Amitriptyline Hydrochloride Tablets

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In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 4 Expert Committee has revised the Amitriptyline Hydrochloride Tablets monograph. The purpose of this revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). “If necessary” was added to the *Medium* deaeration requirement to improve the test flexibility. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

- *Dissolution Test 2* was validated using the Xterra RP-18 brand of 4.6-mm x 15-cm, 5 µm column with L1 packing. The typical retention time for amitriptyline is about 10 min.

The Amitriptyline Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact V. Durga Prasad, Scientific Liaison (+91 40 4448 8723 or durgaprasad.v@usp.org).

Revision Bulletin
Official: May 26, 2023

Amitriptyline Hydrochloride Tablets

DEFINITION

Amitriptyline Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$).

IDENTIFICATION

● **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

● **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**

Buffer: 11.04 g of monobasic sodium phosphate in 900 mL of water. Adjust with phosphoric acid to a pH of 2.5 ± 0.5, and dilute to make 1000 mL.

Mobile phase: Acetonitrile and *Buffer* (42:58)

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

Sample solution: Nominally 0.2 mg/mL of amitriptyline hydrochloride in *Mobile phase*, prepared as follows. Transfer NLT 20 Tablets to a suitable volumetric flask, add 50% of the flask volume of *Mobile phase*, and shake the mixture for 1 h or until the Tablets have disintegrated. Dilute with *Mobile phase* to volume, and filter. Dilute the clear filtrate with *Mobile phase* to obtain a solution with a nominal concentration of 0.2 mg/mL of amitriptyline hydrochloride.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm. For *Identification A*, use a diode array detector in the range of 220–400 nm.

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: NLT 1.5 times the retention time of amitriptyline

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$) in each Tablet 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 = nominal concentration of amitriptyline hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲**Test 1**▲ (RB 26-May-2023)

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Standard solution: (*L*/900) mg/mL of USP Amitriptyline Hydrochloride RS in *Medium*, where *L* is the Tablet label claim in milligrams. Dilute with *Medium*, if necessary.

Sample solution: Pass a portion of solution under test through a suitable filter. Dilute with *Medium*, if necessary.

Instrumental conditions

Analytical wavelength: UV 239 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times D \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

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

D = dilution factor, if necessary

Tolerances: NLT 75% (*Q*) of the labeled amount of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$) is dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.1 N hydrochloric acid; 500 mL, deaerated, if necessary

Apparatus 1: 100 rpm

Time: 30 min

Diluted phosphoric acid: Phosphoric acid and water (1:10)

Buffer: Dissolve 0.87 g of potassium phosphate dibasic in 1 L of water. Adjust with *Diluted phosphoric acid* to a pH of 7.0. Add 1.0 mL of triethylamine. Adjust with *Diluted phosphoric acid* to a pH of 7.0.

Mobile phase: Acetonitrile and *Buffer* (35:65)

Standard solution: (*L*/500) mg/mL of USP Amitriptyline Hydrochloride RS in *Medium*, where *L* is the label claim in mg/Tablet. Sonicate to dissolve, if necessary.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of amitriptyline

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

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

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

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

V = volume of the *Medium*, 500 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$) is dissolved. ▲ (RB 26-May-2023)

- **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

- **Organic Impurities**

Buffer: 1.42 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)

Diluent: Methanol and water (70:30)

Standard solution: 2 µg/mL each of USP Amitriptyline Hydrochloride RS, USP Amitriptyline Related Compound A RS, USP Amitriptyline Related Compound B RS, and USP Nortriptyline Hydrochloride RS in *Diluent*

Sample solution: Nominally 1000 µg/mL of amitriptyline hydrochloride in *Diluent*, prepared as follows. Transfer NLT 10 Tablets to a suitable volumetric flask, add 80% of the flask volume of *Diluent*, and shake the mixture for 1 h or until the Tablets have disintegrated. Dilute with *Diluent* to volume. If needed, a portion of this solution can be further diluted with *Diluent*. Centrifuge a portion of the solution with a nominal concentration of 1000 µg/mL of amitriptyline hydrochloride and use the supernatant. [NOTE—A centrifuge speed of 3000 rpm for about 10 min may be suitable.]

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

Sample: *Standard solution*

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

Suitability requirements

Resolution: NLT 3.0 between amitriptyline related compound B and nortriptyline

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of amitriptyline related compound A, amitriptyline related compound B, and nortriptyline hydrochloride in the portion of Tablets 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 = nominal concentration of amitriptyline hydrochloride in the *Sample solution* (µg/mL)

Calculate the percentage of any other individual degradation product in the portion of Tablets taken:

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

r_U = peak response of any other individual degradation product from the *Sample solution*

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

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

C_U = nominal concentration of amitriptyline hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Amitriptyline related compound A	0.32	0.2
Amitriptyline related compound B	0.48	0.2
Nortriptyline	0.62	0.2
Amitriptyline	1.0	—
Any other individual degradation product	—	0.2
Total degradation products	—	1.0

ADDITIONAL REQUIREMENTS

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

Add the following:

▲● **Labeling:** When more than one *Dissolution Test* is given, the labeling states the test used only if *Test 1* is not used.▲ (RB 26-May-2023)

- **USP Reference Standards** ⟨11⟩

USP Amitriptyline Hydrochloride RS

USP Amitriptyline Related Compound A RS

10,11-Dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-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*]-cyclohepten-5-ol;

Also known as Amitriptynol.

$C_{20}H_{25}NO$ 295.43

USP Nortriptyline Hydrochloride RS

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