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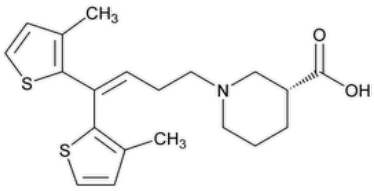
Tiagabine Hydrochloride



• HCl

$C_{20}H_{25}NO_2S_2 \cdot HCl$ 412.00

3-Piperidinecarboxylic acid, 1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-, hydrochloride, (*R*)-;

(−)-(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid, hydrochloride CAS RN®: 145821-59-6; UNII: DQH6T6D8OY.

Free base

$C_{20}H_{25}NO_2S_2$ 375.55 CAS RN®: 115103-54-3; UNII: Z80I64HMNP.

Monohydrate

$C_{20}H_{25}NO_2S_2 \cdot HCl \cdot H_2O$ 430.02 CAS RN®: 145821-57-4.

DEFINITION

Tiagabine Hydrochloride contains NLT 97.5% and NMT 102.5% of tiagabine hydrochloride ($C_{20}H_{25}NO_2S_2 \cdot HCl$), calculated on the anhydrous basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

Sample: Transfer about 5 mg of Tiagabine Hydrochloride to a test tube. Add 4 mL of 2-propanol, and sonicate to dissolve, if necessary. Evaporate the solvent under inert atmosphere at 50°, using a nitrogen evaporator, for 2 h.

Analysis: The IR spectrum of the *Sample* corresponds to that of a similarly prepared USP Tiagabine Hydrochloride RS.

Acceptance criteria: Meets 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: 1.38 g/L of monobasic sodium phosphate. Adjust with phosphoric acid to a pH of 2.0.

Mobile phase: Acetonitrile and *Solution A* (35:65)

Diluent: Methanol and water (50:50)

Internal standard solution: 0.4 mg/mL of butylparaben in *Diluent*

Standard stock solution: 1 mg/mL of USP Tiagabine Hydrochloride RS in *Diluent*

Standard solution: 0.1 mg/mL of USP Tiagabine Hydrochloride RS and 0.04 mg/mL of butylparaben in *Diluent* prepared as follows. Transfer suitable volumes of the *Standard stock solution* and *Internal standard solution* into a suitable volumetric flask and dilute with *Diluent* to volume.

Sample stock solution: 1 mg/mL of Tiagabine Hydrochloride in *Diluent*

Sample solution: 0.1 mg/mL of Tiagabine Hydrochloride and 0.04 mg/mL of butylparaben in *Diluent* prepared as follows. Transfer suitable volumes of the *Sample stock solution* and *Internal standard solution* into a suitable volumetric flask and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 3.5 times the retention time of tiagabine

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 5.5 between tiagabine and butylparaben

Relative standard deviation: NMT 1.5% for the peak response ratios

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of tiagabine hydrochloride ($C_{20}H_{25}NO_2S_2 \cdot HCl$) in the portion of Tiagabine Hydrochloride taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak area ratio of tiagabine hydrochloride to the internal standard from the *Sample solution*

R_S = peak area ratio of tiagabine hydrochloride to the internal standard from the *Standard solution*

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

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

Acceptance criteria: 97.5%–102.5% on the anhydrous basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.2%

• **Limit of (*S*)-(+) Isomer**

Mobile phase: *n*-Hexane, isopropyl alcohol, alcohol, and trifluoroacetic acid (80: 14: 6: 0.5). [Note—Increase or decrease the percentage of *n*-hexane or alcohol, but keep the percentage of isopropyl alcohol constant. Make other adjustments, if necessary (see *Chromatography ⟨621⟩, System Suitability*).]

Standard solution: 0.1 mg/mL of USP Racemic Tiagabine Hydrochloride Mixture RS prepared as follows. Transfer a suitable quantity of USP Racemic Tiagabine Hydrochloride Mixture RS into a suitable volumetric flask, dissolve in a few drops of methanol, and dilute with isopropyl alcohol to volume.

