Tolvaptan Tablets

トルバプタン錠

Tolvaptan Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of tolvaptan ($C_{26}H_{25}N_2C1N_2O_3$: 448.94).

Method of preparation Prepare as directed under Tablets, with Tolvaptan.

Identification Perform the test with 10 μL each of the sample solution and standard solution obtained in the Assay as directed under Liquid Chromatography *<2.01>* according to the following conditions: the retention times of the principal peaks in the chromatograms obtained from the sample solution and standard solution are the same, and both absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.

Operating conditions—

Column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Detector: A photodiode array detector (wavelength: 254 nm, spectrum range of measurement: 210 – 350 nm).

System suitability—

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

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 Tolvaptan Tablets add exactly *V*/6 mL of the internal standard solution, add methanol to make *V* mL so that each mL contains about 0.50 mg of tolvaptan ($C_{26}H_{25}N_2C1N_2O_3$) , sonicate while shaking to disintegrate, then shake thoroughly for 10 minutes. To 2 mL of this solution add methanol to make 10 mL, and filter this solution through a membrane filter with a pore size not exceeding 0.5 μm. Discard 1 mL of the first filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 30 mg of Tolvaptan RS, previously dried at 105°C for 2 hours, add exactly 10 mL of the internal standard solution, and add methanol to make 60 mL. To 2 mL of this solution add methanol to make 10 mL, and use this solution as the standard solution. Then, proceed as directed in the Assay.

Amount (mg) of tolvaptan ($C_{26}H_{25}ClN_2O_3$)
$= M_S \times Q_T / Q_S \times V / 60$

M_S: Amount (mg) of Tolvaptan RS taken

Internal standard solution—A solution of hexyl parahydroxybenzoate in methanol (9 in 5000).

Dissolution *<6.01>* When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of a solution of sodium lauryl sulfate (11 in 5000) as the dissolution medium, the *Q* value in 30 minutes of Tolvaptan Tablets is 80%.

Start the test with 1 tablet of Tolvaptan 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 0.5 μm. Discard not less than 10 mL of the first filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V′* mL so that each mL contains about 8.3 μg of tolvaptan ($C_{26}H_{25}ClN_2O_3$), and use this solution as the sample solution. Separately, weigh accurately about 30 mg of Tolvaptan RS, previously dried at 105°C for 2 hours, and dissolve in methanol to make exactly 100 mL. Pipet 2.5 mL of this solution, add the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the sample solution and standard solution at 268 nm as directed under Ultraviolet-visible Spectrophotometry *<2.24>*.

Dissolution rate (%) with respect to the labeled amount of tolvaptan ($C_{26}H_{25}ClN_2O_3$)
$= M_S \times A_T / A_S \times V' / V \times 1 / C \times 45 / 2$

M_S: Amount (mg) of Tolvaptan RS taken

C: Labeled amount (mg) of tolvaptan ($C_{26}H_{25}ClN_2O_3$) in 1 tablet

Assay Weigh accurately the mass of not less than 20 tablets of Tolvaptan Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 15 mg of tolvaptan ($C_{26}H_{25}ClN_2O_3$), add exactly 9 mL of the internal standard solution, add methanol to make 30 mL, sonicate to disperse, then shake thoroughly for 10 minutes. To 2 mL of this solution add methanol to make 10 mL, and filter this solution through a membrane filter with a pore size not exceeding 0.5 μm. Discard 1 mL of the first filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 50 mg of Tolvaptan RS, previously dried at 105°C for 2 hours, dissolve in methanol to make exactly 50 mL. Pipet 15 mL of this solution, add exactly 9 mL of the internal standard solution, and add methanol to make 30 mL. To 2 mL of this solution add methanol to make 10 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 tolvaptan to that of the internal standard.

Amount (mg) of tolvaptan ($C_{26}H_{25}ClN_2O_3$)
$= M_S \times Q_T / Q_S \times 3 / 10$

M_S: Amount (mg) of Tolvaptan RS taken

Internal standard solution—A solution of hexyl parahydroxybenzoate in methanol (1 in 1000).

Operating conditions—

Proceed as directed in the operating conditions in the Assay under Tolvaptan.

System suitability—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, tolvaptan and the internal standard are eluted in this order with the resolution between these peaks being not less than 15.

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 tolvaptan to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Tight containers.

Add the following to 9.01 (1) Reference Standards:

Tolvaptan RS