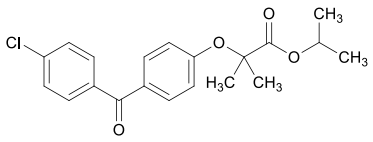
Fenofibrate

フェノフィブラート



$C_{20}H_{21}ClO_4$: 360.83

1-Methylethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate

[*49562-28-9*]

Fenofibrate, when dried, contains not less than 98.5% and not more than 101.0% of fenofibrate ($C_{20}H_{21}ClO_4$).

Description Fenofibrate occurs as a white to pale yellow-white crystalline powder.

It is soluble in ethanol (99.5), and practically insoluble in water.

It shows crystal polymorphism.

Identification **(1)** Determine the absorption spectrum of a solution of Fenofibrate in ethanol (99.5) (1 in 80,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Fenofibrate 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 Fenofibrate, previously dried, 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 dried Fenofibrate RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Perform the test with Fenofibrate as directed under Flame Coloration Test *<1.04>*: a green color appears.

Melting point *<2.60>* 80 – 83℃

Purity **(1)** Heavy metals *<1.07>*—Proceed with 1.0 g of Fenofibrate 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).

(2) Related substances—Conduct this procedure using light-resistant vessels. Dissolve 0.10 g of Fenofibrate in a mixture of acetonitrile and water (7:3) to make 100 mL. To 5 mL of this solution add a mixture of acetonitrile and water (7:3) to make 25 mL, and use this solution as the sample solution. Pipet 3 mL of the sample solution, add a mixture of acetonitrile and water (7:3) to make exactly 50 mL. Pipet 2.5 mL of this solution, add a mixture of acetonitrile and water (7:3) to make exactly 50 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, and determine each peak area by the automatic integration method: the peak area of the related substance A having the relative retention time of about 1.4 to fenofibrate obtained from the sample solution is not larger than 4/5 times the peak area of fenofibrate from the standard solution, and the total area of the peaks other than fenofibrate from the sample solution is not larger than the peak area of fenofibrate from the standard solution.

Operating conditions—

Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 2 times as long as the retention time of fenofibrate, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 5 mL of the standard solution, and add a mixture of acetonitrile and water (7:3) to make exactly 25 mL. Confirm that the peak area of fenofibrate obtained with 20 μL of this solution is equivalent to 15 to 25% of that with 20 μL of the standard solution.

System performance: Dissolve 0.10 g each of Fenofibrate and 4-chlorobenzophenon in 100 mL of a mixture of acetonitrile and water (7:3). To 2 mL of this solution add a mixture of acetonitrile and water (7:3) to make 50 mL. To 1 mL of this solution add a mixture of acetonitrile and water (7:3) to make 50 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, 4-chlorobenzophenon and fenofibrate 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 peak area of fenofibrate is not more than 5%.

Loss on drying *<2.41>* Not more than 0.5% (1 g, in vacuum, phosphorus (V) oxide, 60℃, 4 hours).

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

Assay Conduct this procedure using light-resistant vessels. Weigh accurately about 50 mg each of Fenofibrate and Fenofibrate RS, both previously dried, dissolve each in a mixture of acetonitrile and water (7:3) to make exactly 50 mL. Pipet 2 mL each of these solutions, add exactly 2 mL of the internal standard solution to each, add a mixture of acetonitrile and water (7:3) to make 50 mL, and use these solutions as the sample solution and the standard solution, respectively. 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 fenofibrate to the internal standard.

$$\text{Amount (mg) of fenofibrate } (C_{20}H_{21}ClO_4) = M_S \times Q_T / Q_S$$

M_S: Amount (mg) of Fenofibrate RS taken

Internal standard solution—A solution of 4-chlorobenzophenon in a mixture of acetonitrile and water (7:3) (11 in 10,000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 286 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 acetonitrile and 0.02 mol/L phosphate buffer solution (pH 3.0) (7:3).

Flow rate: Adjust so that the retention time of fenofibrate is about 8 minutes.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the internal standard and fenofibrate 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 fenofibrate to that of the internal standard is not more than 1.0%.

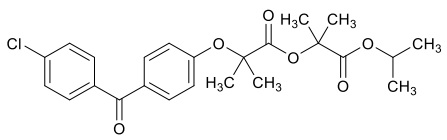
Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Others

Related substance A:

2-Methyl-1-(1-methylethoxy)-1-oxopropan-2-yl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate



Add the following to 9.01 Reference Standards (1):

Fenofibrate RS

Add the following to 9.41 Reagents, Test Solutions:

4-Chlorobenzophenon $C_6H_5COC_6H_4Cl$ A white, crystalline powder or powder.

Identification—Determine the absorption spectrum of a solution of 4-chlorobenzophenon in ethanol (99.5) (3 in 50,000) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits a maximum between 256 nm and 260 nm.

Melting point: 73 – 78℃

Content: not less than 98.0%. Assay—Dissolve 1 g of 4-chlorobenzophenon in acetone to make 10 mL, and use this solution as the sample solution. Perform the test with 1 μL of the sample solution as directed under Gas Chromatography <*2.02*> according to the following conditions. Determine each peak area by the automatic integration method, and calculate the amount of 4-chlorobenzophenon by the area percentage method.

Operating conditions

Detector: A hydrogen flame-ionization detector.

Column: A fused silica column 0.25 mm in inside diameter and 30 m in length, coated with dimethylpolysiloxane for gas chromatography in thickness of 0.25 μm.

Column temperature: A constant temperature of about 220℃.

Injection port temperature: 270℃.

Detector temperature: 250℃.

Carrier gas: Helium.

Flow rate: 1.33 mL per minute.

Split ratio: 1:100.

Time span of measurement: About 3 times as long as the retention time of 4-chlorobenzophenon.

System suitability

System performance: To 1 mL of the sample solution add acetone to make 10 mL. When the procedure is run with 1 μL of this solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of 4-chlorobenzophenon are not less than 50,000 and not more than 1.2, respectively.

System repeatability: To 1 mL of the sample solution add acetone to make 10 mL. When the test is repeated 6 times with 1 μL of this solution under the above operating conditions, the relative standard deviation of the peak area of 4-chlorobenzo-phenon is not more than 2.0%.