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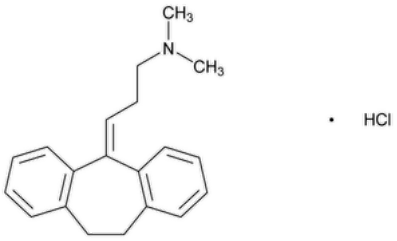
Amitriptyline Hydrochloride

Change to read:



$C_{20}H_{23}N \cdot HCl$ ▲313.87▲ (ERR 1-Jun-2021)

1-Propanamine, 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptен-5-ylidene)-*N*,*N*-dimethyl-, hydrochloride;
10,11-Dihydro-*N*,*N*-dimethyl-5*H*-dibenzo[*a*,*d*]cycloheptene-Δ^{5},γ-propylamine hydrochloride CAS RN®: 549-18-8.

DEFINITION

Amitriptyline Hydrochloride contains NLT 98.0% and NMT 102.0% of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197A or 197K**
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride*: Meets the requirements**

ASSAY

- **Procedure**

Buffer: 1.4 g/L of anhydrous dibasic sodium phosphate in water, adjusted with 1.5 M phosphoric acid TS to a pH of 7.7

Mobile phase: Methanol and *Buffer* (70:30)

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

System suitability stock solution B: 0.4 mg/mL of USP Amitriptyline Hydrochloride RS, 0.6 mg/mL each of USP Amitriptyline Related Compound B RS, USP Cyclobenzaprine Hydrochloride RS, and USP Nortriptyline Hydrochloride RS in *Mobile phase*

Standard solution: 0.2 mg/mL of USP Amitriptyline Hydrochloride RS in *Mobile phase*

System suitability solution: 0.5 µg/mL of USP Amitriptyline Related Compound A RS, 1 µg/mL of USP Amitriptyline Hydrochloride RS, and 1.5 µg/mL each of USP Amitriptyline Related Compound B RS, USP Cyclobenzaprine Hydrochloride RS, and USP Nortriptyline Hydrochloride RS from suitable volumes of *System suitability stock solution A* and *System suitability stock solution B* in *Mobile phase*

Sample solution: 0.2 mg/mL of Amitriptyline Hydrochloride in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 45°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: NLT 1.5 times the retention time of amitriptyline

System suitability

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

[Note—For relative retention times, see *Table 1*.]

Suitability requirements

Resolution: NLT 1.5 between amitriptyline related compound B and nortriptyline, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$) in the portion of Amitriptyline Hydrochloride 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 Amitriptyline Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Amitriptyline 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**

Buffer, Mobile phase, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 0.5 µg/mL of USP Amitriptyline Hydrochloride RS in *Mobile phase*

Standard solution: Use the *System suitability solution*, prepared as directed in the *Assay*.

Sample solution: 1000 µg/mL of Amitriptyline Hydrochloride in *Mobile phase*

System suitability

Samples: *Sensitivity solution* and *Standard solution*

[Note—For relative retention times, see *Table 1*.]

Suitability requirements

Resolution: NLT 1.5 between amitriptyline related compound B and nortriptyline, *Standard solution*

Relative standard deviation: NMT 5.0% each for amitriptyline related compound A, amitriptyline related compound B, nortriptyline, cyclobenzaprine, and amitriptyline, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentages of amitriptyline related compound A, amitriptyline related compound B, and nortriptyline hydrochloride in the portion of Amitriptyline Hydrochloride taken:

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

r_U = peak response of amitriptyline related compound A, amitriptyline related compound B, or nortriptyline from the *Sample solution*

r_S = peak response of amitriptyline related compound A, amitriptyline related compound B, or nortriptyline from the *Standard solution*

C_S = concentration of USP Amitriptyline Related Compound A RS, USP Amitriptyline Related Compound B RS, or USP Nortriptyline Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = concentration of Amitriptyline Hydrochloride in the *Sample solution* (µg/mL)

Calculate the percentage of cyclobenzaprine in the portion of Amitriptyline Hydrochloride taken:

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

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

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

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

C_U = concentration of Amitriptyline Hydrochloride in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of cyclobenzaprine, 275.39

M_{r2} = molecular weight of cyclobenzaprine hydrochloride, 311.85

Calculate the percentage of each unspecified impurity in the portion of Amitriptyline Hydrochloride taken:

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

r_U = peak response of any unspecified impurity from the *Sample solution*

r_S = peak response of USP Amitriptyline Hydrochloride RS from the *Standard solution*

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

C_U = concentration of Amitriptyline Hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 1*. Do not include any peak with a relative retention time less than 0.22. The reporting threshold is 0.05%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Amitriptyline related compound A	0.35	0.05
Amitriptyline related compound B	0.52	0.15
Nortriptyline	0.60	0.15
Cyclobenzaprine	0.76	0.15
Amitriptyline	1.0	—
Any individual unspecified impurity	—	0.10
Total impurities	—	1.0

SPECIFIC TESTS

• **pH** ⟨791⟩

Sample: 10 mg/mL in water

Acceptance criteria: 5.0–6.0

• **Loss on Drying** ⟨731⟩

Analysis: Dry at a pressure not exceeding 5 mm of mercury at 60° to constant weight.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Amitriptyline Hydrochloride RS

USP Amitriptyline Related Compound A RS

10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one;
Also known as Dibenzosuberone.

$C_{15}H_{12}O$ 208.26

USP Amitriptyline Related Compound B RS

5-[3-(Dimethylamino)propyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptene-5-ol;
Also known as Amitriptynol.

$C_{20}H_{25}NO$ ▲295.43▲ (ERR 1-Jun-2021)

USP Cyclobenzaprine Hydrochloride RS

USP Nortriptyline Hydrochloride RS

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

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

Chromatographic Database Information: Chromatographic Database

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