Table 1 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
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.

Add the following:

•• **ORGANIC IMPURITIES, PROCEDURE 2**
Diluent: Acetonitrile and water (25:75)
Solution A: Add 1 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 6.5. 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

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 size: 20 µL
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
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the per centage 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 from *Table 3*

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time*	Relative Response Factor	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[a]	0.23	1.5	0.15
Donepezil pyridine analog (DPMI)[b]	0.49	1.9	0.15
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
Total impurities	—	—	0.5

* Relative retention times are based on 1-mL gradient delay volume.
[a] 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.
[b] 5,6-Dimethoxy-2-(pyridin-4-ylmethyl)indan-1-one.
[c] 1,1-Dibenzyl-4-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidinium.
[d] 1-Benzyl-4-[(5,6-dimethoxyinden-2-yl)methyl]piperidine.
[e] 1-Benzyl-4-[(5,6-dimethoxyindan-2-yl)methyl]piperidine.

● (RB 1-May-2011)

SPECIFIC TESTS

Change to read:

• **WATER DETERMINATION,** *Method Ia* ⟨**921**⟩**:** NMT 0.4% •for the anhydrous form; NMT 7.0% for the monohydrate form ●(RB 1-May-2011)

ADDITIONAL REQUIREMENTS
• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

Add the following:

•• **LABELING:** Label to indicate whether it is the monohydrate form. If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.● (RB 1-May-2011)

Change to read:

• **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.●(RB 1-May-2011)
$C_{24}H_{27}NO_3$ 377.48

Donepezil Hydrochloride Tablets

DEFINITION
Donepezil Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$).

IDENTIFICATION
• **A. ULTRAVIOLET ABSORPTION** ⟨**197U**⟩
Wavelength range: 220–360 nm
Sample solution: Crush a suitable number of T ablets, and transfer an amount of powder, equivalent to 10 mg of

donepezil hydrochloride, to a 100-mL volumetric flask. Add 80 mL of 0.1 N hydrochloric acid, and sonicate for 5 min. Cool the solution to room temperature, and dilute with 0.1 N hydrochloric acid to volume. Transfer a portion to a centrifuge tube, and centrifuge for 15 min. Transfer 5 mL of the clear supernatant to a 25-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume.

Analysis: Using a 1-cm cell, record the UV spectrum of the *Sample solution*.

Acceptance criteria: The solution exhibits absorption maxima at 230, 271, and 315 nm.

- **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**

Diluent: Methanol and 0.1 N hydrochloric acid (3:1)

Mobile phase: Dissolve 2.5 g of sodium decanesulfonate in 650 mL of water, and add 1.0 mL of perchloric acid and 350 mL of acetonitrile. If necessary, adjust with an additional 0.5 mL of perchloric acid to a pH of about 1.8.

System suitability solution: 0.2 mg/mL of USP Donepezil Hydrochloride RS and 0.008 mg/mL of USP Donepezil Related Compound A RS. [NOTE—Dissolve in 40% of the flask volume of methanol, swirl, and dilute with water to volume.]

Standard solution: 0.4 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*. [NOTE—Dissolve in 60% of the flask volume of *Diluent*, swirl, and dilute with *Diluent* to volume.]

Sample solution: 0.4 mg/mL of donepezil hydrochloride in *Diluent*. [NOTE—Dissolve a suitable number of Tablets in 75% of the flask volume of *Diluent*, and sonicate in an ultrasonic bath for 20 min. Swirl the mixture for 30 s, allow to cool to room temperature, and dilute with *Diluent* to volume. Add a magnetic bar to the flask, and mix for 10 min on a magnetic stirrer. Invert the flask at least 10 times to mix the contents, and then allow a few min for the solids to settle. Pass through a suitable filter, discarding the first 2–3 mL of filtrate.]

