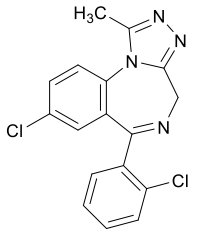
Triazolam

トリアゾラム



$C_{17}H_{12}Cl_2N_4$: 343.21

8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine

[*28911-01-5*]

Triazolam, when dried, contains not less than 98.0% and not more than 102.0% of triazolam ($C_{17}H_{12}Cl_2N_4$).

Description Triazolam occurs as a white crystalline powder.

It is sparingly soluble in *N*,*N*-dimethylformamide, slightly soluble in ethanol (95), and practically insoluble in water.

It shows crystal polymorphism.

Identification **(1)** Determine the absorption spectrum of a solution of Triazolam in ethanol (95) (1 in 200,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Triazolam RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Triazolam, previously dried, as directed in the paste method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum with the Reference Spectrum or the spectrum of dried Triazolam RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Perform the test with Triazolam as directed under Flame Coloration Test *<1.04>* (2): a green to green-blue color appears.

Melting point *<2.60>* 239 – 243℃.

Purity **(1)** Chloride *<1.03>*－To 1.0 g of Triazolam add 50 mL of water, and allow to stand for 1 hour while occasional shaking, and filter. Discard the first 10 mL of the filtrate, pipet 25 mL of the subsequent filtrate, and 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 0.40 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.028%).

(2) Heavy metals－Being specified separately when the drug is granted approval based on the Law.

(3) Related substances－Dissolve 0.14 g of Triazolam in 10 mL of *N*,*N*-dimethylformamide, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add *N*,*N*-dimethylformamide to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 12 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 by the automatic integration method: the area of peak other than triazolam obtained from the sample solution is not larger than 1/5 times the peak area of triazolam from the standard solution, and the total area of the peaks other than triazolam is not larger than the peak area of triazolam from the standard solution. For the areas of the peaks, related substance A having the retention time of about 0.7 to triazolam, related substance B having the retention time of about 1.5, and related substance C having the retention time of about 2.4, multiply their relative response factors, 1.8, 0.6 and 4.3, respectively.

Operating conditions－

Detector, column, column temperature, mobile phase A, mobile phase B, flowing of mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: For 39 minutes after injection, beginning after the solvent peak.

System suitability－

Test for required detectability: Pipet 1 mL of the standard solution, and add *N*,*N*-dimethylformamide to make exactly 10 mL. Confirm that the peak area of triazolam obtained with 12 μL of this solution is equivalent to 7 to 13% of that with 12 μL of the standard solution.

System performance: When the procedure is run with 12 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of triazolam are not less than 4500 and not more than 1.6, respectively.

System repeatability: When the test is repeated 6 times with 12 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of triazolam is not more than 2.0%.

Loss on drying *<2.41>* Not more than 0.5% (1 g, 105℃, 4 hours).

Residue on ignition *<2.44>* Not more than 0.3% (1 g).

Assay Weigh accurately about 55 mg each of Triazolam and Triazolam RS, previously dried, dissolve each in *N*,*N*-dimethylformamide to make exactly 50 mL, and use these solutions as the sample solution and the standard solution,

respectively. Perform the test with 12 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 triazolam in each solution.

$$\text{Amount (mg) of triazolam } (C_{17}H_{12}Cl_2N_4) = M_S \times A_T / A_S$$

M_S: Amount (mg) of Triazolam RS taken

Operating conditions —

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

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with phenylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40℃.

Mobile phase A: A mixture of methanol and diluted acetic acid-ammonium acetate buffer solution (pH 4.5) (1 in 10) (14:11).

Mobile phase B: A mixture of methanol and diluted acetic acid-ammonium acetate buffer solution (pH 4.5) (1 in 10) (19:1).

Flowing of 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 – 14	98	2
14 – 34	98 → 1	2 → 99
34 – 39	1	99

Flow rate: 2.0 mL per minute.

System suitability —

System performance: When the procedure is run with 12 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of triazolam are not less than 4500 and not more than 2.0, respectively.

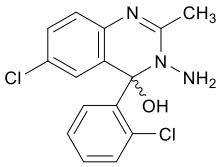
System repeatability: When the test is repeated 6 times with 12 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of triazolam is not more than 1.0%.

Containers and storage Containers — Tight containers.

Others

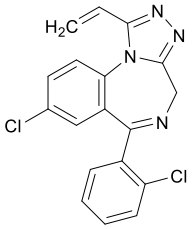
Related substance A:

3-Amino-6-chloro-4-(2-chlorophenyl)-2-methyl-3,4-dihydroquinazolin-4-ol



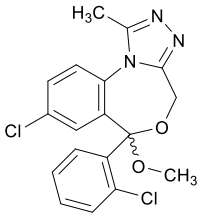
Related substance B:

8-Chloro-6-(2-chlorophenyl)-1-ethenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine



Related substance C:

8-Chloro-6-(2-chlorophenyl)-6-methoxy-1-methyl-4*H*,6*H*-[1,2,4]triazolo[4,3-*a*][4,1]benzoxazepine



Add the following to 9.01 Reference Standards (1):

Triazolam RS