

## Amitriptyline Hydrochloride Tablets

<b>Type of Posting</b>	Notice of Intent to Revise
<b>Posting Date</b>	29-Oct-2021
<b>Targeted Official Date</b>	To Be Determined, Revision Bulletin
<b>Expert Committee</b>	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts and the [Pending Monograph Guideline](#), this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Amitriptyline Hydrochloride Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to accommodate drug products with different dissolution conditions and/or tolerances than the existing dissolution test. *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 column with L1 packing. The typical retention time for amitriptyline is about 10 min.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.<sup>1</sup>

Should you have any questions, please contact Robyn Fales, Scientist IV (240-221-2047 or [rfp@usp.org](mailto:rfp@usp.org)).

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<sup>1</sup> This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the [USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF](#).

## 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  $2.5 \pm 0.5$ , 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  $\times$  30-cm; 10- $\mu$ m packing [L1](#)

**Flow rate:** 2 mL/min

**Injection volume:** 20  $\mu$ L

**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** (TBD)

**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

**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- $\mu$ m 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  $\times$  15-cm; 5- $\mu$ m packing [L1](#)

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection volume:** 10  $\mu$ L

**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. ▲

(TBD)

- **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* ( $\mu\text{g/mL}$ )

$C_U$  = nominal concentration of amitriptyline hydrochloride in the *Sample solution* ( $\mu\text{g/mL}$ )

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* ( $\mu\text{g/mL}$ )

$C_U$  = nominal concentration of amitriptyline hydrochloride in the *Sample solution* ( $\mu\text{g/mL}$ )

**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. ▲ (TBD)

● **USP REFERENCE STANDARDS** (11).

[USP Amitriptyline Hydrochloride RS](#)

[USP Amitriptyline Related Compound A RS](#)

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

Also known as Dibenzosuberone.

$\text{C}_{15}\text{H}_{12}\text{O}$             208.26

[USP Amitriptyline Related Compound B RS](#)

5-[3-(Dimethylamino)propyl]-10,11-dihydro-5H-dibenzo[*a,d*]-cyclohepten-5-ol;

Also known as Amitriptynol.

C<sub>20</sub>H<sub>25</sub>NO            295.43

[USP Nortriptyline Hydrochloride RS](#)

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**Page Information:**

Not Applicable

**Current DocID:**

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