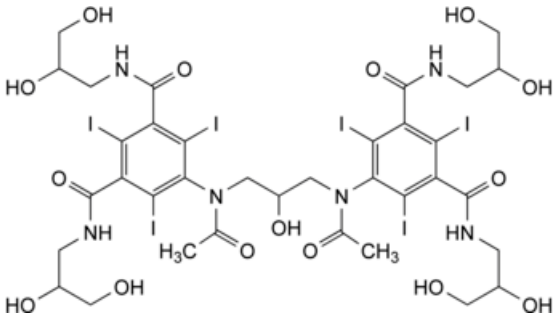
Edition: BP 2025 (Ph. Eur. 11.6 update)

Iodixanol

General Notices

(Ph. Eur. monograph 2215)



$C_{35}H_{44}I_6N_6O_{15}$ 1550 *92339-11-2*

Action and use

Iodinated contrast medium.

Ph Eur

DEFINITION

Mixture of stereoisomers of 5,5′-[(2-hydroxypropane-1,3-diyl)bis(acetylimino)]bis[*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide].

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder, hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *iodixanol CRS*.

B. Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications.

Injection Test solution and reference solution (b).

Results The 3 principal peaks in the chromatogram obtained with the test solution are similar in retention time to the 3 principal peaks in the chromatogram obtained with reference solution (b).

TESTS

Solution S

Dissolve 5.0 g in *water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Heat solution S at about 98 °C for 30 min without boiling, then allow to cool to room temperature. The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_7 (2.2.2, *Method II*).

Impurities E and H

Liquid chromatography (2.2.29).

Test solution Dissolve 0.250 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 5 mg of *iodixanol impurity H CRS* in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (c) Dissolve the contents of a vial of *iodixanol impurity E CRS* in a mixture of 100 µL of the test solution, 100 µL of reference solution (b) and 800 µL of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *aminopropylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *acetonitrile R*, *water for chromatography R* (50:50 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	30	70
2 - 27	30 → 68	70 → 32

Flow rate 1.7 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities E and H.

Relative retention With reference to iodixanol (1st peak) (retention time = about 16 min): impurity E (1st peak) = about 0.7; impurity E (2nd peak) = about 0.8; impurity H = about 1.4.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the 1st peak due to impurity E and the 1st peak due to iodixanol.

Limits:

— *correction factor*: for the calculation of the total content of impurity E, multiply the peak area of the 1st peak due to impurity E by 1.7;

— *impurity H*: not more than 0.6 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.6 per cent);

— *impurity E*: not more than 0.3 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.3 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.250 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*.

Reference solution (b) Dissolve 25 mg of *iodixanol CRS* in *water R* and dilute to 10 mL with the same solvent.

Reference solution (c) Dissolve 5 mg of *iodixanol impurity C CRS* and 5 mg of *iopentol CRS* in *water R* and dilute to 10 mL with the same solvent. Dilute 5 mL of this solution to 100 mL with *water R*.

Reference solution (d) Mix 5 mL of the test solution and 5 mL of reference solution (c) and dilute to 50 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water for chromatography R*;

— *mobile phase B*: *acetonitrile R*, *water for chromatography R* (50:50 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	94	6
2 - 32	94 → 80	6 → 20
32 - 72	80 → 0	20 → 100
72 - 82	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL of the test solution and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurity C and iopentol.

Relative retention With reference to iodixanol (1st peak) (retention time = about 27 min): iopentol (1st peak) = about 0.8; iopentol (2nd peak) = about 0.9; impurity C (1st peak) = about 1.04; overalkylated impurities (a group of peaks) = 1.33-1.70.

System suitability Reference solution (d):

— *resolution*: baseline separation between the 2 peaks due to iopentol;

— *peak-to-valley ratio*: minimum 1.3, where H_p = height above the baseline of the 1st peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the 1st peak due to iodixanol.

Limits:

— *correction factor*: for the calculation of the total content of impurity C, multiply the peak area of the 1st peak due to impurity C by 1.3;

— *impurity C*: not more than 0.4 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *overalkylated impurities (such as impurity I)*: not more than the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 1.5 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (1.5 per cent);

— *disregard limit*: 0.05 times the sum of the areas of the 2 principal peaks in the chromatogram obtained with reference solution (a) (0.05 per cent).

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

Free aromatic amine

Maximum 500 ppm.

Test solution Transfer 0.200 g of the substance to be examined to a 25 mL volumetric flask and dissolve in 15.0 mL of *water R*.

Reference solution Dissolve 5.0 mg of *iohexol impurity J CRS* in *water R* and dilute to 5.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *water R*. Mix 10.0 mL of this solution and 5.0 mL of *water R* in a 25 mL volumetric flask.

