## Donepezil Hydrochloride Tablets

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In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Donepezil Hydrochloride Tablets monograph. The purpose for the revision is to add *Dissolution Test 5* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test. The revision also necessitates a change in the table numbering in the tests for *Organic Impurities, Procedure 1* and *Organic Impurities, Procedure 2*.

- *Dissolution Test 5* was validated using an XTerra RP18 brand of column with L1 packing. The typical retention time for donepezil is about 6 min.

The Donepezil Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison (301-998-6792 or hrj@usp.org).

# Donepezil Hydrochloride Tablets

## DEFINITION

Donepezil Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$).

## IDENTIFICATION

***Change to read:***

- **A. ▲SPECTROSCOPIC IDENTIFICATION TESTS ⟨197⟩,** *Ultraviolet-Visible Spectroscopy*: 197U▲ (CN 1-May-2020)
  **Wavelength range:** 220–360 nm
  **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 VS, and sonicate for 5 min. Cool the solution to room temperature, and dilute with 0.1 N hydrochloric acid VS to volume. Transfer a portion of this solution 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 VS 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 VS (75:25)
  **Mobile phase:** Dissolve 2.5 g of sodium 1-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:** Nominally 0.4 mg/mL of donepezil hydrochloride prepared as follows. 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. [NOTE—If necessary, add a magnetic stirring bar to the flask, and mix for 10 min on the magnetic stirrer, to aid in dissolution.] Allow a few min for the solids to settle. Pass through a suitable filter, discarding the first 2–3 mL of the 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 volume:** 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 the labeled amount 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:** 90.0%–110.0%

## PERFORMANCE TESTS

***Change to read:***

- **DISSOLUTION** ⟨711⟩
  **Test 1**
  **Medium:** 0.1 N hydrochloric acid VS; 900 mL
  **Apparatus 2:** 50 rpm
  **Time:** 30 min
  **Analytical procedure:** Determine the amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved, by using one of the following methods.
  **Chromatographic method**
  **Diluent:** Methanol and 0.1 N hydrochloric acid VS (75:25)
  **Mobile phase:** Acetonitrile, water, and perchloric acid (35: 65: 0.1)
  **Standard stock solution A:** 1.1 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*
  **Standard stock solution B:** 0.11 mg/mL of USP Donepezil Hydrochloride RS from *Standard stock solution A* in *Medium*
  **Standard solution:** (*L*/1000) mg/mL of USP Donepezil Hydrochloride RS from *Standard stock solution B* in *Medium*, where *L* is the label claim in mg/Tablet
  **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 the 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 volume:** 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 the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) 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

**Spectrometric method**

**Standard stock solution:** 0.11 mg/mL of USP Donepezil Hydrochloride RS in water

**Standard solution:** ($L$/900) mg/mL of USP Donepezil Hydrochloride RS from the *Standard stock solution* in *Medium*, where $L$ is the label claim in mg/Tablet

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

**Instrumental conditions**

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

**Mode:** UV

**Analytical wavelength:** 230 nm

**Blank:** *Medium*

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

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

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

**For Tablets which contain 23 mg of donepezil hydrochloride**

**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

**Medium:** pH 6.8 phosphate buffer; 900 mL

**Apparatus 2:** 50 rpm

**Times:** 1, 3, and 8 h

**Buffer:** 5.0 g/L of monobasic ammonium phosphate in water adjusted with phosphoric acid to a pH of 2.3

**Mobile phase:** Acetonitrile and *Buffer* (25:75)

**Standard stock solution:** 0.26 mg/mL of USP Donepezil Hydrochloride RS prepared as follows. Transfer a suitable quantity of USP Donepezil Hydrochloride RS to an appropriate volumetric flask. Add 70% of the flask volume of *Medium*. Sonicate to dissolve and dilute with *Medium* to volume.

**Standard solution:** ($L$/900) mg/mL of USP Donepezil Hydrochloride RS from *Standard stock solution* in *Medium*, where $L$ is the label claim in mg/Tablet. Pass the solution through a suitable filter, discarding the first 3 mL of the filtrate.

