Febuxostat Tablets

フェブキソスタット錠

Febuxostat Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of febuxostat ($C_{16}H_{16}N_2O_3S$: 316.37).

Method of preparation Prepare as directed under Tablets, with Febuxostat.

Identification Perform the test with 20 μL each of the sample solution and standard solution obtained in the Assay as directed under Liquid Chromatography *<2.01>*, according to the following conditions: the retention times of the principal peaks in the chromatograms obtained from the sample solution and standard solution are the same, and both absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.

Operating conditions—

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

Detector: A photodiode array detector (wavelength: 317 nm, spectrum range of measurement: 210 – 350 nm).

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

Purity Related substances—To 5 tablets of Febuxostat Tablets add 3*V*/4 mL of a mixture of acetonitrile and water (3:2), shake vigorously for 30 minutes until the tablets completely disintegrated, then add a mixture of acetonitrile and water (3:2) to make exactly *V* mL so that each mL contains about 1 mg of febuxostat ($C_{16}H_{16}N_2O_3S$). Centrifuge this solution, filter the supernatant liquid, and use the filtrate as the sample solution. Pipet 1 mL of the sample solution, add a mixture of acetonitrile and water (3:2) to make exactly 100 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, and determine each peak area by the automatic integration method: The area of the peaks other than the related substance TA, having the relative retention time of about 0.4 to the related substance A observed in the solution for system suitability test, and febuxostat obtained from the sample solution are not larger than 1/5 times the peak area of febuxostat from the standard solution, respectively. Furthermore, the total area of the peaks other than febuxostat from the sample solution is not larger than 1/2 times the peak area of febuxostat from the standard solution.

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°C.

Mobile phase A: Diluted acetic acid (100) (1 in 5000).

Mobile phase B: A solution of acetic acid (100) in methanol (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
40 − 60	0	100

Flow rate: 0.7 mL per minute.

Time span of measurement: For 60 minutes after injection.

System suitability—

Test for required detectability: Pipet 2mL of the standard solution, and add a mixture of acetonitrile and water (3:2) to make exactly 10 mL. Confirm that the peak area of febuxostat obtained with 40 μL of this solution is equivalent to 14 to 26% of that with 40 μL of the standard solution.

System performance: Dissolve 1 mg of Febuxostat Related Substance A for System Suitability RS in a mixture of acetonitrile and water (3:2) to make 100 mL. To 1 mL of this solution, add 10 mg of Febuxostat RS, add a mixture of acetonitrile and water (3:2) to make 10 mL, and use this solution as the solution for system suitability test. When the procedure is run with 40 μL of the solution for system suitability test 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 2.0.

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%.

Uniformity of dosage units *<6.02>* Perform the test according to the following method: it meets the requirement of the Content uniformity test.

To 1 tablet of Febuxostat Tablets add 3*V*/4 mL of a mixture of acetonitrile and water (3:2), shake vigorously for 30 minutes until the tablets are completely disintegrated, then add a mixture of acetonitrile and water (3:2) to make exactly *V* mL. Centrifuge this solution, pipet a volume of the supernatant liquid, equivalent to about 4 mg of febuxostat ($C_{16}H_{16}N_2O_3S$), add a mixture of acetonitrile and water (3:2) to make exactly 50 mL. Then pipet 2.5 mL of this solution, add a mixture of acetonitrile and water (3:2) to make exactly 20 mL, filter this solution, and use the filtrate as the sample solution. Then, proceed as directed in the Assay.

Amount (mg) of febuxostat ($C_{16}H_{16}N_2O_3S$)
$= M_S \times A_T / A_S \times C / 10$

M_S: Amount (mg) of Febuxostat RS taken
C: Labeled amount (mg) of febuxostat($C_{16}H_{16}N_2O_3S$) in 1 tablet.

Dissolution *<6.10>* When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of disodium hydrogen phosphate-citric acid buffer solution (pH 5.5) as the dissolution medium for 10-mg and 20-mg tablets and 900 mL of 0.05 mol/L disodium hydrogen phosphate-citric acid buffer solution (pH 6.0) as the dissolution medium for a 40-mg tablet, the dissolution rates in 30 minutes of 10-mg and 40-mg tablets are not less than 80%, and that in 60 minutes of a 20-mg tablet is not less than 75%.

Start the test with 1 tablet of Febuxostat Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard not less than 10 mL of the first filtrate, pipet V mL of the subsequent filtrate, add 2nd fluid for disintegration test to make exactly V' mL so that each mL contains about 11 μg of febuxostat ($C_{16}H_{16}N_2O_3S$), and use this solution as the sample solution. Separately, weigh accurately about 11 mg of Febuxostat RS, and dissolve in 2nd fluid for disintegration test to make exactly 50 mL. Pipet 5 mL of this solution, add 2nd fluid for disintegration test to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the sample solution and standard solution at 317 nm as directed under Ultraviolet-visible Spectrophotometry *<2.24>*

Dissolution rate (%) with respect to the labeled amount of febuxostat ($C_{16}H_{16}N_2O_3S$)
$= M_S \times A_T / A_S \times V' / V \times 1 / C \times 90$

M_S: Amount (mg) of Febuxostat RS taken
C: Labeled amount (mg) of febuxostat($C_{16}H_{16}N_2O_3S$) in 1 tablet.

Assay To 10 tablets of Febuxostat Tablets add $3V/4$ mL of a mixture of acetonitrile and water (3:2), shake vigorously for 30 minutes until the tablets are completely disintegrated, then add a mixture of acetonitrile and water (3:2) to make exactly V mL. Centrifuge this solution, pipet a volume of the supernatant liquid, equivalent to about 4 mg of febuxostat ($C_{16}H_{16}N_2O_3S$), add a mixture of acetonitrile and water (3:2) to make exactly 50 mL. Then pipet 2.5 mL of this solution, add a mixture of acetonitrile and water (3:2) to make exactly 20 mL, filter this solution, and use the filtrate as the sample solution. Separately, weigh accurately about 10 mg of Febuxostat RS, dissolve in a mixture of a solution of acetonitrile and water (3:2) to make exactly 200 mL. Pipet 5 mL of this solution, add a mixture of acetonitrile and water (3:2) to make exactly 25 mL, and use this solution 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 determine the peak areas, A_T and A_S, of febuxostat in each solution.

Amount (mg) of febuxostat ($C_{16}H_{16}N_2O_3S$)
$= M_S \times A_T / A_S \times C / 10$

M_S: Amount (mg) of Febuxostat RS taken
C: Labeled amount (mg) of febuxostat($C_{16}H_{16}N_2O_3S$) in 1 tablet.

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 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 6 minutes.

System suitability—

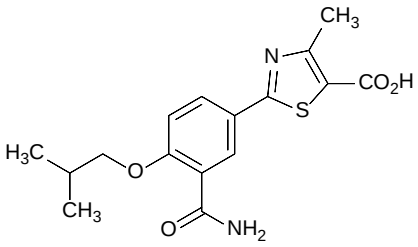
System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the theoretical plates and the symmetry factor of the peak of febuxostat are not less than 1500 and 0.9 to 1.4, respectively.

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 is not more than 1.0%.

Containers and storage Containers—Tight containers.

Others

Related substance TA:
2-[3-Carbamoyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid



Add the following to 9.01 (1) Reference Standards:

Febuxostat RS
Febuxostat Related Substance A for System Suitability RS