Blank solution Transfer 15.0 mL of *water R* to a 25 mL volumetric flask.

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

Place the 3 flasks containing respectively the test solution, the reference solution and the blank solution in iced water, protected from light, for 5 min. Add 1.5 mL of *hydrochloric acid R1* and mix by swirling. Add 1.0 mL of a 20 g/L solution of *sodium nitrite R*, mix and allow to stand for 4 min. Add 1.0 mL of a 40 g/L solution of *sulfamic acid R*, swirl gently until gas liberation has ceased and allow to stand for 1 min. (*CAUTION: considerable pressure is produced*). Add 1.0 mL of a freshly prepared 3 g/L solution of *naphthylethylenediamine dihydrochloride R* in a mixture of 30 volumes of *water R* and 70 volumes of *propylene glycol R* and mix. Remove the flasks from the iced water, dilute to 25.0 mL with *water R*, mix and examine the solutions after 5 min. The solution obtained from the test solution is less coloured than the solution obtained from the reference solution. If the solution obtained from the test solution is about the same colour or darker than the solution obtained from the reference solution, proceed as follows. Concomitantly determine the absorbance (*2.2.25*) at 495 nm of the solution obtained from the test solution and the reference solution in 5 cm cells, using the blank solution as the compensation liquid. The absorbance of the solution obtained from the test solution is not greater than that of the solution obtained from the reference solution.

Free iodine

Transfer 2.0 g to a glass-stoppered tube, add 20 mL of *water R*, 5 mL of *toluene R* and 5 mL of *dilute sulfuric acid R*, shake vigorously and allow the phases to separate: the toluene layer shows no red or pink colour.

Iodide

Maximum 10 ppm.

Dissolve 5.000 g in *water R* and dilute to 20.0 mL with the same solvent. Titrate with *0.001 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*) using a silver indicator electrode and an appropriate reference electrode.

1 mL of *0.001 M silver nitrate* is equivalent to 126.9 µg of iodide.

Ionic compounds (*2.2.38*)

Maximum 0.02 per cent *m/m* calculated as sodium chloride.

Rinse all glassware with distilled water R 5 times before use.

Test solution Dissolve 1.0 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution Dissolve 20.0 mg of *sodium chloride R* in *water R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Measure the specific conductivity of the test solution and the reference solution using a suitable conductivity meter. The specific conductivity of the test solution is not greater than that of the reference solution.

Water (*2.5.12*)

Maximum 4.0 per cent, determined on 0.500 g.

ASSAY

In a 125 mL round-bottomed flask, dissolve 0.200 g in 25 mL of a 50 g/L solution of *sodium hydroxide R*, add 0.5 g of *zinc powder R* and a few glass beads. Boil under a reflux condenser for 1 h. Allow to cool and rinse the condenser with 20 mL of *water R*, adding the rinsings to the flask. Filter through a sintered-glass filter (40) (*2.1.2*) and wash the filter with several quantities of *water R*. Collect the filtrate and washings. Add 5 mL of *glacial acetic acid R* and titrate immediately with *0.1 M silver nitrate*. Determine the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 25.84 mg of $C_{35}H_{44}I_6N_6O_{15}$.

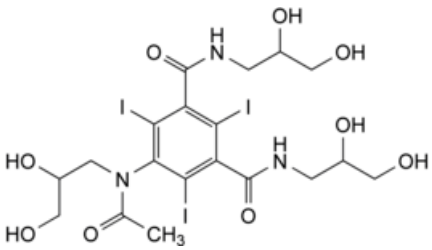
STORAGE

In an airtight container, protected from light.

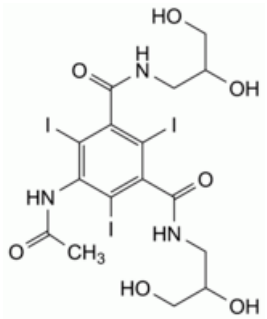
IMPURITIES

Specified impurities *C, E, H, overalkylated impurities.*

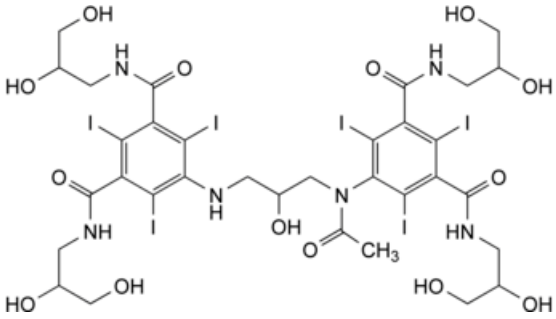
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, F, G.*



