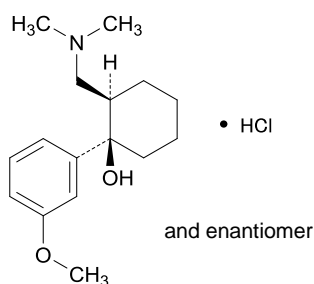


1 Tramadol Hydrochloride

2 トラマドール塩酸塩



4 $C_{16}H_{25}NO_2 \cdot HCl$: 299.84

5 (1*R*S,2*R*S)-2-[(Dimethylamino)methyl]-1-(3-
6 methoxyphenyl)cyclohexanol monohydrochloride
7 [36282-47-0]
8

9 Tramadol Hydrochloride contains not less than 99.0%
10 and not more than 101.0% of tramadol hydrochloride
11 ($C_{16}H_{25}NO_2 \cdot HCl$), calculated on the anhydrous basis.

12 **Description** Tramadol Hydrochloride occurs as a white crystal-
13 line powder.

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

16 A solution of Tramadol Hydrochloride (1 in 20) shows no opti-
17 cal rotation.

18 Tramadol Hydrochloride shows crystal polymorphism.

19 **Identification (1)** Determine the absorption spectrum of a so-
20 lution of Tramadol Hydrochloride in ethanol (95) (1 in 10,000) as
21 directed under Ultraviolet-visible Spectrophotometry <2.24>, and
22 compare the spectrum with the Reference Spectrum: both spectra
23 exhibit similar intensities of absorption at the same wavelengths.

24 **(2)** Determine the infrared absorption spectrum of Tramadol
25 Hydrochloride as directed in the potassium chloride disk method
26 under Infrared Spectrophotometry <2.25>, and compare the spec-
27 trum with the Reference Spectrum: both spectra exhibit similar in-
28 tensities of absorption at the same wave numbers.

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

31 **Melting point** <2.60> 180 – 184°C

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

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

43 **(3)** Related substances—(i) Dissolve 0.10 g of Tramadol
44 Hydrochloride in 2 mL of methanol, and use this solution as the
45 sample solution. Pipet 1 mL of the sample solution, add methanol
46 to make exactly 500 mL, and use this solution as the standard so-
47 lution. Perform the test with these solutions as directed under
48 Thin-layer Chromatography <2.03>. Spot 10 μ L each of the sam-
49 ple solution and standard solution on a plate of silica gel with fluo-
50 rescent indicator for thin-layer chromatography (if necessary, de-
51 velop the plate with methanol to the upper end, and air-dry). Allow
52 the plate to stand in ammonia vapor for 20 minutes, develop with
53 a mixture of toluene, isopropanol and ammonia solution (28)
54 (80:19:1) to a distance of about 15 cm, and air-dry the plate. Allow
55 the plate to stand in iodine vapor for 1 hour, and examine under
56 ultraviolet light (main wavelength: 254 nm): the spot at the *R_f*
57 value of about 0.5 obtained from the sample solution is not more
58 intense than the spot obtained from the standard solution.

59 (ii) Dissolve 0.15 g of Tramadol Hydrochloride in 100 mL of
60 the mobile phase, and use this solution as the sample solution. Pi-
61 pet 1 mL of the sample solution, add the mobile phase to make
62 exactly 100 mL, and use this solution as the standard solution. Per-
63 form the test with exactly 20 μ L each of the sample solution and
64 standard solution as directed under Liquid Chromatography
65 <2.01> according to the following conditions. Determine each
66 peak area by the automatic integration method: the peak area hav-
67 ing the relative retention time of about 0.9 to tramadol from the
68 sample solution is not larger than 1/5 times the peak area of tra-
69 madol from the standard solution, the area of the peak other than
70 tramadol and the peak mentioned above from the sample solution
71 is not larger than 1/10 times the peak area of tramadol from the
72 standard solution, and the total area of the peaks other than tra-
73 madol from the sample solution is not larger than 2/5 the peak area
74 of tramadol from the standard solution.

75 *Operating conditions*—

76 **Detector:** An ultraviolet absorption photometer (wavelength:
77 270 nm).

78 **Column:** A stainless steel column 4.0 mm in inside diameter and
79 25 cm in length, packed with octylsilanized silica gel for liquid
80 chromatography (5 μ m in particle diameter).

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

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

84 **Flow rate:** Adjust so that the retention time of tramadol is about
85 5 minutes.

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

88 *System suitability*—

89 **Test for required detectability:** Pipet 1 mL of the standard
90 solution, add the mobile phase to make exactly 20 mL. Confirm
91 that the peak area of tramadol obtained with 20 μ L of this solution

92 is equivalent to 3.5 to 6.5% of that obtained with 20 μL of the
93 standard solution.

94 System performance: When the procedure is run with 20 μL of
95 the standard solution under the above operating conditions, the
96 number of theoretical plates and the symmetry factor of the peak
97 of tramadol are not less than 5000 and not more than 1.5,
98 respectively.

99 System repeatability: When the test is repeated 6 times with 20
100 μL of the standard solution under the above operating conditions,
101 the relative standard deviation of the peak area of tramadol is not
102 more than 2.0%.

103 **Water** <2.48> Not more than 0.5% (1 g, volumetric titration, di-
104 rect titration).

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

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

111 Each mL of 0.1 mol/L perchloric acid VS
112 = 29.98 mg of $\text{C}_{16}\text{H}_{25}\text{NO}_2\cdot\text{HCl}$

113 **Containers and storage** Containers—Tight containers.

114