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Memantine Hydrochloride Tablets

DEFINITION

Memantine Hydrochloride Tablets contain an amount of memantine hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of memantine hydrochloride ($C_{12}H_{21}N \cdot HCl$).

IDENTIFICATION

Change to read:

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

Analytical range: 4000–400 cm^{-1}

Standard: 6.7 mg/mL of USP Memantine Hydrochloride RS in dichloromethane. Shake for 10 min, and pass through a suitable filter. Evaporate the solvent at room temperature. Collect the residue powder, and dry at 60° for 15 min. Prepare an approximate 1% (w/w) dispersion of the sample in potassium bromide.

Sample: 6.7 mg/mL of memantine hydrochloride in dichloromethane from NLT 20 crushed Tablets. Shake for 10 min, and centrifuge for 10 min. Pass the supernatant through a suitable filter. Evaporate the solvent at room temperature. Collect the residue powder, and dry at 60° for 15 min. Prepare an approximate 1% (w/w) dispersion of the sample in potassium bromide.

Acceptance criteria: Fingerprint region of the *Standard* and *Sample* spectrum exhibit maxima at the same wave numbers.

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

ASSAY

• **Procedure**

Solution A: 200 mg/mL of sodium hydroxide in water

Internal standard solution: 25 µg/mL of USP Amantadine Hydrochloride RS in water

Standard stock solution: 25 µg/mL of USP Memantine Hydrochloride RS prepared as follows. Weigh a suitable quantity of the Standard into a volumetric flask. Add methanol to fill 40% of the final flask volume, and sonicate. Dilute with water to volume.

Standard solution: Pipet 4.0 mL each of the *Internal standard solution* and the *Standard stock solution* into a test tube. Add 2 mL of *Solution A*, and mix on a vortex mixer for 1 min. Add 4.0 mL of toluene, and mix on a vortex mixer for 3 min. Allow the two layers to separate. Inject the toluene layer.

Sample stock solution: Nominally 20 µg/mL of memantine hydrochloride prepared as follows. Transfer a suitable number of Tablets to a volumetric flask to obtain a 0.1 mg/mL memantine hydrochloride solution. Add methanol to fill 40% of the final flask volume, and sonicate for 30 min with intermittent shaking. Add water to fill 40% of the final flask volume, and sonicate for 30 min with intermittent shaking. Dilute with water to volume, and centrifuge a portion for 10 min. Pipet a suitable volume of the clear centrifugate into a volumetric flask, and dilute with water to volume.

Sample solution: Pipet 5.0 mL of the *Sample stock solution*, 4.0 mL of the *Internal standard solution*, and 2 mL of *Solution A* into a test tube, and mix on a vortex mixer for 1 min. Add 4.0 mL of toluene, and mix on a vortex mixer for 5 min. Allow the two layers to separate. Inject the toluene layer.

Blank: To 5.0 mL of 80 µL/mL of methanol in water add 2 mL of *Solution A*, and mix on a vortex mixer for 1 min. Add 4.0 mL of toluene, and mix on a vortex mixer for 5 min. Allow the two layers to separate. Inject the toluene layer.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 30-m × 0.32-mm; 0.25-µm packing G27

Temperatures

Injection port: 210°

Detector: 300°

Oven: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	2
50	20	140	0
140	30	200	5

Carrier gas: Helium

Flow rate: 34.8 psi

Injection volume: 4 µL

Injection type: Split ratio, 1:10

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for amantadine and memantine are 0.97 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between amantadine and memantine

Tailing factor: NMT 2.5 for amantadine; NMT 2.0 for memantine

Relative standard deviation: NMT 2.0% for the ratio of the peak areas of amantadine and memantine

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

Calculate the percentage of the labeled amount of memantine hydrochloride ($C_{12}H_{21}N \cdot HCl$) 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 memantine to amantadine from the *Sample solution*

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: 0.1 N hydrochloric acid with sodium chloride (2 g/L of sodium chloride in water), adjusted with hydrochloric acid to a pH of 1.2; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Standard stock solution: (*L*/900) mg/mL of USP Memantine Hydrochloride RS in *Medium*, where *L* is the label claim in mg/Tablet

Internal standard solution: 28 µg/mL of USP Amantadine Hydrochloride RS in *Medium*

Standard solution

For Tablets labeled to contain 5 mg: Transfer 5 mL of the *Standard stock solution* to a test tube, add 1 mL of the *Internal standard solution* and 2 mL of 5 N sodium hydroxide, and mix for 1 min. Add 3 mL of toluene, and mix for 2 min. Use the toluene layer.

