Mosapramine Hydrochloride Granules

Dissolution <*6.10*> Weigh accurately an amount of Mosapramine Hydrochloride Granules, equivalent to about 25 mg of mosapramine hydrochloride ($C_{28}H_{35}ClN_4O \cdot 2HCl$) according to the labeled amount, and perform the test 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, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 28 mg of Mosapramine Hydrochloride RS, previously dried at 105ºC for 2 hours, and dissolve in water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, at 252 nm of the sample solution and standard solution as directed under Ultraviolet visible Sectrophotometry <*2.24*>.

The requirements are met if Mosapramine Hydrochloride Granules conform to the dissolution requirements.

Dissolution rate (%) with respect to the labeled amount of mosapramine hydrochloride ($C_{28}H_{35}ClN_4O \cdot 2HCl$)

$= M_S/M_T \times A_T/A_S \times 1/C \times 90$

M_S: Amount (mg) of Mosapramine Hydrochloride RS

M_T: Amount (g) of sample

C: Labeled amount (mg) of mosapramine hydrochloride ($C_{28}H_{35}ClN_4O \cdot 2HCl$) in 1 g

Dissolution Requirements

Labeled amount	Specified minute	Dissolution rate
100 mg/g	15 minutes	Not less than 85%

Mosapramine Hydrochloride RS $C_{28}H_{35}ClN_4O \cdot 2HCl$: 551.98 (±)-3-chloro-5-[3-(2-oxo-1,2,3,5,6,7,8,8a-oxtahydroimidazo[1,2-a]pyridine-3-spiro-4'-piperidino)propyl]-10,11-dihydro-5*H*-dibenz[b,f]azepine dihydrochloride. It meets the following reuirements. Purify according to the following method if needed.

Purification method−Conduct this procedure without exposure to light. To 30 g of mosapramine hydrochloride add 100 mL of water, shake for 5 minutes, add 50 mL of ammonia TS, and shake for further 5 minutes. Add 700 mL of diethyl ether, shake, and separate the diethyl ether layer. To the

diethyl ether layer add 30 g of anhydrous sodium sulfate, and immediately filter by suction. Evaporate the filtrate at 30ºC under reduced pressure, lightly crush the residue, and dry with a desiccator (reduced pressure, phosphorus (V) oxide) for 1 hour. To 25 g of the residue add 280 mL of ethanol (99.5), dissolve in a water bath by warming at 80ºC, and filter by suction while hot. Cool the filtrate with ice for 1 hour, and allow to stand in a refrigerator for further 40 hours. Filter the crystals separated, and dry with a desiccator (reduced pressure, phosphorus (V) oxide) for 1 hour. To 14 g of the crystals add 120 mL of 0.5 mol/L hydrochloric acid TS, shake vigorously to dissolve, and filter. Allow the filtrate to stand at room temperature overnight, filter the crystals separated, and dry with a desiccator (reduced pressure, phosphorus (V) oxide) for 5 hours.

Description−Mosapramine Hydrochloride RS occurs as a white, crystalline powder.

Identification−Determine the infrared absorption spectrum of Mosapramine Hydrochloride RS as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>: it exhibits absorption at the wave numbers of about 2950 cm^{-1}, 1721 cm^{-1}, 1589 cm^{-1}, 1474 cm^{-1} and 756 cm^{-1}.

Related substances−Dissolve 0.15 g of Mosaparamine Hydrochloride RS in 10 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 200 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 peak area, A_{Ta} and A_{Tb}, of 3-chloro-5-[3-(2-oxo-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-3-spiro-4'-piperidino)propyl]-10,11-dihydro-5*H*-dibenz [b,f]azepine, having the retention time of about 0.7 with respect to mosapramine obtained from the sample solution, and 5-[3-(2-oxo-1,2,3,5,6,7,8,8a-octahydroimidazo [1,2-a]pyridine-3-spiro-4'-piperidino)propyl]-10,11-dihydro-5*H*-dibenz[b,f]azepine, having the retention time of about 0.8 with respect to mosapramine, is not larger than 3/5 times the peak area, *A*s, of mosapriamine from the standard solution, the 1/6 times the peak area, A_{Tc}, of chloroiminodibenzyl, having the retention time of about 4 with respect to mosapramine from the sample solution is not larger than 1/5 times of *A*s, each peak area of related substances other than the above substances from the sample solution is not larger than 1/5 times of *A*s, and the total amount of the peaks of 1/6 times of A_{Ta}, A_{Tb}, A_{Tc}, and other related substances is not larger than *A*s.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25ºC.

Mobile phase: Dissolve 7.0 g of sodium perchlorate in 1000 mL of water, and adjust the pH to 2.5 with perchloric acid. To 900 mL of this solution add 1100 mL of acetonitrile.

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

Time span of measurement: About 5 times as long as the retention time of mosapramine beginning after the solvent peak.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of mosapramine obtained from 10 μL of this solution is equivalent to 7 to 13% of that from 10 μL of the standard solution.

System performance: Dissolve 0.1 g of Mosapramine Hydrochloride RS and 30 mg of benzophenone in the mobile phase to make 100 mL. When the procedure is run with 5 μL of this solution under the above operating conditions, mosapramine and benzophenone are eluted in this order with the resolution between these peaks being not less than 4.

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 mosapramine is not more than 2.0%.

Loss on drying <2.41>: not more than 0.5% (1 g, 105ºC, 2 hours).

Content: not less than 99.0%. Assay−Weigh accurately about 0.4 g of Mosapramine Hydrochloride RS, previously dried, dissolve in 3.0 mL of formic acid, add 60 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
= 27.60 mg of $C_{28}H_{35}ClN_4O \cdot 2HCl$