EXHIBIT A

US006333045B1

(12) **United States Patent**
Yasueda et al.

(10) **Patent No.: US 6,333,045 B1**
(45) **Date of Patent: Dec. 25, 2001**

(54) **AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION COMPRISED OF GATIFLOXACIN**

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(73) Assignees: **Senju Pharmaceutical Co., Ltd.**, Osaka; **Kyorin Pharmaceutical Co., Ltd.**, Tokyo, both of (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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PCT Pub. Date: **Mar. 2, 2000**

(30) **Foreign Application Priority Data**

Aug. 21, 1998 (JP) 10/235432

(51) **Int. Cl.**[7] **A61F 13/00**; A61K 31/495

(52) **U.S. Cl.** **424/434**; 424/400; 424/422; 424/427; 424/437; 424/78.04; 514/254

(58) **Field of Search** 424/400, 78.04, 424/422, 427, 434, 437

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Assistant Examiner—Charesse L. Evans
(74) *Attorney, Agent, or Firm*—Wenderoth, Lind & Ponack, L.L.P.

(57) **ABSTRACT**

There is provided an aqueous liquid pharmaceutical composition which comprises Gatifloxacin (chemical nomenclature: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid) or its salt and disodium edetate. Further, there are provided a method for raising corneal permeability of Gatifloxacin, a method for preventing precipitation of Gatifloxacin crystals, and a method for preventing coloration of Gatifloxacin by incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt.

11 Claims, No Drawings

AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION COMPRISED OF GATIFLOXACIN

FIELD OF THE INVENTION

The present invention relates to an aqueous liquid pharmaceutical composition comprising as a main component a quinolone carboxylic acid derivative, Gatifloxacin (chemical nomenclature: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid). Further, the present invention relates to a method for raising corneal permeability of Gatifloxacin, a method for preventing precipitation of Gatifloxacin crystals, and a method for preventing coloration of Gatifloxacin.

BACKGROUND OF THE INVENTION

Gatifloxacin is a new quinolone antimicrobial agent which is recognized to exhibit a strong antimicrobial activity against not only Gram-negative bacteria but also Gram-positive bacteria, anaerobes and mycoplasmas. Then, it has been proposed to apply it to ophthalmological infectious diseases such as conjunctivitis, dacryocystitis, hordeolum etc. and otorhinological infectious diseases such as otitis externa, otitis media, sinusitis etc (see JP-B 8-9597).

For designing a pharmaceutical preparation in the form of eye drops containing an antimicrobial agent, an index is to raise corneal permeability of the agent to increase the amount of the agent to transfer to aqueous humor. However, in general, the agent applied to eyes can scarcely pass into inside of the eyes because of dilution with tears and the barrier function of corneas. Then, as a method of improving corneal permeability of the agent, a method using an absorption enhancer has been proposed. In addition, a method using a viscous base material has been proposed to increase the agent-retentivity at the anterior ocular segment.

OBJECTS OF THE INVENTION

With regard to Gatifloxacin, although its application. to ophthalmological or otorhinological infectious diseases has been proposed, there is no report about a study of an aqueous liquid pharmaceutical composition thereof for topical administration, which can be actually applied to eyes, for example, its passing into inside of eyes, stability, etc.

In view of these circumstances, an object of the present invention is to permit actual application of Gatifloxacin in ophthalmological or otorhinological field, in particular, to provide an aqueous liquid pharmaceutical composition comprising as an effective component Gatifloxacin.

SUMMARY OF THE INVENTION

The present inventors have intensively studied to apply Gatifloxacin in ophthalmological field and, consequently, have found that this objective can be achieved by coexistence of Gatifloxacin with disodium edetate.

Disodium edetate is considered to lower the calcium concentration in corneal epithelium cells and expanding intercellular spaces, thereby accelerating passing of a water-soluble medicament into inside of eyes. However, a rise in corneal permeability of a medicament depends on a concentration of disodium edetate (Journal of Pharmaceutical Science, 77: 3–14, 1988) and, normally, at present, disodium edetate should be used at a high concentration as much as 0.5% (Investigative Ophthalmology & Visual Science, 66: 110–113, 1985; Experimental Eye Research, 54: 747–757, 1992; Pharmaceutical Research, 12: 1146–1150). Nevertheless, the present inventors have found that corneal permeability of Gatifloxacin can be improved at a lower concentration of disodium edetate.

Further, it has been known that the solubility of Gatifloxacin depends on pH and its solubility at about physiological pH is very low. Then, in order to dissolve a sufficient amount of Gatifloxacin in an aqueous liquid pharmaceutical composition, pH of the composition should be adjusted to an acidic or alkaline range, which causes a problem such as irritation upon topical administration. However, the present inventors also have found that the solubility of Gatifloxacin at about physiological pH is improved by coexistence thereof with disodium edetate.

The present invention has been completed based on these present inventors' novel findings and, according to the present invention, there is provided an aqueous liquid pharmaceutical composition which comprises Gatifloxacin or its salt and disodium edetate. In particular, the aqueous liquid pharmaceutical composition of the present invention is an aqueous solution containing Gatifloxacin or its salt and disodium edetate.

Further, the present invention provides a method for raising corneal permeability of Gatifloxacin which comprises incorporating disodium edetate into eye drops containing Gatifloxacin or its salt; a method for preventing precipitation of Gatifloxacin crystals which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt; and a method for preventing coloration of Gatifloxacin which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt.

This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, Gatifloxacin or its salt is used as the effective component. Examples of the salt of Gatifloxacin used in the present invention include those with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, etc.; those with organic acids such as methanesulfonic acid, lactic acid, oxalic acid, acetic acid, etc.; or those with sodium, potassium, magnesium, calcium, aluminum, cerium, chromium, cobalt, copper, iron, zinc, platinum, silver, etc.

Normally, the amount of Gatifloxacin or its salt (hereinafter sometimes simply referred to as "Gatifloxacin") to be formulated in the aqueous liquid pharmaceutical composition of the present invention is varied according to the degree of infection of a particular subject, but normally, Gatifloxacin is formulated within the range of 0.1 to 1.0 w/v %, preferably 0.1 to 0.8 w/v %, more preferably 0.3 to 0.5 w/v %.

Normally, disodium edetate is formulated in an amount of 0.001 to 0.2 w/v %, preferably 0.005 to 0.1 w/v %, more preferably 0.01 to 0.1 w/v %.

Normally, the aqueous liquid pharmaceutical composition of the present invention is adjusted to pH 5 to 8, preferably pH 5.5 to 7.5, more preferably pH 6 to 7.

