Amiodarone Hydrochloride Tablets

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Revision Bulletin

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29-Jan-2021

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1-Feb-2021

**Expert Committee**  
Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 2 Expert Committee has revised the Amiodarone 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 tests.

- *Dissolution Test 5* was validated using the Thermo Scientific Hypersil BDS C18 brand of column with L1 packing. The typical retention time for amiodarone is about 11.5 min.

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

Should you have any questions, please contact Yanyin Yang, Scientific Liaison (301-692-3623 or [yanyin.yang@usp.org](mailto:yanyin.yang@usp.org)).
Amiodarone Hydrochloride Tablets

**DEFINITION**
Amiodarone Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of amiodarone hydrochloride (C$_{25}$H$_{29}$I$_2$NO$_3$ · HCl).

**IDENTIFICATION**
- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

**ASSAY**
- **Procedure**
  - **Buffer:** Add 3 mL of acetic acid, glacial to 1 L of water. Adjust with ammonia water, 25 percent to a pH of 3.0.
  - **Mobile phase:** Acetonitrile and Buffer (40:60)
  - **Standard solution:** 0.1 mg/mL of USP Amiodarone Hydrochloride RS in Mobile phase
  - **Sample stock solution:** Nominally 1 mg/mL of amiodarone hydrochloride in Mobile phase prepared as follows. Transfer a quantity, equivalent to 100 mg of amiodarone hydrochloride, from NLT 20 finely powdered Tablets to a 100-mL volumetric flask. Add Mobile phase to about 50% of the final flask volume. Sonicate with occasional shaking to dissolve. Cool the solution and dilute with Mobile phase to volume.
  - **Sample solution:** Nominally 0.1 mg/mL of amiodarone hydrochloride in Mobile phase from Sample stock solution. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and collect the filtrate.

**Chromatographic system**
(See *Chromatography (621), System Suitability,* )
- **Mode:** LC
- **Detector:** UV 240 nm. For Identification B, use a diode array detector in the range of 200–400 nm.
- **Column:** 4.6-mm × 25-cm; 5-µm packing L1
- **Column temperature:** 30°
- **Flow rate:** 1 mL/min
- **Injection volume:** 10 µL
- **Run time:** NLT 2.5 times the retention time of amiodarone

**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 percentage of the labeled amount of amiodarone hydrochloride (C$_{25}$H$_{29}$I$_2$NO$_3$ · HCl) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

\[
r_U = \text{peak response of amiodarone from the Sample solution}
\]
$r_S$ = peak response of amiodarone from the Standard solution

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

$C_U$ = nominal concentration of amiodarone hydrochloride in the Sample solution (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution (711)**

Test 1

**Medium:** 1% (w/v) sodium dodecyl sulfate; 1000 mL

**Apparatus 2:** 100 rpm

**Time:** 60 min

**Standard stock solution:** 0.2 mg/mL of USP Amiodarone Hydrochloride RS prepared as follows. Transfer an appropriate quantity of USP Amiodarone Hydrochloride RS to a suitable volumetric flask and add methanol to 5% of the final flask volume. Sonicate to dissolve and dilute with Medium to volume.

**Standard solution:** 0.01 mg/mL of USP Amiodarone Hydrochloride RS in Medium from Standard stock solution

**Sample solution:** Dilute a portion of the solution under test with Medium to a concentration similar to that of the Standard solution. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and collect the filtrate.

**Instrumental conditions**

(See Ultraviolet-Visible Spectroscopy (857).)

**Mode:** UV

**Analytical wavelength:** 243 nm

**Cell:** 1 cm

**Blank:** Medium

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of amiodarone hydrochloride ($C_{25H_{29}I_2NO_3\cdot HCl}$) dissolved:

\[
\text{Result} = \left( \frac{A_U}{A_S} \right) \times C_S \times D \times V \times \left( \frac{1}{L} \right) \times 100
\]

$A_U$ = absorbance of amiodarone from the Sample solution

$A_S$ = absorbance of amiodarone from the Standard solution

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

$D$ = dilution factor for the Sample solution

$V$ = volume of Medium, 1000 mL

$L$ = label claim of amiodarone hydrochloride (mg/Tablet)

**Tolerances:** NLT 80% ($Q$) of the labeled amount of amiodarone hydrochloride ($C_{25H_{29}I_2NO_3\cdot HCl}$) is dissolved.

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

**Medium:** 0.2% (v/v) polysorbate 80 in 0.05 N hydrochloric acid prepared as follows. Add 26 mL of hydrochloric acid and 12 mL of polysorbate 80 to 6 L of deaerated water; 900 mL.

**Apparatus 2:** 75 rpm
**Time:** 30 min

**Standard solution:** 0.22 mg/mL of USP Amiodarone Hydrochloride RS prepared as follows. Transfer an appropriate quantity of USP Amiodarone Hydrochloride RS to a suitable volumetric flask, and add methanol to 20% of the final flask volume. Sonicate to dissolve and dilute with Medium to volume.

