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

- **A. Ultraviolet Absorption** ⟨197U⟩**:** The spectrum of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the test for *Uniformity of Dosage Units*.
- **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 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 and *Buffer solution* (1:19)
Solution B: Acetonitrile and methanol (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 water, and add 50 mL of methanol. [Note—First dissolve in water, then add methanol.]
Standard solution: 0.62 mg/mL of USP Galantamine Hydrobromide RS in *Diluent*
Sample solution: 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
Column: 4.6-mm × 10-cm; 3-µm L1 packing
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) 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
Standard solution: •(*L*/400) mg/mL of USP Galantamine Hydrobromide RS• (RB 1-Jan-2012) in *Medium*, where *L* is the label claim in mg
Sample solution: Pass portions of the solution through a suitable filter of 0.2-µm pore size.
Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 288 nm
Cell: 5-cm cell for 4-mg and 8-mg Tablets; 1-cm cell 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:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of 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

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, Apparatus 2, Time, Standard solution, Sample solution, and **Analysis:** Proceed as directed for *Test 1*.
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 peak vessels
Time: 20 min
Buffer: Triethylamine and 3.45 g/L of monobasic sodium phosphate in water (1:1000). Adjust with phosphoric acid to a pH of 4.5.
Mobile phase: Acetonitrile, methanol, and *Buffer* (10:10:80). Filtered and de-aerated
Standard solution: (*L*/400) mg/mL of USP Galantamine Hydrobromide RS in water, where *L* is the label claim in mg
Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size. Use the filtrate.

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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: Two times the retention time of galantamine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) dissolved in the portion of Tablets taken:

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

r_U = peak area of the *Sample solution*
r_S = peak area of 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

Tolerances: NLT 80% (*Q*) of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) is dissolved.● (RB 1-Jan-2012)

• **Uniformity of Dosage Units** ⟨905⟩
Procedure for content uniformity
Standard solution: 0.05 mg/mL of USP Galantamine Hydrobromide RS in 0.1 N hydrochloric acid
Sample solution: Add 1 Tablet to each appropriately sized volumetric flask to obtain a final galantamine concentration of 0.04 mg/mL. Add an appropriate amount of 0.1 N hydrochloric acid, equivalent to 75% of the total volume of the volumetric flask, and mechanically shake for 45 min. Dilute with 0.1 N hydrochloric acid to volume. Pass a portion of the solution through a suitable filter of 0.2-µm pore size, and use the filtrate.
Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: Absorption maximum at about 289 nm
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the amount of galantamine ($C_{17}H_{21}NO_3$) dissolved in filtered portions of the *Sample solution* in comparison with the *Standard solution.*
Calculate the percentage of the labeled amount of galantamine ($C_{17}H_{21}NO_3$) dissolved:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Galantamine Hydrobromide RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of the *Sample solution* (mg/mL)
M_{r1} = molecular weight of galantamine, 287.35
M_{r2} = molecular weight of galantamine hydrobromide, 368.27

Acceptance criteria: Meet the requirements for coated Tablets

IMPURITIES
• **Organic Impurities**
Buffer solution, Solution A, Solution B, Mobile phase, Diluent, Standard solution, and **Sample solution:** Prepare as directed in the *Assay*.
System suitability solution: 0.6 mg/mL of USP Galantamine Hydrobromide Related Compounds Mixture RS in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Injection volume: 20 µL
System suitability
Samples: *Standard solution* and *System suitability solution*
Suitability requirements
Resolution: NLT 1.5 between 6*β*-hexahydrogalantamine and 6*β*-octahydrogalantamine, *System suitability solution*
Relative standard deviation: NMT 2.0% for galantamine, *Standard solution*
[Note—Identify the impurities using the approximate relative retention times given in *Table 2*.]
Analysis
Samples: *Standard solution* and *Sample solution*
[Note—Ignore the peak due to bromide near the void volume.]
Calculate the percentage of each of the impurities including the unspecified degradation impurities 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*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
N-Desmethylgalantamine[a]	0.41	1.1	0.5
6*β*-Hexahydrogalantamine (also known as galantamine *N*-oxide)[b]	0.73	1.1	0.75

[a] (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol.
[b] [4a*S*-(4α,6*β*,8a*R**)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol, *N*-oxide.
[c] [4a*S*-(4α,6*β*,8a*R**)]-4a,5,7,8,9,10,11,12-Octahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol.
[d] Impurities are not quantified and are intended for system suitability evaluation only.
[e] [4a*S*-(4aα,6α,8a*R**)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol.
[f] [4a*S*-(4a*R**,8a*R**)]-9,10,11,12-Tetrahydro-3-methoxy-11-methyl-4a*H*-benzofuro[3a,3,2-*ef*][2]benzazepine.

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Table 2 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
6β-Octahydrogalantamine (also known as lycoramine)[c,d]	0.86	—	—
Galantamine hydrobromide	1.00	1.0	—
6α-Hexahydrogalantamine (also known as epigalantamine)[e]	1.15	1.1	0.5
Tetrahydrogalantamine[f,d]	2.09	—	—
Individual, unspecified degradation impurity	—	1.0	0.2
Total impurities	—	—	1.5

[a] (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-Hexahydro-3-methoxy-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol.

[b] [4a*S*-(4α,6β,8a*R**)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol, *N*-oxide.

[c] [4a*S*-(4aα,6β,8a*R**)]-4a,5,7,8,9,10,11,12-Octahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol.

[d] Impurities are not quantified and are intended for system suitability evaluation only.

[e] [4a*S*-(4aα,6α,8a*R**)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol.

[f] [4a*S*-(4a*R**,8a*R**)]-9,10,11,12-Tetrahydro-3-methoxy-11-methyl-4a*H*-benzofuro[3a,3,2-*ef*][2]benzazepine.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **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 Galantamine Hydrobromide RS
  USP Galantamine Hydrobromide Related Compounds Mixture RS
  Contains galantamine hydrobromide, 6β-hexahydrogalantamine, 6β-octahydrogalantamine, 6α-hexahydrogalantamine, and tetrahydrogalantamine.

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