If necessary, the aqueous liquid pharmaceutical composition of the present invention may further contain appropriate additives, for example, an isotonic agent. (e.g., sodium chloride, potassium chloride, boric acid, glycerin,

propylene glycol, mannitol, sorbitol, glucoseetc.); a buffer solution (e.g., phosphate buffer solution, acetate butter solution, borate buffer solution, citrate buffer solution, glutamic acid, ϵ-aminocapronic acid, etc.); a preservative (e.g., benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, p-hydroxybenzoate, etc.), a thickening agent (e.g., methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium hyaluronate, carboxyvinyl polymer, polyvinyl alcohol, polyvinyl pyrrolidone, Macrogol (polyethylene glycol), etc.), a pH adjusting agent (e.g., hydrochloric acid, sodium hydroxide, acetic acid, phosphoric acid, etc.), and the like.

The aqueous liquid pharmaceutical composition of the present invention can be produced by a per se known method. For example, it can be produced by the process described in the section of "Ophthalmic Solutions" or "Liquids and Solutions", General Rules for Preparations, The Japanese Pharmacopoeia Thirteenth Edition.

The aqueous liquid pharmaceutical composition of the present invention has antimicrobial activity and can be used for prophylaxis and therapy of blepharitis, hordeolum, dacryocystitis, conjunctivitis, tarsitis, keratitis, corneal ulcer, postoperative infection, and the like. For this purpose, the composition can be instilled in the eye about three times a day at a dosage of one drop per once. For otitis externa or otitis media, normally, the composition can be instilled in the ear twice a day at a dosage of 6 to 10 drops per once. Further, for sinusitis, normally, the composition can be sprayed and inhaled three times every other day in a week at a dosage of 2 to 4 ml per once, or can be administered in the maxillary sinus once a week at a dosage of 1 ml per once. The dosage can be increased or decreased according to the degree of a particular disease condition.

The present invention will be further illustrated by the following experiments and examples, but the present invention is not limited thereto.

Experiment 1

Effect of disodium edetate on transfer of Gatifloxacin to aqueous humor

Method

According to the formulations of Table 1, eye drops of Gatifloxacin were prepared (formulations A–C). Each of the eye drops (50 μl/eye) was instilled once in the eyes of male Japanese albino rabbits (body weight: about 2 kg). At one hour after the instillation, the aqueous humor was collected and the Gatifloxacin concentration was determined by HPLC.

TABLE 1

Formulations	A	B	C
Gatifloxacin	0.5 g	0.5 g	0.5 g
Disodium edetate	—	—	0.05 g
Sodium chloride	0.9 g	0.9 g	0.9 g
Hydrochloric acid	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml	to total 100 ml
pH	7.0	6.0	6.0

Results

The concentration of Gatifloxacin in the aqueous humor at one hour after the instillation is shown in Table 2.

When pH dropped, the amount of Gatifloxacin transferred to the aqueous humor decreased. For the formulation adjusted to pH 6.0 (formulation C), the amount of Gatifloxacin transferred to the aqueous humor increased by about 1.2 times and 1.5 times as much as those of the formulations A (pH 7.0) and B (pH 6.0) which were used as controls, respectively.

Since the concentration of disodium edetate normally used for raising corneal permeability is 0.5 w/v %, these results show that corneal permeability of Gatifloxacin has been improved even by using disodium edetate in 1/10 amount as much as that normally used.

TABLE 2

Formulations	Gatifloxacin concentration in aqueous humor (μg/ml)
A	1.61 ± 0.43
B	1.30 ± 0.42
C	1.93 ± 0.95

Experiment 2

Effect of disodium edetate on precipitation of Gatifloxacin crystals

Method

According to the formulations of Table 3, aqueous liquid preparations of Gatifloxacin were prepared (formulations B–D). Each solution was filled in 5 ml glass ampoules. The ampoules were subjected to freezing at −30° C. (overnight) and then thawing at room temperature repeatedly to observe precipitation of Gatifloxacin crystals.

TABLE 3

Formulations	B	C	D
Gatifloxacin	0.5 g	0.5 g	0.5 g
Disodium edetate	—	0.05 g	0.1 g
Sodium chloride	0.9 g	0.9 g	0.9 g
Hydrochloric acid	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml	to total 100 ml
pH	6.0	6.0	6.0

Results

In the formulation in which disodium edetate was not formulated (formulation B), crystals were precipitated when freezing and thawing were repeated twice to three times. On the other hand, when disodium edetate was formulated (formulations C and D), no precipitation of crystals was recognized even when freezing and thawing were repeated ten times.

These results show that precipitation of Gatifloxacin crystals under storage conditions at a low temperature is prevented by formulating disodium edetate in an aqueous liquid preparation of Gatifloxacin.

Experiment 3

Effect of disodium edetate on preventing coloration of Gatifloxacin

Method

Sodium chloride (0.86 g) and 0.1 mol/liter hydrochloric acid (5.2 ml) were added to sterilized purified water (80 ml) in a stainless steel (SUS316) beaker of 8 cm diameter and the mixture was stirred. Then, Gatifloxacin (0.32 g) and disodium edetate (at a final concentration of 0%, 0.001%, 0.005%, 0.01% or 0.05%) were added thereto and dissolved therein. The solution was adjusted to pH 6.5 with 0.1 mol/liter sodium hydroxide and the total volume was made

up to 100 ml to obtain an aqueous liquid preparation of Gatifloxacin. A color difference between the aqueous liquid preparation and sterilized purified water was determined with a differential calorimeter (Chroma meter CT-210C manufactured by Minolta, light source Lab table system). As a control, an aqueous liquid preparation of Gatifloxacin prepared in a glass beaker was used.

Results

The color difference determined is shown in Table 4.

The aqueous liquid preparation prepared in the glass beaker and used as the control had the color difference of 1.9 to 2.0 and a pale yellow color. On the other hand, the aqueous liquid preparation prepared in the stainless steel beaker had the color difference of 3.17 in case that disodium edetate was not added and 2.42 in case that 0.01% of disodium edetate was added. They had a light yellow color and a pale yellow color, respectively. Thus, they were discolored by formulating disodium edetate.

In view of these results, it is considered that Gatifloxacin is colored by the metal ion dissolved in the preparation from the stainless steel beaker. Further, these results show that addition of disodium edetate can prevent coloration of Gatifloxacin.

TABLE 4

Concentration of disodium edetate (%)	Color Difference	
	Stainless Steel Beaker	Glass Beaker
0	3.17	1.90
0.001	3.08	1.93
0.005	3.05	2.02
0.01	2.42	1.94
0.05	2.19	1.93

EXAMPLE 1

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Disodium edetate	0.1 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	7.0

EXAMPLE 2

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Disodium edetate	0.05 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.

