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Amantadine Hydrochloride Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-amantadine-hcl-tabs-20221216.

DEFINITION

Amantadine Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$).

IDENTIFICATION

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

  Sample: Transfer an amount equivalent to 200 mg of amantadine hydrochloride from finely powdered Tablets (NLT 10) to a suitable beaker. Add 20 mL of 0.1 N hydrochloric acid solution, sonicate for about 5 min, and filter. Transfer the filtrate to a separatory funnel, add 1 mL of 5 N sodium hydroxide solution, and shake. Add 5 mL of methylene chloride to the solution, shake, and allow the two layers to separate for about 20 min. Pass the lower layer through sodium sulfate anhydrous, then rinse the sodium sulfate with 2 mL of methylene chloride. Evaporate the filtrate under nitrogen and use the dried residue.

  Acceptance criteria: Meet the requirements

- **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**

  Diluent: Methanol and water (40:60)

  Internal standard solution: 0.5 mg/mL of naphthalene in toluene

  Standard stock solution: 4 mg/mL of USP Amantadine Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Amantadine Hydrochloride RS to a suitable volumetric flask. Add 40% of the flask volume of *Diluent* and sonicate for about 5 min. Dilute with *Diluent* to volume.

  Standard solution: Transfer 1 mL of the *Standard stock solution* and 5 mL of 5 N sodium hydroxide solution to a separatory funnel. Add 5 mL of the *Internal standard solution* and shake for about 10 min. Allow the two layers to separate, then collect 4 mL of the clear upper layer and add 500 mg of sodium sulfate anhydrous to remove traces of water. Allow the sodium sulfate to precipitate and use the clear solution for analysis.

  Sample stock solution: Nominally 4 mg/mL of amantadine hydrochloride from Tablets prepared as follows. Transfer a number of Tablets (NLT 10) to a suitable volumetric flask and add 80% of the flask volume of *Diluent*. Sonicate for about 30 min with intermittent shaking. Dilute with *Diluent* to volume. Centrifuge a portion and use the supernatant. [Note—The use of a centrifuge speed of 3000 rpm for 10 min may be suitable.]

  Sample solution: Transfer 1 mL of the *Sample stock solution* and 5 mL of 5 N sodium hydroxide solution to a separatory funnel. Add 5 mL of the *Internal standard solution* and shake for about 10 min. Allow the two layers to separate, then collect 4 mL of the clear upper layer and add 500 mg of sodium sulfate anhydrous to remove traces of water. Allow the sodium sulfate to precipitate and use the clear solution for analysis.

  Chromatographic system

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

  Mode: GC

  Detector: Flame ionization

  Column: 0.32-mm × 30-m fused silica capillary; coated with a 1-µm film of phase G27

  Temperatures

  Injector: 280°

  Detector: 300°

  Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
120	0	120	2
120	30	270	5

Carrier gas: Nitrogen

Flow rate: 2 mL/min

Injection volume: 2 µL

Injection type: Split, split ratio 80:1

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for naphthalene and amantadine are 0.94 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 5.0 between naphthalene and amantadine

Tailing factor: NMT 1.2

Relative standard deviation: NMT 2.0% for the peak response ratio of amantadine to naphthalene

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$) in the portion of Tablets taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak area ratio of amantadine to naphthalene from the *Sample solution*

R_S = peak area ratio of amantadine to naphthalene from the *Standard solution*

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

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

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

▲Test 1▲ (RB 1-Jan-2023)

Medium: Water; 500 mL deaerated

Apparatus 2: 50 rpm; with suitable sinkers

Time: 60 min

Internal standard solution: 0.12 mg/mL of naphthalene in toluene. Sonicate to dissolve if necessary.

Standard stock solution: 0.2 mg/mL of USP Amantadine Hydrochloride RS in *Medium*. Sonicate to dissolve if necessary.

Standard solution: ▲Equivalent to 0.2 mg/mL▲ (RB 1-Jan-2023) of USP Amantadine Hydrochloride RS ▲in upper layer (toluene)▲ (RB 1-Jan-2023) prepared as follows. Transfer 5 mL of the *Standard stock solution* and 2.5 mL of 5 N sodium hydroxide solution to a separatory funnel. Add 5 mL of the *Internal standard solution* and shake for about 10 min. Allow the two layers to separate and use the clear upper layer.

Sample solution: Pass a portion of the solution under test through a filter of 0.45-µm pore size, discarding the first 3 mL of filtrate. Transfer 5 mL of the filtered solution under test and 2.5 mL of 5 N sodium hydroxide solution to a separatory funnel. Add 5 mL of the *Internal standard solution* and shake for about 10 min. Allow the two layers to separate and use the clear upper layer.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-m fused silica capillary; coated with a 1-µm film of phase G27

Temperatures

Injector: 280°

Detector: 300°

Column: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
120	0	120	1
120	25	240	2

Carrier gas: Nitrogen

Flow rate: 1.5 mL/min

Injection volume: 2 µL

Injection type: Split, split ratio 50:1

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for naphthalene and amantadine are 0.94 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 5.0 between naphthalene and amantadine

Relative standard deviation: NMT 5.0% for the peak response ratio of amantadine to naphthalene

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$) dissolved:

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

R_U = peak area ratio of amantadine to naphthalene from the *Sample solution*

R_S = peak area ratio of amantadine to naphthalene from the *Standard solution*

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

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$) is dissolved.

