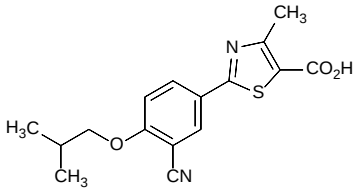
Febuxostat

フェブキソスタット



$C_{16}H_{16}N_2O_3S$: 316.37

2-[3-Cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

[*144060-53-7*]

Febuxostat contains not less than 98.0% and not more than 102.0% of febuxostat ($C_{16}H_{16}N_2O_3S$).

Description Febuxostat occurs as white, crystals or crystalline powder.

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

Melting point: about 209℃ (with decomposition, after drying).

It shows crystal polymorphism.

Identification (1) Determine the absorption spectrum of a solution of Febuxostat in ethanol (99.5) (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 Febuxostat 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 Febuxostat 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 Febuxostat RS: both spectra exhibit similar intensities of absorption at the same wave numbers. If any difference appears between the spectra, recrystallize the sample and the Reference Standard according to the method otherwise specified, filter and dry the crystals, and perform the test with the crystals.

Purity Related substances－(i) Weigh accurately about 50 mg of Febuxostat, dissolve in acetonitrile to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately about 50 mg of Febuxostat RS, dissolve in acetonitrile to make exactly 50 mL. Pipet 10 mL of this solution, add acetonitrile to make exactly 100 mL, then pipet 10 mL of this solution, add acetonitrile to make exactly 200 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, A_T, of related substances obtained from the sample solution and the peak area, A_S, of febuxostat from the standard solution by the automatic integration method, and calculate the amount of each related substance by the following equation. For the peak area of the related substance A having the relative retention time of about 1.2 to febuxostat, multiply the correction factor 1.8.

$$\text{Amount of the related substance (\%)} = M_S / M_T \times A_T / A_S \times 1 / 2$$

M_S: Amount (mg) of Febuxostat RS taken

M_T: Amount (mg) of Febuxostat

Operating conditions–

Detector: An ultraviolet absorption photometer (wavelength: 217 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 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: Diluted acetic acid (100) (1 in 5000).

Mobile phase B: A solution of acetic acid (100) in acetonitrile for liquid chromatography (1 in 5000).

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 － 40	60 → 0	40 → 100

Flow rate: 0.7 mL per minute.

Time span of measurement: For 40 minutes after injection.

System suitability–

Test for required detectability: Pipet 1 mL of the standard solution, and add acetonitrile to make exactly 10 mL. Confirm that the peak area of febuxostat obtained with 40 μL of this solution is equivalent to 7 to 13% of that with 40 μL of the standard solution.

System performance: Dissolve 1 mg of Febuxostat Related Substance A for System Suitability RS in acetonitrile to make 100 mL. To 1 mL of this solution add 10 mg of Febuxostat RS, and add acetonitrile to make 10 mL. When the procedure is run with 40 μL of this solution under the above operating conditions, febuxostat and the related substance A are eluted in this order with the resolution between these peaks being not less than 2.5.

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 febuxostat is not more than 2.0%.

(ii) Weigh accurately about 50 mg of Febuxostat, dissolve in acetonitrile to make exactly 50 mL. Pipet 10 mL of this solution, add 40 mmol/L ammonium acetate TS to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 50 mg of Febuxostat RS, add acetonitrile to make exactly 50 mL. Pipet 10 mL of this solution, add acetonitrile to make exactly 100 mL, and use this solution as the febuxostat stock solution. Pipet 10 mL of the febuxostat stock solution, and add acetonitrile to make exactly 200 mL. Then, pipet 10 mL of this solution, add 40 mmol/L ammonium acetate TS to make exactly 100 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 the peak area A_T of the related substance B, having the relative retention time of about 1.1 to febuxostat, obtained from the sample solution and the peak area A_S of febuxostat from the standard solution by the automatic integration method, and calculate the amount of the related substance B by the following equation.

$$\text{Amount of the related substance B (\%)} = M_S / M_T \times A_T / A_S \times 1 / 2$$

M_S: Amount of Febuxostat RS taken
M_T: Amount of Febuxostat taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 317 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with triacontylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 15°C.

