

BRIEFING

Donepezil Hydrochloride. This monograph was posted on the USP website as a Draft 2 USP Pending Monograph in June 2009 for review and public comments. No comments were received. The Monograph Development—Psychiatrics and Psychoactives Expert Committee approved the monograph as an Authorized USP Pending Monograph.

An authorized version of this Pending Monograph was posted on the USP website in February 2008. Comments received indicated that Donepezil Hydrochloride has other polymorphic forms. The following tests were revised to include all forms:

1. *Identification test A, Infrared Absorption* (197K) was revised to add a note to allow for polymorphic equalization.
2. *Water Determination* was revised from 4.0%–7.0% to NMT 7.0%.
3. The CAS number was revised to be consistent with that in the ACS registry.

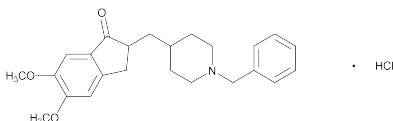
Additionally, the monograph was redesigned to be consistent with the USP monograph redesign initiative.

The gradient elution HPLC method in the *Procedure for Organic Impurities* is based on analyses performed using the Kromasil C-18 brand of L1 column with a retention time of between 12.5 and 15.5 min for the donepezil peak, depending on the gradient delay volume. The isocratic HPLC method for the *Assay* is based on analyses performed using the Kromasil C-18 brand of L1 column with a retention time of about 11.5 min for donepezil.

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Donepezil Hydrochloride

v.2 Authorized April 1, 2010



$C_{24}H_{29}NO_3 \cdot HCl$ 415.95
(±)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride [120011-70-3].

DEFINITION

Donepezil Hydrochloride contains NLT 98.0% and NMT 102.0% of $C_{24}H_{29}NO_3 \cdot HCl$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K): [NOTE—If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the USP Donepezil Hydrochloride RS separately in dichloromethane, evaporate to dryness, and record new spectra using the residues.]
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. IDENTIFICATION TESTS—GENERAL, Chloride** (191)
Sample solution: 10 mg/mL

ASSAY

PROCEDURE

Buffer: 6.8 g/L of potassium dihydrogen phosphate in water. Add 5 mL of triethylamine, and adjust with orthophosphoric acid to a pH of 2.2. Pass through a filter of 0.45- μ m or finer pore size.

Mobile phase: Methanol and *Buffer* (2:3)

Standard solution: 0.1 mg/mL of USP Donepezil Hydrochloride RS in *Mobile phase*. [NOTE—Sonication may be used to aid the dissolution of donepezil hydrochloride.]

Sample solution: 0.1 mg/mL of Donepezil Hydrochloride in *Mobile phase*. [NOTE—Sonication may be used to aid the dissolution of donepezil hydrochloride.]

Chromatographic system

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

Mode: LC

Detector: UV 268 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection size: 20 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Column efficiency: NLT 7000 theoretical plates

Relative standard deviation: NMT 1.0%, for five replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{24}H_{29}NO_3 \cdot HCl$ in the portion of Donepezil Hydrochloride taken:

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

r_U = peak response of donepezil hydrochloride from the *Sample solution*

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

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

C_U = concentration of Donepezil Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **HEAVY METALS, Method II** (231): NMT 20 ppm
- **RESIDUE ON IGNITION** (281): NMT 0.1%

Organic Impurities

PROCEDURE

Diluent: Acetonitrile and water (1:3)

Solution A: Add 1 mL of phosphoric acid in 1 L of water, and mix. Adjust with triethylamine to a pH of 6.5. Pass through a filter of 0.45- μ m or finer pore size.

Solution B: Acetonitrile

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	75	25
10	40	60
40	40	60
41	75	25
50	75	25

Standard solution: 0.01 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*. [NOTE—Sonication may be used to aid the dissolution of donepezil hydrochloride.]

Sample solution: 1.0 mg/mL of Donepezil Hydrochloride in *Diluent*. [NOTE—Sonication may be used to aid the dissolution of donepezil hydrochloride.]

Chromatographic system

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

Mode: LC

Detector: UV 286 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection size: 20 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 40,000 theoretical plates

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%, for five replicate injections

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Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of any individual impurity in the portion of Donepezil Hydrochloride taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times (1/F) \times 100$$

- r_u = peak response of any individual impurity from the *Sample solution*
 r_s = peak response of donepezil hydrochloride from the *Standard solution*
 C_s = concentration of USP Donepezil Hydrochloride RS in the *Standard solution* (mg/mL)
 C_u = concentration of Donepezil Hydrochloride in the *Sample solution* (mg/mL)
 F = relative response factor for each individual impurity (see *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.5%

Impurity Table 1

Name	Relative Retention Time*	Relative Response Factor	Acceptance Criteria, NMT (%)
DNP1 ^a	0.23	1.5	0.15
DPM1 ^b	0.49	1.9	0.15

- * Relative retention times are based on 1 mL gradient delay volume.
^a 2,3-Dihydro-5,6-dimethoxy-2-(4-piperidinyl)methylindan-1-one hydrochloride.
^b 5,6-Dimethoxy-2-(4-pyridyl)methylindan-1-one.
^c 1,1-Dibenzyl-4-[(5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl]piperidinium bromide.
^d 1-Benzyl-4-[(5,6-dimethoxy-1*H*-inden-2-yl)methyl]piperidine hydrochloride.
^e 1-Benzyl-4-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-2-yl)methyl]piperidine hydrochloride.

Impurity Table 1 (continued)

Name	Relative Retention Time*	Relative Response Factor	Acceptance Criteria, NMT (%)
Donepezilbenzyl bromide ^c	0.68	0.73	0.15
Donepezil hydrochloride	1.0	1.0	—
Dehydrodeoxy donepezil ^d	1.72	2.0	0.15
Deoxydonepezil ^e	2.12	0.67	0.15
Any individual unspecified impurity	—	1.0	0.1

- * Relative retention times are based on 1 mL gradient delay volume.
^a 2,3-Dihydro-5,6-dimethoxy-2-(4-piperidinyl)methylindan-1-one hydrochloride.
^b 5,6-Dimethoxy-2-(4-pyridyl)methylindan-1-one.
^c 1,1-Dibenzyl-4-[(5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl]piperidinium bromide.
^d 1-Benzyl-4-[(5,6-dimethoxy-1*H*-inden-2-yl)methyl]piperidine hydrochloride.
^e 1-Benzyl-4-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-2-yl)methyl]piperidine hydrochloride.

SPECIFIC TESTS

- WATER DETERMINATION** (921): NMT 7.0%

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve in well-closed containers and store at controlled room temperature.
- USP REFERENCE STANDARDS** (11)
USP Donepezil Hydrochloride RS