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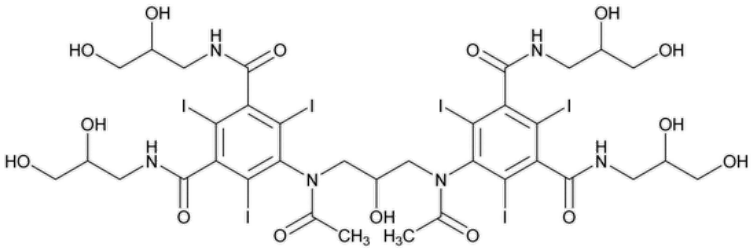
Iodixanol



$C_{35}H_{44}I_6N_6O_{15}$ 1550.18

1,3-Benzenedicarboxamide, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(acetylimino)]bis[*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-;
5,5'-[(2-Hydroxytrimethylene)bis(acetylimino)]bis[*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide] CAS RN®: 92339-11-2; UNII: HW8W27HTXX.

DEFINITION

Iodixanol contains NLT 98.6% and NMT 101.0% of iodixanol ($C_{35}H_{44}I_6N_6O_{15}$), calculated on the anhydrous basis.

IDENTIFICATION

• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**

• **B.** The retention times of the three principal peaks of the *Sample solution* correspond to those of the *Identification solution*, as obtained in the test for *Limit of Iodixanol Related Compound E and Iodixanol Impurity H*. [Note—A third isomer may appear as a minor peak.]

ASSAY

• **Procedure**

Sample solution: Transfer 500 mg of Iodixanol to a glass-stoppered, 125-mL conical flask. Add 25 mL of 1.25 N sodium hydroxide and 500 mg of powdered zinc. Connect the flask to a reflux condenser, and reflux for 1 h. Cool the flask to room temperature, rinse the condenser with 20 mL of water, disconnect the flask from the condenser, and pass the mixture through a filter. Rinse the flask and the filter thoroughly with small portions of water, adding the rinsings to the filtrate. Add 5 mL of glacial acetic acid.

Titrimetric system

(See *Titrimetry* ⟨541⟩.)

Mode: Direct titration

Titrant: 0.1 N silver nitrate VS

Endpoint detection: Potentiometric

Analysis

Sample: *Sample solution*

Titrate the *Sample solution* with the *Titrant*.

Calculate the percentage of iodixanol ($C_{35}H_{44}I_6N_6O_{15}$) in the portion of Iodixanol taken:

$$\text{Result} = [(V \times N \times F)/W] \times 100$$

V = sample titrant volume (mL)

N = *Titrant* normality (meq/mL)

F = equivalent weight of iodixanol, 258.4 mg/meq

W = weight of iodixanol (mg)

Acceptance criteria: 98.6%–101.0% on the anhydrous basis

IMPURITIES

• **Limit of Free Iodide**

Sample solution: 5 g of Iodixanol in 30 mL of water

Titrimetric system

(See *Titrimetry ⟨541⟩*.)

Mode: Direct titration

Titrant: 0.001 N silver nitrate VS

Endpoint detection: Potentiometric

Analysis

Calculate the percentage of free iodide in the portion of Iodixanol taken:

$$\text{Result} = [(V \times N \times F)/W] \times 100$$

V = sample titrant volume (mL)

N = *Titrant* normality (meq/mL)

F = equivalent weight of iodide, 0.1269 mg/meq

W = weight of iodixanol (mg)

Acceptance criteria: NMT 0.001%

• **Limit of Ionic Compounds**

[Note—Rinse all glassware with water.]

Standard solution: 4 µg/mL of sodium chloride in water

Sample solution: 2 g of Iodixanol in 100 mL of water

Acceptance criteria: The specific conductance in the *Sample solution* is NMT that of the *Standard solution* (equivalent to NMT 0.02% of ionic compounds, as sodium chloride).

• **Limit of Free Aromatic Amine**

Solution A: 3 mg/mL of *N*-(1-naphthyl)ethylenediamine dihydrochloride in a mixture of propylene glycol and water (70:30)

Blank solution: Add 15 mL of water to a 25-mL volumetric flask.

Standard stock solution: 10 µg/mL of USP Iohexol Related Compound B RS in water

Standard solution: Transfer 10.0 mL of the *Standard stock solution* and 5 mL of water to a 25-mL volumetric flask.

