

Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Betahistine Mesilate, previously dried, as directed in the potassium bromide disk method under Infrared Spectrophotometry <2.25>, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) A 30 mg portion of Betahistine Mesilate responds to Qualitative Tests <1.09> (2) for mesilate.

**Melting point** <2.60> 110 – 114°C (after drying).

**Purity** (1) Heavy metals <1.07>—Proceed with 1.0 g of Betahistine Mesilate according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(2) Related substances—Dissolve 50 mg of Betahistine Mesilate in 10 mL of a mixture of water and acetonitrile (63:37), and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the mixture of water and acetonitrile (63:37) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20  $\mu$ L 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 betahistine obtained from the sample solution is not larger than 1/10 times the peak area of betahistine from the standard solution, and the total area of the peaks other than the peak of betahistine from the sample solution is not larger than 1/2 times the peak area of betahistine from the standard solution.

**Operating conditions—**

Detector: An ultraviolet absorption photometer (wavelength: 261 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  $\mu$ m in particle diameter).

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

Mobile phase: To 5 mL of diethylamine and 20 mL of acetic acid (100) add water to make 1000 mL. Dissolve 2.3 g of sodium lauryl sulfate in 630 mL of this solution, and add 370 mL of acetonitrile.

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

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

**System suitability—**

Test for required detectability: To exactly 5 mL of the standard solution add the mixture of water and acetonitrile (63:37) to make exactly 50 mL. Confirm that the peak area of betahistine obtained with 20  $\mu$ L of this solution is equivalent to 7 to 13% of that with 20  $\mu$ L of the standard solution.

System performance: Dissolve 10 mg of betahistine mesilate and 10 mg of 2-vinylpyridine in 50 mL of the mixture of water and acetonitrile (63:37). To 2 mL of this solution add the mixture of water and acetonitrile (63:37) to make 50 mL. When the procedure is run with 20  $\mu$ L of this solution under the above operating conditions, 2-vinylpyridine and betahistine 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 20  $\mu$ L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of betahistine is not more than 1.0%

**Loss on drying** <2.41> Not more than 1.0% (1 g, in vacuum, phosphorus (V) oxide, 70°C, 24 hours).

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

**Assay** Weigh accurately about 0.2 g of Betahistine Mesilate, previously dried, dissolve in 1 mL of acetic acid (100), add 50 mL of acetic anhydride, 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  
= 16.42 mg of  $C_8H_{12}N_2 \cdot 2CH_4O_3S$

**Containers and storage** Containers—Tight containers.

## Betahistine Mesilate Tablets

ベタヒスチンメシル酸塩錠

Betahistine Mesilate Tablets contain not less than 93.0% and not more than 107.0% of the labeled amount of betahistine mesilate ( $C_8H_{12}N_2 \cdot 2CH_4O_3S$ ; 328.41).

**Method of preparation** Prepare as directed under Tablets, with Betahistine Mesilate.

**Identification** To 5 mL of the sample solution obtained in the Assay add 0.1 mol/L hydrochloric acid TS to make 100 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry <2.24>: it exhibits a maximum between 259 nm and 263 nm.

**Purity** Related substances—Powder not less than 20 Betahistine Mesilate Tablets. To a portion of the powder, equivalent to about 50 mg of Betahistine Mesilate, add 10 mL of a mixture of water and acetonitrile (63:37), agitate for 10 minutes by sonicating, centrifuge, and use the supernatant liquid as the sample solution. Pipet 1 mL of the sample solution, add the mixture of water and acetonitrile (63:37) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20  $\mu$ L 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, having the relative retention time of about 1.9 to betahistine obtained from the sample solution, is not larger than 3/5 times the peak area of betahistine from the standard solution, and the total area of the peaks other than betahistine from the sample solution is not larger than the peak area of betahistine 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 8 times as long as the retention time of betahistine, beginning after the solvent peak.

**System suitability—**

Test for required detectability: To exactly 5 mL of the standard solution add the mixture of water and acetonitrile (63:37) to make exactly 50 mL. Confirm that the peak area of betahistine obtained with 20  $\mu$ L of this solution is equivalent to 7 to 13% of that with 20  $\mu$ L of the standard solution.

