Iohexol

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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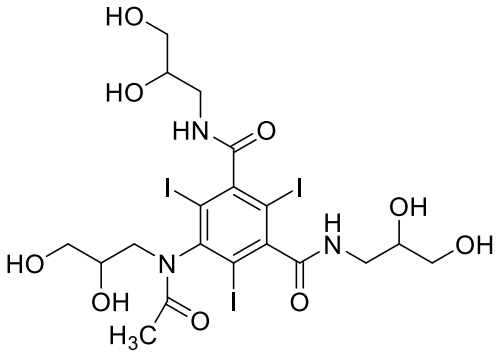
Iohexol



$C_{19}H_{26}I_3N_3O_9$ Mol. Wt. 821.1

Iohexol is 1,3-benzenedicarboxamide, 5-[acetyl(2,3-dihydroxypropyl)amino]-N,N′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo.

Iohexol contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{19}H_{26}I_3N_3O_9$, calculated on the anhydrous basis.

Category. Contrast agent.

Description. A white to off-white, hygroscopic powder.

Identification

A**.** Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *iohexol IPRS* or with the reference spectrum of iohexol.

B. In the Related substances, the principal peak in the chromatogram obtained with the test solution corresponds to the principal peak in the chromatogram obtained with the reference solution.

Tests

Colour of Solution. When examined the absorbance at about 400 nm, at about 420 nm and at about 450 nm (2.4.7), a 64.72 per cent w/v solution shows the absorbance about 0.180, 0.030 and 0.015, respectively.

Limit of ionic compounds. Not more than 0.01 per cent ionic compound as *sodium chloride*.

NOTE- Rinse all glassware five times with distilled water.

Test solution. Dissolve 1 g of substance under examination in 50.0 ml of *water*.

Reference solution. A 0.0002 per cent w/v solution of *sodium chloride* in *water*.

The specific conductance of the test solution is not more than that of the reference solution.

Limit of free iodide. Not more than 0.001 per cent.

Dissolve 5.0 g of the substance under examination in 20 ml of *water*. Titrate with *0.001 M silver nitrate*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.001 M silver nitrate* is equivalent to 0.0001269 g of *iodide*.

Limit of 2-methoxyethanol. Not more than 0.0002 per cent, determined by gas chromatography (2.4.13).

Internal standard solution. A 0.001 per cent w/v solution of *secondary butyl alcohol* in *water*.

Test solution. Transfer 0.25 g of the substance under examination to a headspace vial, add 1.0 ml of the internal standard solution and seal the vial with a septum and crimp cap.

Reference solution (a). A 0.001 per cent w/v solution of *2-methoxyethanol* in the internal standard solution.

Reference solution (b). Transfer 0.25 g of *iohexol IPRS* to a head space vial, add 1.0 ml of reference solution (a) and seal the vial with a septum and crimp cap.

Reference solution (c). A solution containing 0.0005 per cent w/v of *methanol* and 0.001 per cent w/v, each of, *isopropyl alcohol* and *2-methoxyethanol* in internal standard solution.

Blank solution. Transfer 0.25 g of *iohexol IPRS* to a head space vial, add 1.0 ml of the internal standard solution and seal the vial with a septum and crimp cap.

Chromatographic system

– a fused silica column 30 m x 0.53 mm, packed with polyethylene glycol 20 M (film thickness 1.0 µm),
– temperature:
column. 40° for 3 minutes, 40° to 100° @ 8° per minute and hold for 1 minutes,
– autosampler: 105°,
– needle: 130°-140°,
– inlet port at 150° and detector at 200°,
– a flame ionisation detector,
– flow rate: 11 ml per minute, using helium as the carrier gas.

The relative retention times with reference to secondary butyl alcohol for methanol, isopropyl alcohol and 2-methoxyethanol are about 0.5, 0.6 and 1.9, respectively.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to methanol and isopropyl alcohol is not less than 1.0, and the relative standard deviation of the peak area ratio of 2-methoxyethanol to secondary butyl alcohol (internal standard) for replicate injections is not more than 10.0 per cent.

Inject reference solution (b) and the test solution.

Calculate the content of 2-methoxyethanol using ratio of the peak area of 2-methoxyethanol to that of peak area of secondary butyl alcohol (internal standard).

Limit of 3-chloropropane-1,2-diol. Determined by gas chromatography (2.4.13).

Test solution. Transfer 1 g of the substance under examination to a separator, add about 1 ml of *water* and dissolve. Extract with four quantities, each of 2 ml of *ethyl acetate*. Combine the extract and dry with *anhydrous sodium sulphate*. Filter, and wash the filter with a small amount of *ethyl acetate*. Combine the washings with the filtrate. Concentrate the combined extracts on a warm water bath, and stream of nitrogen, to a volume of 0.7 ml. Dilute with *ethyl acetate* to 1 ml.

