofloxacin prepared in Example 1 was added to 90 ml of a mixed solvent containing ethyl acetate, methyl acetate, and water (48.5 : 48.5 : 3). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 4.0 ml of the mixed solvent containing ethyl acetate, methyl acetate, and water (48.5 : 48.5 : 3). The resulting wet cake was dried under reduced pressure to provide 1.7 g of levofloxacin monohydrate (yield: 85 %).

[35] **Example 7. Purification with mixed solvent containing ethyl acetate, methyl acetate, and water**

[36] 1.5 g of the crude levofloxacin prepared in Example 1 was added to 75 ml of a mixed solvent containing ethyl acetate, methyl acetate, and water (77.6 : 19.4 : 3). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 3.0 ml of the mixed solvent containing ethyl acetate, methyl acetate, and water (77.6 : 19.4 : 3). The resulting wet cake was dried under reduced pressure to provide 1.25 g of levofloxacin monohydrate (yield: 83.3 %).

[37] **Example 8. Purification with mixed solvent containing t-butanol, ethyl acetate, and water**

[38] 2.0 g of the crude levofloxacin prepared in Example 1 was added to 54 ml of a mixed solvent containing t-butanol, ethyl acetate, and water (64.7 : 32.3 : 3). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 4.0 ml of the mixed solvent containing t-butanol, ethyl acetate, and water (64.7 : 32.3 : 3). The resulting wet cake was dried under reduced pressure to provide 1.69 g of levofloxacin hemihydrate (yield: 84.5 %).

[39] **Example 9. Purification with mixed solvent containing t-butanol, ethyl acetate, and water**

[40] 2.0 g of the crude levofloxacin prepared in Example 1 was added to 54 ml of a mixed solvent containing t-butanol, ethyl acetate, and water (48.5 : 48.5 : 3). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 4.0 ml of the mixed solvent containing t-butanol, ethyl acetate, and water (48.5 : 48.5 : 3). The resulting wet cake was dried under reduced pressure to provide 1.72 g of levofloxacin hemihydrate (yield: 86 %).

[41] **Example 10. Purification with mixed solvent containing t-butanol, ethyl acetate, and water**

[42] 2.0 g of the crude levofloxacin prepared in Example 1 was added to 64 ml of a mixed solvent containing t-butanol, ethyl acetate, water (32.3 : 64.7 : 3). The reaction

mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 4.0 ml of the mixed solvent containing t-butanol, ethyl acetate, and water (32.3 : 64.7 : 3). The resulting wet cake was dried under reduced pressure to provide 1.75 g of levofloxacin hemihydrate (yield: 87.5 %).

[43] **Example 11. Purification with mixed solvent containing t-butanol, methyl acetate, and water**

[44] 2.0 g of the crude levofloxacin prepared in Example 1 was added to 60 ml of a mixed solvent containing t-butanol, methyl acetate, and water (64.7 : 32.3 : 3). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 4.0 ml of the mixed solvent containing t-butanol, methyl acetate, and water (64.7 : 32.3 : 3). The resulting wet cake was dried under reduced pressure to provide 1.72 g of levofloxacin hemihydrate (yield: 86 %).

[45] **Example 12. Purification with mixed solvent containing t-butanol, methyl acetate, and water**

[46] 2.0 g of the crude levofloxacin prepared in Example 1 was added to 70 ml of a mixed solvent containing t-butanol, methyl acetate, and water (48.5 : 48.5 : 3). The reaction mixture was refluxed for 1 hour and then cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 4.0 ml of the mixed solvent containing t-butanol, methyl acetate, and water (48.5 : 48.5 : 3). The resulting wet cake was dried under reduced pressure to provide 1.69 g of levofloxacin hemihydrate (yield: 84.5%).

