

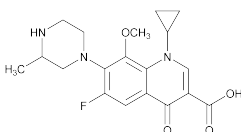
BRIEFING

Gatifloxacin. The authorized version of this USP Pending Monograph was posted on the USP Website in June 2008. Draft 2 is being proposed because of the difficulty in procuring the bulk material for the development of USP Gatifloxacin Related Compound A. 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 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 XTerraRP-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

Draft 2



C₁₉H₂₂FN₃O₄ 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 402.42
 [180200-66-2].
 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

Change to read:

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

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

~~System suitability stock solution: 1 mg/mL each of USP Gatifloxacin RS and USP Gatifloxacin Related Compound A in Diluent~~

~~System suitability solution: 0.1 mg/mL each of USP Gatifloxacin RS and USP Gatifloxacin Related Compound A in water~~

◀(1-May-2010)

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.

Standard 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 column; 5-μm packing L1

Flow rate: 1.5 mL/min

Temperature: 38°

Injection size: 20 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 4.5 between gatifloxacin and gatifloxacin related compound A

▶**Tailing factor:** NMT 1.5

Column efficiency: NLT 7500 theoretical plates ▶(1-May-2010)

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 = response of gatifloxacin from the *Sample solution*

r_S = 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 ▶(1-May-2010)

IMPURITIES

Inorganic Impurities

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

Change to read:

Organic Impurities

PROCEDURE

[NOTE—Protect solutions of gatifloxacin from light.]

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

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 A: Dissolve USP Gatifloxacin RS in acetonitrile (about 10% final volume) using a sonicator, and dilute with water to volume to obtain a solution containing 0.2 mg/mL. Dilute an aliquot of this solution with water to obtain a 0.004 mg/mL solution.

Standard stock solution B: Dissolve USP Gatifloxacin Related Compound A RS in acetonitrile (about 10% final volume) using a sonicator, and dilute with water to obtain a solution containing 0.2 mg/mL. Dilute an aliquot of this solution with water to obtain a 0.004 mg/mL solution.

Standard solution: 1 µg/mL each of Gatifloxacin and Gatifloxacin Related Compound A in *Diluent* from *Standard stock solution A* and *Standard stock solution B*.

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*.^{◀(1-May-2010)}

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%

Resolution: NLT 4.5 between gatifloxacin and gatifloxacin related compound A

Tailing factor: NMT 1.5

Column efficiency: NLT 7500 theoretical plates.^{◀(1-May-2010)}

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 = response of each individual impurity from the *Sample solution*
 r_S = 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%

Table 1

Component	Relative Retention Time (approx.)	Relative Retention Factor (F)	Wave-length (nm)	Limit (%)
Gatifloxacin	1.0	1.0	285	—
Gatifloxacin related compound A ^a	0.75	1.0 (vs gatifloxacin related compound A)	240	0.15
Gatifloxacin related compound B ^b	1.3	2.1 (vs gatifloxacin related compound A)	240	0.10
Gatifloxacin related compound C ^c	2.1	1.3 (vs gatifloxacin related compound A)	240	0.10
Gatifloxacin related compound D ^d	0.6	1 (vs gatifloxacin)	285	0.15
Gatifloxacin related compound E ^e	0.88	1 (vs gatifloxacin)	285	0.15
Any other impurity	—	1 (vs gatifloxacin)	285	0.10
Total impurities	—	—	240 and 285	0.80

^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

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
Difluorohydroxy gatifloxacin ^b	1.3	2.5	240	0.10
Difluoromethoxy gatifloxacin ^c	2.1	1.3	240	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.

Impurity Table 1 (continued)

Name	Relative Retention Time	Relative Response Factor	Wave-length (nm)	Acceptance Criteria, NMT (%)
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.

◀ (1-May-2010)

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.

Change to read:

- **USP REFERENCE STANDARDS** (11)

USP Gatifloxacin RS

~~USP Gatifloxacin Related Compound A RS~~

▶ (1-May-2010)