Sample solution: Transfer 200 mg of Iodixanol to a 25-mL volumetric flask, and add 15 mL of water.

Instrumental conditions

Mode: UV-Vis

Analytical wavelength: 495 nm

Cell: 5 cm

Analysis

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

Treat the *Samples* as follows. Place the flask in an ice bath for 5 min. Add 1.5 mL of 6 N hydrochloric acid, and mix by swirling. Add 1.0 mL of sodium nitrite solution (20 mg/mL), and allow to stand in the ice bath for 4 min. Remove the flask from the ice bath, add 1.0 mL of sulfamic acid solution (40 mg/mL), and swirl gently until gas evolution ceases. [**Caution—**Considerable pressure is produced.] Add 1.0 mL of *Solution A*, dilute with water to volume, and allow to stand for 5 min.

Measure the absorbance of the *Standard solution* and the *Sample solution* against the *Blank solution*.

Acceptance criteria: The absorbance of the *Sample solution* is NMT that of the *Standard solution* (NMT 0.05% of free aromatic amine).

Change to read:

• **Limit of 2-Methoxyethanol**

Internal standard solution: 0.01 mg/mL of secondary butyl alcohol in water

Standard stock solution: 0.005 mg/mL of methanol and 0.01 mg▲/mL▲ (ERR 1-Mar-2022) each of isopropyl alcohol, secondary butyl alcohol, and 2-methoxyethanol in *Internal standard solution*

Standard solution: Transfer about 0.25 g of USP Iodixanol RS and 1.0 mL of *Standard stock solution* to a headspace vial and seal the vial with a septum and crimp cap.

Sample solution: Transfer about 0.25 g of Iodixanol and 1.0 mL of *Internal standard solution* to a headspace vial and seal the vial with a septum and crimp cap.

Chromatographic system

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

Mode: GC with suitable headspace autosampler

Detector: Flame ionization

Column: 0.53-mm × 30-m fused-silica; coated with a 1-µm phase G16

Temperatures

Autosampler: 105°

Needle: 130°–140°

Injection port: 150°

Detector: 200°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	—	40	3
40	8	100	1

Carrier gas: Helium

Flow rate: 11 mL/min

Injection volume: 1 mL of the headspace

System suitability

Sample: *Standard solution*

[NOTE—The typical relative retention times for methanol, isopropyl alcohol, secondary butyl alcohol, and 2-methoxyethanol are 0.5, 0.6, 1.0 and 1.9 respectively.]

Suitability requirements

Resolution: NLT 1.0 between methanol and isopropyl alcohol

Relative standard deviation: NMT 10.0% for the ratio of 2-methoxyethanol to internal standard

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the amount of 2-methoxyethanol in the portion of Iodixanol taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U)$$

R_U = peak response ratio of 2-methoxyethanol to the internal standard from the *Sample solution*

R_S = peak response ratio of 2-methoxyethanol to the internal standard from the *Standard solution*

C_S = concentration of 2-methoxyethanol in the *Standard solution* (µg/mL)

C_U = concentration of Iodixanol in *Sample solution* (g/mL)

Acceptance criteria: NMT 10 µg/g of 2-methoxyethanol

• **ORGANIC IMPURITIES**

Solution A: Water

Solution B: Acetonitrile and water (50:50)

System suitability solution: 0.25 mg/mL of USP Iodixanol RS, 0.0025 mg/mL of USP Iodixanol Related Compound C RS, and 0.005 mg/mL of USP Iodixanol Related Compound D RS in water

Sample solution: 2.5 mg/mL of Iodixanol in water

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	94	6

Time (min)	Solution A (%)	Solution B (%)
2	94	6
32	80	20
72	0	100
82	0	100

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

Use the chromatogram from the *System suitability solution* to identify the peaks based on the relative retention times given in *Table 3*.

Suitability requirements

Resolution: NLT 1.5 between the two peaks due to iodixanol related compound D

Peak-to-valley ratio: NLT 1.3 between the first iodixanol peak and iodixanol related compound C (first peak)

Analysis

Sample: *Sample solution*

[NOTE—If iodixanol related compound C is present, only the first and larger peak with a retention time of 1.04 relative to the main iodixanol peak is seen between the two principal iodixanol peaks; the second iodixanol related compound C peak co-elutes with iodixanol. The area of the first and larger peak corresponds to approximately 80% of the total area of iodixanol related compound C. Determine the peak area of the first peak by drawing a vertical line through the minimum before the peak and a horizontal baseline at the minimum after the peak.]