[47] **Example 13. Purification with mixed solvent containing t-butanol, methyl acetate, and water**

[48] 2.0 g of the crude levofloxacin prepared in Example 1 was added to 70 ml of a mixed solvent containing t-butanol, methyl acetate, and water (32.3 : 64.7 : 3). The reaction mixture was refluxed for 1 hour and cooled to room temperature. The resulting precipitate was filtered under reduced pressure and then washed with 4.0 ml of the mixed solvent containing t-butanol, methyl acetate, and water (32.3 : 64.7 : 3). The resulting wet cake was dried under reduced pressure to provide 1.59 g of levofloxacin hemihydrate (yield: 79.5 %).

[49] Test Example 1.

[50] The levofloxacin hemihydrate or monohydrate prepared in Examples 1 ~ 13 were analyzed by HPLC to determine the concentration of impurities, i.e., decarboxy-levofloxacin (Impurity B), desfluoro-levofloxacin (Impurity C), anti-levofloxacin (Impurity D), desmethyl-levofloxacin (Impurity E) and N-oxide levofloxacin (Impurity F). The results of the HPLC analysis are summarized in the following Table 1.

[51] Table 1.

Ex.	Mixed Solvent	Purity	Imp. B	Imp. C	Imp. D	Imp. E	Imp. F
1	Crude levofloxacin	99.57	0.01	0.01	-	0.01	0.01
2	Methyl acetate: water (97: 3)	99.81	-	-	-	-	-
3	Isobutyl methyl ketone: water (98.5: 1.5)	99.83	-	-	-	-	-
4	Ethyl acetate: water (97: 3)	99.84	-	-	-	-	-
5	Ethyl acetate: methyl acetate: water (19.4: 77.6: 3)	99.86	-	-	-	-	-
6	Ethyl acetate: methyl acetate: water (48.5: 48.5: 3)	99.88	-	-	-	-	-
7	Ethyl acetate: methyl acetate: water (77.6: 19.4: 3)	99.88	-	-	-	-	-
8	t-Butanol: ethyl acetate: water (64.7: 32.3: 3)	99.88	-	-	-	-	-
9	t-Butanol: ethyl acetate: water (48.5: 48.5: 3)	99.90	-	-	-	-	-
10	t-Butanol: ethyl acetate: water (32.3: 64.7: 3)	99.90	-	-	-	-	-
11	t-Butanol: methyl acetate: water (64.7: 32.3: 3)	99.90	-	-	-	-	-
12	t-Butanol: methyl acetate: water (48.5: 48.5: 3)	99.89	-	-	-	-	-
13	t-Butanol: methyl acetate: water (32.3: 64.7: 3)	99.90	-	-	-	-	-

[52] - : not detected

[53] As shown above, according to the process of the present invention, levofloxacin hemihydrate or monohydrate may be obtained with high purity ($\geq 99.8\%$), without impurities, such as Impurities B, C, D, E, and F.

WE CLAIM:

1. A process of preparing levofloxacin hemihydrate or monohydrate without decarboxy-levofloxacin, desfluoro-levofloxacin, anti-levofloxacin, desmethyl-levofloxacin, and N-oxide levofloxacin, the process comprising:

