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Amantadine Hydrochloride Capsules

DEFINITION

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

IDENTIFICATION

Change to read:

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

Cell: 1 mm

Sample solution: Place the contents of Capsules, equivalent to 200 mg of amantadine hydrochloride, in a vessel, dissolve in 0.1 N hydrochloric acid, and filter. Transfer the filtrate to a separator, add 1 mL of 5 N sodium hydroxide, and extract with 5 mL of methylene chloride. Filter the extract through anhydrous sodium sulfate, and rinse the anhydrous sodium sulfate with 2 mL of methylene chloride.

• **B.** The retention time of the amantadine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• Procedure

Internal standard solution: 0.4 mg/mL of naphthalene in hexane

Standard stock solution: 2 mg/mL of USP Amantadine Hydrochloride RS in water

Standard solution: Transfer 25.0 mL of *Standard stock solution* into a 250-mL separator, and add 25 mL of 2 N sodium hydroxide and 50.0 mL of *Internal standard solution*. Shake for about 10 min, and collect the hexane layer.

Sample stock solution: Transfer NLT 20 Capsules to a 200-mL volumetric flask. Add 40 mL of 0.1 N hydrochloric acid and 40 mL of water. Sonicate for 20 min with intermittent shaking, and dilute with water to volume. Centrifuge the solution for 10 min and pass through a suitable filter.

Sample solution: Transfer 5.0 mL of the filtrate into a 250-mL separator, and add 40.0 mL of 1 N sodium hydroxide and 50.0 mL of *Internal standard solution*. Shake for about 10 min, and collect the hexane layer.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-m; coated with a 0.25-µm film of phase G1

Temperatures

Injection port: 250°

Detector: 300°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
100	0	100	3
100	10	200	2

Carrier gas: Helium

Flow rate: 1.4 mL/min

Injection volume: 2 µL

Injection type: Split

Split flow rate: 20 mL/min

System suitability

Sample: *Standard solution*

[Note—The relative retention times for naphthalene and amantadine are 0.90 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between naphthalene and amantadine

Tailing factor: NMT 2.0 for the amantadine peak

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 Capsules taken:

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

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

R_S = peak response 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

• **Dissolution** ⟨711⟩

Test 1

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

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

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

Standard solution: Transfer 15.0 mL of *Standard stock solution* into a 50-mL screw-capped test tube, add 5.0 mL of 5 N sodium hydroxide and 10.0 mL of *Internal standard solution*, and shake for 60 min. Collect the hexane layer.

Sample solution: Transfer 15.0 mL of the filtered solution under test, and place into a 50-mL screw-capped test tube. Pipet 5.0 mL of 5 N sodium hydroxide and 10.0 mL of the *Internal standard solution* into the test tube, and shake for 60 min. Collect the hexane layer.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-m; coated with a 0.25-µm film of phase G1

Temperatures

Injection port: 250°

Detector: 300°

Column: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
100	0	100	3
100	10	200	2

Carrier gas: Helium

Flow rate: 1.4 mL/min

Injection volume: 2 µL

Injection type: Split

Split flow rate: 20 mL/min

System suitability

Sample: *Standard solution*

[Note—The relative retention times for naphthalene and amantadine are 0.90 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between naphthalene and amantadine

Tailing factor: NMT 2.0 for the amantadine peak

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 dissolved:

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

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

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

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

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

Tolerances: NLT 75% (*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

Apparatus 2: 75 rpm, with sinkers. [NOTE—A suitable sinker is available as catalog number CAPWHT-2S from www.qla-llc.com or www.tabletdissolution.com or www.labhut.com.]

Time: 45 min

Internal standard solution: 0.06 mg/mL of naphthalene in hexane

Standard stock solution: 0.12 mg/mL of USP Amantadine Hydrochloride RS in *Medium*

Standard solution: Transfer 60.0 mL of the *Standard stock solution* to a 200-mL volumetric flask. Add 20 mL of 5 N sodium hydroxide and 40.0 mL of *Internal standard solution*. Shake the flask for approximately 10 min, and allow the layers to separate. Use the top layer for injection. The final concentration is about 0.18 mg/mL.

