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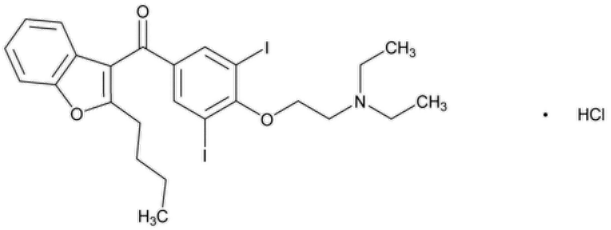
Amiodarone Hydrochloride



$C_{25}H_{29}I_2NO_3 \cdot HCl$ 681.77

Methanone, (2-butyl-3-benzofuranyl)[4-[2-(diethyl amino)ethoxy]-3,5-diiodophenyl]- hydrochloride;

2-Butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride CAS RN®: 19774-82-4; UNII: 976728SY6Z.

2-Butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone CAS RN®: 1951-25-3; UNII: N3RQ532IUT.

DEFINITION

Amiodarone Hydrochloride contains NLT 98.5% and NMT 101.0% of $C_{25}H_{29}I_2NO_3 \cdot HCl$, calculated on the dried basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K
- **B. Identification Tests—General, *Chloride* ⟨191⟩:** Meets the requirements

ASSAY

- **Procedure**

Buffer: Dissolve 6.80 g of monobasic potassium phosphate in 900 mL of water, and add 1.0 mL of triethylamine. Adjust with phosphoric acid to a pH of 6.00 ± 0.05, and dilute with water to 1000 mL.

Diluent: Acetonitrile and water (1:1)

Mobile phase: Acetonitrile and *Buffer* (1:1)

Standard stock solution: 0.5 mg/mL of USP Amiodarone Hydrochloride RS in methanol

Standard solution: 0.1 mg/mL USP Amiodarone Hydrochloride RS in *Diluent* from *Standard stock solution*

Sample stock solution: 0.5 mg/mL of Amiodarone Hydrochloride in methanol

Sample solution: 0.1 mg/mL of Amiodarone Hydrochloride in *Diluent* from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 3.9-mm × 15-cm; 5-µm packing L26

Flow rate: 1.5 mL/min

Injection size: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{25}H_{29}I_2NO_3 \cdot HCl$ in the portion of Amiodarone Hydrochloride taken:

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

r_U = peak response of amiodarone in the *Sample solution*

r_S = peak response of amiodarone in 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: 98.5%–101.0%, on the dried basis

IMPURITIES

Inorganic Impurities

- **Residue on Ignition ⟨281⟩:** NMT 0.1% on a 1-g sample

Organic Impurities

[Note—The product meets the requirements for both *Procedure 1* and *Procedure 2*.]

- **Procedure 1**

Potassium iodobismuthate solution: Dissolve 100 g of tartaric acid in 400 mL of water, and add 8.5 g of bismuth subnitrate. Shake for 1 h, add 200 mL of a 400 g/L solution of potassium iodide, and shake well. Allow to stand for 24 h, filter, and protect from light.

Standard solution A: 0.02 mg/mL of USP Amiodarone Related Compound H RS in methylene chloride

Standard solution B: *Standard solution A* and *Sample solution* (1:1).

Sample solution: 100 mg/mL of Amiodarone Hydrochloride in methylene chloride

Chromatographic system

(See *Chromatography ⟨621⟩, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: Suitable layer of chromatographic silica gel and fluorescent indicator with maximum absorbance at 254 nm

Application volume

Standard solution A: 50 µL

Standard solution B: 100 µL

Sample solution: 50 µL

Developing solvent system: Methylene chloride, methanol, and anhydrous formic acid (17:2:1)

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Develop the plate in the *Developing solvent system* until the solvent front has moved NLT two-thirds the length of the plate, and dry in a current of cold air. Spray the plate with *Potassium iodobismuthate solution* and then with 3% hydrogen peroxide solution. Examine immediately in daylight: the spot from *Standard solution B* due to amiodarone related compound H is clearly visible.

Acceptance criteria: Any spot with the same R_F as the spot due to amiodarone related compound H from the *Sample solution* is not more intense than the spot from *Standard solution A* (0.02%).

- **Procedure 2**

Buffer: Add 3 mL of glacial acetic acid to 800 mL of water. Adjust with diluted ammonia solution to a pH of 4.9, and dilute with water to 1000 mL.

Mobile phase: Acetonitrile: methanol: *Buffer* (4:3:3 v/v/v).