Calculate the percentage of each impurity in the *Sample solution*:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

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

r_T = sum of all peak responses greater than 0.05% of the principal peaks in the *Sample solution*

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. Disregard any impurity less than or equal to 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Iodixanol related compound D (first peak)	0.8	1.0	Sum of both peaks 0.1% if present
Iodixanol related compound D (second peak)	0.9	1.0	
Iodixanol (first peak)	1.0	—	—
Iodixanol related compound C (first peak)	1.04	0.76	0.4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Overalkylated impurities	1.3–1.7	1.0	(Sum of all) 1.0
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.5

- **Limit of Iodixanol Related Compound E and Iodixanol Impurity H**

Solution A: Acetonitrile and water (50:50)

Solution B: Acetonitrile

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	30	70
2	30	70
27	68	32

System suitability solution: 0.25 mg/mL of USP Iodixanol RS and 0.025 mg/mL of USP Iodixanol Related Compound E RS in water

Identification solution: 2.5 mg/mL of USP Iodixanol RS in water

Sample solution: 2.5 mg/mL of Iodixanol in water

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L8

Flow rate: 1.7 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

[Note—See *Table 5* for relative retention times.]

Suitability requirements

Resolution: NLT 5.0 between iodixanol related compound E (first peak) and iodixanol (first peak)

Analysis

Samples: *Identification solution* and *Sample solution*

[Note—Iodixanol related compound E exhibits two peaks, the second of which may partly overlap with one of iodixanol peaks; use only the area of the first and larger peak of iodixanol related compound E, which corresponds to approximately 60% of the total area of iodixanol related compound E.]

Use the chromatograms obtained from the *Identification solution* and *Sample solution* for *Identification* test *B*.

Calculate the percentage of iodixanol related compound E and iodixanol impurity H in the *Sample solution*:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

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

r_T = sum of all peak responses greater than 0.05% of the principal peaks in the *Sample solution*

F = relative response factor (see *Table 5*)

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Iodixanol related compound E (first peak)	0.7	0.58	Sum of both peaks 0.3
Iodixanol related compound E (second peak)	0.8	1.0	
Iodixanol (first peak)	1.0	—	—
Iodixanol impurity H[a]	1.4	1.0	0.6

[a] 5-[[3-[[3-[[[3-[[3-[[3,5-bis-[[[2,3-Dihydroxypropyl]amino]carbonyl]-2,4,6-triiodophenyl](acetylimino)]-2-hydroxypropyl](acetylimino)]-5-[[[2,3-dihydroxypropyl]amino]carbonyl]-2,4,6-triiodophenyl]carbonyl]amino]-2-hydroxypropyl]oxy]-2-hydroxypropyl](acetylimino)]-*N*,*N*'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzendicarboxamide.

SPECIFIC TESTS

• **Water Determination,** *Method I*⟨921⟩**:** NMT 4.0%

ADDITIONAL REQUIREMENTS

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

• **USP Reference Standards** ⟨11⟩

USP Iodixanol RS

USP Iodixanol Related Compound C RS

5-[Acetyl[3-[[3,5-bis[[(2,3-dihydroxypropyl)amino]carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]*N*,*N*'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide.

$C_{33}H_{42}I_6N_6O_{14}$ 1508.15

USP Iodixanol Related Compound D RS

5-[Acetyl(2-hydroxy-3-methoxypropyl)amino]-*N*,*N*'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide.

$C_{20}H_{28}I_3N_3O_9$ 835.16

USP Iodixanol Related Compound E RS

(5-{*N*-[3-(*N*-{3-Carbamoyl-5-[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl}acetamido)-2-hydroxypropyl]acetamido}-*N*1,*N*3-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide.

USP Iohexol Related Compound B RS

5-Amino-*N*,*N*'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide.

$C_{14}H_{18}I_3N_3O_6$ 705.02

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

Topic/Question	Contact	Expert Committee
IODIXANOL	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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