Toremifene Citrate Tablets

Dissolution <6.10> Perform the test with 1 tablet of Toremifene Citrate 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 0.45 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 44 μg of toremifene ($C_{26}H_{28}ClNO$) according to the labeled amount, and use this solution as the sample solution. Separately, weigh accurately about 30 mg of Toremifene Citrate RS, previously dried at 105ºC for 2 hours, add 4 mL of methanol to dissolve, and add 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0 to make exactly 100 mL. Pipet 5 mL of this solution, add 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0 to make exactly 20 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, at 277 nm of the sample solution and standard solution as directed under Ultraviolet-visible Spectrophotometry <2.24>, using 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0 as the blank.

The requirements are met if Toremifene Citrate Tablets conform to the dissolution requirements.

Dissolution rate (%) with respect to the labeled amount of toremifene ($C_{26}H_{28}ClNO$)

$= M_S \times A_T/A_S \times V'/V \times 1/C \times 225 \times 0.679$

M_S: Amount (mg) of Toremifene Citrate RS

C: Labeled amount (mg) of toremifene ($C_{26}H_{28}ClNO$) in 1 tablet

Dissolution Requirements

Labeled amount*	Specified minute	Dissolution rate
40.0 mg	30 minutes	Not less than 75%
60.0 mg	30 minutes	Not less than 75%

*as Toremifene

Toremifene Citrate RS $C_{26}H_{28}ClNO \cdot C_6H_8O_7$: 598.08 2-[4-〔(*Z*)-4-chloro-1,2-diphenyl-1-butenyl〕phenoxy]-*N*,*N*-dimethylethylamine citrate. It meets the following requirements.

Description—Toremifene Citrate RS occurs as a white, crystalline powder.

Identification (1) Infrared absorption spectrum−Determine the infrared absorption spectrum of Toremifene Citrate RS as directed in the potassium bromide disk method under Infrared Spectrophotometry <2.25>: it exhibits absorption at the wave numbers of about 1741 cm^{-1}, 1703 cm^{-1}, 1585 cm^{-1}, 1241 cm^{-1}, and 706 cm^{-1}.

(2) Nuclear magnetic resonance spectrum−Determine the ^{1}H spectrum of a solution of Toremifene Citrate RS in deuterated dimethylsulfoxide for nuclear magnetic spectroscopy (1 in 25), using tetramethlsilane for nuclear magnetic resonance spectroscopy as an internal reference compound, as directed under Nuclear Magnetic Resonance Spectroscopy <2.21>: it exhibits a quartet signal A at around σ 2.6 ppm, a single signal B at around σ 2.6 ppm, triple signals C, D, E and F, at around σ 2.9 ppm, at around σ 3.2 ppm, at around σ 3.4 ppm and at around σ 4.1 ppm, double signals G and H, at around σ 6.7 ppm and at around σ 6.8 ppm, multiple signals I and J, at around σ 7.2 ppm and at around σ 7.4 ppm, and a signal K composed of a broad absorption at around σ 10.8 ppm. The ratio of the integrated intensity of each signal, A:B:C:D:E:F:G:H:I:J:K, is about 4:6:2:2:2:2:2:2:5:5:3.

Purity (1) E-isomer−Dissolve 50 mg of Toremifene Citrate RS in exactly 5 mL of methanol. Pipet 2 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add the mobile phase to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 25 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, and determine each peak area by the automatic integration method: the peak area of E-isomer having the relative retention time of about 0.9 with respect to toremifene, obtained from sample solution, is not larger than the peak area of toremifene from the standard solution. (not more than 0.2%).

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 (5 μm in particle diameter).

Column temperature: A constant temperature of about 35ºC.

Mobile phase: Dissolve 1.6 g of sodium dihydrogen phosphate dehydrate in water to make 1000 mL, and adjust the pH to 2.0 with phosphoric acid. To 1000 mL of this solution add 7.9 g of *N*,*N*-dimethyl-*n*-octylamine, and adjust the pH to 2.0 with phosphoric acid. To 450 mL of this solution add 550 mL of a mixture of methanol and acetonitrile (1:1), and adjust the pH to 2.0 with phosphoric acid.

Flow rate: Adjust the flow rate so that the retention time of toremifene is about 18 minutes.

System suitability

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of

toremifene are not less than 5000 and not more than 1.5, respectively.

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 toremifene is not more than 3.0%.

(2) Other Related substances−Dissolve 50 mg of Toremifene Citrate RS in exactly 5 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of this solution, and add methanol to make exactly 100 mL. Pipet 10 mL, 4 mL and 2 mL of this solution, add methanol to make them exactly 20 mL, and use these solutions as the standard solution (1), standard solution (2) and standard solution (3). Pipet 10 mL of the standard solution (3), add methanol to make exactly 20 mL, and use this solution as the standard solution (4). Perform the test with these solutions as directed under Thin-layer Chromatography *<2.03>*. Spot 10 μL each of the sample solution, standard solution (1), standard solution (2), standard solution (3) and standard solution (4) on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of toluene and triethylamine (9:1) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm) and compare to the spot with the standard solution with the spots other than the principal spot and the spot of the starting point with the sample solution: the total amount of these spots is not more than 0.5%.

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

Content: not less than 99.5%. Assay−Weigh accurately about 0.4 g of Toremifene Citrate RS, previously dried, dissolve in 50 mL of acetic acid (100), 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
= 59.81 mg of $C_{26}H_{28}ClNO \cdot C_6H_8O_7$