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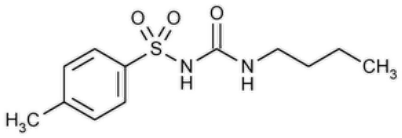
Tolbutamide



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

Benzenesulfonamide, *N*-[(butylamino)carbonyl]-4-methyl-;

1-Butyl-3-(*p*-tolylsulfonyl)urea;

N-(Butylcarbamoyl)-4-methylbenzenesulfonamide CAS RN®: 64-77-7; UNII: 982XCM1FOI.

DEFINITION

Tolbutamide contains NLT 97.0% and NMT 103.0% of tolbutamide ($C_{12}H_{18}N_2O_3S$), calculated on the dried basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197M, 197K, or 197A
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**

Buffer: 1.36 g/L of potassium phosphate, monobasic in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and *Buffer* (35:65)

Diluent: Acetonitrile and *Buffer* (70:30)

System suitability solution: 1 mg/mL of USP Tolbutamide RS and 10 µg/mL of USP Tolazamide RS in *Diluent*

Standard solution: 0.1 mg/mL of USP Tolbutamide RS in *Diluent*

Sample solution: 0.1 mg/mL of Tolbutamide in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm x 25-cm; 5-µm packing L1

Autosampler temperature: 4°

Flow rate: 1.5 mL/min

Injection volume: 30 µL

Run time: NLT 1.5 times the retention time of tolbutamide

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between tolbutamide and tolazamide, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of tolbutamide ($C_{12}H_{18}N_2O_3S$) in the portion of Tolbutamide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of tolbutamide from the *Sample solution*

r_S = peak response of tolbutamide from the *Standard solution*

C_S = concentration of USP Tolbutamide RS in the *Standard solution* (mg/mL)

C_U = concentration of tolbutamide in the *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–103.0% on the dried basis

IMPURITIES

Change to read:

• ▲**Selenium** ⟨291⟩, *Procedures, Procedure 1*▲ (CN 1-Jun-2023)

Sample: Mix 100 mg of tolbutamide with 100 mg of magnesium oxide.

Acceptance criteria: NMT 0.003%

• **Organic Impurities**

Buffer, Mobile phase, Diluent, System suitability solution, and **Chromatographic system:** Proceed as directed in *Assay*.

Standard solution: 0.001 mg/mL of USP Tolbutamide RS in *Diluent*

Sensitivity solution: 0.5 µg/mL of USP Tolbutamide RS in *Diluent* from the *Standard solution*

Sample solution: 1 mg/mL of Tolbutamide in *Diluent*

System suitability

Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*

Suitability requirements

Resolution: NLT 2.0 between tolbutamide and tolazamide, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tolbutamide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of tolbutamide from the *Standard solution*

C_S = concentration of USP Tolbutamide RS in the *Standard solution* (mg/mL)

C_U = concentration of Tolbutamide in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*. The reporting threshold is 0.05%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tosylurea[a]	0.21	1.3	0.1
Tosylamide[b]	0.26	1.3	0.1
Tolbutamide	1.00	—	—
Tolazamide	1.14	0.85	0.1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any other individual impurity	—	—	0.1
Total impurities	—	—	0.3

[a] *N*-Carbamoyl-4-methylbenzenesulfonamide.

[b] 4-Methylbenzenesulfonamide.

SPECIFIC TESTS

• **Loss on drying** ⟨731⟩

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 0.5%

• **Sterility Tests** ⟨71⟩**:** Where the label states that Tolbutamide is sterile, it meets the requirements.

• **Bacterial Endotoxins Test** ⟨85⟩**:** Where the label states that Tolbutamide must be subjected to further processing during the preparation of injectable dosage forms, the levels of bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Tolbutamide is used is met.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

• **Labeling:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

• **USP Reference standards** ⟨11⟩

USP Tolazamide RS

USP Tolbutamide RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
TOLBUTAMIDE	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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