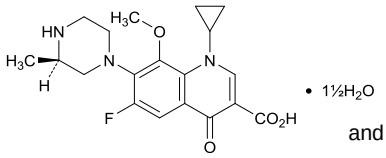
Gatifloxacin Hydrate

ガチフロキサシン水和物



and enantiomer

$C_{19}H_{22}FN_3O_4.1\frac{1}{2}H_2O$: 402.42

1-Cyclopropyl-6-fluoro-8-methoxy-7-[(3*RS*)-3-methylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid sesquihydrate [*180200-66-2*]

Gatifloxacin Hydrate contains not less than 98.5% and not more than 101.5% of gatifloxacin ($C_{19}H_{22}FN_3O_4$: 375.39), calculated on the anhydrous basis.

Description Gatifloxacin Hydrate occurs as white to pale yellow, crystals or crystalline powder.

It is slightly soluble in methanol and in ethanol (99.5), and very slightly soluble in water.

It dissolves in sodium hydroxide TS.

It is gradually colored to pale yellow by light.

A solution of Gatifloxacin Hydrate in dilute sodium hydroxide TS (1 in 100) shows no optical rotation.

Identification **(1)** Determine the absorption spectrum of a solution of Gatifloxacin Hydrate in dilute sodium hydroxide TS (1 in 100,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Gatifloxacin RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Gatifloxacin Hydrate as directed in the potassium bromide disk method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum with the Reference Spectrum or the spectrum of Gatifloxacin RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity **(1)** Clarity and color of solution—Dissolve 1.0 g of Gatifloxacin Hydrate in 10 mL of sodium hydroxide TS: the solution is clear. Perform the test with the solution as directed under Methods for Color Matching *<2.65>*: the solution has no more color than diluted Matching Fluid O (1 in 5).

(2) Heavy metals *<1.07>*—Proceed with 1.0 g of Gatifloxacin Hydrate according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Related substances—Dissolve 20 mg of Gatifloxacin Hydrate in 50 mL of the dissolving solution, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add the dissolving solution to make exactly 100 mL. Pipet 2 mL of this solution, add the dissolving solution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine each peak area by the automatic integration method: the peak area of the related substance A, having the relative retention time of about 1.2 to gatifloxacin, obtained from the sample solution is not larger than 2 times the peak area of gatifloxacin from the standard solution, and the area of the peak other than gatifloxacin and the peak mentioned above from the sample solution is not larger than the peak area of gatifloxacin from the standard solution. Furthermore, the total area of the peaks other than gatifloxacin from the sample solution is not larger than 3 times the peak area of gatifloxacin from the standard solution.

Dissolving solution: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (4:1).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 325 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35℃.

Mobile phase A: A mixture of diluted triethylamine (1 in 100), adjusted to pH 4.3 with phosphoric acid, and acetonitrile (22:3).

Mobile phase B: A mixture of diluted triethylamine (1 in 100), adjusted to pH 4.3 with phosphoric acid, and acetonitrile (1:1).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 － 15	100	0
15 － 30	100 → 0	0 → 100
30 － 40	0	100

Flow rate: 1.0 mL per minute (the retention time of gatifloxacin is about 16 minutes).

Time span of measurement: About 2.5 times as long as the retention time of gatifloxacin, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 5 mL of the standard solution, and add the dissolving solution to make exactly 10 mL. Confirm that the peak area of gatifloxacin obtained with 20 μL of this solution is equivalent to 40 to 60% of that with 20 μL of the standard solution.

System performance: Dissolve 20 mg of methyl 4-aminobenzoate in 50 mL of the dissolving solution. To 5 mL of this solution add 1 mL of the sample solution and the dissolving solution to make 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, gatifloxacin and methyl 4-aminobenzoate are eluted in this order with the resolution between these peaks being not less than 4.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of gatifloxacin is not more than 3.0%.

Water *<2.48>* 6.0 – 9.0% (0.1 g, volumetric titration, direct titration).

Residue on ignition *<2.44>* Not more than 0.1% (1 g).

Assay Weigh accurately about 50 mg of Gatifloxacin Hydrate, and dissolve in the dissolving solution to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 2 mL of the internal standard solution, add the dissolving solution to make 25 mL, and use this solutions as the sample solution. Separately, weigh accurately about 50 mg of Gatifloxacin RS (separately determine the water *<2.48>* in the same manner as Gatifloxacin Hydrate), and dissolve in the dissolving solution to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 2 mL of the internal standard solution, add the dissolving solution to make 25 mL, and use this solutions as the standard solution. Perform the test with 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of gatifloxacin to that of the internal standard.

Amount (mg) of gatifloxacin ($C_{19}H_{22}FN_3O_4$)
$= M_S \times Q_T / Q_S$

M_S: Amount (mg) of Gatifloxacin RS taken, calculated on the anhydrous basis

Internal standard solution—A solution of methyl 4-aminobenzoate in the dissolving solution (1 in 4000).

Dissolving solution: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (4:1).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4 mm in inside diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40℃.

Mobile phase: To 10 mL of triethylamine add water to make 1000 mL, and adjust to pH 4.5 with phosphoric acid. To 870 mL of this solution add 130 mL of acetonitrile.

Flow rate: Adjust so that the retention time of gatifloxacin is about 5 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, gatifloxacin and the internal standard are eluted in this order with the resolution between these peaks being not less than 4.

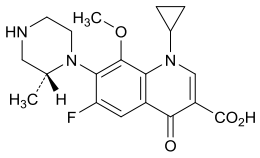
System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of gatifloxacin to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Others

Related substance A: 1-Cyclopropyl-6-fluoro-8-methoxy-7-[(2*RS*)-2-methylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



and enantiomer

Add the following to 9.01 Reference Standards (1):

Gatifloxacin RS

Add the following to 9.41 Reagents, Test Solutions:

Methyl 4-aminobenzoate $H_2NC_6H_4COOCH_3$ Pale yellow, crystals or crystalline powder.

Melting point <2.60>: 111 – 114℃