For Tablets labeled to contain 10 mg: Transfer 5 mL of the *Standard stock solution* to a test tube, add 2 mL of the *Internal standard solution* and 2 mL of 5 N sodium hydroxide, and mix for 1 min. Add 3 mL of toluene, and mix for 2 min. Use the toluene layer.

Sample solution: Pass a portion of the solution under test through a suitable filter.

For Tablets labeled to contain 5 mg: Transfer 5 mL of the filtrate to a test tube, add 1 mL of the *Internal standard solution* and 2 mL of 5 N sodium hydroxide, and mix for 1 min. Add 3 mL of toluene, and mix for 2 min. Use the toluene layer.

For Tablets labeled to contain 10 mg: Transfer 5 mL of the filtrate to a test tube, add 2 mL of the *Internal standard solution* and 2 mL of 5 N sodium hydroxide, and mix for 1 min. Add 3 mL of toluene, and mix for 2 min. Use the toluene layer.

Chromatographic system

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

Mode: GC, splitless

Detector: Flame ionization

Column: 30-m × 0.32-mm; 0.25-µm packing G27

Flow rate: 34.8 psi

Temperatures

Injection port: 210°

Detector: 300°

Oven: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	2
50	20	140	0
140	30	200	5

Carrier gas: Helium

Injection volume: 4 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between amantadine and memantine

Tailing factor: NMT 2.0 each for amantadine and memantine

Relative standard deviation: NMT 2.0% for the ratio of memantine to amantadine peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of memantine hydrochloride ($C_{12}H_{21}N \cdot HCl$) dissolved:

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

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

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

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of memantine hydrochloride ($C_{12}H_{21}N \cdot HCl$) is dissolved.

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

IMPURITIES

• **Limit of Memantine–Lactose Adduct**

[Note—Perform this test if lactose is present in the formulation.]

Solution A: 40 mg/mL of sodium hydroxide in water

Buffer: Dissolve 3.3 g of monobasic potassium phosphate and 2.3 g of sodium 1-octane sulfonate in 1 L of water. Adjust with *Solution A* to a pH of 6.1.

Mobile phase: Acetonitrile, methanol, and *Buffer* (26:4:70)

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

Sample solution: Nominally 10 mg/mL of memantine hydrochloride from NLT 25 crushed Tablets, prepared as follows. Transfer an amount of powder equivalent to 100 mg of memantine hydrochloride to a 20-mL volumetric flask. Add 10 mL of *Mobile phase*, and sonicate for 30 min. Centrifuge, and pass a portion of the centrifugate through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: Refractive index

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

Temperatures

Column: 40°

Detector: 35°

Flow rate: 1.3 mL/min

Injection volume: 50 µL

Run time: 1.3 times the retention time of the memantine peak

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 3.5

Relative standard deviation: NMT 10.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the memantine–lactose adduct in the portion of Tablets taken:

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

r_U = peak response of the memantine–lactose adduct from the *Sample solution*

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

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

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

F = relative response factor of the memantine–lactose adduct (see *Table 3*)

Acceptance criteria: See *Table 3*.

Disregard all peaks other than the memantine–lactose adduct peak.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Memantine–lactose adduct	0.41	0.53	1.4
Memantine	1.0	1.0	—

• **Organic Impurities**

Solution A: 1 N sodium hydroxide

System suitability stock solution A: 0.5 mg/mL each of USP Memantine Related Compound A RS, USP Memantine Related Compound B RS, USP Memantine Related Compound C RS, USP Memantine Related Compound D RS, and USP Memantine Related Compound E RS in *n*-hexane

System suitability stock solution B: Transfer 75 mg of USP Memantine Hydrochloride RS into a suitable container, add 9 mL of 1.0 N sodium hydroxide and 6 mL of *n*-hexane, and mix for 10 min.