System performance: Dissolve 10 mg of betahistine mesilate and 10 mg of 2-vinylpyridine in 50 mL of the mixture of

water and acetonitrile (63:37). To 2 mL of this solution add the mixture of water and acetonitrile (63:37) to make 50 mL. When the procedure is run with 20  $\mu$ L of this solution under the above operating conditions, 2-vinylpyridine and betahistine 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 20  $\mu$ L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of betahistine is not more than 1.0%.

**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 Betahistine Mesilate Tablets add exactly  $V$  mL of 0.1 mol/L hydrochloric acid TS so that each mL contains about 0.4 mg of betahistine mesilate ( $C_8H_{12}N_2 \cdot 2CH_4O_3S$ ), agitate for about 10 minutes by sonicating to disintegrate the tablet, then centrifuge, and use the supernatant liquid as the sample solution. Proceed as directed in the Assay.

$$\begin{aligned} \text{Amount (mg) of betahistine mesilate } (C_8H_{12}N_2 \cdot 2CH_4O_3S) \\ = M_S \times A_T/A_S \times V/250 \end{aligned}$$

$M_S$ : Amount (mg) of betahistine mesilate for assay taken

**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 Betahistine Mesilate Tablets is not less than 85%.

Start the test with 1 tablet of Betahistine Mesilate Tablets, 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  $\mu$ m. Discard not less than 10 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 6.7  $\mu$ g of betahistine mesilate ( $C_8H_{12}N_2 \cdot 2CH_4O_3S$ ), and use this solution as the sample solution. Separately, weigh accurately about 17 mg of betahistine mesilate for assay, previously dried under reduced pressure with phosphorous (V) oxide at 70°C for 24 hours, and dissolve in water to make exactly 100 mL. Pipet 4 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20  $\mu$ L 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 betahistine in each solution.

$$\begin{aligned} \text{Dissolution rate (\%)} \text{ with respect to the labeled amount} \\ \text{of betahistine mesilate } (C_8H_{12}N_2 \cdot 2CH_4O_3S) \\ = M_S \times A_T/A_S \times V'/V \times 1/C \times 36 \end{aligned}$$

$M_S$ : Amount (mg) of betahistine mesilate for assay taken

$C$ : Labeled amount (mg) of betahistine mesilate ( $C_8H_{12}N_2 \cdot 2CH_4O_3S$ ) in 1 tablet

#### Operating conditions—

Proceed as directed in the operating conditions in the Assay.

#### System suitability—

**System performance:** When the procedure is run with 20  $\mu$ L of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of betahistine are not less than 2000 and not more than 1.5, respectively.

**System repeatability:** When the test is repeated 6 times with 20  $\mu$ L of the standard solution under the above operat-

ing conditions, the relative standard deviation of the peak area of betahistine is not more than 2.0%.

**Assay** Weigh accurately the mass of not less than 20 Betahistine Mesilate Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 20 mg of betahistine mesilate ( $C_8H_{12}N_2 \cdot 2CH_4O_3S$ ), add 40 mL of 0.1 mol/L hydrochloric acid TS, agitate for 10 minutes by sonicating, and add 0.1 mol/L hydrochloric acid TS to make exactly 50 mL. Centrifuge, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 0.1 g of betahistine mesilate for assay, previously dried under reduced pressure with phosphorous (V) oxide at 70°C for 24 hours, and dissolve in 0.1 mol/L hydrochloric acid TS to make exactly 50 mL. Pipet 10 mL of this solution, add 0.1 mol/L hydrochloric acid TS to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 5  $\mu$ L 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 betahistine in each solution.

$$\begin{aligned} \text{Amount (mg) of betahistine mesilate } (C_8H_{12}N_2 \cdot 2CH_4O_3S) \\ = M_S \times A_T/A_S \times 1/5 \end{aligned}$$

$M_S$ : Amount (mg) of betahistine mesilate for assay taken

#### Operating conditions—

**Detector:** An ultraviolet absorption photometer (wavelength: 261 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  $\mu$ m in particle diameter).

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

**Mobile phase:** To 5 mL of diethylamine and 20 mL of acetic acid (100) add water to make 1000 mL. In 630 mL of this solution dissolve 2.3 g of sodium lauryl sulfate, and add 370 mL of acetonitrile.

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

#### System suitability—

**System performance:** When the procedure is run with 5  $\mu$ L of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of betahistine are not less than 2000 and not more than 1.5, respectively.

**System repeatability:** When the test is repeated 6 times with 5  $\mu$ L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of betahistine is not more than 1.0%.

**Containers and storage** Containers—Tight containers.