-continued

Ingredients	Amount
sterilized purified water	up to 100 ml
pH	7.0

EXAMPLE 3

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Disodium edetate	0.1 g
Sodium dihydrogen phosphate	0.1 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	7.0

EXAMPLE 4

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.3 g
Disodium edetate	0.05 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	6.0

EXAMPLE 5

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Sodium edetate	0.01 g
Glycerin	2.6 g
Benzalkonium chloride	0.005 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	7.5

EXAMPLE 6

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Sodium edetate	0.05 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	5.5

EXAMPLE 7

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.3 g
Disodium edetate	0.05 g
Sodium chloride	0.9 g
Hydroxypropylmethyl cellulose	0.1 g
Methyl p-hydroxybenzoate	0.026 g
Propyl p-hydroxybenzoate	0.014 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	6.0

EXAMPLE 8

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Disodium edetate	0.01 g
Sodium chloride	0.83 g
Benzalkonium chloride	0.005 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	5.5

EXAMPLE 9

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.3 g
Disodium edetate	0.01 g

-continued

Ingredients	Amount
Sodium chloride	0.86 g
Benzalkonium chloride	0.005 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	6.0

As shown in Experiment 1, according to the eye drops of the present invention, corneal permeability of the effective component, Gatifloxacin, can be improved even by using disodium edetate in 1/10 amount as much as that normally used. Further, as shown in Experiment 2, the aqueous liquid preparation of the present invention can. prevent precipitation of Gatifloxacin crystals under storage conditions as a low temperature. Furthermore, as shown in Experiment 3, coloration of Gatifloxacin by a metal ion can be prevented. Thus, the aqueous liquid preparation of the present invention is very useful.

What is claimed is:

1. An aqueous liquid pharmaceutical composition which comprises Gatifloxacin or its salt and disodium edetate.

2. The aqueous liquid pharmaceutical composition according to claim **1**, wherein pH of the composition is within the range of 5 to 8.

3. The aqueous liquid pharmaceutical composition according to claim **1**, where the composition is in the form of eye drops.

4. The aqueous liquid pharmaceutical composition according to claim **1**, where the composition is in the form of ear drops.

5. The aqueous liquid pharmaceutical composition according to claim **1**, where the composition is in the form of nasal drops.

6. A method for raising corneal permeability of Gatifloxacin which comprises incorporating disodium edetate into eye drops containing Gatifloxacin or its salt.

7. A method for preventing precipitation of Gatifloxacin crystals which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt.

8. A method for preventing coloration of Gatifloxacin which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt.

9. The aqueous liquid pharmaceutical composition according to claim **2**, where the composition is in the form of eye drops.

10. The aqueous liquid pharmaceutical composition according to claim **2**, where the composition is in the form of ear drops.

11. The aqueous liquid pharmaceutical composition according to claim **2**, where the composition is in the form of nasal drops.

* * * * *

EXHIBIT B

US005880283A

United States Patent [19]

Matsumoto et al.

[11] Patent Number: 5,880,283

[45] Date of Patent: *Mar. 9, 1999

[54] **8-ALKOXYQUINOLONECARBOXYLIC ACID HYDRATE WITH EXCELLENT STABILITY AND PROCESS FOR PRODUCING THE SAME**

[75] Inventors: **Toyomi Matsumoto**, Kamiina-gun; **Masamoto Hara**, Okaya; **Kunio Miyashita**; **Yukihiro Kato**, both of Okaya, all of Japan

[73] Assignee: **Kyorin Pharmaceutical Co., Ltd.**, Tokyo, Japan

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **860,325**

[22] PCT Filed: **Dec. 5, 1995**

[86] PCT No.: **PCT/JP95/02477**

§ 371 Date: **Jun. 23, 1997**

§ 102(e) Date: **Jun. 23, 1997**

[87] PCT Pub. No.: **WO96/19472**

PCT Pub. Date: **Jun. 27, 1996**

[30] **Foreign Application Priority Data**

Dec. 21, 1994 [JP] Japan 6-335569

[51] **Int. Cl.**[6] **C07D 401/10**; C07D 401/04

[52] **U.S. Cl.** **544/363**

[58] **Field of Search** 544/363

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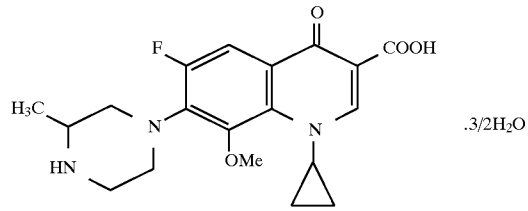
5,597,923	1/1997	Nagano et al.	546/156

Primary Examiner—Mukund J. Sham
Assistant Examiner—Ann Kessinger
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier, & Neustadt, P.C.

[57] **ABSTRACT**

The invention provides 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate with excellent stability represented by a following formula (1),



(1)

and process for producing the same.

