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Galantamine Tablets

DEFINITION

Galantamine Tablets contain an amount of Galantamine Hydrobromide equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of galantamine ($C_{17}H_{21}NO_3$).

IDENTIFICATION

Change to read:

• **A.** ▲The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

• **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

Change to read:

• **Procedure**

Buffer solution: 5.34 g/L of dibasic sodium phosphate dihydrate in water. Adjust with phosphoric acid to a pH of 6.5.

Solution A: ▲Methanol▲ (USP 1-May-2021) and *Buffer solution* (1:19)

Solution B: ▲Acetonitrile and methanol▲ (USP 1-May-2021) (19:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
40.0	75	25
45.0	60	40
46.0	40	60
55.0	40	60
56.0	100	0
61.0	100	0

Diluent: Dissolve 35.4 g of edetate disodium in 950 mL of water, and add 50 mL of ▲methanol.▲ (USP 1-May-2021) [Note—First dissolve in water, and then add ▲methanol.]

System suitability solution: 0.6 mg/mL of USP Galantamine Hydrobromide Related Compounds Mixture RS in *Diluent*▲ (USP 1-May-2021)

Standard solution: 0.62 mg/mL of USP Galantamine Hydrobromide RS▲(equivalent to 0.48 mg/mL of galantamine)▲ (USP 1-May-2021) in *Diluent*

Sample solution: ▲Nominally▲ (USP 1-May-2021) 0.48 mg/mL of galantamine from powdered Tablets (NLT 10) in *Diluent*. Pass through a PTFE filter of 0.45-µm or finer pore size.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm. ▲For *Identification A*, use a diode array detector in the range of 200–300 nm.▲ (USP 1-May-2021)

Column: 4.6-mm × 10-cm; 3-µm packing L1

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Samples: ▲*System suitability solution* and▲ (USP 1-May-2021) *Standard solution*

▲[NOTE—See *Table 2* for the relative retention times.]▲ (USP 1-MAY-2021)

Suitability requirements

▲**Resolution:** NLT 1.5 between galantamine *N*-oxide and dihydrogalantamine, *System suitability solution*▲ (USP 1-May-2021)

Relative standard deviation: NMT ▲1.0%,▲ (USP 1-May-2021) *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

M_{r1} = molecular weight of galantamine, 287.35

M_{r2} = molecular weight of galantamine hydrobromide, 368.27

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION ⟨711⟩**

Test 1

Medium: Water; 500 mL

Apparatus 2: 50 rpm

Time: 20 min

▲Analyze the sample under test using either the *Instrumental procedure* or *Chromatographic procedure*.

Instrumental procedure▲ (USP 1-May-2021)

Standard solution: (*L*/400) mg/mL of USP Galantamine Hydrobromide RS in *Medium*, where *L* is the label claim in mg▲/Tablet▲ (USP 1-May-2021)

Sample solution: Pass ▲a portion▲ (USP 1-May-2021) of the solution through a suitable filter of 0.2-µm pore size.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

Mode: UV

Analytical wavelength: 288 nm

Cell: 5-cm for 4-mg and 8-mg Tablets; 1-cm for 12-mg Tablets

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) dissolved in the portion of Tablets taken:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times V \times 100$$

A_U = absorbance of galantamine from the *Sample solution*

A_S = absorbance of galantamine from the *Standard solution*

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

L = label claim (mg/Tablet)

M_{r1} = molecular weight of galantamine, 287.35

M_{r2} = molecular weight of galantamine hydrobromide, 368.27

V = volume of *Medium*, 500 mL

▲**Chromatographic procedure**

Buffer: 3.45 g/L of monobasic sodium phosphate in water. To each liter, add 1 mL of triethylamine. Adjust with phosphoric acid to a pH of 4.5.

