Aripiprazole Tablets

アリピプラゾール錠

Aripiprazole Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$:448.39).

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

Identification Perform the test with 10 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 the standard solution are the same, and both absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelength.

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: 254 nm, spectrum range of measurement: 230 – 350 nm).

System suitability—

Proceed as directed in the system suitability in the Assay.

Purity Related substances—This is applied to 1-mg tablets.

Conduct this procedure using light-resistant vessels. To a quantity of powdered Aripiprazole Tablets, equivalent to 4 mg of Aripiprazole, add 8 mL of a mixture of water, acetonitrile and acetic acid (100) (60:40:1), shake for 10 minutes, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 1 mL of the filtrate, and use the subsequent filtrate as the sample solution. Perform the test with 20 μL of the sample solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method, and calculate their amounts by the area percentage method: the amounts of the related substances TA and TB, having the relative retention times of about 0.43 and about 0.48 to aripiprazole, are not more than 0.2%, respectively, and the amount of the peak other than aripiprazole and the peaks mentioned above is not more than 0.1%.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 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 25℃.

Mobile phase: Dissolve 2.88 g of sodium lauryl sulfate, 9.63 g of diammonium hydrogen citrate and 1.57 g of citric acid monohydrate in water to make 1000 mL. To 550 mL of this solution add 450 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of aripiprazole is about 21 minutes.

Time span of measurement: About 1.8 times as long as the retention time of aripiprazole, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 1 mL of the sample solution, add a mixture of water, acetonitrile and acetic acid (100) (60:40:1) to make exactly 100 mL, and use this solution as the solution for system suitability test. Pipet 2 mL of the solution for system suitability test, add a mixture of water, acetonitrile and acetic acid (100) (60:40:1) to make exactly 20 mL. Confirm that the peak area of aripiprazole obtained with 20 μL of this solution is equivalent to 7 to 13% of that with 20 μL of the solution for system suitability test.

System performance: When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of aripiprazole are not less than 8000 and not more than 1.2, respectively.

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

To 1 tablet of Aripiprazole Tablets add 35 mL of the mobile phase, shake thoroughly until the tablet is disintegrated, add the mobile phase to make exactly 50 mL, shake thoroughly for 10 minutes, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard 1 mL of the first filtrate, pipet V mL of the subsequent filtrate, add exactly V'／20 mL of the internal standard solution, add the mobile phase to make V' mL so that each mL contains about 10 μg of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$), and use this solution as the sample solution. Separately, weigh accurately about 50 mg of Aripiprazole RS, previously dried at 105℃ for 3 hours, dissolve in the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 5 mL of the internal standard solution, add the mobile phase to make 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 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 aripiprazole to that of the internal standard.

$$\text{Amount (mg) of aripiprazole } (C_{23}H_{27}Cl_2N_3O_2) = M_S \times Q_T / Q_S \times V'/V \times 1/100$$

M_S: Amount (mg) of Aripiprazole RS taken

Internal standard solution—A solution of propyl parahydroxybenzoate in the mobile phase (1 in 6000).

Operating conditions—

Proceed as directed in the operating conditions in the Assay.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, aripiprazole and the internal standard are eluted in this order with the resolution between these peaks being not less than 8.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of aripiprazole to that of the internal standard is not more than 1.0%.

Dissolution *<6.10>* **(1)** 1-mg and 3-mg tablets When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of a solution prepared by dissolving 1.97 g of acetic acid (100) and 9.15 g of sodium acetate trihydrate in water to make 1000 mL as the dissolution medium, the dissolution rates in 30 minutes of 1-mg and 3-mg tablets are not less than 70%.

Start the test with 1 tablet of Aripiprazole 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 the mobile phase to make exactly *V'* mL so that each mL contains about 0.56 μg of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$), and use this solution as the sample solution. Separately, weigh accurately about 28 mg of Aripiprazole RS, previously dried at 105°C for 3 hours, dissolve in the mobile phase to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 100 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 aripiprazole in each solution.

Dissolution rate (%) with respect to the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$)

$$= M_S \times A_T / A_S \times V'/V \times 1/C \times 9/5$$

M_S: Amount (mg) of Aripiprazole RS taken

C: Labeled amount (mg) of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) in 1 tablet

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 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 25°C.

Mobile phase: Dissolve 2.84 g of anhydrous sodium sulfate in water to make 1000 mL. To 500 mL of this solution add 400 mL of acetonitrile for liquid chromatography, 100 mL of methanol and 10 mL of acetic acid (100).

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

System suitability—

System performance: When the procedure is run with 100 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of aripiprazole are not less than 3000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 100 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of aripiprazole is not more than 2.0%.

(2) 6-mg and 12-mg tablets When the test is performed at 75 revolutions per minute according to the Paddle method, using 900 mL of a solution prepared by dissolving 1.97 g of acetic acid (100) and 9.15 g of sodium acetate trihydrate in water to make 1000 mL as the dissolution medium, the dissolution rate in 30 minutes of a 6-mg tablet is not less than 70%, and that in 60 minutes of a 12-mg tablet is not less than 70%.

Start the test with 1 tablet of Aripiprazole 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 the dissolution medium to make exactly *V'* mL so that each mL contains about 6.7 μg of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$), and use this solution as the sample solution. Separately, weigh accurately about 56 mg of Aripiprazole RS, previously dried at 105°C for 3 hours, dissolve in ethanol (95) to make exactly 50 mL. Pipet 3 mL of this solution, add the dissolution medium to make exactly 500 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 249 nm as directed under Ultraviolet-visible Spectrophotometry *<2.24>* using the dissolution medium as the control.

Dissolution rate (%) with respect to the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$)

$$= M_S \times A_T / A_S \times V'/V \times 1/C \times 54/5$$

M_S: Amount (mg) of Aripiprazole RS taken

C: Labeled amount (mg) of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) in 1 tablet

Assay Weigh accurately not less than 20 Aripiprazole Tablets, and powder. Weigh accurately a quantity of the powder, equivalent to about 10 mg of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$), add 20 mL of the mobile phase, add exactly 10 mL of the internal standard solution, shake thoroughly for 10 minutes, then add the mobile phase to make 50 mL, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard 1 mL of the first filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 50 mg of Aripiprazole RS, previously dried at 105°C for 3 hours, dissolve in the mobile phase to make exactly 50 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 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 aripiprazole to that of the internal standard.

$$\text{Amount (mg) of aripiprazole } (C_{23}H_{27}Cl_2N_3O_2) = M_S \times Q_T / Q_S \times 1/5$$

M_S: Amount (mg) of Aripiprazole RS taken

Internal standard solution—A solution of propyl parahydroxybenzoate in the mobile phase (1 in 3000)

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 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 25°C.

Mobile phase: Dissolve 2.84 g of anhydrous sodium sulfate in water to make 1000 mL. To 560 mL of this solution add 330 mL of acetonitrile for liquid chromatography, 110 mL of methanol and 10 mL of acetic acid (100).

Flow rate: Adjust so that the retention time of aripiprazole is about 10 minutes.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, aripiprazole and the internal standard are eluted in this order with the resolution between these peaks being not less than 8.

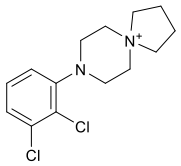
System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of aripiprazole to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Others

Related substance TA:

8-(2,3-Dichlorophenyl)-5,8-diazaspiro[4.5]decan-5-ium



Related substance TB:

4-(2,3-Dichlorophenyl)-1-{4-[(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy]butyl}piperazine 1-oxide