

Internal standard solution—A solution of tolbutamide in ethanol-free chloroform (3 in 2000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 30 cm in length, packed with silica gel for liquid chromatography (5 μ m in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of hexane, water-saturated hexane, tetrahydrofuran, ethanol (95) and acetic acid (100) (475:475:20:15:9).

Flow rate: Adjust the flow rate so that the retention time of tolbutamide is about 12 minutes.

System suitability—

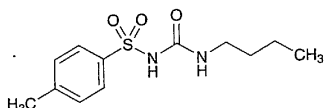
System performance: When the procedure is run with 10 μ L of the standard solution under the above operating conditions, the internal standard and tolbutamide are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 6 times with 10 μ L of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of tolbutamide to that of the internal standard is not more than 1.0%.

Containers and storage Containers—Well-closed containers.

Tolbutamide

トルブタミド



$C_{12}H_{18}N_2O_3S$: 270.35

N-(Butylcarbamoyl)-4-methylbenzenesulfonamide
[64-77-7]

Tolbutamide, when dried, contains not less than 99.0% of $C_{12}H_{18}N_2O_3S$.

Description Tolbutamide occurs as white crystals or crystalline powder. It is odorless or has a slight, characteristic odor. It is tasteless.

It is soluble in ethanol (95), slightly soluble in diethyl ether, and practically insoluble in water.

Identification (1) Boil 0.2 g of Tolbutamide with 8 mL of diluted sulfuric acid (1 in 3) under a reflux condenser for 30 minutes. Cool the solution in ice water, collect the precipitated crystals, recrystallize from water, and dry at 105°C for 3 hours: the crystals melt between 135°C and 139°C.

(2) Render the filtrate obtained in (1) alkaline with about 20 mL of a solution of sodium hydroxide (1 in 5), and heat: an ammonia-like odor is perceptible.

Melting point 126 – 132°C

Purity (1) Acid—Warm 3.0 g of Tolbutamide with 150 mL of water at 70°C for 5 minutes, allow to stand for 1 hour in ice water, and filter. To 25 mL of the filtrate add 2 drops of methyl red TS and 0.20 mL of 0.1 mol/L sodium hydroxide VS: a yellow color develops.

(2) Chloride—To 40 mL of the filtrate obtained in (1) add 6 mL of dilute nitric acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.011%).

(3) Sulfate—To 40 mL of the filtrate obtained in (1) add 1 mL of dilute hydrochloric acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid VS (not more than 0.021%).

(4) Heavy metals—Proceed with 2.0 g of Tolbutamide according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

Loss on drying Not more than 0.5% (1 g, 105°C, 3 hours).

Residue on ignition Not more than 0.10% (1 g).

Assay Weigh accurately about 0.5 g of Tolbutamide, previously dried, and dissolve in 30 mL of neutralized ethanol. Add 20 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 27.035 mg of $C_{12}H_{18}N_2O_3S$

Containers and storage Containers—Well-closed containers.

Tolbutamide Tablets

トルブタミド錠

Tolbutamide Tablets contain not less than 95% and not more than 105% of the labeled amount of tolbutamide ($C_{12}H_{18}N_2O_3S$: 270.35).

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

Identification Shake a quantity of powdered Tolbutamide Tablets, equivalent to 0.5 g of Tolbutamide according to the labeled amount, with 50 mL of chloroform, filter, and evaporate the filtrate to dryness. Proceed with the residue as directed in the Identification under Tolbutamide.

Dissolution test Take 1 tablet of Tolbutamide Tablets at 100 revolutions per minute according to the Method 2 under the Dissolution Test, using 900 mL of phosphate buffer solution, pH 7.4, as the test solution. Take 20 mL or more of the dissolved solution 30 minutes after the start of the test, and filter through a membrane filter (less than 0.8 μ m in pore size). Discard the first 10 mL of the filtrate, pipet the subsequent V mL, add water to make exactly V' mL of a solution containing about 10 μ g of tolbutamide ($C_{12}H_{18}N_2O_3S$) per mL according to the labeled amount, and use this solution as the sample solution. Separately, weigh accurately about 0.050 g of Tolbutamide Reference Standard, previously

dried at 105°C for 3 hours, dissolve in 10 mL of methanol, and add phosphate buffer solution, pH 7.4, to make exactly 100 mL. Pipet 2 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 , of the sample solution and the standard solution at 226 nm as directed under the Ultraviolet-visible Spectrophotometry, respectively.