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 size: 20 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for donepezil related compound A and donepezil are about 0.92 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 1.5 between donepezil related compound A and donepezil, *System suitability solution*
Tailing factor: NMT 1.5 for the donepezil peak, *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 Tablets 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 = nominal concentration of donepezil hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 93.0%–107.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Diluent: Methanol and 0.1 N hydrochloric acid (3:1)
Mobile phase: Acetonitrile, water, and perchloric acid (350:650:1)
Standard stock solution: 1.1 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*. Dilute this solution with *Medium* to obtain a final concentration of 0.11 mg/mL.
Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of L/1000 mg/mL, where L is the Tablet label claim in mg.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45- µm pore size, discarding the first few mL of filtrate.
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: 1.0 mL/min
Injection size: 50 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Column efficiency: NLT 5000 theoretical plates
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of donepezil hydrochloride dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of donepezil hydrochloride is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

Organic Impurities

- **PROCEDURE**

Diluent, 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 *Diluent*
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for donepezil related compound A and donepezil are about 0.92 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 1.5 between donepezil related compound A and donepezil, *System suitability solution*
Relative standard deviation: NMT 8.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
[NOTE—Identify the impurities using the relative retention times given in *Impurity Table 1*.]
Calculate the percentage of any individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each 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 = nominal concentration of donepezil hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor (see *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[a]	0.33	1.0	0.5
Donepezil open ring[b]	0.70	0.6	0.5
Donepezil hydrochloride	1.0	—	—
Donepezil *N*-oxide[c]	1.2	1.0	0.5
Any individual unspecified degradation product	—	—	0.2

[a] 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.
[b] 2-(3-(1-Benzylpiperidin-4-yl)-2-oxopropyl)-4,5-dimethoxybenzoic acid.
[c] 2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dimethoxyindan-1-one *N*-oxide.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **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

Donepezil Hydrochloride Orally Disintegrating Tablets

DEFINITION

Donepezil Hydrochloride Orally Disintegrating Tablets contains NLT 93.0% and NMT 107.0% of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION** ⟨197U⟩
  Sample solution: Crush a suitable number of Tablets, and transfer an amount of powder, equivalent to 10 mg of donepezil hydrochloride, to a 100-mL volumetric flask. Add 80 mL of 0.1 N hydrochloric acid, and sonicate for 5 min. Cool to room temperature, and dilute with 0.1 N hydrochloric acid to volume. Transfer a portion to a centrifuge tube, and centrifuge for 15 min. Transfer 5 mL of the clear supernatant to a 25-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume.
  Analysis
  Wavelength range: 220–360 nm
  Acceptance criteria: 230, 271, and 315 nm
- **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**
  Diluent: Methanol and 0.1 N hydrochloric acid (3:1)
  Mobile phase: Dissolve 2.5 g of sodium decanesulfonate in 650 mL of water, and add 1.0 mL of perchloric acid and 350 mL of acetonitrile. If necessary, adjust with an additional 0.5 mL of perchloric acid to a pH of about 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 by dissolving in 40% of the flask volume of methanol and diluting with water to volume.
  Standard solution: 0.4 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*
  Sample solution: 0.4 mg/mL of donepezil hydrochloride in *Diluent*, prepared by transferring a suitable number of Tablets to an appropriate volumetric flask containing 10 mL of 0.1 N hydrochloric acid. Shake to disintegrate the Tablets. Add 60% of the flask volume of *Diluent*, sonicate for 10 min, allow to cool to room temperature, and dilute with *Diluent* to volume.
  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 size: 20 µL
  System suitability
  Samples: *System suitability solution* and *Standard solution*
  [NOTE—The relative retention times of donepezil related compound A and donepezil are about 0.92 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 1.5 between donepezil related compound A and donepezil, *System suitability solution*
  Tailing factor: NMT 1.5 for donepezil, *System suitability solution*
  Relative standard deviation: NMT 2.0%, *Standard solution*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of $C_{24}H_{29}NO_3 \cdot HCl$ in the portion of Tablets 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 = nominal concentration of donepezil hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 93.0%–107.0%

PERFORMANCE TESTS

- **DISINTEGRATION** ⟨701⟩
  Time: NMT 60 s
- **DISSOLUTION** ⟨711⟩
  Medium: 0.1 N hydrochloric acid; 900 mL
  Apparatus 2: 50 rpm
  Time: 30 min
  Diluent: Methanol and 0.1 N hydrochloric acid (3:1)
  Mobile phase: Acetonitrile, perchloric acid, and water (350:1:650)
  Standard stock solution: 1.1 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*. Dilute with *Medium* to obtain a concentration of 0.11 mg/mL.
  Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a concentration of L/1000 mg/mL, where L is the Tablet label claim in mg.
  Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45- µm pore size.