Mobile phase: Acetonitrile, methanol, and *Buffer* (10:10:80), filtered and deaerated

Standard solution: (*L*/400) mg/mL of USP Galantamine Hydrobromide RS in water, where *L* is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size. Use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of galantamine

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 galantamine ($C_{17}H_{21}NO_3$) dissolved in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times V \times 100$$

r_U = peak area of galantamine from the *Sample solution*

r_S = peak area of galantamine from the *Standard solution*

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

L = label claim (mg/Tablet)

M_{r1} = molecular weight of galantamine, 287.35

M_{r2} = molecular weight of galantamine hydrobromide, 368.27

V = volume of *Medium*, 500 mL▲ (USP 1-May-2021)

Tolerances: NLT 80% (*Q*) of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) is dissolved.

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

▲**Medium:** Water; 500 mL

Apparatus 2: 50 rpm

Time: 20 min

Standard solution: (*L*/400) mg/mL of USP Galantamine Hydrobromide RS in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution through a suitable filter of 0.2-µm pore size.

Instrumental conditions

(See Ultraviolet-Visible Spectroscopy ⟨857⟩.)

Mode: UV

Analytical wavelength: 288 nm

Cell: 5-cm for 4-mg and 8-mg Tablets; 1-cm for 12-mg Tablets

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) dissolved in the portion of Tablets taken:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times V \times 100$$

A_U = absorbance of galantamine from the *Sample solution*

A_S = absorbance of galantamine from the *Standard solution*

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

L = label claim (mg/Tablet)

M_{r1} = molecular weight of galantamine, 287.35

M_{r2} = molecular weight of galantamine hydrobromide, 368.27

V = volume of *Medium*, 500 mL▲ (USP 1-May-2021)

Tolerances: NLT 70% (*Q*) of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

Medium: Water; 500 mL

Apparatus 2: 50 rpm. Use apex vessels and adjust the position of the paddle so that the distance between the tip of the peak and the bottom of the paddle is 1 cm.

Time: 20 min

Buffer: ▲3.45 g/L of monobasic sodium phosphate in water. To each liter, add 1 mL of triethylamine.▲ (USP 1-May-2021) Adjust with phosphoric acid to a pH of 4.5.

Mobile phase: ▲Acetonitrile, methanol,▲ (USP 1-May-2021) and *Buffer* (10:10:80), filtered and deaerated

Standard solution: (*L*/400) mg/mL of USP Galantamine Hydrobromide RS in water, where *L* is the label claim in mg▲/Tablet▲ (USP 1-May-2021)

Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size. Use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: ▲NLT 2▲ (USP 1-May-2021) times the retention time of galantamine

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 galantamine ($C_{17}H_{21}NO_3$) dissolved in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times V \times 100$$

r_U = peak area of ▲galantamine from▲ (USP 1-May-2021) the *Sample solution*

r_S = peak area of ▲galantamine from▲ (USP 1-May-2021) the *Standard solution*

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

L = label claim (mg/Tablet)

M_{r1} = molecular weight of galantamine, 287.35

M_{r2} = molecular weight of galantamine hydrobromide, 368.27

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) is dissolved.

Change to read:

• **Uniformity of Dosage Units ⟨905⟩, *Content Uniformity*:** ▲Meet the requirements▲ (USP 1-May-2021)

IMPURITIES

Change to read:

• **Organic Impurities**

Buffer solution, Solution A, Solution B, Mobile phase, Diluent, ▲System suitability solution,▲ (USP 1-May-2021) Standard solution, and **Sample solution:** Prepare as directed in the *Assay*.

▲Sensitivity solution: 0.6 µg/mL of USP Galantamine Hydrobromide RS (equivalent to 0.5 µg/mL of galantamine) from the *Standard solution* in *Diluent*▲ (USP 1-May-2021)

Chromatographic system

(See Chromatography ⟨621⟩, System Suitability.)