Mobile phase: A mixture of diluted trifluoroacetic acid (1 in 2000) and a solution of trifluoroacetic acid in acetonitrile for liquid chromatography (1 in 2000) (11:9).

Flow rate: Adjust so that the retention time of febuxostat is about 47 minutes.

System suitability–

Test for required detectability: Weigh accurately 1 mg of Febuxostat Related Substance B for System Suitability RS, dissolve in acetonitrile to make exactly 100 mL. and use this solution as the related substance B solution. Pipet 2 mL of the febuxostat stock solution, add acetonitrile to make exactly 20 mL, and use this solution as the febuxostat 10 times dilution solution. Pipet 1 mL each of febuxostat 10 times dilution solution and the related substance B solution, add acetonitrile to make exactly 20 mL. Pipet 2 mL of this solution, and add 40 mmol/L ammonium acetate TS to make exactly 20 mL. Confirm that the peak areas of febuxostat and the related substance B obtained with 20 μL of this solution are equivalent to 7 to 13% of those with 20 μL of the solution for system suitability test.

System performance: Pipet 2.5 mL each of febuxostat 10 times dilution solution and the related substance B solution, add 40 mmol/l ammonium acetate TS to make exactly 50 mL, and use this solution as the solution for system suitability test. When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, febuxostat and the related substance B are eluted in this order with the resolution between these peaks being not less than 3.

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 febuxostat is not more than 2.0%.

(iii) Each amount of the related substances determined in (i) and (ii) is not more than 0.10%, and the total amount of the related substances is not more than 0.5%.

Loss on drying *<2.41>* Not more than 0.5% (1 g, 105°C, 4 hours).

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

Assay Weigh accurately about 50 mg of Febuxostat, dissolve in acetonitrile to make exactly 50 mL. Pipet 10 mL of this solution, add acetonitrile to make exactly 100 mL. Pipet 25 mL of this solution and 10 mL of the internal standard solution, add acetonitrile to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 50 mg of Febuxostat RS, dissolve in acetonitrile to make exactly 50 mL. Then, proceed as in the same manner as the sample solution, and use the solution so obtained 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 feboxostat to that of the internal standard.

$$\text{Amount (mg) of febuxostat } (C_{16}H_{16}N_2O_3S) = M_S \times Q_T / Q_S$$

M_S: Amount (mg) of Febuxostat RS taken

Internal standard solution — A solution of diphenyl in acetonitrile (1 in 2500).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 217 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°C.

Mobile phase: A mixture of a solution of acetic acid (100) in acetonitrile for liquid chromatography (1 in 500) and diluted acetic acid (100) (1 in 500) (3:2).

Flow rate: Adjust so that the retention time of febuxostat is about 7 minutes.

System suitability–

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, febuxostat and the internal standard are eluted in this order with the resolution being not less than 10.

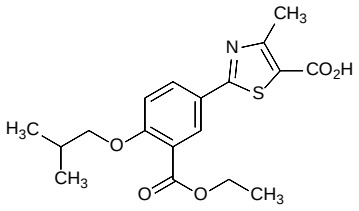
System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of febuxostat to that of the internal standard is not more than 1.0%.

Containers and storage Containers— Tight containers.

Others

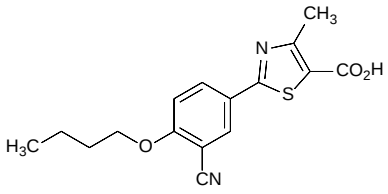
Related substance A:

2-[3-Ethoxycarbonyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid



Related substance B:

2-(4-Butoxy-3-cyanophenyl)-4-methyl-1,3-thiazole-5-carboxylic acid



Add the following to 9.01 Reference Standards (1):

Febuxostat RS

Febuxostat Related Substance A for System Suitability RS

Febuxostat Related Substance B for System Suitability RS

Add the following to 9.41 Reagents, Test Solutions:

40 mmol/L ammonium acetate TS Dissolve 3.08 g of ammonium acetate in water to make 1000 mL.