9 Claims, 7 Drawing Sheets

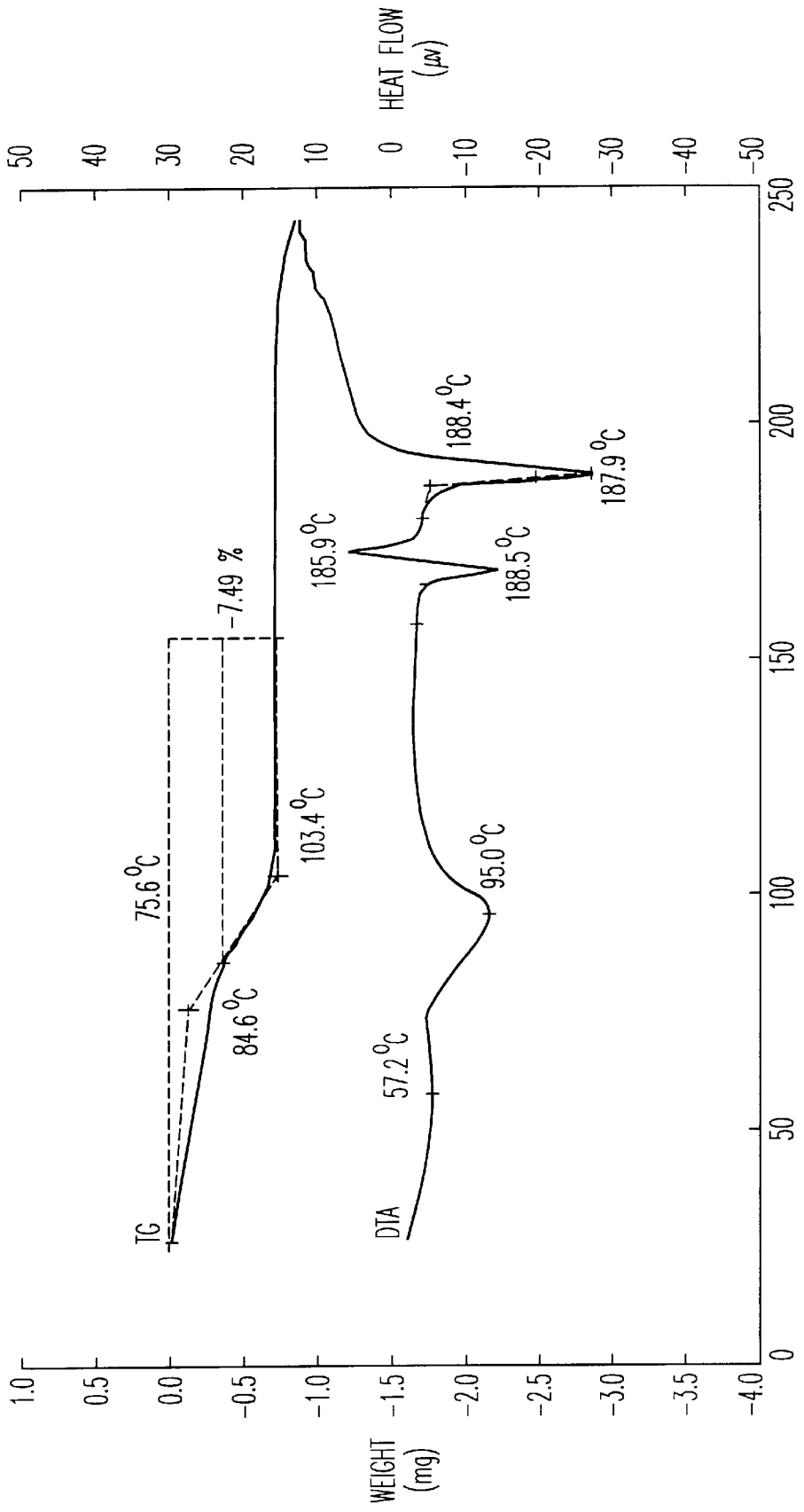

HEAT FLOW (μV)
50
40
30
20
10
0
-10
-20
-30
-40
-50
250
200
150
100
50
0
TEMPERATURE (°C)
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
WEIGHT (mg)
TG
DTA
75.6°C
84.6°C
103.4°C
-7.49 %
57.2°C
95.0°C
185.9°C
188.5°C
188.4°C
187.9°C

FIG. 1

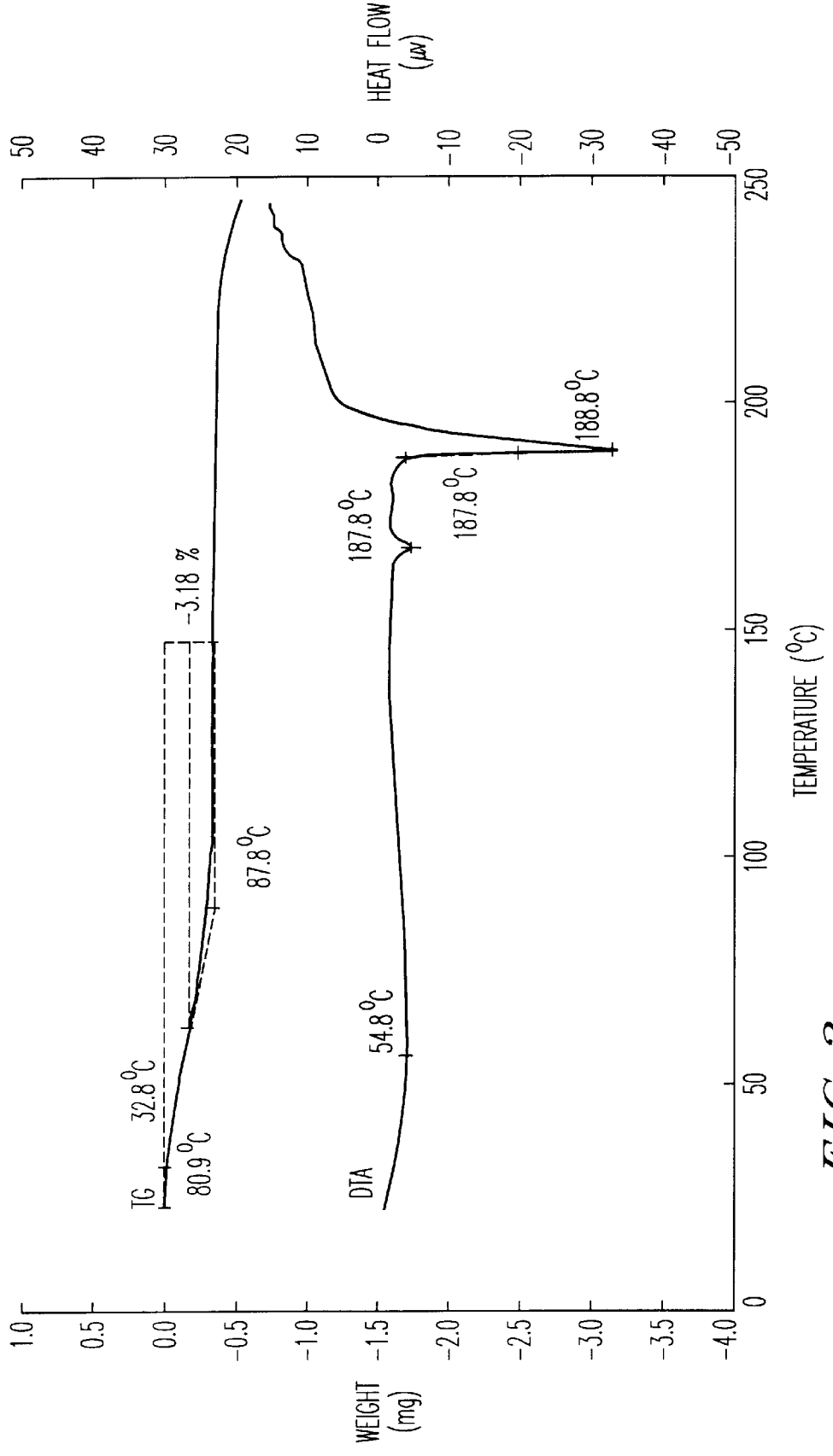
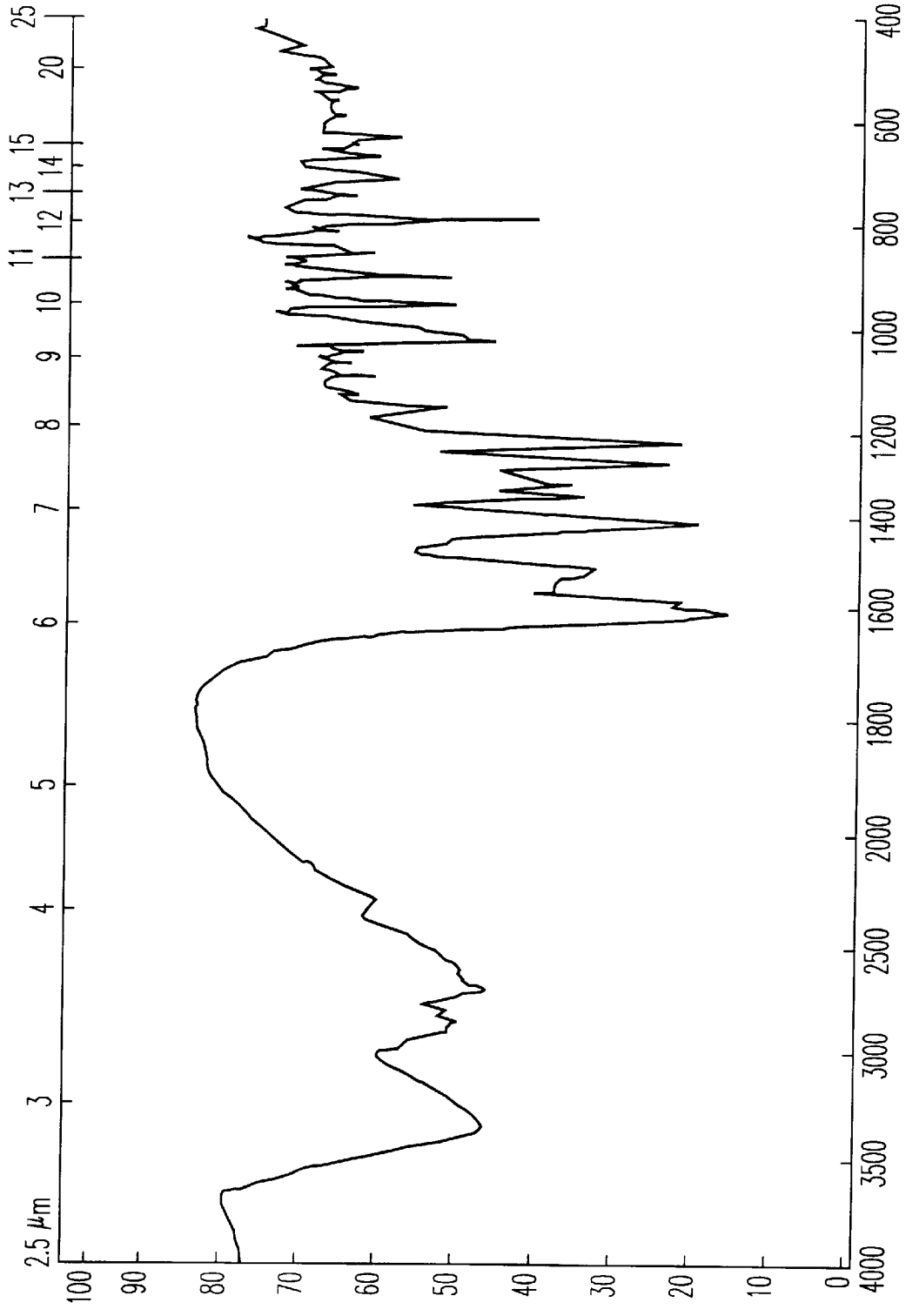

