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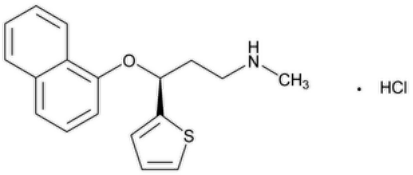
Duloxetine Hydrochloride



$C_{18}H_{19}NOS \cdot HCl$ 333.88

2-Thiophenepropanamine, *N*-methyl-γ-(1-naphthalenyloxy)-, hydrochloride, (*S*)-;

(+)-(*S*)-*N*-Methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride CAS RN®: 136434-34-9; UNII: 9044SC542W.

DEFINITION

Duloxetine Hydrochloride contains NLT 97.0% and NMT 102.0% of duloxetine hydrochloride ($C_{18}H_{19}NOS \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the duloxetine *S*-isomer from the *System suitability solution* in the test for *Limit of Duloxetine Related Compound A*.

• **C.** Identification Tests—General, *Chloride* ⟨191⟩

Sample solution: 5 mg/mL in methanol

Acceptance criteria: Meets the requirements

ASSAY

• **Procedure**

Protect solutions of duloxetine from light.

Buffer: 2.9 g/L of phosphoric acid in water. Adjust with sodium hydroxide solution to a pH of 2.5. To each L of this solution add 10.3 g of sodium 1-hexanesulfonate monohydrate, and dissolve.

Mobile phase: Acetonitrile, *n*-propanol, and *Buffer* (13:17:70)

Diluent: Acetonitrile and water (25:75)

System suitability solution: 0.2 mg/mL of USP Duloxetine Hydrochloride RS (contains duloxetine related compound F) in *Mobile phase*. Heat the solution to at least 40° for a minimum of 1 h. [Note—The resulting solution contains duloxetine alcohol, duloxetine 4-naphthyl isomer, α-naphthol, duloxetine β-naphthol-1-yl isomer, and duloxetine related compound F.]

Standard solution: 0.1 mg/mL of USP Duloxetine Hydrochloride RS in *Diluent*

Sample solution: 0.1 mg/mL of Duloxetine Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

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

Column temperature: 40 ± 3°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 2 times the retention time of duloxetine

System suitability

Sample: *System suitability solution*

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

Suitability requirements

Resolution: NLT 1.5 between duloxetine and duloxetine related compound F

Tailing factor: NMT 1.5 for duloxetine

Relative standard deviation: NMT 1.0% for duloxetine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of duloxetine hydrochloride ($C_{18}H_{19}NOS \cdot HCl$) in the portion of sample 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 Duloxetine Hydrochloride RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 97.0%–102.0% on the dried basis

IMPURITIES

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

• **Organic Impurities**

Protect solutions of duloxetine from light.

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

Sensitivity solution: 0.2 µg/mL of USP Duloxetine Hydrochloride RS in *Diluent*

Sample solution: 0.2 mg/mL of Duloxetine Hydrochloride in *Diluent*

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

Run time: 2.4 times the retention time of duloxetine

System suitability

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

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

Suitability requirements

Resolution: NLT 1.5 between duloxetine 4-naphthyl isomer and α-naphthol; NLT 1.5 between duloxetine and duloxetine related compound F, *System suitability solution*

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

Relative standard deviation: NMT 1.0% for duloxetine, *System suitability solution*

Signal-to-noise ratio: NLT 20 for the duloxetine peak, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of any individual impurity in the portion of Duloxetine 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 the responses of all the peaks from the *Sample solution*

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Duloxetine alcohol[a]	0.15	0.36	0.1
Duloxetine 4-napthyl isomer[b]	0.43	1.0	0.1
α-Napthol[c]	0.48	1.8	0.1
Duloxetine β-naphthol-1-yl isomer[d]	0.74	1.0	0.1
Duloxetine	1.0	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Duloxetine related compound F[e]	1.1	1.0	0.5
Fluoronaphthalene[f]	1.4	0.51	0.1
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.6

[a] 3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol.

[b] 4-[3-(Methylamino)-1-(thiophen-2-yl)propyl]naphthalen-1-ol.

[c] Naphthalen-1-ol.

[d] 2-[3-(Methylamino)-1-(thiophen-2-yl)propyl]naphthalen-1-ol.

[e] (*S*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-3-yl)propan-1-amine.

[f] 1-Fluoronaphthalene.

• **Limit of Duloxetine Related Compound A**

Mobile phase: Hexane and isopropyl alcohol (83:17). To 1 L of this mixture add 2 mL of diethylamine.

System suitability solution: 0.1 mg/mL each of USP Duloxetine Hydrochloride RS and USP Duloxetine Related Compound A RS in *Mobile phase*. Sonication may be used to aid in dissolution.

Sensitivity solution: 0.1 µg/mL of USP Duloxetine Hydrochloride RS in *Mobile phase*

Sample solution: 0.1 mg/mL of Duloxetine Hydrochloride in *Mobile phase*. Sonication may be used to aid in dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

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

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 2 times the retention time of duloxetine

System suitability

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

[Note—The relative retention times for duloxetine and duloxetine related compound A are 1.0 and 1.3, respectively.]

Suitability requirements

Resolution: NLT 3.5 between duloxetine and duloxetine related compound A, *System suitability solution*

Tailing factor: 0.8–1.5 each for duloxetine and duloxetine related compound A, *System suitability solution*

Relative standard deviation: NMT 5.0% for duloxetine, *System suitability solution*

Signal-to-noise ratio: NLT 3, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of duloxetine related compound A in the portion of Duloxetine Hydrochloride taken:

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

r_U = peak response of duloxetine related compound A from the *Sample solution*

r_T = sum of the peak responses of duloxetine and duloxetine related compound A from the *Sample solution*

Acceptance criteria: NMT 0.5%

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Protect from light. Store at room temperature.
- **USP Reference Standards** ⟨11⟩

USP Duloxetine Hydrochloride RS

USP Duloxetine Related Compound A RS

(*R*)-*N*-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine hydrochloride.

$C_{18}H_{19}NOS \cdot HCl$ 333.88

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

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

Chromatographic Database Information: Chromatographic Database

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