Tramadol Hydrochloride

1. **Tramadol Hydrochloride**

   ![Chemical Structure](image)

   C_{16}H_{21}NO_2.HCl: 299.84

   (1RS,2RS)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol monohydrochloride

   [3682-47-0]

2. **Description**

   Tramadol Hydrochloride occurs as a white crystalline powder.

   It is very soluble in water, and freely soluble in methanol, in ethanol (95%) and in acetic acid (100%).

   A solution of Tramadol Hydrochloride (1 in 20) shows no optical rotation.

   Tramadol Hydrochloride shows crystal polymorphism.

3. **Identification**

   (1) Determine the absorption spectrum of a solution of Tramadol Hydrochloride in ethanol (95%) (1 in 10,000) as directed under Ultraviolet-visible Spectrophotometry <2.24>, 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 Tramadol Hydrochloride as directed in the potassiumchloride disk method under Infrared Spectrophotometry <2.25>, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

   (3) A solution of Tramadol Hydrochloride (1 in 100) responds to Qualitative Tests <1.09> (2) for chloride.

4. **Melting point**

   <2.60° >  180 – 184°C

5. **Purity**

   (1) Acidity or alkalinity — Dissolve 1.0 g of Tramadol Hydrochloride in water to make 20 mL. To 10 mL of this solution add 0.2 mL of methyl red TS for acidity or alkalinity test and 0.2 mL of 0.01mol/L hydrochloric acid VS: a red color develops. To this solution add 0.01 mol/L sodium hydroxide VS until the color of the solution changes from red to yellow: the consumed volume is not more than 0.4 mL.

   (2) Heavy metals <1.07> — Proceed with 1.0 g of Tramadol Hydrochloride according to Method 1, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

   (3) Related substances — (i) Dissolve 0.10 g of Tramadol Hydrochloride in 2 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 500 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <2.03>. Spot 10 µL of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography (if necessary, develop the plate with methanol to the upper end, and air-dry). Allow the plate to stand in ammonia vapor for 1 hour, and examine under ultraviolet light (main wavelength: 254 nm): the spot at the RI value of about 0.5 obtained from the sample solution is not more intense than the spot obtained from the standard solution.

   (ii) Dissolve 0.15 g of Tramadol Hydrochloride in 100 mL of the mobile phase, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 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 peak area having the relative retention time of about 0.9 to tramadol from the sample solution is not larger than 1/5 times the peak area of tramadol from the standard solution, the area of the peak other than tramadol and the peak mentioned above from the sample solution is not larger than 1/10 times the peak area of tramadol from the standard solution, and the total area of the peaks other than tramadol from the sample solution is not larger than 2/5 the peak area of tramadol from the standard solution.

5. **Operating conditions**

   Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

   Column: A stainless steel column 4.0 mm in inside diameter and 25 cm in length, packed with octysilanized silica gel for liquid chromatography (5 µm in particle diameter).

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

   Mobile phase: A mixture of trifluoroacetic acid (1 in 500) and acetonitrile (141:59).

   Flow rate: Adjust so that the retention time of tramadol is about 5 minutes.

   Time span of measurement: About 4 times as long as the retention time of tramadol, beginning after the solvent peak.

6. **System suitability**

   Test for required detectability: Pipet 1 mL of the standard solution, add the mobile phase to make exactly 20 mL. Confirm that the peak area of tramadol obtained with 20 µL of this solution
is equivalent to 3.5 to 6.5% of that obtained with 20 \( \mu \text{L} \) of the standard solution.

System performance: When the procedure is run with 20 \( \mu \text{L} \) of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of tramadol are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 \( \mu \text{L} \) of the standard solution under the above operating conditions, the relative standard deviation of the peak area of tramadol is not more than 2.0%.

Water <2.48> Not more than 0.5% (1 g, volumetric titration, direct titration).

Residue on ignition <2.44> Not more than 0.1% (1 g).

Assay Weigh accurately about 0.18 g of Tramadol Hydrochloride, dissolve in 25 mL of acetic acid(100), add 10 mL of acetic anhydride, and titrate <2.50> with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS

\[ = 29.98 \text{ mg of } \text{C}_{16}\text{H}_{25}\text{NO}_2\cdot\text{HCl} \]

Containers and storage Containers—Tight containers.