Midodrine Hydrochloride Orally Disintegrating Tablets

Midodrine Hydrochloride Orally Disintegrating Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of midodrine hydrochloride (C₁₂H₁₈N₂O₄·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 Ultra violet-visible Spectrophotometry <2.27>; 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 substances 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

\[ \text{Amount} = \frac{M_s}{M_T} \times \frac{A_T}{A_S} \times \frac{M_{TS}}{C} \times \frac{1}{25} \]

Mₜ: Amount (mg) of Midodrine Hydrochloride RS taken
M₄: Amount (mg) of Midodrine Hydrochloride Orally Disintegrating Tablets taken
M₅: Average mass of 1 tablet (mg)
A₄: Peak area of midodrine obtained from the standard solution
A₅: Peak area of each related substance obtained from the sample solution
C: Labeled amount (mg) of midodrine hydrochloride (C₁₂H₁₈N₂O₄·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 trimethylsilylized 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_{2}O_{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_{2}O_{4}·HCl)**

\[ M_S = M_S \times \frac{Q_T}{Q_S} \times V \times 250 \]

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

110  **Dissolution** 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%.

111  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 \( \mu \)m. 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 \( \mu \)g of midodrine hydrochloride (C_{12}H_{18}N_{2}O_{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.

112  Perform the test with exactly 100 \( \mu \)L each of the sample solution and standard solution as directed under Liquid Chromatography according to the following conditions, and determine the peak areas, \( A_T \) and \( A_S \), of midodrine in each solution.

113  Dissolution rate (%) with respect to the labeled amount of midodrine hydrochloride (C_{12}H_{18}N_{2}O_{4}·HCl)

\[ = M_S \times \frac{A_T}{A_S} \times V' / V \times \frac{1}{C} \times 9/2 \]

**M_S: Amount (mg) of Midodrine Hydrochloride RS taken**

114  **Operating conditions**

115  Detector: An ultraviolet absorption photometer (wavelength: 290 nm)

116  **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 \( \mu \)m in particle diameter).

117  **Flow rate:** Adjust so that the retention time of midodrine is about 6 minutes.

**System suitability**

118  System performance: When the procedure is run with 100 \( \mu \)L 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.

119  System repeatability: When the test is repeated 6 times with 100 \( \mu \)L 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%.

120  **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_{2}O_{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 \( \mu \)L each of the sample solution and standard solution as directed under Liquid Chromatography 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.

121  Amount (mg) of midodrine hydrochloride (C_{12}H_{18}N_{2}O_{4}·HCl)

\[ = M_S \times \frac{Q_T}{Q_S} \times 2/25 \]

122  **M_S: Amount (mg) of Midodrine Hydrochloride RS taken**

123  **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).

124  **Detector**: An ultraviolet absorption photometer (wavelength: 220 nm)

125  **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 \( \mu \)m 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