Bopindolol Malonate Tablets

Dissolution <*6.10*> Perform the test with 1 tablet of Bopindolol Malonate Tablets at 50 revolutions per minute according to the Paddle method, using 900 mL of 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0, 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 0.5 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0 to make exactly *V'* mL so that each mL contains about 0.71 μg of bopindolol malonate ($C_{23}H_{28}N_2O_3 \cdot C_3H_4O_4$) according to the labeled amount. Pipet 4 mL of this solution, add acetonitrile to make exactly 5 mL, and use this solution as the sample solution. Separately, weigh accurately about 28 mg of Bopindolol Malonate RS, previously dried at 80ºC for 3 hours under reduced pressure (not more than 0.67 kPa), and dissolve in 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0 to make exactly 200 mL. Pipet 1 mL of this solution, add 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0 to make exactly 200 mL. Pipet 20 mL of this solution, add acetonitrile to make exactly 25 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 bopindolol of both solutions.

The requirements are met if Bopindolol Malonate Tablets conform to the dissolution requirements.

Dissolution rate (%) with respect to the labeled amount of bopindolol malonate ($C_{23}H_{28}N_2O_3 \cdot C_3H_4O_4$)

$= M_S \times A_T/A_S \times V'/V \times 1/C \times 9/4$

M_S: Amount (mg) of Bopindolol Malonate RS

C: Labeled amount (mg) of bopindolol malonate ($C_{23}H_{28}N_2O_3 \cdot C_3H_4O_4$) in 1 tablet

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 268 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 1.45 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust the pH to 3.0 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile, and mix.

Flow rate: Adjust the flow rate so that the retention time of bopindolol is about 5 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 bopindolol are not less than 3000 and not more than 2.5, 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 bopindolol is not more than 2.0%.

Dissolution Requirements

Labeled amount	Specified minute	Dissolution rate
0.6365 mg	15 minutes	Not less than 80%
1.273 mg	30 minutes	Not less than 85%

Bopindolol Malonate RS $C_{23}H_{28}N_2O_3 \cdot C_3H_4O_4$: 484.54 (±)-4-[2'-benzoyloxy-3'-(tert-butylamino)propoxy]-2-methylindol malonic acid. It meets the following requirements. Purify according to the following method if needed.

Purification method−Dissolve Bopindolol Malonate RS in acetone by warming. After cooling, separate the crystals produced, and wash with acetone. Repeat the recrystallization in the same manner, and dry the crystals so obtained under reduced pressure by warming.

Description−Bopindolol Malonate RS occurs as white to pale yellow reddish-white crystalline powder.

Identification (1) Determine the absorption spectrum of Bopindolol Malonate RS in ethanol (95) (1 in 40000) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits a maximum between 266 nm and 270 nm.

(2) Determine the infrared absorption spectrum of Bopindolol Malonate RS, previously dried, as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>: it exhibits absorption at the wave numbers of about 3340cm^{-1}, 1719 cm^{-1}, 1266 cm^{-1}, 1236 cm^{-1}, 1096 cm^{-1} and 897 cm^{-1}.

Absorbance <*2.24*> $E_{1cm}^{1\%}$ (268 nm): 214 - 236 (0.05 g, ethanol (95), 2000 mL).

Purity Related substances−Dissolve 0.10 g of Bopindolol Malonate RS in 20 mL of a mixture of water and acetonitrile (1:1), and use this solution as the sample solution. Pipet 1 mL of this solution, add a mixture of water and acetonitrile (1:1) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 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 other than bopindolol

obtained from the sample solution is not larger than the peak area of bopindolol from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 248 nm).

Column: A stainless steel column 4.0 mm in inside diameter and 12.5 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 A: A mixture of a solution of ammonium carbonate (1 in 100), acetonitrile and tetrahydrofuran (14:5:1).

Mobile phase B: A mixture of acetonitrile, a solution of ammonium carbonate (1 in 100) and tetrahydrofuran (17:5:3).

Flowing of the mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 30	100 → 0	0 → 100
30 – 38	0	100

Flow rate: 1.1 mL per minute.

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

System suitability

Test for required detectability: Pipet 2 mL of the standard solution, and add a mixture of water and acetonitrile (1:1) to make exactly 10 mL. Confirm that the peak area of bopindolol obtained from 20 μL of this solution is equivalent to 4 to 26% of that from 20 μL of the standard solution.

System performance: Dissolve 50 mg of Bopindolol Malonate RS and 10 mg of benzophenone in 250 mL of a mixture of water and acetonitrile (1:1). When the procedure is run with 20 μL of this solution under the above operating conditions, benzophenone and bopindolol are eluted in this order with the resolution between these peaks being not less than 10.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of bopindolol is not more than 2.0%.

Loss on drying <2.41>: not more than 0.5% (1 g, reduced pressure not exceeding 0.67 kPa, 80ºC, 3 hours).

Content: not less than 99.0%. Assay−Weigh accurately about 0.3 g of Bopindolol Malonate RS, previously dried, dissolve in 50 mL of a mixture of acetic acid (100) and acetic anhydride (1:1), 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
= 48.45 mg of $C_{23}H_{28}N_2O_3 \cdot C_3H_4O_4$