HEAT FLOW (μv)
50
40
30
20
10
0
-10
-20
-30
-40
-50
250
200
150
100
50
0
TEMPERATURE (°C)
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
WEIGHT (mg)
TG
DTA
32.8°C
80.9°C
87.8°C
-3.18 %
54.8°C
187.8°C
187.8°C
188.8°C

FIG. 2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30
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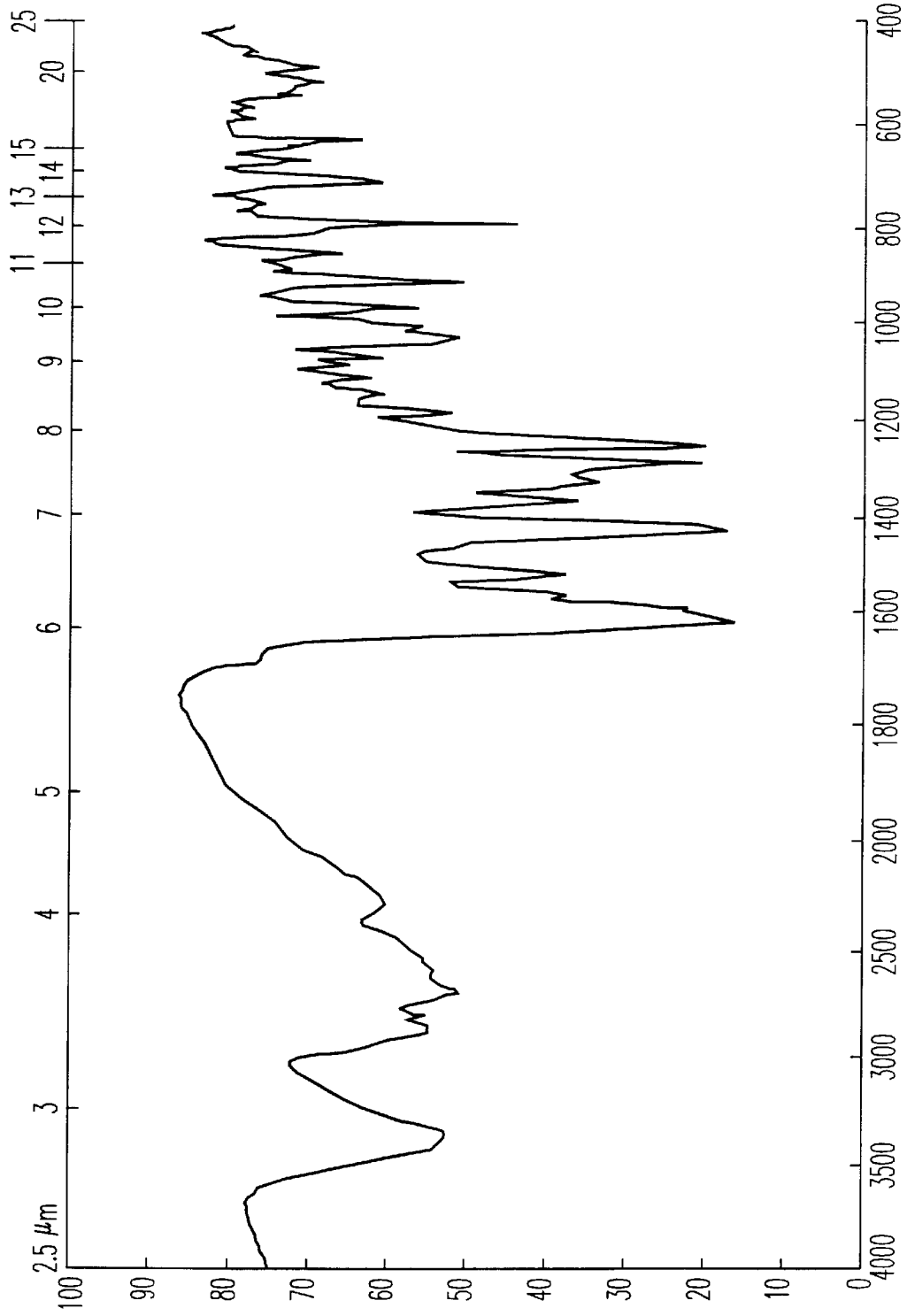
WAVE NUMBER CM^{-1}