adding crude levofloxacin to

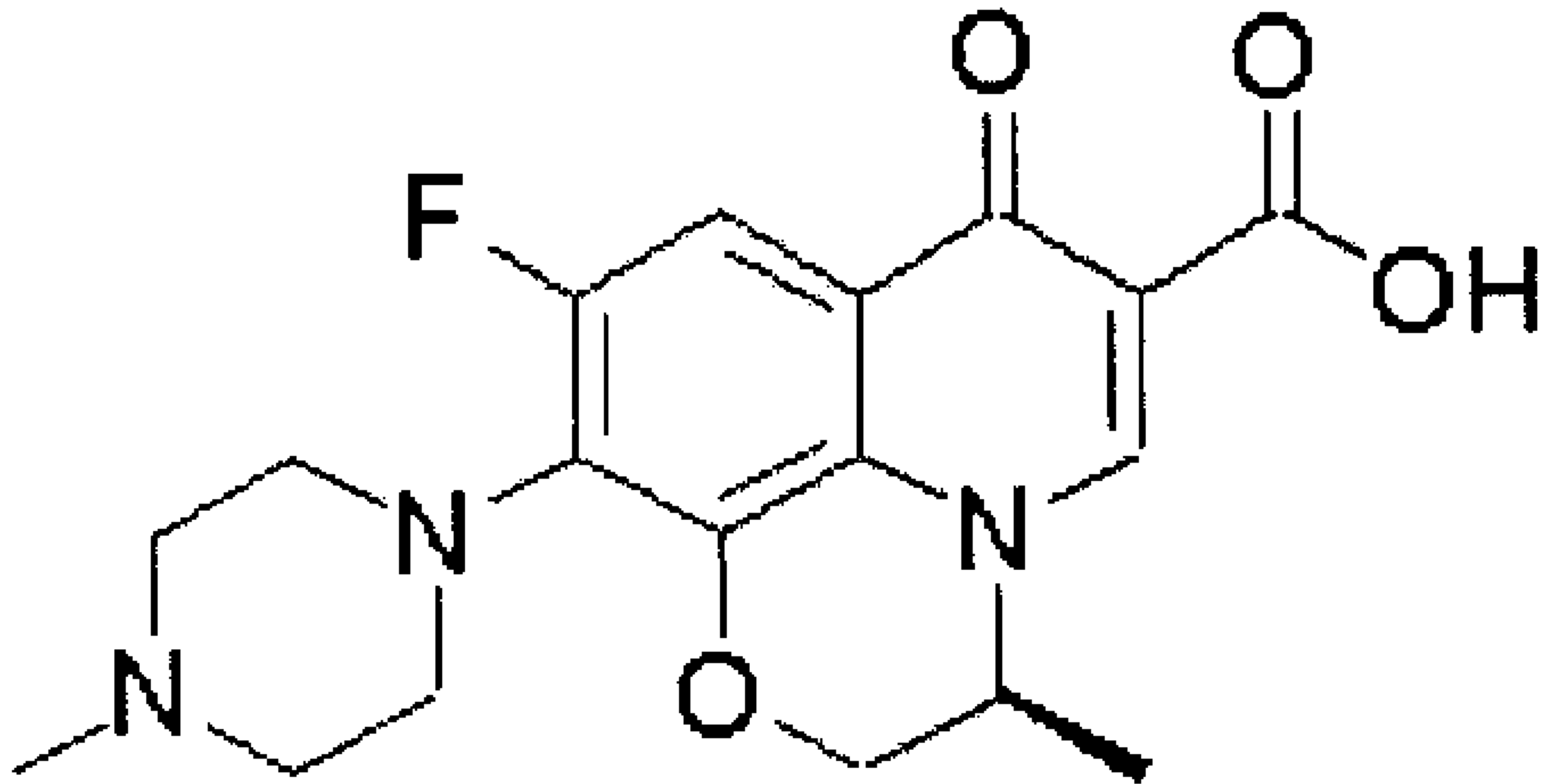
a mixed solvent (A) containing water and an organic solvent selected from the group consisting of methyl acetate, ethyl acetate, and isobutyl methyl ketone; or

a mixed solvent (B) containing water and two organic solvents selected from the group consisting of t-butanol, isopropyl acetate, methyl acetate, ethyl acetate, and isobutyl methyl ketone,

refluxing the mixture obtained in the adding the crude levofloxacin to the mixed solvent (A) or (B) to form a solution, followed by cooling the solution, and

recovering the precipitated levofloxacin hemihydrate or monohydrate from the solution by filtration or distillation.

2. The process of claim 1, wherein the water content in the mixed solvent (A) or (B) is 1.5 ~ 6.0 % (v/v).
3. The process of claims 1 or 2, wherein the mixed solvent (B) contains t-butanol, ethyl acetate, and water.
4. The process of claim 3, wherein the volume ratio of t-butanol, ethyl acetate and water is 32.3 : 64.7 : 3.



(I)