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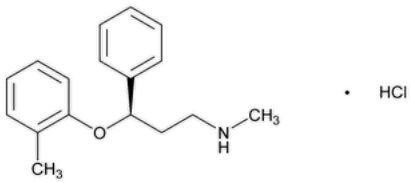
Atomoxetine Hydrochloride

Change to read:



$C_{17}H_{21}NO \cdot HCl$ 291.82

Benzenepropanamine, *N*-methyl-γ-(2-methylphenoxy)-, hydrochloride, (-);

(-)-*N*-Methyl-3-phenyl-3-(*o*-tolyloxy)propylamine hydrochloride;

▲(*R*)-▲ (USP 1-May-2023) *N*-Methyl-3-phenyl-3-(2-tolyloxy)propylamine hydrochloride CAS RN®: 82248-59-7; UNII: 57WVB6I2W0.

DEFINITION

Atomoxetine Hydrochloride contains NLT 98.0% and NMT 102.0% of atomoxetine hydrochloride ($C_{17}H_{21}NO \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

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

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the atomoxetine *R*-isomer from the *System suitability solution*, as obtained in the test for *Organic Impurities, Procedure 2*.

• **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride*:** Meets the requirements

ASSAY

• **Procedure**

Solution A: 280 g/L of potassium hydroxide in water

Buffer: 2.9 g/L of phosphoric acid in water. Adjust with *Solution A* to a pH of 2.5. To 1 L of this solution add 5.9 g of octanesulfonic acid sodium salt monohydrate.

Mobile phase: *n*-Propyl alcohol and *Buffer* (27:73). [Note—The ratio of *n*-propyl alcohol in *Buffer* can be varied between 26:74 and 29:71 to meet system suitability requirements.]

System suitability solution: 0.1 mg/mL of USP Mandelic Acid RS, 0.15 mg/mL of USP Atomoxetine Related Compound A RS, and 0.25 mg/mL of USP Atomoxetine Hydrochloride RS in *Mobile phase*

Standard solution: 0.25 mg/mL of USP Atomoxetine Hydrochloride RS in *Mobile phase*. Sonication may be used to aid in dissolution.

Sample solution: 0.25 mg/mL of Atomoxetine Hydrochloride in *Mobile phase*. Sonication may be used to aid in dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L7

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 1.3 times the retention time of atomoxetine

System suitability

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

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 5.0 between mandelic acid and atomoxetine related compound A, *System suitability solution*

Tailing factor: NMT 1.5 for atomoxetine, *System suitability solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of atomoxetine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) in the portion of Atomoxetine Hydrochloride taken:

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

r_U = peak response of atomoxetine from the *Sample solution*

r_S = peak response of atomoxetine from the *Standard solution*

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

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

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Organic Impurities, Procedure 1**

[Note—It is required to perform *Organic Impurities, Procedure 1* and *Organic Impurities, Procedure 2*.]

Buffer, Mobile phase, and **System suitability solution:** Prepare as directed in the *Assay*.

Sensitivity solution: 0.0013 mg/mL of USP Atomoxetine Hydrochloride RS in *Mobile phase*

Standard solution: 0.0025 mg/mL of USP Atomoxetine Hydrochloride RS in *Mobile phase*

Sample solution: 2.5 mg/mL of Atomoxetine Hydrochloride in *Mobile phase*

Chromatographic system: Proceed as directed in the *Assay*, except for *Run time*.

Run time: NLT 2.6 times the retention time of atomoxetine

System suitability

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

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 5.0 between mandelic acid and atomoxetine related compound A, *System suitability solution*

Tailing factor: NMT 1.5 for atomoxetine, *System suitability solution*

Relative standard deviation: NMT 5%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Atomoxetine Hydrochloride taken:

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

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

r_S = peak response of atomoxetine from the *Standard solution*

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

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

Acceptance criteria: See *Table 1*. The reporting threshold is 0.05%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Mandelic acid	0.20	0.10
Atomoxetine related compound A	0.27	0.10
Desmethyl atomoxetine[a]	0.73	0.3
Atomoxetine	1.0	—
Any individual unspecified impurity	—	0.10
Total impurities	—	0.5

[a] (*R*)-*N*-Methyl-3-phenoxy-3-phenylpropan-1-amine.

• **Organic Impurities, Procedure 2**

Mobile phase: Isopropyl alcohol, diethylamine, trifluoroacetic acid, and chromatographic solvent hexane (150: 1.5: 2.0: 846.5)

System suitability solution: 3.5 mg/mL of USP Atomoxetine Hydrochloride RS, 17.5 µg/mL of USP Atomoxetine S-Isomer RS, and 3.5 µg/mL of USP Atomoxetine Related Compound B RS, prepared by first dissolving the Reference Standards in absolute alcohol, using 25% of the final volume. Dilute with chromatographic solvent hexane to volume.

Sensitivity solution: 0.0018 mg/mL of USP Atomoxetine Hydrochloride RS prepared by first dissolving it in absolute alcohol, using 25% of the final volume. Dilute with chromatographic solvent hexane to volume.

Sample solution: 3.5 mg/mL of Atomoxetine Hydrochloride prepared by first dissolving it in absolute alcohol, using 25% of the final volume. Dilute with chromatographic solvent hexane to volume.

Chromatographic system

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

Mode: LC

Detector: UV 273 nm

Column: 4.6-mm × 25-cm; 5-µm packing L40

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 1.3 times the retention time of atomoxetine

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

[Note—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.75 between atomoxetine *S*-isomer and atomoxetine related compound B, *System suitability solution*

Tailing factor: NMT 1.8 for atomoxetine, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of atomoxetine related compound B, atomoxetine related compound C, and atomoxetine *S*-isomer in the portion of Atomoxetine Hydrochloride taken:

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

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

r_T = sum of all the peak responses of atomoxetine related compound B, atomoxetine related compound C, atomoxetine *S*-isomer, and atomoxetine from the *Sample solution*

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Atomoxetine *S*-isomer	0.47	0.5
Atomoxetine related compound C[a]	0.52	0.1
Atomoxetine related compound B	0.56	0.1
Atomoxetine	1.0	—

[a] (*R*)-*N*-Methyl-3-phenyl-3-(4-tolyloxy)propan-1-amine; also known as (*R*)-*N*-Methyl-3-phenyl-3-(*p*-tolyloxy)propan-1-amine.

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry under vacuum at 105° for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Store at room temperature.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Atomoxetine Hydrochloride RS

USP Atomoxetine Related Compound A RS
3-(Methylamino)-1-phenylpropan-1-ol.
$C_{10}H_{15}NO$ 165.23

USP Atomoxetine Related Compound B RS

▲▲ (USP 1-May-2023)
(*R*)-*N*-Methyl-3-phenyl-3-(3-tolyloxy)propan-1-amine hydrochloride.
$C_{17}H_{21}NO \cdot HCl$ 291.82

▲▲ (USP 1-May-2023)

USP Atomoxetine S-Isomer RS
(*S*)-*N*-Methyl-3-phenyl-3-(2-tolyloxy)propan-1-amine hydrochloride; also known as (*S*)-*N*-Methyl-3-phenyl-3-(*o*-tolyloxy)propan-1-amine hydrochloride.
$C_{17}H_{21}NO \cdot HCl$ 291.82

USP Mandelic Acid RS
2-Hydroxy-2-phenylacetic acid.
$C_8H_8O_3$ 152.15

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
ATOMOXETINE HYDROCHLORIDE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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