Tofisopam

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\text{C}_{22}\text{H}_{30}\text{N}_{2}\text{O}_{4}\text{C}: 382.45} \\
(RS)-1-(3,4-	ext{Dimethoxyphenyl})-5-	ext{ethyl}-7,8-	ext{dimethoxy-4-	ext{methyl-5H-2,3-benodiazepine [22345-47-7]}}
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Tofisopam, when dried, contains not less than 98.0\% of \(\text{C}_{22}\text{H}_{30}\text{N}_{2}\text{O}_{4}\).

**Description**

Tofisopam occurs as a pale yellowish white, crystalline powder.

It is freely soluble in acetic acid (100), soluble in acetone, sparingly soluble in ethanol (95), slightly soluble in diethyl ether, and practically insoluble in water.

A solution of Tofisopam in ethanol (95) (1 in 100) shows no optical rotation.

**Identification**

(1) Determine the absorption spectrum of a solution of Tofisopam in ethanol (95) (1 in 100,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

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

**Melting point**

155 – 159\^\circ\text{C}

**Purity**

(1) Heavy metals—Proceed with 1.0 g of Tofisopam according to Method 2, and perform the test. Prepare the control solution with 1.0 mL of Standard Lead Solution (not more than 10 ppm).

(2) Arsenic—Prepare the test solution with 1.0 g of Tofisopam according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(3) Related substances—Dissolve 0.05 g of Tofisopam in 10 mL of acetone, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add acetone to make exactly 25 mL, pipet 1 mL of this solution, add acetone to make exactly 20 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10 \(\mu\text{L}\) 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 a mixture of ethyl acetate, acetone, methanol and formic acid (24:12:2:1) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main 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, silica gel, 60°C, 3 hours).

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

**Assay** Weigh accurately about 0.2 g of Tolisopam, previously dried, dissolve in 50 mL of acetic acid (100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS = 38.246 mg of C_{16}H_{20}N_{2}O_{4}

**Containers and storage** Containers—Tight containers.

Storage—Light-resistant.

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**Tolazamide**

トルザミド

C_{16}H_{20}N_{2}O_{4}S: 311.40
4-Methyl-N-(azepan-1-ylcarbamoyl)benzenesulfonamide [1156-19-0]

Tolazamide, when dried, contains not less than 97.5% and not more than 102.0% of C_{16}H_{21}N_{2}O_{3}S.

**Description** Tolazamide occurs as a white to pale yellow, crystalline powder. It is odorless.

It is freely soluble in chloroform, soluble in acetone, slightly soluble in ethanol (95) and in n-butylamine, and practically insoluble in water and in diethyl ether.

Melting point: about 168°C (with decomposition).

**Identification** (1) Dissolve 0.02 g of Tolazamide in 5 mL of water and 1 mL of n-butylamine, add 2 to 3 drops of copper (II) sulfate TS, and shake well. Shake well this solution with 5 mL of chloroform, and allow to stand: a green color develops in the chloroform layer.

(2) Determine the absorption spectrum of a solution of Tolazamide in ethanol (95) (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 Tolazamide 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 Tolazamide, 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 Tolazamide Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers.

**Purity** (1) Heavy metals—Proceed with 1.0 g of Tolazamide according to Method 2, and perform the test.

Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(2) Arsenic—Prepare the test solution with 1.0 g of Tolazamide according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(3) Related substances—Dissolve 0.20 g of Tolazamide in acetone to make exactly 10 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add acetone to make exactly 200 mL, and use this solution as the standard solution (1). Separately, dissolve 0.020 g of p-toluenesulfonamide in acetone to make exactly 200 mL, and use this solution as the standard solution (2). Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10 μL each of the sample solution and the standard solutions (1) and (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol, cyclohexane and dilute ammonia solution 28:10:20 (100:60:23) to a distance of about 12 cm, and air-dry the plate. Heat the plate at 110°C for 10 minutes, and immediately expose to chlorine for 2 minutes. Expose the plate to cold wind until a very pale blue color develops when 1 drop of potassium iodide-starch TS is placed on a site below the starting line on the plate. Spray evenly potassium iodide-starch TS on the plate: the spot from the sample solution corresponding to the spot from the standard solution (2) is not more intense than the spot from the standard solution (2), and the spots other than the principal and above spots from the sample solution are not more intense than the spot from the standard solution (1).

(4) N-Aminohexamethyleneimine—To 0.50 g of Tolazamide add 2.0 mL of acetone, stopper the flask tightly, shake vigorously for 15 minutes. Add 8.0 mL of disodium hydrogenphosphate-citric acid buffer solution, pH 5.4, shake, allow to stand for 15 minutes, and filter. To the filtrate add 1.0 mL of trisodium ferrous pentacyanoamine TS, and shake: the color developing within 30 minutes is not deeper than that of the following control solution.

Control solution: Dissolve 0.125 g of N-aminohexamethyleneimine in acetone to make exactly 100 mL. Pipet 1 mL of this solution, and add acetone to make exactly 100 mL. To 2.0 mL of this solution add 8.0 mL of disodium hydrogenphosphate-citric acid buffer solution, pH 5.4, shake, and proceed in the same manner.

**Loss on drying** Not more than 0.5% (1 g, in vacuum, 60°C, 3 hours).

**Residue on ignition** Not more than 0.20% (1 g).

**Assay** Weigh accurately about 0.03 g each of Tolazamide and Tolazamide Reference Standard, previously dried, dissolve each in 10 mL of the internal standard solution, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 10 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of tolazamide to that of the internal standard, respectively.

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\text{Amount (mg) of C}_{16}\text{H}_{20}\text{N}_{2}\text{O}_{4}\text{S} = \frac{\text{Amount (mg) of Tolazamide Reference Standard} \times Q_T}{Q_S}
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