**Sample solution:** Pass a portion of the solution under test through a suitable filter, discarding the first 3 mL of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 210 nm

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

**Column temperature:** 35°

**Flow rate:** 1.5 mL/min

**Injection volume:** 50 µL

**Run time:** NLT 1.7 times the retention time of donepezil

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 1.5

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the concentration ($C_i$) of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) in the sample withdrawn from the vessel at each time point ($i$):

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

$r_U$ = peak response of donepezil from the *Sample solution*
$r_S$ = peak response of donepezil from the *Standard solution*
$C_S$ = concentration of USP Donepezil Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at each time point ($i$):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of donepezil hydrochloride in the portion of the sample withdrawn at the specified time point (mg/mL)
$V$ = volume of *Medium*, 900 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of the *Sample solution* withdrawn at each time point (mL)

**Tolerances:** See *Table 1*.

**Table 1**

| Time Point ($i$) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | NMT 20 |
| 2 | 3 | 35–60 |
| 3 | 8 | NLT 80 |

The percentages of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

**Medium:** pH 6.8 phosphate buffer; 900 mL

**Apparatus 2:** 50 rpm

**Times:** 1, 3, and 10 h

**Standard stock solution:** 0.25 mg/mL of USP Donepezil Hydrochloride RS prepared as follows. Transfer a suitable quantity of USP Donepezil Hydrochloride RS to an appropriate volumetric flask. Add 70% of the flask volume of water. Sonicate to dissolve and allow to cool to room temperature. Dilute with water to volume.

**Standard solution:** (*L*/900) mg/mL of USP Donepezil Hydrochloride RS from *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet
**Sample solution:** Pass a portion of the solution under test through a suitable filter.
**Instrumental conditions**
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
**Mode:** UV-Vis
**Analytical wavelength:** 315 nm
**Blank:** *Medium*
**System suitability**
**Sample:** *Standard solution*
**Suitability requirements**
**Relative standard deviation:** NMT 2.0%
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the concentration ($C_i$) of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) in the sample withdrawn from the vessel at each time point (*i*):

$$\text{Result}_i = (A_U/A_S) \times C_S$$

$A_U$ = absorbance of donepezil from the *Sample solution*
$A_S$ = absorbance of donepezil from the *Standard solution*
$C_S$ = concentration of USP Donepezil Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of donepezil hydrochloride in the portion of the sample withdrawn at the specified time point (mg/mL)
$V$ = volume of *Medium*, 900 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of the *Sample solution* withdrawn at each time point (mL)

**Tolerances:** See *Table 2*.

**Table 2**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | 10–30 |
| 2 | 3 | 33–53 |
| 3 | 10 | NLT 80 |

The percentages of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
**Medium:** 0.05 M sodium phosphate buffer, pH 6.8 [0.1 N hydrochloric acid VS and 76 g/L of tribasic sodium phosphate (25:75) adjusted with 2 N hydrochloric acid TS or 2 N sodium hydroxide TS to a pH of 6.8]; 900 mL, degassed
**Apparatus 2:** 50 rpm, with sinkers; see *Dissolution* ⟨711⟩, *Figure 2a*.
**Times:** 1, 3, and 8 h
**Buffer:** 1.36 g/L of monobasic potassium phosphate prepared as follows. To each 1 L of 1.36 g/L of monobasic potassium phosphate in water, add 3 mL of triethylamine and adjust with phosphoric acid to a pH of 2.8.
**Mobile phase:** Methanol and *Buffer* (47:53)
**Diluent:** Methanol and water (50:50)
**Standard stock solution:** 0.53 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*
**Standard solution:** 0.027 mg/mL of USP Donepezil Hydrochloride RS from *Standard stock solution* in *Medium*
**Sample solution:** Pass a portion of the solution under test through a suitable filter. Replace the portion removed with the same volume of *Medium*.
**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 268 nm
**Column:** 4.6-mm × 15-cm; 5-µm packing L7
**Flow rate:** 1.3 mL/min
**Injection volume:** 20 µL
**Run time:** NLT 1.7 times the retention time of donepezil
**System suitability**
**Sample:** *Standard solution*
**Suitability requirements**
**Tailing factor:** NMT 1.5
**Relative standard deviation:** NMT 1.0%
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the concentration ($C_i$) of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) in the sample withdrawn from the vessel at each time point (*i*):

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

$r_U$ = peak response of donepezil from the *Sample solution*
$r_S$ = peak response of donepezil from the *Standard solution*
$C_S$ = concentration of USP Donepezil Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$C_i$ = concentration of donepezil hydrochloride in the portion of the sample withdrawn at time point *i* (mg/mL)
$V$ = volume of *Medium*, 900 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