FIG. 3


2.5 μm
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12
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14
15
20
25
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
WAVE NUMBER CM^{-1}

FIG. 4

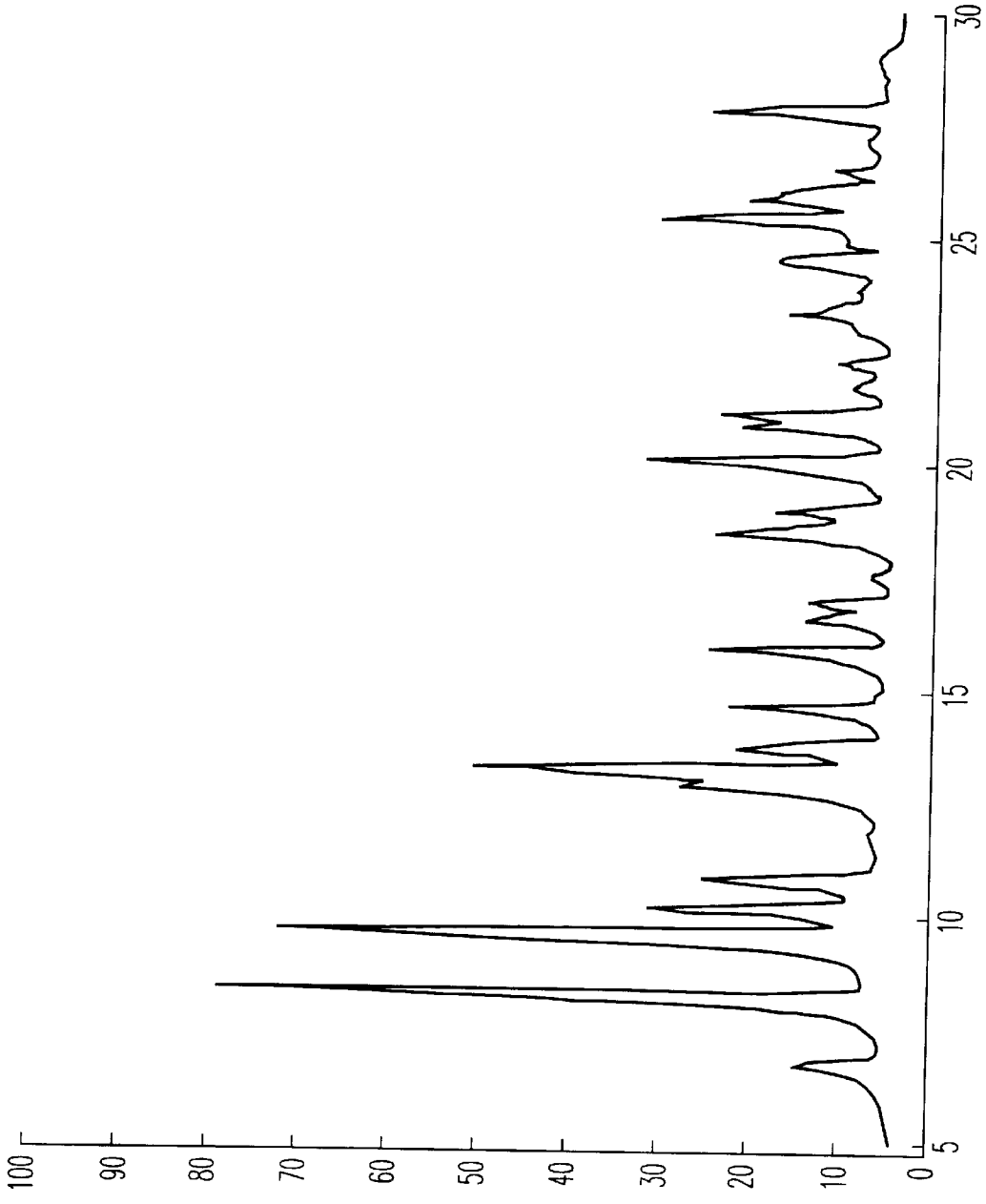


FIG. 5

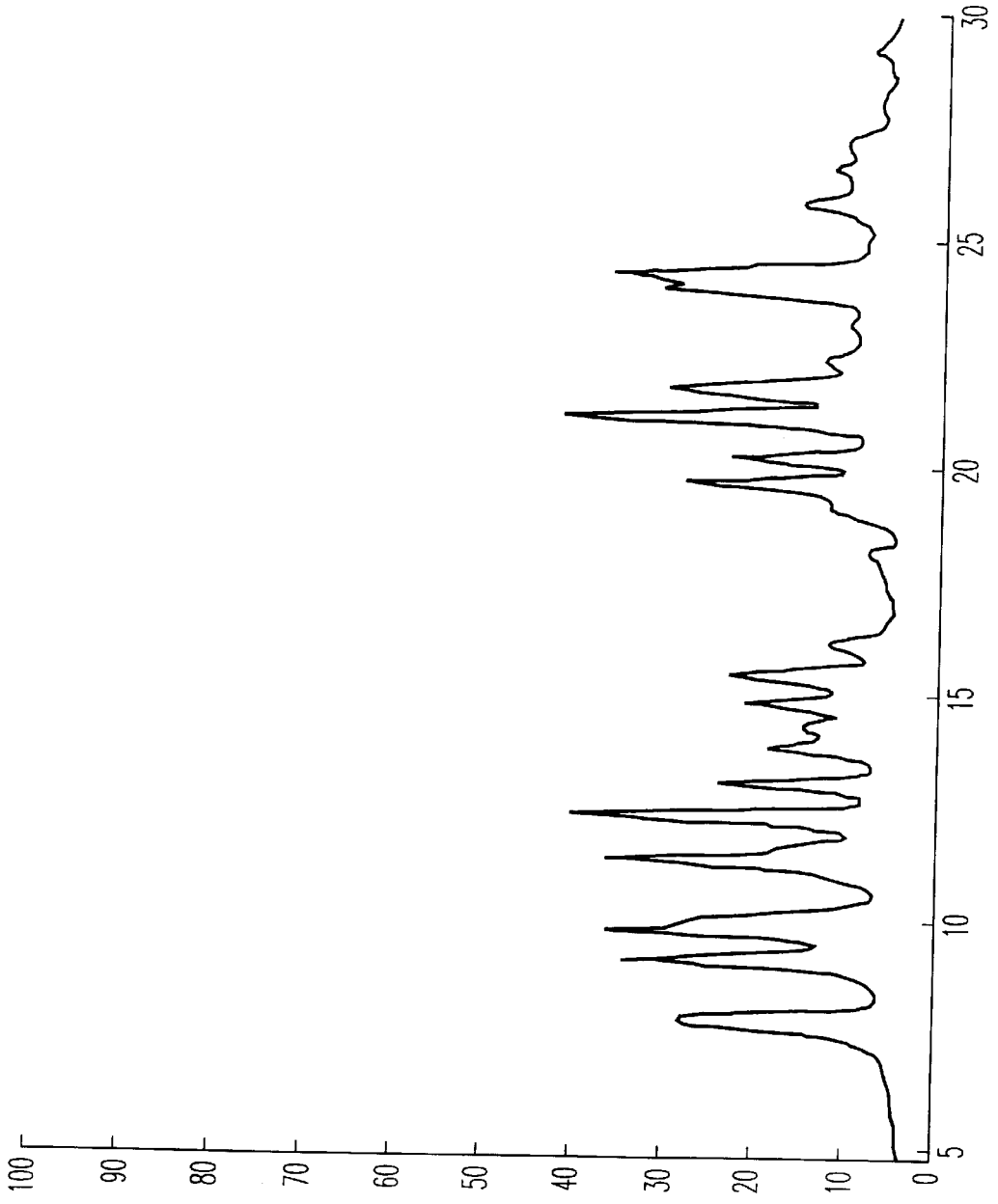


FIG. 6

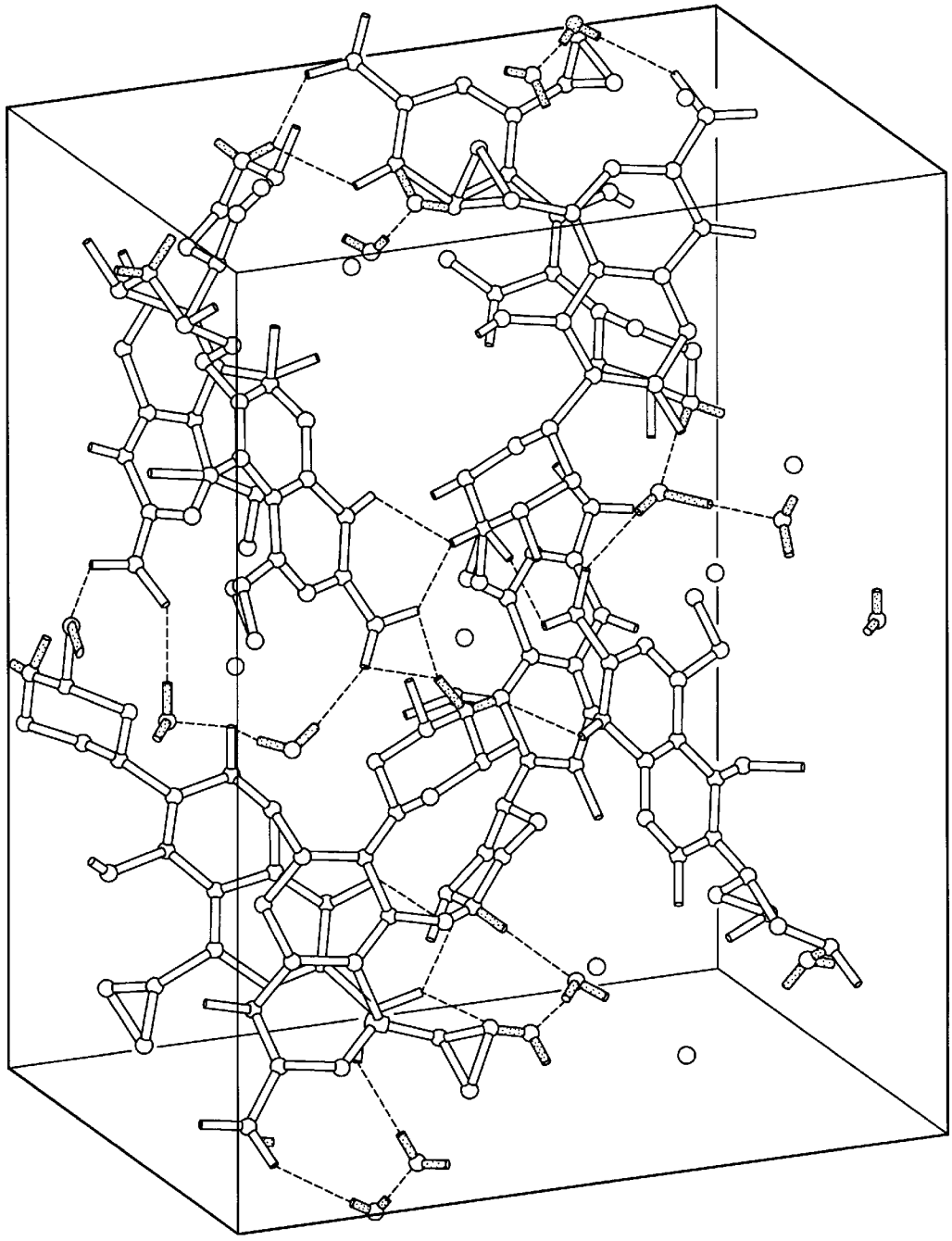


FIG. 7

8-ALKOXYQUINOLONECARBOXYLIC ACID HYDRATE WITH EXCELLENT STABILITY AND PROCESS FOR PRODUCING THE SAME

TECHNICAL FIELD

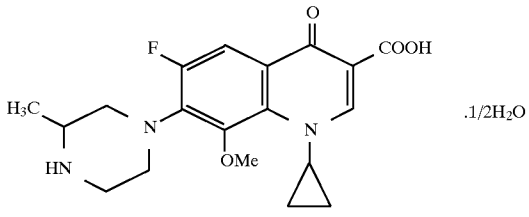
The present invention relates to 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate with excellent stability and process for producing the same.

BACKGROUND TECHNOLOGY

Antibacterial agents of the quinolonecarboxylic acid class have achieved a striking progress in recent years. Because of broad antibacterial spectrum and potent bactericidal activity ranging from Gram-positive bacteria to negative bacteria, they have become to be used for surgical infectious diseases as well as urinary tract infectious disease and their usefulness is highly appreciated, leading to great contribution in the clinical practice.

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid is particularly noted because of not only its potent antibacterial activity but also higher selectivity against bacteria from mammalian cells, which brings on an excellent selective toxicity.

In Japanese Unexamined Patent Publication No. Sho 62-252772, hemihydrate of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid represented by a formula (2) is disclosed.

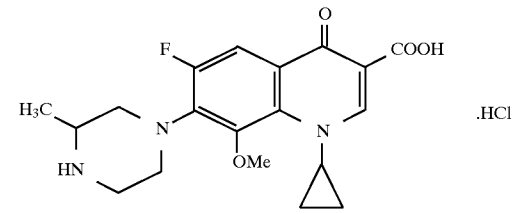


(2)

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid tends to make a hydrate because of its strong hygroscopicity, and it easily forms a hemihydrate when recrystallizing from water-containing organic solvent or when drying crystals obtained by the recrystallization method by neutralization according to acid-alkali recrystallization.

