add 15 mL of methanol, mix, and sonicate for not less than 8 minutes. Add 22.5 mL of *0.02 M Potassium phosphate buffer*, cool to room temperature, dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer about 38 mg of Torsemide, accurately weighed, to a 100-mL volumetric flask, add 30 mL of methanol, mix, and sonicate for not less than 8 minutes. Add 45 mL of *0.02 M Potassium phosphate buffer*, cool to room temperature, dilute with *Mobile phase* to volume, and mix.

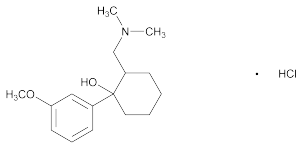
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 288-nm detector and a 4.6-mm × 15-cm column that contains 7-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in mg, of $C_{16}H_{20}N_4O_3S$ in the portion of Torsemide taken by the formula:

$$100C(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of USP Torsemide RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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 [36282-47-0].

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

IDENTIFICATION
- **A. Infrared Absorption** ⟨197K⟩
- **B. Identification Tests—General,** *Chloride* ⟨191⟩**:** An aqueous solution (1 in 100) meets the requirements.

ASSAY
- **Procedure**

Solution A: Dissolve 0.5 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 Hydrochloride Related Compound A RS in *Mobile phase*
Standard solution: 1.5 mg/mL USP Tramadol Hydrochloride RS in *Mobile phase*
Sample solution: 1.5 mg/mL 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 size: 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 $C_{16}H_{25}NO_2 \cdot HCl$ in the portion of Tramadol Hydrochloride taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Tramadol Hydrochloride in the *Standard solution* (mg/mL)
C_U = nominal concentration of Tramadol Hydrochloride in the *Sample solution* (mg/mL)
Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES
Inorganic Impurities
- **Residue on Ignition** ⟨281⟩**:** NMT 0.1%
- **Heavy Metals,** *Method I* ⟨231⟩**:** 20 ppm
- **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 thiocynate VS, determining the endpoint potentiometrically, and using a silver–glass electrode system. Each mL of 0.1 N ammonium thiocynate is equivalent to 3.545 mg of chloride.
Acceptance criteria: 11.6%–12.1% of chloride is found.

Organic Impurities
- **Procedure 1: Limit of Tramadol Related Compound B** (2-(dimethylaminomethyl)-1-cyclohexanone hydrochloride)

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture
Standard solution: 0.1 mg/mL USP Tramadol Related Compound B RS in methanol
Sample solution: 50 mg/mL Tramadol Hydrochloride in methanol
Developing solvent system: Toluene, isopropyl alcohol, and 25% ammonia water (80:19:1)
Sodium nitrite solution: 50 mg/mL sodium nitrite in water
Analysis: 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 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%

- **Procedure 2**

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 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.
USP Tramadol Related Compound B RS
2-(Dimethylaminomethyl)-1-cyclohexanone hydrochloride.

Tramadol Hydrochloride Tablets

DEFINITION
Tramadol Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$).

IDENTIFICATION
- **A. INFRARED ABSORPTION** ⟨**197K**⟩
Sample solution: Transfer powdered Tablets, equivalent to 200 mg of tramadol hydrochloride, into a 50-mL volumetric flask, add 20 mL of dichloromethane, and sonicate. Filter, and transfer the clear supernatant to a separating funnel. Extract the dichloromethane layer with two 10-mL portions of 2 N sodium hydroxide, and discard the aqueous layer. Dry the dichloromethane layer over anhydrous sodium sulfate, and filter. Evaporate this solution to dryness under a stream of nitrogen.
Acceptance criteria: Meet the requirements
- **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**
Solution A: Dissolve 5 mL of perchloric acid in 950 mL of water in a 1-L volumetric flask. Add 4 mL of 25% ammonia water, dilute with water to volume, and mix. Adjust with 25% ammonia water to a pH of 2.2 ± 0.2.
Mobile phase: Acetonitrile and *Solution A* (23:77)
Standard solution: 0.1 mg/mL of USP Tramadol Hydrochloride RS in 0.1 N hydrochloric acid
Sample solution: Finely powder NLT 20 Tablets. Transfer a portion of the powder, equivalent to 50 mg of tramadol hydrochloride, into a 100-mL volumetric flask. Add 70 mL of 0.1 N hydrochloric acid, sonicate for 5 min, and shake for 10 min. Dilute with 0.1 N hydrochloric acid to volume, and mix. Pass a portion of this solution through a suitable filter, discarding the first 20 mL of the filtrate. Transfer 10 mL of the clear filtrate into a 50-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 273 nm
Column: 3.9-mm × 15-cm; packing L7
Flow rate: 2 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of tramadol hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨**711**⟩
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Time: 30 min
Solution A, Mobile phase, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.
Standard solution: 0.055 mg/mL of USP Tramadol Hydrochloride RS in *Medium*
Sample solution: Withdraw 9 mL from the dissolution vessel, and pass through a ▲suitable▲ *USP35* filter. Discard the first 3 mL of the filtrate.
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) is dissolved.
- **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩**:** Meet the requirements
Procedure for content uniformity
Solution A, Mobile phase, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.
Sample solution: Transfer 1 whole Tablet to a 100-mL volumetric flask, add 70 mL of 0.1 N hydrochloric acid, sonicate until the Tablet is completely disintegrated, and shake for 10 min. Dilute with 0.1 N hydrochloric acid to volume, and mix. Pass a portion of this solution through a suitable filter, discarding the first 20 mL of the filtrate. Transfer 10 mL of the clear filtrate into a 50-mL volumetric