**Tolerances:** See *Table 3*.

**Table 3**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | 10–30 |
| 2 | 3 | 40–60 |
| 3 | 8 | NLT 80 |

The percentages of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 5:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

**Medium:** 0.05 M potassium phosphate buffer (6.8 g/L of monobasic potassium phosphate and 0.9 g/L of sodium hydroxide in water adjusted with dilute phosphoric acid in water or dilute sodium hydroxide in water to a pH of 6.80); 900 mL

**Apparatus 2:** 50 rpm, with suitable sinkers

**Times:** 1, 3, and 9 h

**Buffer:** 6.8 g/L of monobasic potassium phosphate in water; adjusted with phosphoric acid to a pH of 3.0

**Mobile phase:** Methanol and *Buffer* (40:60)

**Diluent:** Methanol and water (50:50)

**Standard stock solution:** 0.5 mg/mL of USP Donepezil Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Donepezil Hydrochloride RS to an appropriate volumetric flask and dissolve in 50% of the flask volume of *Diluent*. Sonicate for NLT 1 min to promote dissolution then dilute with *Diluent* to volume.

**Standard solution:** 0.025 mg/mL of USP Donepezil Hydrochloride RS from *Standard stock solution* in *Medium*

**Sample solution:** Pass a portion of the solution under test through a suitable filter discarding the first NLT 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:** 30°
**Flow rate:** 1 mL/min
**Injection volume:** 50 µL
**Run time:** NLT 1.5 times the retention time of donepezil

**System suitability**
**Sample:** *Standard solution*
**Suitability requirements**
**Tailing factor:** NMT 2.0
**Relative standard deviation:** NMT 2.0%

**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the concentration ($C_i$) of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) in the sample withdrawn from the vessel at each time point ($i$):

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

$r_U$ = peak response of donepezil from the *Sample solution*
$r_S$ = peak response of donepezil from the *Standard solution*
$C_S$ = concentration of USP Donepezil Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at each time point ($i$):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of donepezil hydrochloride in the portion of the sample withdrawn at the specified time point (mg/mL)
$V$ = volume of *Medium*, 900 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of the *Sample solution* withdrawn at each time point (mL)

**Tolerances:** See *Table 4*.

**Table 4**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | 15–35 |
| 2 | 3 | 40–60 |
| 3 | 9 | NLT 80 |

The percentages of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-May-2020)

- **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

## IMPURITIES

***Change to read:***

- **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 7*▲ (RB 1-May-2020) are potential degradation products.]

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

**Standard solution:** 0.0008 mg/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 ▲*Table 5*▲ (RB 1-May-2020).]
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 ▲*Table 5*▲ (RB 1-May-2020))

**Acceptance criteria:** See ▲*Table 5*.

**Table 5** ▲(RB 1-May-2020)

| 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.

***Change to read:***

- **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 6*.

**Table 6** ▲(RB 1-May-2020)

| 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:** Nominally 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**
**Sample:** *Standard solution*
**Suitability requirements**
**Tailing factor:** NMT 1.5
**Relative standard deviation:** NMT 2.0%, for five replicate injections
**Analysis**
**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each specified impurity or any individual degradation product 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 for the corresponding impurity peak from ▲*Table 7*▲ (RB 1-May-2020)

**Acceptance criteria:** See ▲*Table 7*.

**Table 7** ▲(RB 1-May-2020)

| Name | Relative Retention Time[a] | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| Desbenzyl donepezil[b] | 0.23 | 1.5 | 0.15 |
| Donepezil pyridine analog[c] | 0.49 | 1.9 | 0.15 |
| Donepezil quaternary salt[d] | 0.68 | 0.74 | 0.15 |
| Donepezil hydrochloride | 1.0 | 1.0 | — |
| Donepezil indene analog[e] | 1.7 | 2.2 | 0.15 |
| Deoxydonepezil[f] | 2.1 | 1.3 | 0.15 |
| Any individual degradation product | — | 1.0 | 0.1 |
| Total degradation products | — | — | 1.0 |

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

## ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **LABELING:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies. If a test for *Dissolution* other than *Test 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-dimeth oxyindan-1-one.
$C_{24}H_{27}NO_3$ 377.48