It was revealed by us, however, that the measured weight of this hemihydrate increases with the rise of environmental humidity. It was further revealed by us that the tablet containing the hemihydrate has poor disintegration and dissolution rates, leading to disadvantages in pharmaceutical manufacturing.

Moreover, in Japanese Unexamined Patent Publication No. Sho 63-198664, hydrochloride of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid represented by a formula (3) is disclosed.



(3)

However, with respect to this hydrochloride (3), too, the instability due to the hygroscopicity of drug substance same as or more than that of hemihydrate (2) and the problems of poor disintegration and dissolution rate when converted to tablets have become evident.

DISCLOSURE OF THE INVENTION

As a result of studies for the purpose of solving the problems of said 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid hemihydrate and hydrochloride, the inventors have found that 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate is a stable compound and excellent also in pharmaceutical manufacturing. Namely, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate has been found to be stable under different conditions of humidity, and the disintegration and dissolution rates of the tablets manufactured have also found to be good.

In addition, as a means to obtain 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate, we have found that the target compound can be obtained efficiently by heating an aqueous suspension of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid under stirring, leading to the completion of the invention.

Here, the aqueous suspension represents a suspension after neutralization in the acid-alkali recrystallization during the process for purification, a suspension of isolated crystals added with water, or the like, and it is possible to manipulate with amount of water 3 to 20 times as much as crystals, but it is preferable to use 3 to 5 times for obtaining the target compound in high yield.

It is optimum to stir for 10 to 30 minutes at a temperature of, for example, 50° to 100° C., preferably 80° to 90° C.

The pH of aqueous suspension is preferable to be in the vicinity of neutrality (6.0–8.0).

After collecting the first crop of the target compound by filtration, the second crop can be obtained by cooling the filtrate to room temperature, which may result in an increase of overall yield.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a diagram showing the result of thermal analysis of the inventive substance, FIG. **2** is a diagram showing the result of thermal analysis of comparative substance, FIG. **3** is a diagram showing infrared spectrum of the inventive substance, FIG. **4** is a diagram showing infrared spectrum of comparative substance, FIG. **5** is a diagram showing the result of X-ray diffraction of the inventive substance, FIG. **6** is a diagram showing the result of X-ray diffraction of comparative substance, and FIG. **7** is an illustrative diagram showing the crystal structure of the inventive substance.

BEST EMBODIMENT FOR PUTTING THE INVENTION INTO PRACTICE

In following, the invention will be illustrated in more detail showing an example, but the invention is not subject to any restriction by this example.

(EXAMPLE 1)

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (85 g) was suspended into water (425 ml, 5 times volume) and stirred for 10 minutes at an inner temperature of 80° to 85° C. After hot filtration at the same temperature, the crystals were dried to obtain the target compound (84.43 g) at a yield of 92.7%.

Elemental analysis: $C_{19}H_{22}FN_3O_4.3/2H_2O$

	C	H	N	Water content
Calculated	56.71	6.26	10.44	6.7
Found	56.79	6.15	10.44	7.3

(1) Instruments Used

TG/DTA: Rigaku Corporation (TAS-200; Control section), TG8101D2 (Measuring apparatus)

Infrared spectrophotometer: Hitachi, Ltd., Model 270-30

Powder X-ray diffraction apparatus: Rigaku Corporation, Model 2013

Single crystal X-ray diffraction apparatus: Rigaku Corporation Model AFC5R

Karl Fischer moisture meter: Kyoto Electronics Manufacturing Co., Ltd., Model MKA-3P

1) Thermal analysis (TG/DTA)

Employing each about 10 mg of samples of the inventive substance and comparative untreated substance without hot water treatment, heating was performed from room temperature to 240° C. at a temperature-raising velocity of 5° C./min, using α-alumina as a reference, and the gravimetric behavior and the thermal behavior at that time were measured, respectively. The results are shown in FIG. **1** for the inventive substance and in FIG. **2** for the comparative substance.

2) Infrared absorption spectrometry

Each sample of the inventive substance and untreated substance without hot water treatment was measured by KBr-transmission method. The results are shown in FIG. **3** for the inventive substance and in FIG. **4** for the comparative substance, respectively.

3) Powder X-ray diffraction

Each sample of the inventive substance and comparative substance was pulverized and measured using a glass sample plate. The results are shown in FIG. **5** for the inventive substance and in FIG. **6** for the comparative substance, respectively.

4) Single crystal X-ray diffraction

The crystal structure obtained as a result of X-ray diffraction is shown in FIG. **7**.

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate retained a constant amount of water under ordinary preservation conditions and was stable.

When comparing the measurement data of thermal analysis (TG/DTA), infrared absorption spectrometry and powder X-ray diffraction between the untreated substance and the inventive hot water-treated substance, the patterns differ obviously, hence it has become clear that the hot water-treated substance and the untreated substance have different crystal forms.

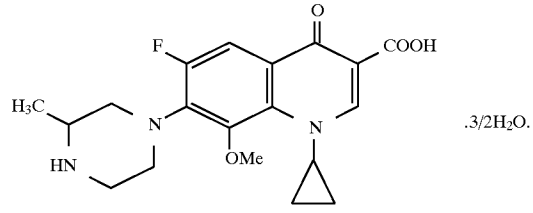
In addition, from the result of single crystal X-ray diffraction, it has been proved that 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate contains 8 molecules of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid and 12 molecules of water in a unit cell.

Utilizability in the Industry

The inventive 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate is excellent in the disintegration and dissolution rate and stable, hence it is very useful for pharmaceutical manufacturing.

Scope of the claim:

1. 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate represented by a formula (1)



(1)

.3/2H2O.

2. A process for producing the compound of claim **1**, characterized in that an aqueous suspension of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid is treated by heating under stirring.

3. The process of claim **2** wherein said aqueous suspension is heated at a temperature of 50° to 100° C.

4. The process of claim **3** wherein said temperature is 80° to 90° C.

5. The process of claim **2** wherein said aqueous suspension is at a pH in the range 6.0 to 8.0.

6. The process of claim **2** wherein said suspension is hot filtered at the same temperature at which it is treated.

7. The process of claim **6** wherein, after collecting a first crop of crystals, a second crop is obtained by cooling the filtrate to room temperature.

8. The process of claim **3** wherein, after collecting a first crop of crystals, a second crop is obtained by cooling the filtrate to room temperature.

9. The process of claim **2** wherein said aqueous suspension is the suspension obtained after neutralization in the acid-alkali recrystallization during the process of purifying said 1-cyclopropyl-6-fluoro-1,4 dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid.

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