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

Medium: Water; 900 mL deaerated

Apparatus 2: 50 rpm

Time: 45 min

Internal standard solution: 0.054 mg/mL of naphthalene in chromatographic solvent hexane

Standard stock solution: 0.1 mg/mL of USP Amantadine Hydrochloride RS in *Medium*

Standard solution: Equivalent to 0.15 mg/mL of USP Amantadine Hydrochloride RS in upper layer (hexane) prepared as follows. Transfer 30.0 mL of the *Standard stock solution* and 10 mL of 5 N sodium hydroxide solution to a suitable volumetric flask. Add 20.0 mL of the *Internal standard solution* and shake for about 60 min. Allow the two layers to separate and use the clear upper layer.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.7-µm pore size, discarding the first 10 mL of filtrate. Transfer 15.0 mL of the filtered solution under test and 5 mL of 5 N sodium hydroxide solution to a suitable centrifuge tube. Add 10.0 mL of the *Internal standard solution* and shake for about 60 min. Allow the two layers to separate and use the clear upper layer.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.25-mm × 30-m fused silica capillary; coated with a 0.25-µm film of phase G1

Temperatures

Injection port: 250°

Detector: 300°

Column: See *Table 3*.

Table 3

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
100	0	100	0
100	10	200	2

Carrier gas: Helium

Flow rate: 1.4 mL/min

Injection volume: 3.0 µL

Injection type: Split, split ratio 40:1

System suitability

Sample: *Standard solution*

[Note—The relative retention times for naphthalene and amantadine are 0.89 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 4.0 between naphthalene and amantadine

Tailing factor: NMT 2.0 for amantadine

Relative standard deviation: NMT 2.0% for the peak response ratio of amantadine to naphthalene

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$) dissolved:

$$\text{Result} = (R_U/R_S) \times C_S \times V \times D \times (1/L) \times 100$$

R_U = peak area ratio of amantadine to naphthalene from the *Sample solution*

R_S = peak area ratio of amantadine to naphthalene from the *Standard solution*

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

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*, 0.667

L = label claim (mg/Tablet)

Tolerances: NLT 75% (*Q*) of the labeled amount of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$) is dissolved. ▲ (RB 1-Jan-2023)

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

IMPURITIES

Change to read:

• **Organic Impurities**

Internal standard solution: 0.5 mg/mL of adamantane in toluene

Standard stock solution: 1.6 mg/mL of USP Amantadine Hydrochloride RS prepared as follows. Transfer 50 mg of USP Amantadine Hydrochloride RS and 20 mL of 5 N sodium hydroxide solution to a suitable container and sonicate for about 15 min with intermittent shaking. Add 10 mL of the *Internal standard solution* and sonicate for about 15 min with intermittent shaking. Centrifuge the solution. Transfer 3 mL of the supernatant to a suitable container and add 300 mg of sodium sulfate anhydrous to remove traces of water. Allow the sodium sulfate to precipitate and use the clear solution for preparation of the *Standard solution*. [Note—The use of a centrifuge speed of 3000 rpm for 10 min may be suitable.]

Standard solution: 0.16 mg/mL of USP Amantadine Hydrochloride RS prepared as follows. Transfer 1 mL of the *Standard stock solution* to a 10-mL volumetric flask. Dilute with the *Internal standard solution* to volume.

Sample solution: Nominally 16.7 mg/mL of amantadine hydrochloride from Tablets prepared as follows. Transfer a portion of powder, equivalent to 500 mg of amantadine hydrochloride, from Tablets (NLT 20) and 20 mL of 5 N sodium hydroxide solution to a suitable container. Sonicate for about 15 min with intermittent shaking. Add 10 mL of the *Internal standard solution* and sonicate for about 15 min with intermittent shaking. Centrifuge the solution. Transfer 3 mL of the supernatant and add 300 mg of sodium sulfate anhydrous to remove traces of water. Allow the sodium sulfate to precipitate and use the clear solution for analysis. [Note—The use of a centrifuge speed of 3000 rpm for 10 min may be suitable.]

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m fused silica capillary; coated with a 1-µm film of phase G27

Temperatures

Injector: 220°

Detector: 300°

Column: See ▲*Table 4*.

Table 4 ▲ (RB 1-Jan-2023)

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
70	0	70	5
70	10	250	17

Carrier gas: Helium

Flow rate: 4 mL/min

Injection volume: 1 µL

Injection type: Split, split ratio 50:1

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for adamantane and amantadine are 0.83 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 20 between adamantane and amantadine

Relative standard deviation: NMT 5.0% for the peak response ratio of amantadine to adamantane

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak area ratio of each degradation product to adamantane from the *Sample solution*

R_S = peak area ratio of amantadine to adamantane from the *Standard solution*

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

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

Acceptance criteria: The reporting threshold is 0.10%.

Any unspecified degradation product: NMT 0.2%

Total degradation products: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light and moisture. 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 1-Jan-2023)

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Amantadine Hydrochloride RS

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

Topic/Question	Contact	Expert Committee
AMANTADINE HYDROCHLORIDE TABLETS	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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