System suitability solution: Pipet 4.0 mL of the *n*-hexane layer from *System suitability stock solution B* into a 10-mL volumetric flask. Add 0.5 mL of *System suitability stock solution A*, and dilute with *n*-hexane to volume.

Standard stock solution: 1.3 mg/mL of USP Memantine Hydrochloride RS in *n*-hexane prepared as follows. Weigh a suitable quantity of the Standard into a volumetric flask. Add *Solution A* to fill 30% of the final flask volume, and mix for 5 min. Add *n*-hexane to fill 40% of the final flask volume, and shake for 10 min. Transfer the contents of the flask into a separator. Allow the layers to separate, and filter a portion of the top *n*-hexane layer through anhydrous sodium sulfate. Use the clear solution.

Standard solution: Pipet 2.0 mL of the clear solution from the *Standard stock solution* into a 100-mL volumetric flask, and dilute with *n*-hexane to volume.

Sample solution: Nominally 5 mg/mL of memantine hydrochloride in *n*-hexane from NLT 20 crushed Tablets, prepared as follows. Transfer a weighed amount of powder equivalent to 100 mg of memantine hydrochloride to a suitable volumetric flask. Add *Solution A* to fill 15% of the final flask volume. Shake to disperse the material, and then shake for 5 min. Sonicate for 5 min with intermittent shaking. Add *n*-hexane to fill 20% of the final flask volume, and shake for 10 min. Transfer the contents into a separator. Allow the layers to separate, and filter a portion of the top hexane layer through anhydrous sodium sulfate. Use the clear solution.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 50-m × 0.32-mm; 0.52-µm packing G27

Temperatures

Injection port: 220°

Detector: 300°

Oven: See *Table 4*.

Table 4

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	2
50	5	145	0
145	10	250	20

Carrier gas: Helium

Flow rate: 4.0 ± 0.2 mL/min

Injection volume: 3 µL

Injection type: Split ratio, 1:20

System suitability

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

[NOTE—See *Table 5* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between memantine and memantine related compound B; NLT 2.0 between memantine related compound B and memantine related compound C, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of memantine related compound E or any 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 memantine related compound E or any individual degradation product from the *Sample solution*

r_S = peak response of memantine hydrochloride from the *Standard solution*

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

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

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Memantine related compound A[a]	0.77	—
Memantine	1.0	—
Memantine related compound B[a]	1.03	—
Memantine related compound C[a]	1.1	—
Memantine related compound D[a]	1.2	—
Memantine related compound E	1.4	0.3
Any individual unspecified degradation product	—	0.20
Total impurities[b]	—	0.5

[a] Process impurities controlled in the drug substance and are included for identification only. Not reported for the drug product and not included in the total impurities.

[b] Excludes memantine–lactose adduct monitored in the test for *Limit of Memantine–Lactose Adduct*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Amantadine Hydrochloride RS

USP Memantine Hydrochloride RS

USP Memantine Related Compound A RS
1,3-Dimethyladamantane.
$C_{12}H_{20}$ 164.29

USP Memantine Related Compound B RS
3,5-Dimethyladamantane-1-ol.
$C_{12}H_{20}O$ 180.29

USP Memantine Related Compound C RS
1-Chloro-3,5-dimethyladamantane.
$C_{12}H_{19}Cl$ 198.73

USP Memantine Related Compound D RS
1-Bromo-3,5-dimethyladamantane.
$C_{12}H_{19}Br$ 243.18

USP Memantine Related Compound E RS
N-3,5-Dimethyladamantan-1-yl formamide.
$C_{13}H_{21}NO$ 207.31

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

Topic/Question	Contact	Expert Committee
MEMANTINE HYDROCHLORIDE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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