Terguride Tablets

Dissolution <*6.10*> Perform the test with 1 tablet of Terguride Tablets at 50 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium. 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 the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add 2nd fluid for dissolution test to make exactly V' mL so that each mL contains about 0.56 μg of terguride ($C_{20}H_{28}N_4O$) according to the labeled amount, and use this solution as the sample solution. Separately, weigh accurately about 17 mg of Terguride RS (previously determine the water <*2.48*> with 0.1 g by direct titration in volumetric titration), and dissolve in methanol to make exactly 100 mL. Pipet 2 mL of this solution, and add 2nd fluid for dissolution test to make exactly 50 mL. Further, pipet 2 mL of this solution, add 2nd fluid for dissolution test to make exactly 25 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 terguride in each solution.

The requirements are met if Terguride Tablets conform to the dissolution requirements.

Dissolution rate (%) with respect to the labeled amount of terguride ($C_{20}H_{28}N_4O$)

$= M_S \times A_T/A_S \times V'/V \times 1/C \times 72/25$

M_S: Amount (mg) of Teguride RS, calculated on the anhydrous basis

C: Labeled amount (mg) of terguride ($C_{20}H_{28}N_4O$) in 1 tablet

Operating conditions —

Detector: An ultraviolet absorption photometer (wavelength: 224 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 25ºC.

Mobile phase: A mixture of water, acetonitrile, phosphate buffer solution, pH 7.0, and dehydrated trifluoroacetic acid (1300:700:60:1).

Flow rate: Adjust the flow rate so that the retention time of terguride is about 4 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 terguride are not less than 2000 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 terguride is not more than 2.0%.

Dissolution Requirements

Labeled amount	Specified minute	Dissolution rate
0.5mg	60 minutes	Not less than 70%

Terguride RS $C_{20}H_{28}N_4O$:340.46 (+)-1,1-diethyl-3-(6-methyl-8α-ergolinyl)urea. It meets the following requirements. Purify by the following method if needed.

Purification method—To 8.5 g of terguride add 280 mL of acetone, and dissolve at 34 to 36ºC by heating. Filter by warming, allow to stand the filtrate at room temperature overnight, and filter the crystals. Recrystallize in the same manner, and dry the crystals in vacuum for 3 hours.

Description—Terguride RS occurs as white to pale yellowish white crystalline powder.

I*dentification*—Determine the infrared absorption spectrum of Terguride RS as directed in the paste method under Infrared Spectrophotometry *<2.25>*: it exhibits absorption at the wave numbers of about 3480 cm^{-1}, 3200 cm^{-1}, 1625 cm^{-1}, 1514 cm^{-1} and 753 cm^{-1}.

Related substances—Weigh accurately about 20 mg of Terguride RS, dissolve in methanol to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 1 mg each of lisuride (previously determine the water *<2.48>* with 0.1 g by direct titration in volumetric titration), amine 8 (previously determine the water *<2.48>* with 0.1 g by direct titration in volumetric titration) and dimer (previously determine the water *<2.48>* with 0.1 g by direct titration in volumetric titration), and dissolve in methanol to make exactly 100 mL. Pipet 10 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the lisuride, amine 8 and dimer standard stock solution. Pipet 1 mL of the sample solution and 10 mL of the lisuride, amine 8 and dimer standard stock solution, add methanol to make exactly 100 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. Determine each peak area of both solutions by the automatic integration method, and calculate the amounts of lisuride, dimer and amine 8: not more than 0.1%, respectively. Further, determine the principal peak obtained from the sample solution and other than the peaks mentioned above, and the peak area of terguride obtained from the standard solution by the automatic integration method, and calculate the amount of other related substances: not more than 0.25%. The total amount of the related substances is not more than 0.5%.

Operating conditions

Detector: Amine 8, dimer and other related substances—A fluorophotometer (excitation wavelength: 280 nm, fluorescence wavelength: 340 nm).

Lisuride－A fluorophotometer (excitation wavelength: 325 nm, fluorescence wavelength: 420 nm).

Column: A stainless steel column 3.9 mm in inside diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25ºC.

Mobile phase: A mixture of water, acetonitrile, phosphate buffer solution, pH 7.0, and dehydrated trifluoroacetic acid (1300:700:60:1).

Flow rate: Adjust the flow rate so that the retention time of terguride is about 4 minutes.

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

System suitability

Test for required detectability: To exactly 1 mL of the standard solution add methanol to make exactly 10 mL. Confirm that the peak area of terguride obtained from 20 μL of this solution is equivalent to 7 to 13% of that from 20 μL of the standard solution.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, amine 8, dimer, terguride and lisuride are eluted in this order with the complete separation between these peaks.

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 terguride is not more than 2.0%.

Water *<2.48>*: not more than 5.5% (0.1g, volumetric titration, direct titration).

Content: not less than 99.0%, calculated on the dehydrated basis. Assay—Weigh accurately about 0.2 g of Terguride RS, dissolve in 50 mL of a mixture of acetone and acetic acid (100) (9:1), and titrate *<2.50>* with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.05 mg of $C_{20}H_{28}N_4O$

Phosphate buffer solution, pH 7.0 To a solution, prepared by dissolving 6.8 g of potassium dihydrogen phosphate in water to make 500 mL, add about 300 mL of 0.1 mol/L sodium hydroxide VS, to adjust to pH 7.0 ± 0.1, and add water to make 1000 mL.

Lisuride $C_{20}H_{26}N_4O$ 3-(9,10-didehydro-6-methyl-8α-ergolinyl)-1,1-diethylurea

Description－White to pale yellowish white crystals.