The dissolution rate of Tolbutamide Tablets after 30 minutes should be not less than 80%.

Dissolution rate (%) to labeled amount of tolbutamide ($C_{12}H_{18}N_2O_3S$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{90}{C} \times \frac{1}{5}$$

W_S : Amount (mg) of Tolbutamide Reference Standard.

C : Labeled amount (mg) of tolbutamide ($C_{12}H_{18}N_2O_3S$) per tablet.

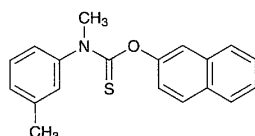
Assay Weigh accurately and powder not less than 20 Tolbutamide Tablets. Weigh accurately a portion of the powder, equivalent to about 0.5 g of tolbutamide ($C_{12}H_{18}N_2O_3S$), dissolve in 50 mL of neutralized ethanol, add 25 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 27.035 mg of $C_{12}H_{18}N_2O_3S$

Containers and storage Containers—Well-closed containers.

Tolnaftate

トルナフタート



$C_{19}H_{17}NOS$: 307.41

O-Naphthalen-2-yl *N*-methyl-*N*-(3-methylphenyl)thiocarbamate [2398-96-1]

Tolnaftate, when dried, contains not less than 98.0% of $C_{19}H_{17}NOS$.

Description Tolnaftate occurs as a white powder. It is odorless.

It is freely soluble in chloroform, sparingly soluble in diethyl ether, slightly soluble in methanol and in ethanol (95), and practically insoluble in water.

Identification (1) To 0.2 g of Tolnaftate add 20 mL of potassium hydroxide-ethanol TS and 5 mL of water, and heat under a reflux condenser for 3 hours. After cooling, to 10 mL of this solution add 2 mL of acetic acid (100), and shake with 1 mL of lead (II) acetate TS: a black precipitate is formed.

(2) Determine the absorption spectrum of a solution of Tolnaftate in methanol (1 in 100,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of a

solution of Tolnaftate Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared absorption spectrum of Tolnaftate, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of previously dried Tolnaftate Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers.

Melting point 111 – 114°C (after drying).

Purity (1) Heavy metals—Carbonize 1.0 g of Tolnaftate by gentle heating. After cooling, add 5 mL of nitric acid and 1 mL of sulfuric acid, and heat until white fumes are evolved. After cooling, add 2 mL of nitric acid, and heat until white fumes are evolved. After cooling, add 2 mL of nitric acid and 0.5 mL of perchloric acid, and heat gradually until white fumes are evolved. Repeat this procedure twice, and heat until white fumes are no longer evolved. Incinerate the residue by igniting between 500°C and 600°C for 1 hour. Proceed according to Method 2, and perform the test with 50 mL of the test solution so obtained. Prepare the control solution as follows: to 11 mL of nitric acid add 1 mL of sulfuric acid, 1 mL of perchloric acid and 2 mL of hydrochloric acid, proceed in the same manner as the test solution, and add 2.0 mL of Standard Lead Solution and water to make 50 mL (not more than 20 ppm).

(2) Related substances—Dissolve 0.50 g of Tolnaftate in 10 mL of chloroform, and use this solution as the sample solution. Pipet 2 mL of the sample solution, and add chloroform to make exactly 100 mL. Pipet 5 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10 μ L each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with toluene to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand in iodine vapor for 5 minutes, and examine under ultraviolet light (wavelength: 254 nm): the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

Loss on drying Not more than 0.5% (1 g, in vacuum at a pressure not exceeding 0.67 kPa, 65°C, 3 hours).

Residue on ignition Weigh accurately about 2.0 g of Tolnaftate, and carbonize by gradual heating. Moisten the substance with 1 mL of sulfuric acid, heat gradually until white fumes are no longer evolved, and ignite between 450°C and 550°C for about 2 hours to constant mass: the residue is not more than 0.1%.

Assay Weigh accurately about 0.05 g of Tolnaftate and Tolnaftate Reference Standard, previously dried, dissolve each in 200 mL of methanol by warming in a water bath, cool, and add methanol to make exactly 250 mL. Pipet 5 mL each of the solutions, to each add methanol to make exactly 100 mL, and use these solutions as the sample solution and the standard solution, respectively. Determine the absorbances, A_T and A_S , of the sample solution and the standard solution at 257 nm as directed under the Ultraviolet-visible Spectrophotometry.