Gatifloxacin Ophthalmic Solution

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Gatifloxacin Ophthalmic Solution is an aqueous ophthalmic preparation.

It contains not less than 95.0% and not more than 107.0% of the labeled amount of gatifloxacin ($C_{19}H_{22}FN_3O_4$: 375.39).

Method of preparation Prepare as directed under Ophthalmic Liquids and Solutions, with Gatifloxacin Hydrate.

Description Gatifloxacin Ophthalmic Solution is a clear, pale yellow liquid.

Identification To a volume of Gatifloxacin Ophthalmic Solution, equivalent to 6 mg of Gatifloxacin, add diluted sodium hydroxide TS (1 in 10) to make 30 mL. To 1 mL of this solution add diluted sodium hydroxide TS (1 in 10) to make 20 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry *<2.24>*: it exhibits maxima between 238 nm and 242 nm, between 287 nm and 291 nm, and between 336 nm and 340 nm.

Osmotic pressure ratio Being specified separately when the drug is granted approval based on the Law.

pH Being specified separately when the drug is granted approval based on the Law.

Purity Related substance—To a volume of Gatifloxacin Ophthalmic Solution, equivalent to 6 mg of Gatifloxacin, add the diluting solution to make 30 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the diluting solution to make exactly 100 mL. Pipet 2 mL of this solution, add the diluting solution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 40 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.

Diluting 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 40℃.

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

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

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

Time span of measurement: For 40 minutes after injection, beginning after the solvent peak.

System suitability—

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

System performance: Dissolve 20 mg of methyl 4-aminobenzoate in 100 mL of the diluting solution. To 5 mL of this solution and 1 mL of the sample solution add the diluting solution to make 100 mL. When the procedure is run with 40 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 40 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%.

Foreign insoluble matter *<6.11>* It meets the requirement.

Insoluble particulate matter *<6.08>* It meets the requirement.

Sterility *<4.06>* Perform the test according to the Membrane filtration method: it meets the requirement.

Assay Pipet a volume of Gatifloxacin Ophthalmic Solution, equivalent to 6 mg of Gatifloxacin, and add the diluting solution to make exactly 30 mL. Pipet 2 mL of this solution, add exactly 3 mL of the internal standard solution, add the diluting solution to make 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 22 mg of Gatifloxacin RS (separately determine the water *<2.48>* in the same manner as Gatifloxacin Hydrate), and dissolve in the diluting solution to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 3 mL of the internal standard solution, add the diluting solution to make 20 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.

$$\text{Amount (mg) of gatifloxacin } (C_{19}H_{22}FN_3O_4) = M_S \times Q_T / Q_S \times 3/10$$

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

Internal standard solution—A solution of methyl 4-aminobenzoate in the diluting solution (1 in 10,000).

Diluting 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 4.6 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 40℃.

Mobile phase: A mixture of water, acetonitrile and triethylamine (81:18:1), adjusted to pH 4.5 with phosphoric acid.

Flow rate: Adjust so that the retention time of gatifloxacin is about 6 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 10.

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.

Others

Related substances A: Refer to it described in Gatifloxacin Hydrate.

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℃