Diluent: Acetonitrile and water (1:1)

Standard stock solution: Dissolve equal quantities of USP Amiodarone Related Compound D RS, USP Amiodarone Related Compound E RS, and USP Amiodarone Hydrochloride RS in a known amount of methanol.

Standard solution: 0.01 mg/mL each of USP Amiodarone Related Compound D RS, USP Amiodarone Related Compound E RS, and USP Amiodarone Hydrochloride RS, in *Diluent* from *Standard stock solution*

Sample solution: 5 mg/mL of Amiodarone Hydrochloride in *Diluent*

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 size: 10 µL

Run time: 2 times the retention time of amiodarone

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 3.5 between amiodarone related compound D and amiodarone related compound E

Analysis

[Note—Disregard any peak that is less than 0.05%.]

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Amiodarone Hydrochloride taken:

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

r_U = peak response of each impurity in the *Sample solution*

r_S = peak response of amiodarone in 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

Individual impurities: See *Impurity Table I*.

Total impurities: NMT 0.5%

Impurity Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Amiodarone related compound A[a]	0.26	0.2
Amiodarone related compound D[b]	0.29	0.2
Amiodarone related compound E[c]	0.37	0.2
Amiodarone related compound B[d]	0.49	0.2
Amiodarone related compound C[e]	0.55	0.2
Amiodarone related compound G[f]	0.62	0.2
Amiodarone related compound F[g]	0.69	0.2
Amiodarone hydrochloride	1.00	—
Any other individual impurity	—	0.10

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

[b] (2-Butylbenzofuran-3-yl)(4-hydroxy-3,5-diiodophenyl)methanone.

[c] (2-Butylbenzofuran-3-yl)(4-hydroxyphenyl)methanone.

[d] (2-Butylbenzofuran-3-yl){4-[2-(ethylamino)ethoxy]-3,5-diiodophenyl}methanone.

[e] (2-Butylbenzofuran-3-yl){4-[2-(diethylamino)ethoxy]-3-iodophenyl}methanone.

[f] [2-[(1*RS*)-1-Methoxybutyl]benzofuran-3-yl][4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone.

[g] (2-Butylbenzofuran-3-yl)(4-hydroxy-3-iodophenyl)methanone.

SPECIFIC TESTS

• **Limit of Iodides**

Solution A: Add 1.50 g of Amiodarone Hydrochloride to 40 mL of water at 80°, and shake until completely dissolved. Cool, and dilute with water to 50.0 mL.

Standard solution: To 15.0 mL of *Solution A* add 1.0 mL of 0.1 M hydrochloric acid, 1.0 mL of an 88.2 mg/L solution of potassium iodide, and 1.0 mL of 0.05 M potassium iodate. Dilute with water to 20.0 mL. Allow to stand protected from light for 4 h.

Sample solution: To 15.0 mL of *Solution A* add 1.0 mL of 0.1 M hydrochloric acid and 1.0 mL of 0.05 M potassium iodate. Dilute with water to 20.0 mL. Allow to stand protected from light for 4 h.

Analysis: Measure the absorbances of the *Standard solution* and the *Sample solution* at 420 nm, using a mixture of 15.0 mL of *Solution A* and 1.0 mL of 0.1 M hydrochloric acid diluted with water to 20.0 mL to serve as the blank. The absorbance of the *Sample solution* is NMT half the absorbance of the *Standard solution*.

Acceptance criteria: NMT 150 ppm

• **pH** ⟨791⟩**:** 3.2–3.8. Dissolve 1 g of Amiodarone Hydrochloride in water by heating at 80°. Cool, and dilute with water to 20 mL.

• **Loss on Drying** ⟨731⟩**:** Use 1 g of sample, and dry under vacuum (NMT 0.3 kPa) at 50° for 4 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in light-resistant, tight containers. Store at controlled room temperature.

Change to read:

- **USP Reference Standards ⟨11⟩**

USP Amiodarone Hydrochloride RS

USP Amiodarone Related Compound D RS

(2-Butylbenzofuran-3-yl)(4-hydroxy-3,5-diiodophenyl) methanone.

$C_{19}H_{16}I_2O_3$ 546.14

USP Amiodarone Related Compound E RS

(2-Butylbenzofuran-3-yl)(4-hydroxyphenyl) methanone.

$C_{19}H_{18}O_3$ 294.34

USP Amiodarone Related Compound H RS

2-Chloro-*N*,*N*-diethylethanamine ▲hydrochloride▲ (ERR 1-Dec-2020) ·

$C_6H_{14}ClN$▲ · HCl 172.09▲ (ERR 1-Dec-2020)

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

Topic/Question	Contact	Expert Committee
AMIODARONE HYDROCHLORIDE	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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