Sample solution: Transfer 3.0 mL of the solution under test to a centrifuge tube. Add 1.0 mL of 5 N sodium hydroxide and 2.0 mL of *Internal standard solution*. Shake the tube for approximately 10 min, and allow the layers to separate. Use the top layer for injection.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-m; 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	3
100	10	200	2

Carrier gas: Helium

Flow rate: 1.4 mL/min

Injection volume: 2 µL

Injection type: Split

Split flow rate: 20 mL/min

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2 between naphthalene and amantadine

Tailing factor: NMT 2.0 for the amantadine peak

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 dissolved:

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

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

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

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

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

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

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

IMPURITIES

• **Organic Impurities**

Internal standard solution: 0.1 mg/mL of adamantane in *n*-heptane

Peak identification solution: 0.03 mg/mL each of USP Amantadine Related Compound A RS and USP Amantadine Related Compound B RS in *Internal standard solution* prepared as follows. Transfer suitable amounts of USP Amantadine Related Compound A RS and USP Amantadine Related Compound B RS to a suitable volumetric flask. Add methylene chloride to about 5% of the flask volume to dissolve, and dilute with *Internal standard solution* to volume.

Standard stock solution: 0.03 mg/mL of USP Amantadine Hydrochloride RS in water

Standard solution: Transfer 25 mL of *Standard stock solution*, 10 mL of 5 N sodium hydroxide solution, and 25 mL of *Internal standard solution* to a separatory funnel and shake for 10 min. Collect the upper layer of *n*-heptane and swirl with anhydrous sodium sulfate to remove traces of water.

Sample stock solution (for hard gelatin Capsules)**:** Nominally 10 mg/mL of amantadine hydrochloride prepared as follows. Combine the contents of NLT 20 Capsules and transfer a portion equivalent to 500 mg of amantadine hydrochloride to a 100-mL flask. Add 20 mL of 0.1 N hydrochloric acid using a volumetric pipette. Heat gently to dissolve and cool. Add 20 mL of water and sonicate for 15 min. Cool and add 10 mL of water. Centrifuge the solution for 10 min and collect the supernatant.

Sample solution

For hard gelatin Capsules: Transfer 25 mL of *Sample stock solution* and 10 mL of 5 N sodium hydroxide solution to a separatory funnel. Add 25 mL of *Internal standard solution* and shake for 10 min. Collect the upper layer of *n*-heptane and swirl with anhydrous sodium sulfate to remove traces of water.

For soft gelatin Capsules: Transfer 2 Capsules to a 200-mL flask and add 10 mL of water. Heat gently and cool. Add 5.0 mL of 5 N sodium hydroxide, 3.0 mL of concentrated sodium chloride, and 50.0 mL of *Internal standard solution*. Shake the contents for 20 min and collect the upper layer of *n*-heptane.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m; base deactivated fused-silica coated with a 1.0-µm film of stationary phase G27

Temperatures

Injection port: 220°

Detector: 300°

Column: See *Table 4*.

Table 4

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
120	0	120	3
120	8	250	10

Carrier gas: Helium

Flow rate: 4 mL/min

Injection volume: 2 µL

Injection type: Split ratio, 5:1 (deactivated split liner with glass wool)

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for adamantane and amantadine are 0.7 and 1.0, respectively.]

Suitability requirements

Relative standard deviation: NMT 3.0% for the peak response ratio of amantadine to adamantane

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual unspecified impurity in the portion of Capsules taken:

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

R_U = peak response ratio of any individual unspecified impurity to adamantane from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Amantadine	1.0	—
Amantadine related compound A[a]	1.2	—
Amantadine related compound B[a]	1.9	—
Any individual unspecified impurity	—	0.2
Total impurities	—	1.5

[a] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Amantadine Hydrochloride RS

USP Amantadine Related Compound A RS

1-Chloroadamantane.

$C_{10}H_{15}Cl$ 170.68

USP Amantadine Related Compound B RS

N-(Adamantan-1-yl)acetamide.

$C_{12}H_{19}NO$ 193.29

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

Topic/Question	Contact	Expert Committee
AMANTADINE HYDROCHLORIDE CAPSULES	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 43(4)
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