Apparatus 1: 100 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_7H_7NO_3$ dissolved, employing the procedure set forth in the *Assay*, making any necessary modifications.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_7H_7NO_3$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Limit of *m*-aminophenol—

Mobile phase and *Internal standard solution*—Prepare as directed in the *Assay* under *Aminosalicylic Acid*.

Standard solution and *Chromatographic system*—Prepare as directed in the test for *Limit of m-aminophenol* under *Aminosalicylic Acid*.

Test solution—Use the *Assay preparation*, prepared as directed in the *Assay*.

Procedure—Proceed as directed for *Procedure* in the test for *Limit of m-aminophenol* under *Aminosalicylic Acid*. Calculate the percentage of *m*-aminophenol, in relation to the quantity of aminosalicylic acid in the portion of T ablets taken by the formula:

$$100(C / W)(R_U / R_S)$$

in which *C* is the concentration, in µg per mL, of USP *m*-Aminophenol RS in the *Standard solution; W* is the quantity of aminosalicylic acid, in mg, in the portion of T ablets taken, as determined in the *Assay;* and R_U and R_S are the ratios of the response of the *m*-aminophenol peak to the response of the sulfanilamide peak obtained from the *Test solution* and the *Standard solution*, respectively: not more than 1.0% of *m*-aminophenol is found.

Assay—

Mobile phase, Internal standard solution, Standard preparation, and *Chromatographic system*—Prepare as directed in the *Assay* under *Aminosalicylic Acid*.

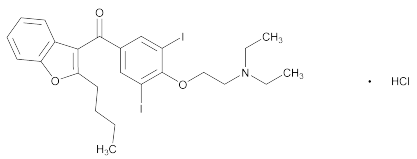
Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg of aminosalicylic acid, to a 100-mL low-actinic volumetric flask. Add 50 mL of *Mobile phase*, and shake for about 5 minutes. Dilute with *Mobile phase* to volume, and mix. Filter, and transfer 10.0 mL of the clear filtrate to a 100-mL low-actinic volumetric flask containing 10.0 mL of *Internal standard solution*, dilute with *Mobile phase* to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Aminosalicylic Acid*. Calculate the quantity, in mg, of aminosalicylic acid ($C_7H_7NO_3$) in the portion of T ablets taken by the formula:

$$1000C(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of USP Aminosalicylic Acid RS in the *Standard preparation;* and R_U and R_S are the ratios of the response of the aminosalicylic acid peak to the response of the acetaminophen peak obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Amiodarone Hydrochloride



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

Methanone, (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]- hydrochloride;
2-Butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride [19774-82-4].
2-Butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone [1951-25-3].

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. Infrared Absorption** ⟨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
- **Heavy Metals**

Buffer: Dissolve 25.0 g of ammonium acetate in 25 mL of water, and add 38.0 mL of 70% hydrochloric acid. Adjust, if necessary, with diluted hydrochloric acid or diluted ammonia solution to a pH of 3.5. Dilute with water to 100.0 mL.
Lead standard stock solution (1000 ppm Pb): 1.6 mg/mL of lead nitrate in water
Lead standard solution: 10 ppm of lead in water from *Lead standard stock solution*. [Note—Prepare immediately before use.]

Phenolphthalein solution: Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol, and dilute with water to 100 mL.

Thioacetamide solution: Prepare a solution of 40 g/L of thioacetamide in water. To 0.2 mL of the freshly prepared solution, add 1 mL of a mixture of 85% glycerol, 1 M sodium hydroxide, and water (4:3:1). Heat in a water bath for 20 s.

Sample solution: Place about 1 g of Amiodarone Hydrochloride in a silica crucible along with 4 mL of magnesium sulfate solution (250 g/L of diluted sulfuric acid). Mix using a fine glass rod, and heat cautiously. If the mixture is a liquid, evaporate gently to dryness on a water bath. Progressively heat to ignition, and continue heating until an almost white or a mostly grayish residue is obtained. Carry out the ignition at a temperature not exceeding 800°. Allow to cool. Moisten the residue with a few drops of dilute sulfuric acid. Evaporate, ignite again, and allow to cool. The total period of ignition must not exceed 2 h. Dissolve the residue in two portions, 5 mL each, of 20% hydrochloric acid. Add 0.1 mL of *Phenolphthalein solution* followed by 25% ammonia water until a pink color is obtained. Cool, add glacial acetic acid until the solution is decolorized, and add 0.5 mL in excess. Filter if necessary, wash the filter, and dilute with water to 20 mL.

