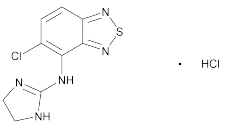
Tizanidine Hydrochloride



$C_9H_8ClN_5S \cdot HCl$ 290.17

2,1,3-Benzothiadiazol-4-amine, 5-chloro-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-, monohydrochloride.

5-Chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole monohydrochloride [64461-82-1].

» Tizanidine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_9H_8ClN_5S \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards ⟨11⟩**—**
USP Tizanidine Hydrochloride RS
USP Tizanidine Related Compound A RS
4-Amino-5-chloro-2,1,3-benzothiadiazole.
$C_6H_4ClN_3S$ 185.63
USP Tizanidine Related Compound B RS
N-Acetyltizanidine.
$C_{11}H_{10}ClN_5OS$ 295.75
USP Tizanidine Related Compound C RS
1-Acetylimidazolidine-2-thione.
$C_5H_8N_2OS$ 144.20

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

C: A solution of 10 mg per mL in water meets the requirements of the silver nitrate precipitate test for *Chloride* ⟨191⟩.

pH ⟨791⟩**:** between 4.3 and 5.3, in a 1% (w/v) solution.

Loss on drying ⟨731⟩**—**Dry about 0.5 g of sample at 105° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals ⟨231⟩**:** 0.002%.

Related compounds—

Phosphoric acid solution—Transfer 6.0 mL of phosphoric acid to a 50-mL volumetric flask, and dilute with water to volume.

Buffer solution—Dissolve about 3.5 g of sodium 1-pentanesulfonate in 1000 mL of water, and adjust with *Phosphoric acid solution* or 1 N sodium hydroxide to a pH of 3.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Tizanidine related compound A solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Tizanidine related compound B solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Tizanidine related compound C solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound C RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Resolution solution—Transfer about 23 mg of USP Tizanidine Hydrochloride RS to a 100-mL volumetric flask, add 20 mL of *Mobile phase* and 10 mL each of *Tizanidine related compound A solution, Tizanidine related compound B solution,* and *Tizanidine related compound C solution.* Sonicate to dissolve the USP Tizanidine Hydrochloride RS, and dilute with *Mobile phase* to volume.

Standard solution—Dissolve an accurately weighed quantity of USP Tizanidine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.046 mg per mL.

Test solution—Transfer about 57 mg of Tizanidine Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 50°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are given in *Table 1;* the resolution, *R,* between tizanidine and tizanidine related compound C is not less than 4.0; and the resolution, *R,* between tizanidine and tizanidine related compound B is not less than 4.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major analyte peaks, disregarding the peaks due to the solvent. Calculate the percentage of each impurity in the portion of Tizanidine Hydrochloride taken by the formula:

$$(253.71/290.17)100(C_S / C_T)(1/F)(r_I / r_S)$$

in which 253.71 and 290.17 are the molecular weights of tizanidine and tizanidine hydrochloride, respectively; C_S and C_T are the concentration, in mg per mL, of tizanidine hydrochloride in the *Standard solution* and the *Test solution; F* is the relative response factor for each impurity relative to tizanidine and is given in *Table 1; r_I* is the peak area for each impurity obtained from the *Test solution;* and r_S is the peak area of tizanidine obtained from the *Standard solution.* The limits for the impurities are specified in *Table 1.*

Table 1

Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
Tizanidine related compound C	about 0.8	1.0	0.1
Tizanidine	1.0	—	—
Tizanidine related compound B	about 1.4	1.1	0.1
Tizanidine related compound A	about 10.2	1.1	0.1
Individual unknown	—	1.0	0.1
Total	—	—	0.3

Assay—

Buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water, and adjust with 5.3 N potassium hydroxide to a pH of 7.5 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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System suitability preparation—Dissolve suitable quantities of USP Tizanidine Hydrochloride RS and USP Tizanidine Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution containing about 46 µg per mL and 0.12 µg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Tizanidine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.046 mg per mL.

Assay preparation—Transfer about 23 mg of Tizanidine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 35°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for tizanidine related compound C and 1.0 for tizanidine; the resolution, *R,* between tizanidine and tizanidine related compound C is not less than 6; and the tailing factor for the tizanidine peak is not more than 2.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* 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 percentage of $C_9H_8ClN_5S \cdot HCl$ in the portion of Tizanidine Hydrochloride taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S and C_U are the concentrations of tizanidine hydrochloride, in mg per mL, in the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Tizanidine Tablets

DEFINITION

Tizanidine Tablets contain Tizanidine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of tizanidine ($C_9H_8ClN_5S$).

IDENTIFICATION

- 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: Water and phosphoric acid (44:6)

Buffer: 3.5 g/L of sodium 1-pentanesulfonate. Adjust with *Solution A* or 1 N sodium hydroxide to a pH of 3.0 ± 0.05.

Mobile phase: Acetonitrile and *Buffer* (1:4)

Tizanidine related compound A solution: 0.1 mg/mL of USP Tizanidine Related Compound A RS in methanol

Tizanidine related compound B solution: 0.1 mg/mL of USP Tizanidine Related Compound B RS in methanol

Tizanidine related compound C solution: 0.1 mg/mL of USP Tizanidine Related Compound C RS in methanol

System suitability solution: Transfer 23 mg of USP Tizanidine Hydrochloride RS to a 100-mL volumetric flask, add 20 mL of *Mobile phase* and 10 mL each of *Tizanidine related compound A solution*, *Tizanidine related compound B solution*, and *Tizanidine related compound C solution*. Sonicate to dissolve the USP Tizanidine Hydrochloride RS, and dilute with *Mobile phase* to volume.

Standard solution: 0.046 mg/mL of USP Tizanidine Hydrochloride RS in *Mobile phase*

Sample solution: Transfer a weighed portion of finely powdered Tablets (NLT 20), equivalent to 20 mg of tizanidine, to a 500-mL volumetric flask. Add 250 mL of *Buffer* solution, sonicate for 15 min with occasional shaking, and shake by mechanical means for 15 min. Add 100 mL of acetonitrile, and mix. Allow to cool, and dilute with *Buffer* solution to volume. Centrifuge a portion of this solution at 2000 rpm or higher for 10 min. Pass a portion of this solution through a filter having a 0.45-µm or finer pore size, and use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; packing L1

Temperature: Column is maintained at 50°.

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times are listed in *Impurity Table 1*.]

Suitability requirements

Resolution: NLT 4.0 between tizanidine and tizanidine related compound C; NLT 4.0 between tizanidine and tizanidine related compound B

Column efficiency: NLT 5000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_9H_8ClN_5S$ in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

M_{r1} = molecular weight of tizanidine, 253.71

M_{r2} = molecular weight of tizanidine hydrochloride, 290.17

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

Test 1

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Time: 15 min

Sample solution: Sample per *Dissolution* ⟨711⟩. Dilute with *Medium* to a concentration that is similar to the *Standard solution*.

Solution A, Buffer, and **Mobile phase:** Proceed as directed in the *Assay*.

Standard solution: (L/500) mg/mL of USP Tizanidine Hydrochloride RS in *Medium*, where L is the label claim in mg

Chromatographic system

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

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