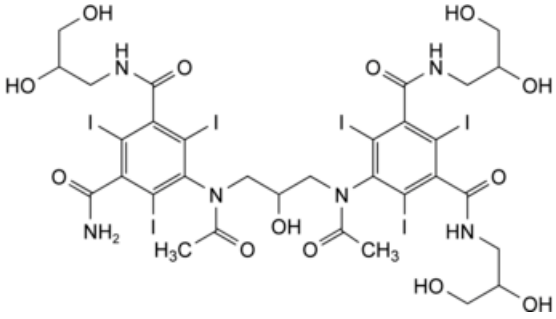
A. 5-[acetyl(2,3-dihydroxypropyl)amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide (iohexol),



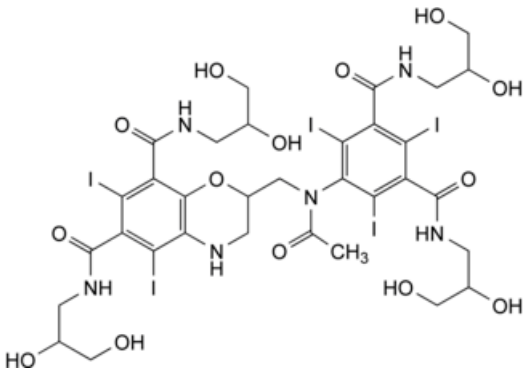
B. 5-acetamido-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



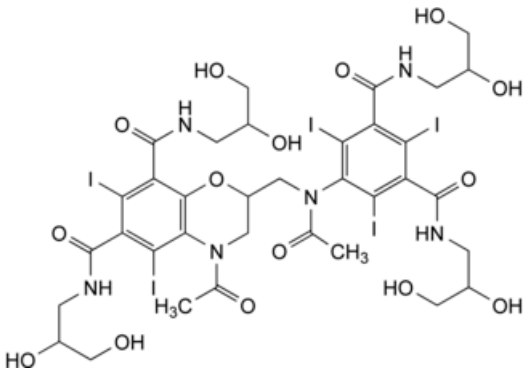
C. 5-[acetyl[3-[[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



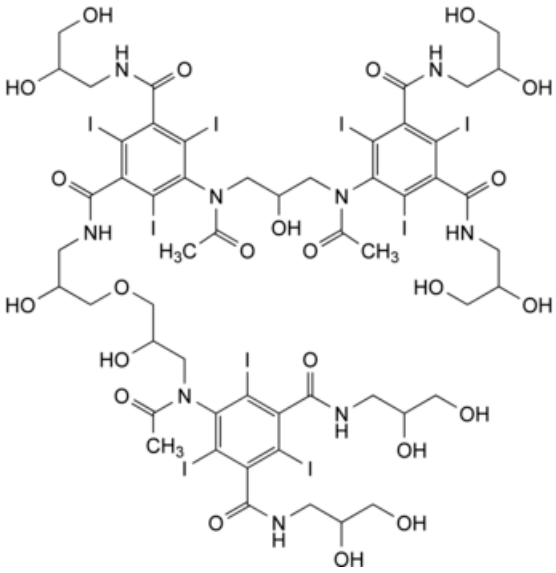
E. 5-[acetyl[3-[acetyl[3-carbamoyl-5-[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



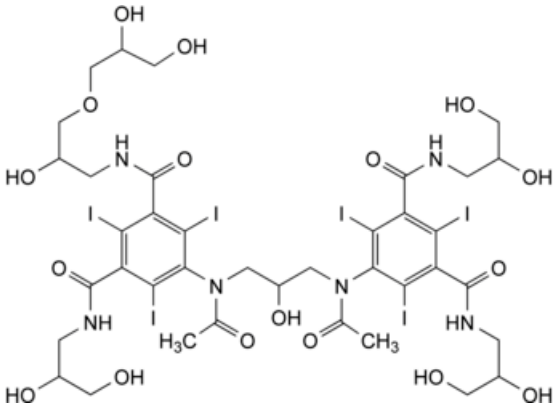
F. 2-[[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]methyl]-*N*,*N*′-bis(2,3-dihydroxypropyl)-5,7-diiodo-3,4-dihydro-2*H*-1,4-benzoxazine-6,8-dicarboxamide,



G. 4-acetyl-2-[[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]methyl]-*N*,*N*′-bis(2,3-dihydroxypropyl)-5,7-diiodo-3,4-dihydro-2*H*-1,4-benzoxazine-6,8-dicarboxamide,



H. 5-[acetyl[3-[acetyl[3-[[3-[3-[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropoxy]-2-hydroxypropyl]carbamoyl]-5-[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



I. overalkylated impurities (an example): 5-[acetyl[3-[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*-[3-(2,3-dihydroxypropoxy)-2-hydroxypropyl]-*N*′-(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide.
