

BRIEFING

Gatifloxacin. This monograph was posted on the USP Pending Monographs Website as a Draft 2 on October 30, 2009 for public comment. The Monograph Development—Antivirals and Antimicrobials Expert Committee has reviewed the comments that were received and has approved the monograph as an Authorized USP Pending Monograph, Version 2. The following is a summary of the comments received and the Expert Committee's responses.

Comment 1: The system suitability requirement of NLT 7500 theoretical plates proposed for the *Assay* and *Organic Impurities* tests could not be met consistently using the specified brand of column. The number of theoretical plates is not a suitable parameter to be used as a system suitability criteria for a gradient HPLC procedure. Hence, the commenters proposed to remove the column efficiency requirement because other requirements such as tailing factor and percent relative standard deviation are included.

Response 1: Comment incorporated.

Comment 2: Commenter requests to widen the acceptance criterion for the tailing factor system suitability requirement for the *Assay* and *Organic Impurities* tests, because the proposed requirement was not consistently met using the specified brand of column.

Response 2: Comment not incorporated because the monograph sponsor's data showed that this requirement was consistently met and also other commenters were able to meet the proposed requirement.

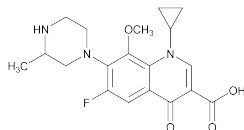
The Authorized Version 1 of this USP Pending Monograph was posted on the USP Website on June 27, 2008. Version 2 is being proposed because of the difficulty in procuring the bulk material for the development of USP Gatifloxacin Related Compound A RS. The use of this reference standard is being removed from the monograph. Therefore, new system suitability requirements based on the gatifloxacin peak are proposed in the *Assay* and in the test for *Organic Impurities*. In addition, the relative response factors for the corresponding gatifloxacin impurities are revised and calculated based on the gatifloxacin peak. Common names are provided for impurities to be consistent with USP style. The monograph is redesigned to be consistent with the USP monograph redesign initiative.

The HPLC procedure used in the *Assay* and in the test for *Organic Impurities* is based on analyses performed with the XTerra RP-18 brand of L1 column. The typical retention time for the gatifloxacin peak is about 9.5 min.

(MD-AA: H. Ramanathan, B. Davani.) RTS—C69776

Gatifloxacin

v.2 Authorized May 1, 2010



C ₁₉ H ₂₂ FN ₃ O ₄	375.39
Quinoline-3-carboxylic acid, 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro, (±); (±)-1-Cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [112811-59-3].	
Sesquihydrate [180200-66-2].	402.42
Dihydrate	411.42

DEFINITION

Gatifloxacin contains NLT 98.0% and NMT 102.0% of C₁₉H₂₂FN₃O₄, calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION (197K)**
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **PROCEDURE**

Buffer: Dissolve 6.6 mL of a 40% tetrabutylammonium hydroxide solution in water and 6.6 g of dibasic ammonium phosphate in 500 mL of water, and dilute with water to 1000 mL. Adjust with ammonium hydroxide to a pH of 9.5.

Diluent: Acetonitrile and water (1:9)

Solution A: Acetonitrile and *Buffer* (7:43)

Solution B: Acetonitrile, methanol, and *Buffer* (2:1:7)

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
8	100	0
15	70	30
15.1	100	0
20	100	0

Standard stock solution: 0.2 mg/mL of USP Gatifloxacin RS. Dissolve USP Gatifloxacin RS in acetonitrile (about 10% final volume) using a sonicator, and dilute with water to volume.

Diluent solution: 0.02 mg/mL of USP Gatifloxacin RS in *Diluent* from *Standard stock solution*

Sample stock solution: 0.2 mg/mL of Gatifloxacin. Dissolve Gatifloxacin in acetonitrile (about 10% final volume) using a sonicator, and dilute with water to volume.

