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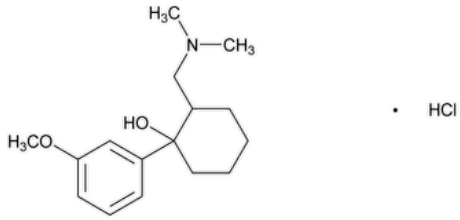
Tramadol Hydrochloride



$C_{16}H_{25}NO_2 \cdot HCl$ 299.84

(±)-*cis*-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride;

(±)-*cis*-2-[(Dimethylamino)methyl]-1-(*m*-methoxyphenyl) cyclohexanol hydrochloride CAS RN®: 36282-47-0; UNII: 9N7R477WCK.

DEFINITION

Tramadol Hydrochloride contains NLT 98.0% and NMT 102.0% of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)

• **B.** **Identification Tests—General,** *Chloride* ⟨191⟩**:** An aqueous solution (1 in 100) meets the requirements.

• **C.** 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**

Solution A: Dissolve 2 mL of trifluoroacetic acid in 1000 mL of water.

Mobile phase: Acetonitrile and *Solution A* (30:70)

System suitability solution: 0.05 mg/mL each of USP Tramadol Hydrochloride RS and USP Tramadol Related Compound A RS in *Mobile phase*

Standard solution: 1.5 mg/mL of USP Tramadol Hydrochloride RS in *Mobile phase*

Sample solution: 1.5 mg/mL of Tramadol Hydrochloride in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

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

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for tramadol related compound A and tramadol are about 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between tramadol related compound A and tramadol

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) in the portion of Tramadol Hydrochloride taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Content of Chloride**

Sample solution: 150 mg of Tramadol Hydrochloride in 40 mL of water

Analysis: To the *Sample solution* add, with stirring, 7.5 mL of 4 N nitric acid and 15.0 mL of 0.1 N silver nitrate, and titrate with 0.1 N ammonium thiocyanate VS, determining the endpoint potentiometrically, and using a silver–glass electrode system. Each mL of 0.1 N ammonium thiocyanate is equivalent to 3.545 mg of chloride.

Acceptance criteria: 11.6%–12.1% of chloride is found.

- **Limit of Tramadol Related Compound B** (2-[(Dimethylamino)methyl]cyclohexanone hydrochloride)

Standard solution: 0.1 mg/mL of USP Tramadol Related Compound B RS in methanol

Sample solution: 50 mg/mL of Tramadol Hydrochloride in methanol

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Developing solvent system: Toluene, isopropyl alcohol, and 25% ammonia water (80:19:1)

Sodium nitrite solution: 50 mg/mL of sodium nitrite in water

Analysis: Place the plate in a chromatographic chamber saturated with ammonia vapor from stronger ammonia water, and allow to stand for NLT 20 min. Separately apply about 10 µL each of the *Sample solution* and the *Standard solution* to the plate, and develop the plate until the solvent front is NLT 10 cm above the line of application. Remove the plate, spray with Dragendorff's TS, and air-dry for 5 min. Spray the dried plate with *Sodium nitrite solution* until the spot from tramadol related compound B in the *Standard solution* is visible. Any secondary spot from the *Sample solution* corresponding to tramadol related compound B is not more intense than a corresponding spot from the *Standard solution*.

Acceptance criteria: NMT 0.2%

- **Organic Impurities**

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

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Tramadol Hydrochloride taken:

$$\text{Result} = (r_U/r_T) \times 100$$

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

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria

Tramadol related compound A: NMT 0.2%

Individual impurities: NMT 0.1%

Total impurities: NMT 0.4%

SPECIFIC TESTS

- **Water Determination, *Method Ia* ⟨921⟩:** NMT 0.5%
- **Acidity**

Sample solution: 500 mg of Tramadol Hydrochloride in 10 mL of water

Analysis: To the *Sample solution* add 0.2 mL of methyl red TS and 0.2 mL of 0.01 N hydrochloric acid VS, and titrate with 0.01 N sodium hydroxide VS.

Acceptance criteria: NMT 0.4 mL of 0.01 N sodium hydroxide VS is required to produce a yellow color.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Tramadol Hydrochloride RS

USP Tramadol Related Compound A RS

(*RS*,*SR*)-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl)cyclohexanol hydrochloride.

$C_{16}H_{25}NO_2 \cdot HCl$ 299.84

USP Tramadol Related Compound B RS

(2-[(Dimethylamino)methyl]cyclohexanone hydrochloride).

$C_9H_{17}NO \cdot HCl$ 191.70

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

Topic/Question	Contact	Expert Committee
TRAMADOL HYDROCHLORIDE	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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