

BRIEFING

Galantamine Hydrobromide. A proposal was published in *PF* 33(2) [Mar.–Apr. 2007], page 334 for this drug substance, which contained a capillary electrophoresis method for determining the *Limit of 4R,8R-stereoisomer*. USP has received comments from companies that hold tentatively approved ANDAs requesting the inclusion of an HPLC method for the test for *Limit of 4R,8R-stereoisomer*. The proposed USP Pending Standard draft for the HPLC method is based on the analyses performed with Chiral AGP 150.4 column containing L41 packing, manufactured by Chromtech. The method has also been validated using Chiral AGP 150.2 containing L41 packing, manufactured by Chromtech. The retention times are about 5.3 and 8.1 minutes for 4R,8R and galantamine, respectively. It is also proposed to include the test for *Related compounds* published in *PF* 33(2) with a USP Pending Standard draft that includes two new impurities with appropriate limits and includes the limits for two specified impurities that do not have any limits currently. Therefore draft proposals to add another test for *Limit of 4R,8R-stereoisomer* and changes to the test for *Related compounds* will be considered for inclusion in the *USP–NF* via a flexible monograph approach pending FDA approval of the sponsor's ANDA.

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Galantamine Hydrobromide

Draft 1.0

Add the following:

■ **Limit of 4R,8R-stereoisomer**—[NOTE—Use low-actinic glassware and vials. It is recommended that precautions be taken to protect all solutions from light.]

Buffer—Dissolve 4.1 g of sodium acetate in 500 mL of water.

Mobile phase—Prepare a filtered degassed mixture of *Buffer* and acetonitrile (49 : 1). Adjust the pH to 6.5 with acetic acid.

System suitability solution—Dissolve suitable quantities of USP Galantamine Hydrobromide RS and USP Galantamine Hydrobromide Racemic RS in water to obtain a final solution having a concentration of about 1.2 mg per mL of galantamine hydrobromide and 3.6 µg per mL of galantamine racemic mixture. [NOTE—This solution will have about 1.8 µg per mL of 4R,8R-stereoisomer.]

Test solution—Prepare a solution having a nominal concentration of about 1.2 mg per mL of Galantamine Hydrobromide.

Chromatographic system—The liquid chromatograph is equipped with a 230-nm detector and a 4.0-mm × 15.0-cm column containing 5-µm packing L41. The flow rate is 0.8 mL per minute. [NOTE—Alternatively a 2.0-mm × 15.0-cm column containing 5-µm packing L41 can be used with a recommended flow rate of about 0.2 mL per minute.] Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*: the 4R,8R-stereoisomer elutes first as the minor peak followed by the major peak due to galantamine (as 4S,8S-stereoisomer); the resolution, *R*, between 4R,8R-stereoisomer and galantamine is not less than 3.0; and the relative standard deviation for the 4R,8R-stereoisomer peak is not more than 5.0%.

Procedure—Inject a volume (about 5 µL) of the *Test solution* into the chromatograph, and measure the responses for the 4R,8R-stereoisomer and galantamine peaks. Calculate the percentage of 4R,8R-stereoisomer in the portion of Galantamine Hydrobromide taken using the formula:

$$100[r_{4R,8R} / (r_{4R,8R} + r_{4S,8S})]$$

in which $r_{4R,8R}$ is the peak area of 4R,8R-stereoisomer and $r_{4S,8S}$ is the peak area of galantamine peak obtained from the *Test solution*: not more than 0.10% of 4R,8R-stereoisomer is found.

Related compounds—

Buffer solution—Dissolve 0.79 g of dibasic sodium phosphate dihydrate and 2.46 g of monobasic sodium phosphate anhydrous in 1 L of water.

Solution A—To 950 mL of the *Buffer solution*, pipet exactly 50 mL of methanol, and mix.

Solution B: acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

Diluent—Prepare a mixture of water and methanol (95 : 5).

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Resolution solution—Dissolve an accurately weighed quantity of USP Galantamine Hydrobromide Related Compounds Mixture RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a concentration of about 1 mg per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Galantamine Hydrobromide RS in *Diluent*, and dilute with *Diluent* quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 5.0 µg per mL.

Test solution—Dissolve an accurately weighed quantity of Galantamine Hydrobromide in *Diluent*, and dilute with *Diluent* quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 1.0 mg per mL.

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 10-cm column that contains 3.5-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 55°. The chromatograph is programmed as follows.

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0–6.0	100	0	isocratic
6.0–20.0	100→95	0→5	linear gradient
20.0–35.0	95→85	5→15	linear gradient
35.0–50.0	85→80	15→20	linear gradient
50.0–51.0	80→40	20→60	linear gradient
51.0–55.0	40	60	isocratic
55.0–56.0	40→100	60→0	linear gradient
56.0–60.0	100	0	re-equilibration

Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure*. Identify the peaks using the relative retention times given in *Table 1*: the resolution, *R*, between galantamine and 6α-hexahydrogalantamine is not less than 4.5; the tailing factor for galantamine hydrobromide is not more than 2.0. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the chromatograms. Identify the impurities, based on the relative retention times given in *Table 1*, and measure the peak responses. [NOTE—Ignore the peak due to bromide near the void volume and any peak below 0.05%. The approximate relative retention times in *Table 1* are for peak identification purposes only.] Calculate the percentage of each of the galantamine hydrobromide related compounds in the portion of Galantamine Hydrobromide, taken on the dried basis, by the formula:

$$100(C_s/C_v)(r_v/r_s)(1/F)(100/100 - L)$$

in which C_s and C_v are the concentrations, in mg per mL, of galantamine hydrobromide in the *Standard solution* and the *Test solution*, respectively; r_v is the peak response of each impurity obtained from the *Test solution*; r_s is the peak response of galantamine hydrobromide obtained from the *Standard solution*; F is the relative response factor for each of the impurities relative to galantamine hydrobromide; and L is the loss on drying, in percent, as determined in the test for *Loss on drying*. The limits are given in *Table 1*.

Table 1

Related Compound	Relative Retention Time	Relative Response Factor (<i>F</i>)	Limit (% w/w)
<i>N</i> -Desmethylgalantamine ¹	0.29	1.2	NMT 0.20
<i>O</i> -Desmethylgalantamine ²	0.35	1.1	NMT 0.20
Galantamine- <i>N</i> -oxide ³	0.65	0.96	NMT 0.20
6β-Octahydrogalantamine ⁴	0.82	0.81	NMT 0.35
Galantamine hydrobromide	1.00	1.0	—
6α-Hexahydrogalantamine ⁵	1.16	0.95	NMT 0.20
Tetrahydrogalantamine ⁶	2.05	1.2	NMT 0.40
Individual unspecified impurity	—	1.0	NMT 0.10
Total impurities ⁷	—	—	NMT 1.0

¹ (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.

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

³ [4a*S*-(4a*α*,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.

⁴ [4a*S*-(4a*α*,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.

⁵ [4a*S*-(4a*α*,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.; also known as epigalantamine.

⁶ [4a*S*-(4a*R**,8a*R**)]-9,10,11,12-Tetrahydro-3-methoxy-11-methyl-4a*H*-benzofuro[3a,3,2-*ef*][2]benzazepine.

⁷ Do not include the 4*R*,8*R*-stereoisomer measure from the test for *Limit of 4*R*,8*R*-stereoisomer*. ■