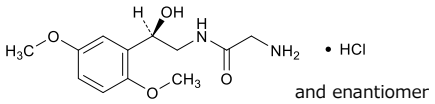
Midodrine Hydrochloride

ミドドリン塩酸塩



and enantiomer

$C_{12}H_{18}N_2O_4$.HCl: 290.74

2-Amino-*N*-[(*2RS*)-2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]acetamide monohydrochloride

[*43218-56-0*]

Midodrine Hydrochloride, when dried, contains not less than 98.0% and not more than 102.0% of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl).

Description Midodrine Hydrochloride occurs as a white crystalline powder.

It is soluble in water, and slightly soluble in ethanol (95).

A solution of Midodrine Hydrochloride (1 in 25) shows no optical rotation.

Melting point: about 200°C (with decomposition).

It shows crystal polymorphism.

Identification **(1)** Determine the absorption spectrum of a solution of Midodrine Hydrochloride in 0.01 mol/L hydrochloric acid TS (3 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 Midodrine Hydrochloride 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 Midodrine Hydrochloride, previously dried, as directed in the potassium chloride disk method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum with the Reference Spectrum or the spectrum of dried Midodrine Hydrochloride RS: both spectra exhibit similar intensities of absorption at the same wave numbers. If any difference appears between the spectra, recrystallize Midodrine Hydrochloride from a mixture of ethanol (95) and water (7:3), filter and dry the crystals, and perform the test with the crystals.

(3) A solution of Midodrine Hydrochloride (1 in 50) responds to Qualitative Tests *<1.09>* for chloride.

Purity **(1)** Sulfate *<1.14>*—Perform the test with 1.0 g of Midodrine Hydrochloride. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid VS (not more than 0.048%).

(2) Related substances—Dissolve 50 mg of Midodrine Hydrochloride in 50 mL of a mixture of water and acetonitrile for liquid chromatography (3:2), and use this solution as the sample solution. Pipet 1 mL of the sample solution, add a mixture of water and acetonitrile for liquid chromatography (3:2) to make exactly 200 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. Determine each peak area by the automatic integration method: the peak area of the related substance A, having the relative retention time of about 1.2 to midodrine, obtained from the sample solution is not larger than 2/5 times the peak area of midodrine from the standard solution, the area of the peak other than midodrine and the peak mentioned above from the sample solution is not larger than 3/10 times the peak area of midodrine from the standard solution, and the total area of the peaks other than midodrine from the sample solution is not larger than 1.1 times the peak area of midodrine from the standard solution.

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: About 3 times as long as the retention time of midodrine, beginning after the solvent peak.

System suitability—

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

Test for required detectability: Pipet 2 mL of the standard solution, add a mixture of water and acetonitrile for liquid chromatography (3:2) to make exactly 20 mL. Confirm that the peak area of midodrine obtained with 10 μL of this solution is equivalent to 7 to 13% of that with 10 μL of the standard solution.

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 peak area of midodrine is not more than 2.0%.

Loss on drying *<2.41>* Not more than 0.3% (1 g, 105°C, 2 hours).

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

Assay Weigh accurately about 25 mg each of Midodrine Hydrochloride and Midodrine Hydrochloride RS, previously dried, dissolve each in a mixture of water and acetonitrile for liquid chromatography (3:2) by sonicating, and add a mixture of water and acetonitrile for liquid chromatography (3:2) to make exactly 25 mL. Pipet 2 mL each of these solutions, add a mixture of water and acetonitrile for liquid chromatography (3:2) to make exactly 20 mL and use these solutions as the sample solution and the standard solution, respectively. 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

determine the peak areas, A_T and A_S, of midodrine in each solution.

Amount (mg) of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl) $= M_S \times A_T / A_S$

M_S: Amount (mg) of Midodrine Hydrochloride RS taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 290 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 50°C.

Mobile phase: A mixture of a solution of sodium lauryl sulfate (1 in 100), acetonitrile for liquid chromatography and phosphoric acid (600:400:1).

Flow rate: Adjust so that the retention time of midodrine is about 8 minutes.

System suitability—

System performance: Dissolve 20 mg of Midodrine Hydrochloride in dilute sodium hydroxide TS to make 20 mL, and allow to stand in a water bath at 80°C for 3 hours. After cooling, to 1 mL of this solution add a mixture of water and acetonitrile for liquid chromatography (3:2) to make 50 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, midodrine and the related substance A are eluted in this order with the resolution between these peaks being not less than 5.

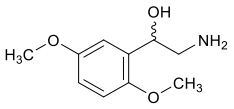
System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of midodrine is not more than 1.0%.

Containers and storage Containers — Well-closed containers.

Others

Related substance A:

2-Amino-1-(2,5-dimethoxyphenyl)ethanol



Add the following to 9.01 Reference Standards (1):

Midodrine Hydrochloride RS