Standard solution: Proceed as directed for *Sample solution*, using 2 mL of *Lead standard solution* instead of Amiodarone Hydrochloride. To 10 mL of the solution obtained, add 2 mL of the *Sample solution*.

Monitor solution: Proceed as directed for *Sample solution*, adding 2 mL of *Standard solution* to 1 g of Amiodarone Hydrochloride.

Blank solution: 10 mL of water and 2 mL of *Sample solution*

Analysis

Samples: *Standard solution*, *Sample solution*, *Blank solution*, and *Monitor solution*

To 12 mL each of the *Standard solution*, *Sample solution*, *Blank solution*, and *Monitor solution* add 2 mL of *Buffer solution*, and mix. Add 1.2 mL of *Thioacetamide solution*, and immediately mix again. Examine the solutions after 2 min. The test is invalid if the *Standard solution* does not show a slight brown color compared to the *Blank solution* or if the *Monitor solution* is not comparable with the *Standard solution*.

Acceptance criteria: Any brown color in the *Sample solution* is not more intense than that in the *Standard solution* (20 ppm). [NOTE—If the result is difficult to judge, pass the solutions through a membrane filter having a porosity of 3 µm. Carry out the filtration slowly and uniformly, applying moderate and constant pressure. Compare the spots on the filters obtained from the different solutions.]

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: 0.5-mm 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 *Standard solution B* 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.

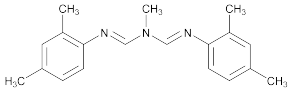
SPECIFIC TESTS

- **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 ser ve 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 dr y 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.
- **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.
  $C_6H_{14}ClN$ 135.64

Amitraz



$C_{19}H_{23}N_3$ 293.41
Methanimidamide, *N*′-(2,4-dimethylphenyl)-[[*N*-(2,4-dimethylphenyl)imino]methyl-*N*]-methyl-.
N-Methyl-*N*′-2,4-xylyl-*N*-(*N*-2,4-xylylformimidoyl)formamidine.
N-Methylbis(2,4-xylyliminomethyl)amine [33089-61-1].

» Amitraz contains not less than 95.0 per cent and not more than 101.5 per cent of $C_{19}H_{23}N$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩**—**
USP Amitraz RS

Labeling—Label it to indicate that it is for veterinar y use only.

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: Proceed as directed in the test for *Related compounds*, except to prepare a test solution of Amitraz in toluene containing 2 mg per mL and a *Standard solution* of USP Amitraz RS in toluene containing 2 mg per mL: the R_F value of the principal spot in the chromatogram obtained from the test solution corresponds to that in the chromatogram obtained from the *Standard solution*.

C: The retention time of the major peak in the chromatogram of the *Reference solution* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Water, *Method I* ⟨921⟩: not more than 0.1%, anhydrous pyridine being used in place of methanol in the titration vessel.

Residue on ignition ⟨281⟩: not more than 0.2%.

Related compounds—Prepare a test solution of Amitraz in toluene containing 100 mg per mL. Prepare a solution of USP Amitraz RS in toluene having a concentration of 2.0 mg per mL (*Standard solution 1*). Prepare a solution of 2,4-dimethylaniline in toluene having a concentration of 0.30 mg per mL (*Standard solution 2*). Prepare a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture as follows. Stand the plate to a depth of 3.5 cm in a solution prepared by dissolving 35 g of acetamide in 100 mL of methanol, adding 100 mL of triethylamine, and diluting to 250 mL with methanol. Allow to stand the wet plate in a current of cold air for about 30 seconds. Immediately apply separately to the plate, at a level about 1 cm below the top of the impregnated zone, 2 µL each of the test solution, *Standard solution 1*, and *Standard solution 2*. Promptly develop the chromatogram in a solvent system consisting of a mixture of cyclohexane, ethyl acetate, and triethylamine (5:3:2) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, allow it to air-dr y, and examine it under short-wavelength UV light. Any secondar y spot in the chromatogram obtained from the test solution is not more intense than the spot in the chromatogram obtained from *Standard solution 1* (2.0%). Expose the plate to the vapor of hydrochloric acid for about 10 minutes, then expose it to the vapor of nitrogen dioxide (prepared by the reaction of nitric acid and zinc) for 10 minutes, remove any excess nitric oxide by air exhaust, and spray the plate with a 0.5% solution of *N*-(1-naphthyl)ethylenediamine dihydrochloride in methanol, and examine the plate. Any secondary spot in the chromatogram obtained from the test solution corresponding to 2,4-dimethylaniline is not more intense than the spot in the chromatogram obtained from *Standard solution 2* (0.30%).