Identification－Determine the infrared absorption spectrum of Lisuride as directed in the paste

method under Infrared Spectrophotometry <2.25>: it exhibits absorption at the wave numbers of about 3330 cm^{-1}, 3060 cm^{-1}, 1623 cm^{-1}, 1539 cm^{-1} and 741 cm^{-1}. If these absorption are not observed, dissolve in diluted ethanol (99.5) (7 in 10), then evaporate the dilute ethanol (99.5) (7 in 10), and repeat the test on the residues.

Purity —Dissolve 5 mg of Lisuride in 50 mL of acetonitrile, and use this solution as the sample solution. Perform the test with 10 μL of this solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine each peak area by the automatic integration method, and calculate the amount of lisuride by the area percentage method: the amount of lisuride is not less than 95%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 227 nm).

Column: A stainless steel column 3.9 mm in inside diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25ºC.

Mobile phase: A mixture of a solution of sodium dihydrogen phosphate (3 in 500) and acetonitrile (10:7).

Flow rate: Adjust the flow rate so that the retention time of lisuride is about 12.5 minutes.

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

System suitability

Test for required detectability: To exactly 5 mL of the sample solution, add acetonitrile 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, and add acetonitrile to make exactly 10 mL. Confirm that the peak area of lisuride obtained from 10 μL of this solution is equivalent to 15 to 25% of that from 10 μL of the solution for system suitability test.

System performance: Dissolve 1 mg each of Lisuride and Terguride RS in 50 mL of acetonitrile. When the procedure is run with 10 μL of this solution under the above operating conditions, terguride and lisuride 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 10 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of lisuride is not more than 2.0%.

Amine 8 $C_{15}H_{19}N_3$ 6-methyl-8α-ergolinylamine

Description —White to pale yellowish white crystals.

Identification —Determine the infrared absorption spectrum of Amine 8 as directed in the paste method under Infrared Spectrophotometry <2.25>: it exhibits absorption at the wave numbers of about 3360 cm^{-1}, 3290 cm^{-1}, 3090 cm^{-1}, 1609 cm^{-1}, 1576 cm^{-1} and 747 cm^{-1}.

Purity —Dissolve 2 mg of Amine 8 in 10 mL of the mobile phase, and use this solution as the sample solution. Perform the test with 10 μL of this solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine each peak area by the automatic integration method, and calculate the amount of amine 8 by the area percentage method: the amount of amine 8 is not less than 95%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 224 nm).

Column: A stainless steel column 3.9 mm in inside diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25ºC.

Mobile phase: A mixture of phosphate buffer solution, pH 2.1 and acetonitrile (4:1).

Flow rate: Adjust the flow rate so that the retention time of amine 8 is about 3.5 minutes.

Time span of measurement: About 3 times as long as the retention time of amine 8 beginning after the solvent peak.

System suitability

Test for required detectability: To exactly 1 mL of the sample solution add the mobile phase to make exactly 100 mL, and use this solution as the solution for system suitability test. Pipet 1 mL of the solution for system suitability test, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of amine 8 obtained from 10 μL of this solution is equivalent to 7 to 13% of that from 10 μL of the solution for system suitability test.

System performance: Dissolve 1 mg each of Amine 8 and Terguride RS in 50 mL of the mobile phase. When the procedure is run with 10 μL of this solution under the above operating conditions, amine 8 and terguride are eluted in this order with the resolution between these peaks being not less than 1.5.

System repeatability: When the test is repeated 6 times with 10 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of amine 8 is not more than 2.0%.

Dimer $C_{31}H_{36}N_6O$ 1,3-bis(6-methyl-8α-ergolinyl)-urea

Description —A white to pale yellowish white crystalline powder.

Identification —Determine the infrared absorption spectrum of Dimer as directed in the paste method under Infrared Spectrophotometry <2.25>: it exhibits absorption at the wave numbers of about 3400 cm^{-1}, 3120 cm^{-1}, 3060 cm^{-1}, 1633 cm^{-1}, 1571 cm^{-1} and 755 cm^{-1}.

Purity —Dissolve 5 mg of Dimer in 10 mL of the mobile phase, and use this solution as the sample solution. Perform the test with 10 μL of this solution as directed under Liquid Chromatography <2.01> according to the following conditions. Determine each peak area by the automatic integration method,

and calculate the amount of dimer by the area percentage method: the amount of dimmer is not less than 95%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 224 nm).

Column: A stainless steel column 3.9 mm in inside diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25ºC.

Mobile phase: A mixture of water, acetonitrile, phosphate buffer solution, pH 7.0, and dehydrated trifluoroacetic acid (1300:700:60:1).

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

Time span of measurement: About 4 times as long as the retention time of dimer beginning after the solvent peak.

System suitability

Test for required detectability: To exactly 1 mL of the sample solution add the mobile phase to make exactly 100 mL, and use this solution as the solution for system suitability test. Pipet 1 mL of the solution for system suitability test, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of dimer obtained from 10 μL of this solution is equivalent to 7 to 13% of that from 10 μL of the solution for system suitability test.

System performance: Dissolve 1 mg each of Dimer and Terguride RS in 50 mL of the mobile phase. When the procedure is run with 10 μL of this solution under the above operating conditions, dimer and terguride 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 10 μL of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of dimer is not more than 2.0%.

Phosphate buffer solution, pH 2.1 To a solution, prepared by dissolving 6.8 g of potassium dihydrogen phosphate in water to make 600 mL, add phosphoric acid to adjust to pH 2.1, and add water to make 1000 mL.