**Sample solution:** Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and collect the filtrate.

**Instrumental conditions**
- **Mode:** UV
- **Analytical wavelength:** 244 nm
- **Cell:** 0.1 cm
- **Blank:** Medium

**Analysis**
- **Samples:** Standard solution and Sample solution
  Calculate the percentage of the labeled amount of amiodarone hydrochloride \((C_{25}H_{29}I_2NO_3 \cdot HCl)\) dissolved:

\[
\text{Result} = \left( \frac{A_U}{A_S} \right) \times C_S \times V \times \frac{1}{L} \times 100
\]

- \(A_U\) = absorbance of amiodarone from the Sample solution
- \(A_S\) = absorbance of amiodarone from the Standard solution
- \(C_S\) = concentration of USP Amiodarone Hydrochloride RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(L\) = label claim of amiodarone hydrochloride (mg/Tablet)

**Tolerances:** NLT 75% \((Q)\) of the labeled amount of amiodarone hydrochloride \((C_{25}H_{29}I_2NO_3 \cdot HCl)\) is dissolved.

**Test 3:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.
- **Medium:** 1% (w/v) sodium dodecyl sulfate in acetate buffer prepared as follows. Dissolve 60 g of sodium dodecyl sulfate in about 5 L of water. Add 81.6 g of sodium acetate or 49.2 g of sodium acetate, anhydrous. Add 10 mL of acetic acid and adjust with acetic acid to a pH of 5.0. Dilute with water to 6 L; 900 mL.
- **Apparatus 2:** 100 rpm
- **Time:** 60 min

**Standard stock solution:** 0.5 mg/mL of USP Amiodarone Hydrochloride RS in methanol. Sonicate to dissolve if necessary.

**Standard solution:** 0.01 mg/mL of USP Amiodarone Hydrochloride RS in Medium from Standard stock solution

**Sample solution:** Pass a portion of the solution through a suitable filter. Dilute with Medium to a concentration similar to that of the Standard solution.

**Instrumental conditions**
- **Mode:** UV
- **Analytical wavelength:** 243 nm
- **Blank:** Medium

**Analysis**
- **Samples:** Standard solution and Sample solution
  Calculate the percentage of the labeled amount of amiodarone hydrochloride \((C_{25}H_{29}I_2NO_3 \cdot HCl)\) dissolved:
Result = \( \frac{A_U}{A_S} \times C_S \times D \times V \times \left( \frac{1}{L} \right) \times 100 \)

- \( A_U \) = absorbance of amiodarone from the Sample solution
- \( A_S \) = absorbance of amiodarone from the Standard solution
- \( C_S \) = concentration of USP Amiodarone Hydrochloride RS in the Standard solution (mg/mL)
- \( D \) = dilution factor for the Sample solution
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim of amiodarone hydrochloride (mg/Tablet)

**Tolerances:** NLT 70% (Q) of the labeled amount of amiodarone hydrochloride \((C_{25}H_{29}I_2NO_3\cdot HCl)\) is dissolved.

**Test 4:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4.

**Medium:** 1% (w/v) polysorbate 80 in acetate buffer prepared as follows. Dissolve 60 g of polysorbate 80 in about 5 L of water. Add 40.8 g of sodium acetate or 24.6 g of sodium acetate, anhydrous. Adjust with acetic acid to a pH of 4.0. Dilute with water to 6 L; 900 mL.

**Apparatus 1:** 50 rpm

**Time:** 60 min

**Standard stock solution:** 0.4 mg/mL of USP Amiodarone Hydrochloride RS prepared as follows. Transfer an appropriate quantity of USP Amiodarone Hydrochloride RS to a suitable volumetric flask and add methanol to 5% of the final flask volume. Sonicate to dissolve and dilute with Medium to volume.

**Standard solution:** 0.04 mg/mL of USP Amiodarone Hydrochloride RS in Medium from Standard stock solution

**Sample solution:** Pass a portion of the solution through a suitable filter. Dilute with Medium to a concentration similar to that of the Standard solution.

**Instrumental conditions**

- **Mode:** UV
- **Analytical wavelength:** 303 nm
- **Blank:** Medium

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of amiodarone hydrochloride \((C_{25}H_{29}I_2NO_3\cdot HCl)\) dissolved:

\[
\text{Result} = \left( \frac{A_U}{A_S} \right) \times C_S \times D \times V \times \left( \frac{1}{L} \right) \times 100
\]

- \( A_U \) = absorbance of amiodarone from the Sample solution
- \( A_S \) = absorbance of amiodarone from the Standard solution
- \( C_S \) = concentration of USP Amiodarone Hydrochloride RS in the Standard solution (mg/mL)
- \( D \) = dilution factor for the Sample solution
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim of amiodarone hydrochloride (mg/Tablet)

**Tolerances:** NLT 70% (Q) of the labeled amount of amiodarone hydrochloride \((C_{25}H_{29}I_2NO_3\cdot HCl)\) is dissolved.