Sample solution: 0.02 mg/mL of Gatifloxacin in *Diluent* from *Sample stock solution*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 285 nm

Column: 4.6-mm × 25-cm; 5-μm packing L1

Flow rate: 1.5 mL/min

Temperature: 38°

Injection size: 20 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of C₁₉H₂₂FN₃O₄ in the portion of Gatifloxacin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of gatifloxacin from the *Sample solution*

r_S = peak response of gatifloxacin from the *Standard solution*

C_S = concentration of USP Gatifloxacin RS in the *Standard solution* (mg/mL)

C_U = concentration of Gatifloxacin in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

• **HEAVY METALS, Method II (231):** 20 ppm

Organic Impurities

• **PROCEDURE**

[NOTE—Protect solutions of gatifloxacin from light.]

Buffer, Diluent, Solution A, and Solution B: Proceed as directed in the *Assay*.

2 / **Gatifloxacin**

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
8	100	0
30	0	100
30.1	100	0
35	100	0

Standard stock solution: Dissolve USP Gatifloxacin RS in acetonitrile (about 10% final volume) using a sonicator, and dilute with water to obtain a 0.2-mg/mL solution. Dilute an aliquot of this solution with water to obtain a 4-µg/mL solution.

Standard solution: 1 µg/mL of USP Gatifloxacin RS in Diluent, from Standard stock solution

Sample solution: 1 mg/mL of Gatifloxacin. Dissolve Gatifloxacin in acetonitrile (about 10% final volume) using a sonicator, and dilute with water to volume.

Chromatographic system: Proceed as directed in the Assay. (See Chromatography <621>, System Suitability.)

Detector: UV 240 nm and 285 nm

System suitability

Sample: Standard solution

Suitability requirements

Relative standard deviation: NMT 10.0%

Tailing factor: NMT 1.5

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of each impurity in the portion of Gatifloxacin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the Sample solution

r_S = peak response of gatifloxacin from the Standard solution

C_S = concentration of USP Gatifloxacin RS in the Standard solution (mg/mL)

C_U = concentration of Gatifloxacin in the Sample solution (mg/mL)

F = relative response factor (see Impurity Table 1)

Acceptance criteria

Individual impurities: See Impurity Table 1.

Total impurities: NMT 0.80%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Wave-length (nm)	Acceptance Criteria, NMT (%)
Gatifloxacin	1.0	1.0	285	—
8-Hydroxy gatifloxacin ^a	0.8	1.2	240	0.15

^a 1-Cyclopropyl-6-fluoro-8-hydroxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

^b 1-Cyclopropyl-6,7-difluoro-8-hydroxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

^c 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

^d 1-Cyclopropyl-6-fluoro-8-methoxy-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

^e 1-Cyclopropyl-6-fluoro-8-methoxy-7-(2-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

Impurity Table 1 (continued)

Name	Relative Retention Time	Relative Response Factor	Wave-length (nm)	Acceptance Criteria, NMT (%)
Difluorohydroxy gatifloxacin ^b	1.3	2.5	240	0.10
Difluoromethoxy gatifloxacin ^c	2.1	1.3	240	0.10
Desmethyl gatifloxacin ^d	0.6	1.0	285	0.15
Isogatifloxacin gatifloxacin ^e	0.9	1.0	285	0.15
Any other impurity	—	1.0	285	0.10

^a 1-Cyclopropyl-6-fluoro-8-hydroxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

^b 1-Cyclopropyl-6,7-difluoro-8-hydroxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

^c 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

^d 1-Cyclopropyl-6-fluoro-8-methoxy-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

^e 1-Cyclopropyl-6-fluoro-8-methoxy-7-(2-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

SPECIFIC TESTS

- **RESIDUE ON IGNITION (281):** NMT 0.1%
- **WATER DETERMINATION (921):** 7.5%–10.0%, if labeled as dihydrate

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, protect from light, and store in a refrigerator.
- **USP REFERENCE STANDARDS (11)**
USP Gatifloxacin RS