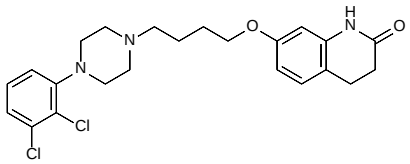
Aripiprazole

アリピプラゾール



$C_{23}H_{27}Cl_2N_3O_2$: 448.39

7-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1*H*)-one

[*129722-12-9*]

Aripiprazole contains not less than 98.0% and not more than 102.0% of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$), calculated on the dried basis.

Description Aripiprazole occurs as white, crystals or crystalline powder.

It is freely soluble in dichloromethane, and practically insoluble in water, in acetonitrile, in methanol and in ethanol (99.5).

It shows crystal polymorphism.

Identification **(1)** Determine the absorption spectrum of a solution of Aripiprazole in methanol (1 in 50,000) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Aripiprazole 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 Aripiprazole 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 Aripiprazole RS: both spectra exhibit similar intensities of absorption at the same wave numbers. If any difference appears between the spectra, dissolve Aripiprazole and Aripiprazole RS in dichloromethane, respectively, then evaporate the dichloromethane to dryness, and repeat the test on the residues.

Purity Related substances—Conduct this procedure using light-resistant vessels. Use the sample solution obtained in the Assay as the sample solution. Pipet 1 mL of the sample solution, add the dissolving solution to make exactly 100 mL. Pipet 5 mL of this solution, add the dissolving solution 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 area of the peak other than aripiprazole obtained from the sample solution is not larger than the peak area of aripiprazole from the standard solution, and the total area of the peaks other than aripiprazole from the sample solution is not larger than 3 times the peak area of aripiprazole from the standard solution. For the areas of the related substance A having the retention time of about 0.2 to aripiprazole and the related substance B having the retention time of about 0.8, multiply the correction factor 0.7, respectively.

Dissolving solution—A mixture of water, acetonitrile, methanol and acetic acid (100) (60:30:10:1).

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: For 25 minutes after injection, beginning after the solvent peak.

System suitability—

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

Test for required detectability: To 1 mL of the sample solution and add the dissolving solution to make 20 mL. To 2 mL of this solution add the dissolving solution to make 20 mL, and use this solution as the solution for system suitability test. Pipet 2 mL of the solution for system suitability test, and add the dissolving solution 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 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 aripiprazole is not more than 2.0%.

Loss on drying <*2.41*> Not more than 0.1% (1 g, 105°C, 3 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 Aripiprazole and Aripiprazole RS, both dried previously, dissolve each in the dissolving solution to make exactly 50 mL. Pipet 5 mL each of these solutions, add dissolving solution to make exactly 50 mL, and use these solutions as the sample solution and the standard solution, respectively. 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 the peak areas, A_T and A_S, of aripiprazole in each solution.

$$\text{Amount (mg) of aripiprazole } (C_{23}H_{27}Cl_2N_3O_2) = M_S \times A_T / A_S$$

M_S: Amount (mg) of Aripiprazole RS taken

Dissolving solution—A mixture of water, acetonitrile, methanol and acetic acid (100) (60:30:10:1).

Operating conditions —

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 25℃.

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

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

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 — 2	80	20
2 — 10	80 → 65	20 → 35
10 — 20	65 → 10	35 → 90
20 — 25	10	90

Flow rate: 1.2 mL per minute.

System suitability —

System performance: Dissolve 5 mg each of Aripiprazole RS and Aripiprazole *N*-oxide for System Suitability RS in 100 mL of the dissolving solution. To 1 mL of this solution add the dissolving solution to make 50 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, aripiprazole and aripiprazole *N*-oxide are eluted in this order with the resolution being not less than 2.0, and the symmetry factor of the peak of aripiprazole is not more than 1.5.

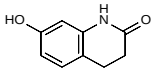
System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of aripiprazole is not more than 1.0%.

Containers and storage Containers—Tight containers.

Others

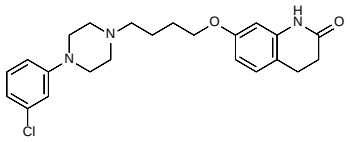
Related substance A:

7-Hydroxy-3,4-dihydroquinolin-2(1*H*)-one



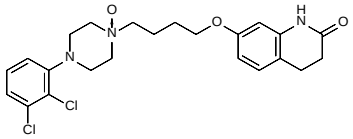
Related substance B:

7-{4-[4-(3-Chlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1*H*)-one



Aripiprazole *N*-oxide:

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



Add the following to 9.01 Reference Standards (1):

Aripiprazole RS

Aripiprazole *N*-oxide for System Suitability RS