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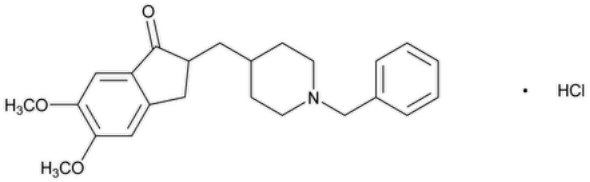
Donepezil Hydrochloride



$C_{24}H_{29}NO_3 \cdot HCl$ 415.95
$C_{24}H_{29}NO_3 \cdot HCl \cdot H_2O$ 433.97
5,6-Dimethoxyindan-1-one, 2-[(1-benzyl-4-piperidyl)methyl]-, (±)-, hydrochloride;
(±)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride CAS RN®: 120011-70-3; UNII: 3O2T2PJ89D.
Monohydrate CAS RN®: 884740-09-4.

DEFINITION

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

IDENTIFICATION

Change to read:

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

[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

Acceptance criteria: Meets the requirements

ASSAY

• **Procedure**

Buffer: 3.9 g/L of sodium 1-decane sulfonate in water

Mobile phase: Acetonitrile and *Buffer* (35:65). Adjust with perchloric acid to a pH of 1.8.

System suitability solution: 0.4 mg/mL of USP Donepezil Hydrochloride RS and 0.016 mg/mL of USP Donepezil Related Compound A RS prepared as follows. Dissolve suitable quantities of USP Donepezil Hydrochloride RS and USP Donepezil Related Compound A RS using 40% of the flask volume of methanol, and dilute with water to volume.

Standard solution: 0.4 mg/mL of USP Donepezil Hydrochloride RS in *Mobile phase*

Sample solution: 0.4 mg/mL of Donepezil Hydrochloride in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 271 nm

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

Column temperature: 35°

Flow rate: 1.4 mL/min

Injection volume: 20 µL

System suitability

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

[Note—Refer to *Table 1* under *Organic Impurities, Procedure 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between donepezil related compound A and donepezil, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) 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

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Organic Impurities, Procedure 1**

[Note—On the basis of the synthetic route, perform either *Procedure 1* or *Procedure 2*. *Procedure 2* is recommended if any of the impurities included in *Table 3* are potential related compounds.]

Mobile phase, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.8 µg/mL of USP Donepezil Hydrochloride RS in *Mobile phase*

System suitability

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

[Note—Refer to *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between donepezil related compound A and donepezil, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Donepezil Hydrochloride taken:

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

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)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[a]	0.33	0.2
Hydroxydonepezil[b]	0.54	0.2
Donepezil related compound A[c]	0.92	0.1
Donepezil hydrochloride	1.0	—
Any individual unspecified impurity	—	0.1
Total impurities	—	1.0

[a] 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.

[b] 2-[(1-Benzylpiperidin-4-yl)(hydroxy)methyl]-5,6-dimethoxyindan-1-one.

[c] (*E*)-2-[(1-Benzylpiperidin-4-yl)methylene]-5,6-dimethoxyindan-1-one.

• **Organic Impurities, Procedure 2**

Solution A: Add 1 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 6.6 ± 0.1. Pass through a filter of 0.45-µm or finer pore size.

Solution B: Acetonitrile

Mobile phase: See *Table 2*.

Table 2

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

[NOTE—The gradient was established on an HPLC system with a dwell volume of approximately 0.65 mL.]

Diluent: Acetonitrile and water (25:75)

System suitability solution: 1 mg/mL of USP Donepezil Hydrochloride RS and 0.002 mg/mL of USP Donepezil Related Compound A RS in *Diluent*

Sensitivity solution: 0.0015 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*

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

Sample solution: 1.0 mg/mL of Donepezil Hydrochloride in *Diluent*. Sonication may be used to aid the dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 286 nm

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

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between donepezil and donepezil related compound A, *System suitability solution*

Tailing factor: NMT 1.5 for donepezil, *Standard solution*

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

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

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 the corresponding impurity peak (see *Table 3*)

Acceptance criteria: See *Table 3*. Disregard peaks less than 0.03%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[a]	0.24	1.2	0.2
Donepezil alkene pyridine *N*-oxide[b]	0.32	2.3	0.15
Donepezil-*N*-oxide[c]	0.46	1.1	0.1
Donepezil pyridine analog (DPMI)[d]	0.52	1.4	0.15
3-Hydroxydonepezil[e]	0.59	1.0	0.15
Hydroxydonepezil[f]	0.68	0.86	0.2
Donepezil quaternary salt (donepezilbenzyl)[g]	0.77	0.74	0.15
Donepezil	1.0	—	—
Donepezil related compound A	1.08	3.4	0.1
Donepezil indene (dehydrodeoxy donepezil)[h]	1.63	2.2	0.15
Deoxydonepezil[i]	1.94	1.2	0.15
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	1.0

[a] 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.

[b] (*E*)-4-[(5,6-Dimethoxy-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl]pyridine 1-oxide.

[c] 1-Benzyl-4-[(5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl]piperidine 1-oxide.

[d] 5,6-Dimethoxy-2-(pyridin-4-ylmethyl)indan-1-one.

[e] 2-[(1-Benzylpiperidin-4-yl)methyl]-3-hydroxy-5,6-dimethoxy-1*H*-indan-one.

[f] 2-[(1-Benzylpiperidin-4-yl)(hydroxy)methyl]-5,6-dimethoxyindan-1-one.

[g] 1,1-Dibenzyl-4-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidinium.

[h] 1-Benzyl-4-[(5,6-dimethoxyinden-2-yl)methyl]piperidine.

[i] 1-Benzyl-4-[(5,6-dimethoxyindan-2-yl)methyl]piperidine.

SPECIFIC TESTS

• **Water Determination,** *Method Ia* ⟨921⟩

Acceptance criteria

Anhydrous form: NMT 0.4%

Anhydrous form-I: NMT 7.0%

Monohydrate form: NMT 7.0%

ADDITIONAL REQUIREMENTS

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

• **Labeling:** Where it is the anhydrous form-I or the hydrated form, the label so indicates. If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.

• **USP Reference Standards** ⟨11⟩

USP Donepezil Hydrochloride RS

USP Donepezil Related Compound A RS

(*E*)-2-[(1-Benzylpiperidin-4-yl)methylene]-5,6-dimethoxyindan-1-one.

$C_{24}H_{27}NO_3$ 377.48

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

Topic/Question	Contact	Expert Committee
DONEPEZIL HYDROCHLORIDE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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