Mode: LC

Injection volume: 20 µL

System suitability

Samples: *System suitability solution*, *Standard solution*, ▲and *Sensitivity solution*

[Note— See *Table 2* for the relative retention times.]▲ (USP 1-May-2021)

Suitability requirements

Resolution: NLT 1.5 between ▲galantamine *N*-oxide and dihydrogalantamine,▲ (USP 1-May-2021) *System suitability solution*

Relative standard deviation: NMT 2.0% for galantamine, *Standard solution*

▲Signal-to-noise ratio: NLT 10, *Sensitivity solution*▲ (USP 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

▲▲ (USP 1-May-2021)

Calculate the percentage of ▲any unspecified impurity▲ (USP 1-May-2021) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (100/F)$$

r_U = peak area of each impurity from the *Sample solution*

r_S = peak area of galantamine from the *Standard solution*

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

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

M_{r1} = molecular weight of galantamine, 287.35

M_{r2} = molecular weight of galantamine hydrobromide, 368.27

F = relative response factor for each of the impurities relative to galantamine (see *Table 2*)

Acceptance criteria: See *Table 2*. ▲Disregard the bromide peak near the void volume. The reporting threshold is 0.1%.▲ (USP 1-May-2021)

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
▲*N*-Desmethyl galantamine▲ (USP 1-May-2021) [a]	0.41	1.1	0.5
▲Galantamine *N*-oxide▲ (USP 1-May-2021) [b]	0.73	1.1	0.75
▲Dihydrogalantamine▲ (USP 1-May-2021) [c,d]	0.86	—	—
Galantamine hydrobromide	1.00	1.0	—
▲6*S*-Galantamine▲ (USP 1-May-2021) [e]	1.15	1.1	0.5
▲Anhydrogalantamine▲ (USP 1-May-2021) [f,d]	2.09	—	—
▲Any unspecified impurity▲ (USP 1-May-2021)	—	1.0	0.2
Total impurities	—	—	1.5

a ▲(4a*S*,6*R*,8a*S*)-3-Methoxy-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.▲ (USP 1-May-2021)

b ▲(4a*S*,6*R*,8a*S*)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepine 11-oxide.▲ (USP 1-May-2021)

c ▲(4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-4a,5,7,8,9,10,11,12-octahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.▲ (USP 1-May-2021)

d This is a process impurity and is listed for information only. It is controlled in the drug substance.

e ▲(4a*S*,6*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.▲ (USP 1-May-2021)

f ▲(4a*S*,8a*S*)-3-Methoxy-11-methyl-9,10,11,12-tetrahydro-4a*H*-benzo[2,3]benzofuro[4,3-*cd*]azepine.▲ (USP 1-May-2021)

ADDITIONAL REQUIREMENTS

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

Change to read:

• **Labeling:** ▲▲ (USP 1-May-2021) The labeling states the *Dissolution* test used only if *Test 1* is not used.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Galantamine Hydrobromide RS

USP Galantamine Hydrobromide Related Compounds Mixture RS

▲Contains a mixture of the following 5 compounds:

Galantamine hydrobromide.
Galantamine *N*-oxide;
(4a*S*,6*R*,8a*S*)-6-Hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepine 11-oxide.
$C_{17}H_{21}NO_4$ 303.35
Dihydrogalantamine;
(4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-4a,5,7,8,9,10,11,12-octahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.
$C_{17}H_{23}NO_3$ 289.37
6*S*-Galantamine;
(4a*S*,6*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol.
$C_{17}H_{21}NO_3$ 287.35
Anhydrogalantamine;
(4a*S*,8a*S*)-3-Methoxy-11-methyl-9,10,11,12-tetrahydro-4a*H*-benzo[2,3]benzofuro[4,3-*cd*]azepine.
$C_{17}H_{19}NO_2$ 269.34

[NOTE—The contents have previously been referred to as galantamine hydrobromide, 6β-hexahydrogalantamine, 6β-octahydrogalantamine, 6α-hexahydrogalantamine, and tetrahydrogalantamine, respectively.]▲ (USP 1-MAY-2021)

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

Topic/Question	Contact	Expert Committee
GALANTAMINE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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