Midodrine Hydrochloride Orally Disintegrating Tablets

ミドドリン塩酸塩口腔内崩壊錠

Midodrine Hydrochloride Orally Disintegrating Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl: 290.74).

Method of preparation Prepare as directed under Tablets, with Midodrine Hydrochloride.

Identification To a quantity of Midodrine Hydrochloride Orally Disintegrating Tablets, equivalent to 6 mg of Midodrine Hydrochloride, add 0.01 mol/L hydrochloric acid TS, shake to disperse the tablets, add 0.01 mol/L hydrochloric acid TS to make 200 mL, and shake vigorously. Filter the solution through a membrane filter with a pore size not exceeding 0.45 μm, and determine the absorption spectrum of the filtrate as directed under Ultraviolet-visible Spectrophotometry *<2.24>*: it exhibits a maximum between 288 nm and 292 nm.

Purity Related substances — Weigh accurately not less than 20 Midodrine Hydrochloride Orally Disintegrating Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 2 mg of Midodrine Hydrochloride, add exactly 10 mL of a mixture of water and acetonitrile for liquid chromatography (13:7), and disperse the particles into small particles by sonicating with occasional shaking. Centrifuge this solution, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 25 mg of Midodrine Hydrochloride RS, previously dried at 105°C for 2 hours, and dissolve in a mixture of water and acetonitrile for liquid chromatography (13:7) to make exactly 25 mL. Pipet 2 mL of this solution, and add a mixture of water and acetonitrile for liquid chromatography (13:7) to make exactly 20 mL. Pipet 1 mL of this solution, add a mixture of water and acetonitrile for liquid chromatography (13:7) to make exactly 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. Determine each peak area by the automatic integration method, and calculate the amounts of the related substances by the following formula. The amounts of the related substance having the relative retention time of about 0.25 to midodrine and the related substance A having the relative retention time of about 1.2 are not more than 0.6%, and the amount of each of other related substances is not more than 0.2%. Furthermore, the total amount of the related substances is not more than 2.0%.

Amount (%) of related substances

$$= M_S / M_T \times A_T / A_S \times M_M / C \times 1/25$$

M_S: Amount (mg) of Midodrine Hydrochloride RS taken

M_T: Amount (mg) of Midodrine Hydrochloride Orally Disintegrating Tablets taken

M_M: Average mass of 1 tablet (mg)

A_S: Peak area of midodrine obtained from the standard solution

A_T: Peak area of each related substance obtained from the sample solution

C: Labeled amount (mg) of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl) in 1 tablet

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 trimethylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35°C.

Mobile phase: A mixture of a solution of sodium lauryl sulfate (1 in 100), acetonitrile for liquid chromatography and phosphoric acid (650:350:1).

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

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

System suitability—

Test for required detectability: Pipet 5 mL of the standard solution, and add a mixture of water and acetonitrile for liquid chromatography (13:7) to make exactly 25 mL. Confirm that the peak area of midodrine obtained with 10 μL of this solution is equivalent to 14 to 26% of that of the standard solution.

System performance: Dissolve 20 mg of Midodrine Hydrochloride RS 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 (13:7) to make 100 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 3.

System reproducibility: When the test is repeated 6 times using 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 4.5%.

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 Midodrine Hydrochloride Orally Disintegrating Tablets add the internal standard solution to make exactly V mL so that each mL contains about 0.1 mg of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl), and disperse the particles into small particles by sonicating with occasional shaking. Centrifuge this solution, and use the supernatant liquid as the sample solution. Then, proceed as directed in the Assay.

Amount (mg) of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl)
$= M_S \times Q_T / Q_S \times V / 250$

M_S: Amount of Midodrine Hydrochloride RS taken

Internal standard solution—A solution of thymol in a mixture of 0.01 mol/L hydrochloric acid TS and methanol (1:1) (1 in 20,000).

Disintegration Being specified separately when the drug is granted approval based on the Law.

Dissolution *<6.10>* When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rate in 15 minutes of Midodrine Hydrochloride Orally Disintegrating Tablets is not less than 85%.

Start the test with 1 tablet of Midodrine Hydrochloride Orally Disintegrating Tablets, withdraw not less than 10 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 5 mL of the first filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 2.2 μg of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl), and use this solution as the sample solution. Separately, weigh accurately about 50 mg of Midodrine Hydrochloride RS, previously dried at 105°C for 2 hours, and dissolve in water to make exactly 50 mL. Pipet 5 mL of this solution, and add water to make exactly 100 mL. Pipet 5 mL of this solution, add water 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 midodrine in each solution.

Dissolution rate (%) with respect to the labeled amount of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl)
$= M_S \times A_T / A_S \times V' / V \times 1 / C \times 9 / 2$

M_S: Amount (mg) of Midodrine Hydrochloride RS taken
C: Labeled amount (mg) of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl) in 1 tablet

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 6 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 midodrine are not less than 5000 and not more than 1.5, 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 midodrine is not more than 1.5%.

Assay Weigh accurately not less than 20 Midodrine Hydrochloride Orally Disintegrating Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 2 mg of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl), add exactly 20 mL of the internal standard solution, and disperse the particles into small particles by sonicating with occasional shaking. Centrifuge this solution, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 25 mg of Midodrine Hydrochloride RS, previously dried at 105°C for 2 hours, and dissolve in the internal standard solution to make exactly 25 mL. Pipet 2 mL of this solution, add the internal standard solution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 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 midodrine to that of the internal standard.

Amount (mg) of midodrine hydrochloride ($C_{12}H_{18}N_2O_4$.HCl)
$= M_S \times Q_T / Q_S \times 2 / 25$

M_S: Amount (mg) of Midodrine Hydrochloride RS taken

Internal standard solution—A solution of thymol in a mixture of 0.01 mol/L hydrochloric acid TS and methanol (1:1) (1 in 20,000).
Operating conditions—
Detector: An ultraviolet absorption photometer (wavelength: 220 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 45°C.

Mobile phase: A mixture of a solution of sodium lauryl sulfate (1 in 100), acetonitrile for liquid chromatography and phosphoric acid (550:450:1).

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

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, midodrine and the internal standard 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 standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of midodrine to that of the internal standard is not more than 1.0%.

Containers and storage Containers — Tight containers (Moisture-proof packaging).

Storage — Light-resistant.

Others

Related substance A: Refer to it described in Midodrine Hydrochloride.

9.01 Add the following to Reference Standards (1) section.

Midodrine Hydrochloride RS