**Test 5:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 5.
Medium: 1% (w/v) polysorbate 80 in pH 4.0 acetate buffer prepared as follows. Dissolve 3.0 g of sodium acetate and 6 mL of acetic acid, glacial in 1 L of water. Adjust with acetic acid, glacial to a pH of 4.0 if needed. To 20% of this solution, add 10 g of polysorbate 80 and sonicate to dissolve. Combine the resulting solution with the remaining quantity; 900 mL.

**Apparatus 1:** 75 rpm

Time: 30 min

**Solution A:** Dissolve 5.0 mL of triethylamine in 1000 mL of water.

**Mobile phase:** Acetonitrile, methanol, and Solution A (37.5: 37.5: 25). Adjust with phosphoric acid to a pH of 6.5.

**Diluent:** Acetonitrile and water (25:75)

**Standard stock solution:** 0.22 mg/mL of USP Amiodarone Hydrochloride RS in Medium. Sonicate to dissolve as needed.

**Standard solution:** 0.022 mg/mL of USP Amiodarone Hydrochloride RS from Standard stock solution in Diluent

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size. Dilute with Diluent to a concentration similar to that of the Standard solution.

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

**Mode:** LC

**Detector:** UV 240 nm

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

**Column temperature:** 40°

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 1.3 times the retention time of amiodarone.

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

- **Tailing:** NMT 2.0
- **Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of amiodarone hydrochloride (C_{25}H_{29}I_{2}NO_{3}·HCl) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times D \times V \times \left( \frac{1}{L} \right) \times 100
\]

- \( r_U \) = peak response of amiodarone from the Sample solution
- \( r_S \) = peak response of amiodarone from the Standard solution
- \( C_S \) = concentration of USP Amiodarone Hydrochloride RS in the Standard solution (mg/mL)
- \( D \) = dilution factor for the Sample solution
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim of amiodarone hydrochloride (mg/Tablet)

**Tolerances:** NLT 80% \((Q)\) of the labeled amount of amiodarone hydrochloride (C_{25}H_{29}I_{2}NO_{3}·HCl) is dissolved.▲ (RB 1-Feb-2021)

- **Uniformity of Dosage Units** (905): Meet the requirements
IMPURITIES

• Organic Impurities

Buffer: Add 3 mL of acetic acid, glacial to 800 mL of water. Adjust with 10% (v/v) ammonium hydroxide solution to a pH of 4.9. Dilute with water to 1000 mL.

Mobile phase: Acetonitrile, methanol, and Buffer (40:30:30)

Diluent: Acetonitrile and water (50:50)

Standard solution: 0.01 mg/mL of USP Amiodarone Hydrochloride RS in Diluent

Sensitivity solution: 0.3 µg/mL of USP Amiodarone Hydrochloride RS in Diluent from Standard solution

Sample solution: Nominally 1 mg/mL of amiodarone hydrochloride in Diluent prepared as follows. Transfer a quantity equivalent to 50 mg of amiodarone hydrochloride from NLT 20 finely powdered Tablets to a 50-mL volumetric flask. Add Diluent to 50% of the final flask volume. Sonicate with occasional shaking to dissolve. Cool the solution and dilute with Diluent to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and collect the filtrate.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 240 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 1.7 times the retention time of amiodarone for the Standard solution; NLT 3.4 times the retention time of amiodarone for the Sample solution

System suitability

Samples: Standard solution and Sensitivity solution

Suitability requirements

Relative standard deviation: NMT 10.0%, Standard solution

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

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of amiodarone related compound D or any unspecified degradation product in the portion of Tablets taken:

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

- \(r_U\) = peak response of amiodarone related compound D or any unspecified degradation product from the Sample solution

- \(r_S\) = peak response of amiodarone from the Standard solution

- \(C_S\) = concentration of USP Amiodarone Hydrochloride RS in the Standard solution (mg/mL)

- \(C_U\) = nominal concentration of amiodarone hydrochloride in the Sample solution (mg/mL)

- \(F\) = relative response factor (see Table 1)

Acceptance criteria: See Table 1. The reporting threshold is 0.03%.

Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Relative Retention Time</td>
<td>Relative Response Factor</td>
<td>Acceptance Criteria, NMT (%)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------</td>
<td>----------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Amiodarone related compound A&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.22</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Amiodarone related compound D&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.29</td>
<td>0.90</td>
<td>0.5</td>
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<tr>
<td>Amiodarone</td>
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<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>1.00</td>
<td>0.2</td>
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<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> (2-Butylbenzofuran-3-yl){4-[2-(diethylamino)ethoxy]phenyl}methanone.

<sup>b</sup> Process impurity included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total degradation products for the drug product.

<sup>c</sup> (2-Butylbenzofuran-3-yl)(4-hydroxy-3,5-diiodophenyl)methanone.

<sup>d</sup> (2-Butylbenzofuran-3-yl){4-[2-(diethylamino)ethoxy]-3-iodophenyl}methanone.

### ADDITIONAL REQUIREMENTS
- **Packaging and Storage:** Preserve in tight and light-resistant containers, and store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- **USP Reference Standards (11):**
  - USP Amiodarone Hydrochloride RS

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**Page Information:**
Not Applicable

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