Ondansetron Hydrochloride Tablets

Dissolution <*6.10*> Perform the test with 1 tablet of Ondansetron Hydrochloride Tablets at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium. Start the test, 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 μm. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 2.5 μg of ondansetron hydrochloride ($C_{18}H_{19}N_3O$·HCl) according to the labeled amount, and use this solution as the sample solution. Separately, weigh accurately about 28 mg of Ondasetron Hydrochloride RS (separately, determine the water <*2.48*> with 50 g by direct titration in volumetric titration), and dissolve in the water to make exactly 200 mL. Pipet 4 mL of this solution, add water to make exactly 200 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 ondansetron of both solutions.

The requirements are met if Ondansetron Hydrochloride Tablets conform to the dissolution requirements.

Dissolution rate (%) with respect to the labeled amount of ondansetron ($C_{18}H_{19}N_3O$)
$= M_S \times A_T/A_S \times V'/V \times 1/C \times 9 \times 0.890$

M_S: Amount (mg) of Ondansetron Hydrochloride RS, calculated on the anhydrous basis
C: Labeled amount (mg) of ondansetron ($C_{18}H_{19}N_3O$) in 1 tablet

Operating conditions−

Detector: An ultraviolet absorption photometer (wavelength: 216 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 25ºC.

Mobile phase: Dissolve 1.56 g of sodium dihydrogen phosphate dihydrate in 500 mL of water, and adjust the pH to 5.4 with sodium hydroxide TS. To 500 mL of this solution add 500 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ondansetron 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

ondansetron are not less than 2000 and not more than 2.0, 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 ondansetron is not more than 1.5%.

Dissolution Requirements

Labeled amount*	Specified minute	Dissolution rate
2 mg	15 minutes	Not less than 80%
4 mg	15 minutes	Not less than 80%

*as Ondansetron

Ondansetron Hydrochloride RS $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$: 365.85 (±)-2,3-dihydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl]carbazol-4-(1*H*)-one monohydrochloride dihydrate. It meets the following reuirements. Purify according to the following method if needed.

Purification method−Recrystalize ondansetron hydrochloride hydrate in a mixture of 2-propanol and water (2:1), previously dried under reduced pressure at 50ºC for 3 hours, and allow to stand in an incubator at 25ºC and 75% relative humidity for more than 12 hours.

Description−Ondansetron Hydrochloride RS occurs as a white to pale yellowish white crystalline powder. A solution of Ondansetron Hydrochloride RS (1 in 50) shows no optical rotation.

Identification (1) Determine the infrared absorption spectrum of Ondansetron Hydrochloride RS as directed in the paste method under Infrared Spectrophotometry <*2.25*>: it exhibits absorption at the wave numbers of about 3180 cm^{-1}, 1640 cm^{-1}, 1282 cm^{-1}, 761 cm^{-1}, and 751 cm^{-1}.

(2) Determine the ^1H spectrum of a solution of Ondansetron Hydrochloride RS in deuterated dimethylsulfoxide for nuclear magnetic resonance spectroscopy (1 in 100), using tetramethylsilane for nuclear magnetic resonance spectroscopy as an internal reference compound, as directed under Nuclear Magnetic Resonance Spectroscopy <*2.21*>: it exhibits single signals A and B, at around δ 2.7 ppm and at around δ 3.7 ppm, and AMX-type quartet signals C and D, at around δ 4.3 ppm and at around δ4.7 ppm. The ratio of the integrated intensity of each signal, A:B:C:D, is about 3:3:1:1.

Purity (1) Related substances−

(i) Dissolve 20 mg of Ondansetron Hydrochloride RS in 200 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add the mobile phase to make exactly 50 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 20 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 of both solutions by the automatic integration

method: the total area of the peaks other than ondansetron obtained from the sample solution is not larger than the peak area of ondansetron from the standard solution. For this calculation, use the areas of the peaks, having the relative retention time of about 0.29 with respect to ondansetron, after multiplying by the sensitivity factor, 0.77.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 216 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 20 cm in length, packed with cyanopropylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25ºC.

Mobile phase: Dissolve 1.56 g of sodium dihydrogen phosphate dihydrate in 500 mL of water, and adjust the pH to 5.4 with sodium hydroxide TS. To 500 mL of this solution add 500 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ondansetron is about 6 minutes.

Time span of measurement: About 2 times as long as the retention time of ondansetron beginning after the solvent peak.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of ondansetron obtained from 10 μL of this solution is equivalent to 14 to 26% of that from 10 μL of the standard solution.

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of ondansetron are not less than 2000 and not more than 2.0, respectively.

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 ondansetron is not more than 5.0%.

(ii) Dissolve 12.5 mg of Ondansetron Hydrochloride RS in 1 mL of methanol, and use this solution as the sample solution. Pipet 0.5 mL of this solution, and add methanol to make exactly 25 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 20 μL each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, ethyl acetate, methanol and ammonia solution (28)(90:50:40:1) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots obtained with other than the principal spot is not more intense than that with the standard solution.

(2) 2-propanol Weigh accurately about 0.1 g of Ondansetron Hydrochloride RS, transfer to a 3 mL glass bottle, add exactly 2 mL of the internal standard solution, and stopper tightly. Warm the

glass bottle in a water bath at 50ºC for 10 to 15 minutes, dissolve with shaking, cool to room temperature, and use this solution as the sample solution. Separately, weigh accurately 40 μL of 2-propanol, add the internal standard solution to make exactly 40 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the sample solution and standard solution as directed under Gas Chromatography <2.02> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of 2-propanol to that of the internal standard of each solution: the amount of 2-propanol is not more than 0.2%.

Amount (%) of 2-propanol
$= Q_T/Q_S \times 1/W \times 1/5 \times 0.79$

M: Amount (g) of sample
0.79: Density (g/mL) of 2-propanol

Internal standard solution−Diluted ethanol (99.5) (1 in 500).

Operating conditions

Detector: A hydrogen flame-ionization detector.

Column: A glass column 3 mm in inside diameter and 2 m in length, packed with porous ethylvinylbenzene-divinylbenzene copolymer for gas chromatography (150 to 180 μm in particle diameter) (0.0075 μm in average pore size, 500 − 600m^2/g).

Column temperature: A constant temperature of about 170ºC.

Carrier gas: Nitrogen.

Flow rate: Adjust the flow rate so that the retention time of the internal standard is about 3 minutes.

System suitability

System performance: When the procedure is run with 1 μL of the standard solution under the above operating conditions, the internal standard and 2-propanol 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 1 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of 2-propanol to that of the internal standard is not more than 1.5%.

Water <2.48>: 9.6 − 10.2% (50 mg, volumetric titration, direct titration).

Content: not less than 99.5%, calculated on the anhydrous basis. Assay−Weigh accurately about 50 mg of Ondansetron Hydrochloride RS, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid for nonaqueous titration (7:3), 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 0.01 mol/L perchloric acid VS
= 3.298 mg of $C_{18}H_{19}N_3O \cdot HCl$