Sample solution: 2 mg/mL of Tiagabine Hydrochloride prepared as follows. Transfer a suitable quantity of Tiagabine Hydrochloride in a suitable volumetric flask, dissolve in a few drops of methanol, and dilute with isopropyl alcohol to volume.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 25-cm; 10-µm packing L40

Flow rate: 0.8 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention of the (*R*)-(−) isomer

System suitability

Sample: *Standard solution*

[Note—The relative retention times of the (*S*)-(+) isomer and the (*R*)-(−) isomer are about 0.76 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between the (*S*)-(+) and (*R*)-(−) isomers

Analysis

Sample: *Sample solution*

Calculate the percentage of the (*S*)-(+) isomer in the portion of Tiagabine Hydrochloride taken:

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

r_U = peak response of the (*S*)-(+) isomer from the *Sample solution*

r_T = sum of the peak responses of the (*S*)-(+) isomer and (*R*)-(−) isomer from the *Sample solution*

Acceptance criteria: NMT 0.5%

• **Organic Impurities**

Solution A: Water adjusted with phosphoric acid to a pH of 2.3

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
30	45	55
40	10	90
45	10	90

Standard stock solution: 1 mg/mL of USP Tiagabine Hydrochloride RS in water

Standard solution: 0.001 mg/mL of USP Tiagabine Hydrochloride RS in water from the *Standard stock solution*

System suitability stock solution: 1 mg/mL of USP Tiagabine Related Compound A RS in water

System suitability solution: 0.1 mg/mL each of USP Tiagabine Hydrochloride RS and USP Tiagabine Related Compound A RS in water prepared from *Standard stock solution* and *System suitability stock solution*

Sample solution: 1 mg/mL of Tiagabine Hydrochloride in water

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

Suitability requirements

Resolution: NLT 9.0 between tiagabine hydrochloride and tiagabine related compound A, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Sample: *Sample solution*

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

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

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

r_T = sum of all the peak responses, excluding the solvent peaks, from the *Sample solution*

F = relative response factor for each impurity (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tiagabine diol analog[a]	0.51	0.75	0.2
Tiagabine keto analog[b]	0.79	0.63	0.1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desmethyl tiagabine[c]	0.93	1.00	0.1
Tiagabine	1.0	—	—
Tiagabine isomers[d]	1.13	1.00	0.6
Tiagabine methyl ester[e]	1.32	1.01	0.2
Tiagabine related compound A	1.39	1.04	0.2
Tiagabine alcohol analog[f]	1.98	0.97	0.2
Bisthiophenylmethanone[g]	2.27	0.39	0.1
Tiagabine alcohol mesylate[h]	2.33	0.96	0.1
Bisthiophenyl tetrahydrofuran[i]	2.54	0.94	0.1
Any unknown impurity	—	1.00	0.1
Total impurities	—	—	1.0

[a] (3*R*)-1-[3,4-Dihydroxy-4,4-bis(3-methylthiophen-2-yl)butyl]piperidine-3-carboxylic acid.

[b] (*R*)-1-[4,4-Bis(3-methylthiophen-2-yl)-3-oxobutyl]piperidine-3-carboxylic acid.

[c] (*R*,*ZE*)-1-[4-(3-Methylthiophen-2-yl)-4-(thiophen-2-yl)but-3-en-1-yl]piperidine-3-carboxylic acid.

[d] (*R*)-1-[4-(*x*-Methylthiophen-2-yl)-4-(*y*-methylthiophen-2-yl)but-3-en-1-yl]piperidine-3-carboxylic acid; where possible, *x*,*y* combinations include (3,4), (4,3), (4,4), (5,5), (4,5), (5,4), (3,5), and (5,3).

[e] Methyl (*R*)-1-[4,4-bis(3-methylthiophen-2-yl)but-3-en-1-yl]piperidine-3-carboxylate.

[f] 4,4-Bis(3-methylthiophen-2-yl)but-3-en-1-ol.

[g] Bis(3-methylthiophen-2-yl)methanone.

[h] 4,4-Bis(3-methylthiophen-2-yl)but-3-en-1-yl methanesulfonate.

[i] 2,2-Bis(3-methylthiophen-2-yl)tetrahydrofuran.

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method I*:** NMT 6.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at a temperature not higher than 30°.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Racemic Tiagabine Hydrochloride Mixture RS

(*S*)-(+),(*R*)-(−)-1-[4,4-Bis(3-methyl-2-thienyl)-3 butenyl]nipecotic acid, hydrochloride.

$C_{20}H_{25}NO_2S_2 \cdot HCl$ 412.00

USP Tiagabine Hydrochloride RS

▲▲ (ERR 1-Nov-2021)

USP Tiagabine Related Compound A RS

(*R*)-Ethyl-1-[4,4-bis(3-methy-2-thienyl)-3-butenyl]-3-piperidinecarboxylate, hydrochloride.

$C_{22}H_{29}NO_2S_2 \cdot HCl$ 440.06

Topic/Question	Contact	Expert Committee
TIAGABINE HYDROCHLORIDE	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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