Reference solution. A 0.0025 per cent w/v solution of *3-chloropropane-1,2-diol* in *ethyl acetate.*

Chromatographic system
– a fused silica capillary column 30 m × 0.32 mm, packed with 86 per cent methylpolysiloxane and 14 per cent cyanopropylphenyl (film thickness 1.0 µm),
– temperature:
column. 80° for 2 minutes, 80° to 275° @ 15° per minute and hold for 2 minutes,
– inlet port at 230° and detector at 250°,
– a flame ionisation detector,
– flow rate: 1 ml per minute, using helium as the carrier gas.
– injection volume: 2 µl.

The retention time of 3-chloropropane-1,2-diol peak is about 8 min.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 10.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of the principal peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.0025 per cent).

Limit of free aromatic amine.

Solution A. a 0.3 per cent w/v solution of *N-(1-naphthyl) ethylenediamine dihydrochloride* in a mixture of 70 volumes of *propylene glycol* and 30 volumes of *water*.

Test solution. Transfer 0.2 g of the substance under examination to a 25-ml volumetric flask, add 15 ml of *water* and mix to dissolve.

Reference solution. A 0.001 per cent w/v solution of *iohexol related compound B IPRS* (5-amino-N, N'-bis (2,3-dihydroxy propyl)-2,4.6-triiodo-1,3-benzenedicarbonamide) in *water.* Mix 10.0 ml of the solution with 5.0 ml of *water* in a 25-ml volumetric flask.

Blank solution. Transfer 15.0 ml of *water* to a 25-ml volumetric flask.

NOTE- In conducting the following steps, keep the flasks in iced water and protected as much as possible from light until all of the reagent have been added.

Place the three flasks containing respectively the test solution, the reference solution and the blank solution in iced water, protected from light for 5 minutes, add 1.5 ml of *6M hydrochloric acid* and mix by swirling. Add 1.0 ml of a 2 per cent w/v solution of *sodium nitrite*, mix and allow to stand for 4 minutes. Remove the flasks from ice bath, add 1.0 ml of a 4 per cent w/v solution of *sulphamic acid*, swirl gently until gas liberation has ceased and allow to stand for 1 minute (*NOTE- Considerable pressure is produced*). Add 1.0 ml of solution A, mix and dilute to volume with *water*, allow to stand for 5 minutes, simultaneously measure the absorbance at maximum at about 495 nm (2.4.7) of the reference solution and the test solution in 5 cm cells, using blank solution as compensation liquid. The absorbance of the test solution is not greater than that of the reference solution.

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 0.15 g of the substance under examination in *water* and dilute to 100.0 mL with *water*.

Reference solution. A solution containing 0.15 per cent w/v of *iohexol IPRS* and 0.0075 per cent w/v of *iohexol related compound A IPRS* in *water*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Inertsil ODS 3V),
- mobile phase: A. *acetonitrile*,
  B. *water*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	1	99
60	13	87
65	1	99
70	1	99

Name	Relative Retention time
Iohexol Related compound A[1]	0.85
Iohexol endo-isomer	0.96
Iohexol exo-isomer	1.0
O-alkylated compounds	1.1-1.4

[1]5-(Acetylamino)-N,N′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide.

NOTE: Iohexol may give two non-resolved peaks in the chromatogram due to endo-exo isomerism. In addition, a small peak (also due to iohexol) usually appears at the leading edge of the first principal peak. This small peak has a retention time about 1.2 min less than the first principal peak.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to iohexol related compound A and the exo-isomer (the second and greater peak) of iohexol is not less than 5.0.

Inject the test solution. The area of any peak due to *o*-alkylated compounds is not more than 0.6 per cent. The area of any other secondary peak is not more than 0.1 per cent and the sum of areas of all the secondary peaks other than *o*-alkylated compounds is not more than 0.3 per cent, calculated by area normalization.

Water (2.3.43). Not more than 4.0 per cent.

Assay. To 0.5 g in a 125-ml round-bottomed flask, add 25 ml of *1.25 M sodium hydroxide* and 0.5 g of *zinc powder* and a few glass beads. Boil under a reflux condenser for 60 minutes. Allow to cool and rinse the condenser with 20 ml of *water*, adding the rinsings to the flask. Filter through a sintered-glass filter and wash the filter with several quantities of *water*. Collect the filtrate and washings. Add 5.0 ml of *glacial acetic acid* and titrate immediately with

0.1 M silver nitrate. Determine the end-point potentiometrically (2.4.25), using a suitable electrode system such as silver-mercurous sulphate. Carry out a blank titration.

1 ml of *0.1 M silver nitrate* is equivalent to 0.02737 g of $C_{19}H_{26}I_3N_3O_9$.

Storage. Store protected from light and moisture at a temperature not exceeding 30°.

Solubility. Very soluble in *water* and in *methanol*; practically insoluble or insoluble in *ether* and in *chloroform*.