STORAGE

Store in an airtight container, protected from light and at a temperature of – 70 °C.

01/2008:0031

IODINE

Iodum

I_2 M_r 253.8
[7553-56-2]

DEFINITION

Content: 99.5 per cent to 100.5 per cent of I.

CHARACTERS

Appearance: greyish-violet, brittle plates or fine crystals with a metallic sheen.

Solubility: very slightly soluble in water, very soluble in concentrated solutions of iodides, soluble in ethanol (96 per cent), slightly soluble in glycerol.

It volatilises slowly at room temperature.

IDENTIFICATION

A. Heat a few fragments in a test-tube. Violet vapour is evolved and a bluish-black crystalline sublimate is formed.

B. To a saturated solution add *starch solution R*. A blue colour is produced. Heat until decolourised. On cooling, the colour reappears.

TESTS

Solution S. Triturate 3.0 g with 20 mL of *water R*, filter, wash the filter with *water R* and dilute the filtrate to 30 mL with the same solvent. To the solution add 1 g of *zinc powder R*. When the solution is decolourised, filter, wash the filter with *water R* and dilute to 40 mL with the same solvent.

Bromides and chlorides: maximum 250 ppm.

To 10 mL of solution S add 3 mL of *ammonia R* and 6 mL of *silver nitrate solution R2*. Filter, wash the filter with *water R* and dilute the filtrate to 20 mL with the same solvent. To 10 mL of the solution add 1.5 mL of *nitric acid R*. After 1 min, any opalescence in the solution is not more intense than that in a standard prepared at the same time by mixing 10.75 mL of *water R*, 0.25 mL of *0.01 M hydrochloric acid*, 0.2 mL of *dilute nitric acid R* and 0.3 mL of *silver nitrate solution R2*.

Non-volatile substances: maximum 0.1 per cent.

Heat 1.00 g in a porcelain dish on a water-bath until the iodine has volatilised. Dry the residue at 100-105 °C. The residue weighs a maximum of 1 mg.

ASSAY

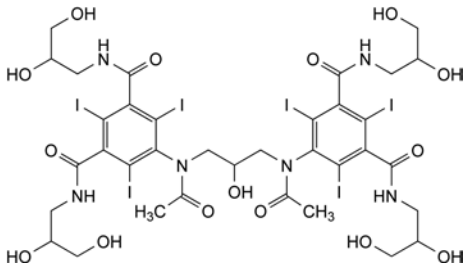
Introduce 0.200 g into a flask containing 1 g of *potassium iodide R* and 2 mL of *water R* and add 1 mL of *dilute acetic acid R*. When dissolution is complete, add 50 mL of *water R* and titrate with *0.1 M sodium thiosulfate*, using *starch solution R* as indicator.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 12.69 mg of I.

07/2010:2215

IODIXANOL

Iodixanolum



$C_{35}H_{44}I_6N_6O_{15}$ M_r 1550
[92339-11-2]

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 E CRS* and 5 mg of *iodixanol impurity H CRS* in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (c). Mix 5.0 mL of the test solution with 5.0 mL of reference solution (b) and dilute to 50.0 mL with *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 R* (50:50 *V/V*);
– *mobile phase B*: *acetonitrile R*;

Monographs I-L

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 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 10.0 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 10.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with *water R*.

Reference solution (d). Mix 5.0 mL of the test solution with 5.0 mL of reference solution (c) and dilute to 50.0 mL with *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

– *mobile phase A*: *water R*;

– *mobile phase B*: *acetonitrile R, water 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 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 with 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.

Heavy metals (*2.4.8*): maximum 10 ppm.

12 mL of solution S complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

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

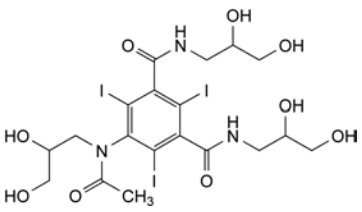
STORAGE

In an airtight container, protected from light.

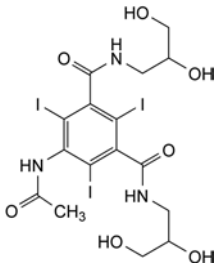
IMPURITIES

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

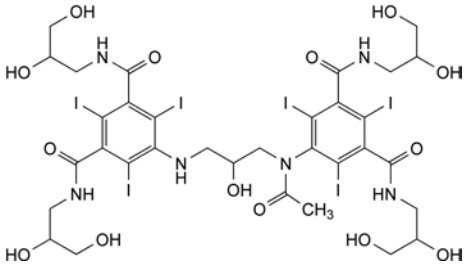
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities. It is therefore not necessary to identify these impurities for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



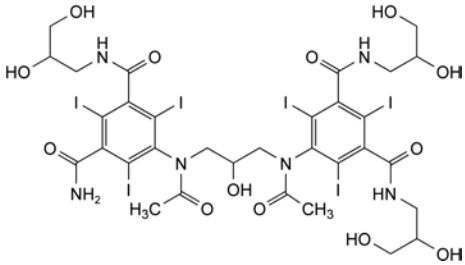
A. 5-[acetyl(2,3-dihydroxypropyl)amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide (iohexol),



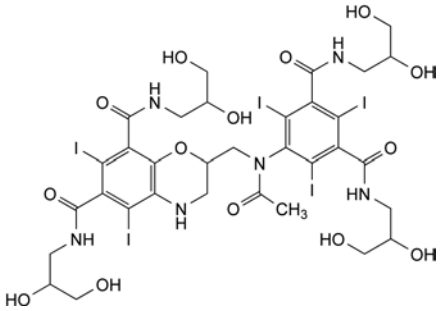
B. 5-acetamido-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



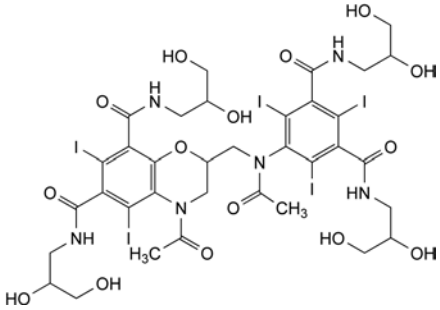
C. 5-[acetyl[3-[[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



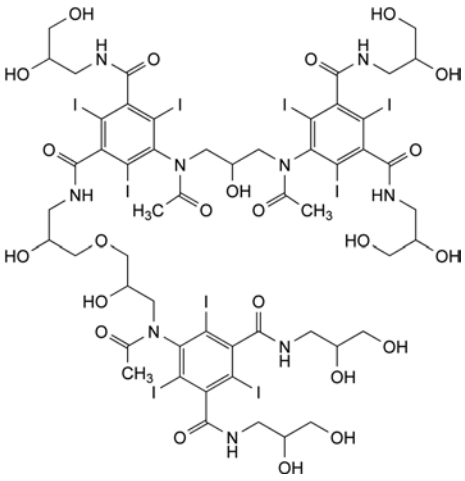
E. 5-[acetyl[3-[acetyl[3-carbamoyl-5-[(2,3-dihydroxypropyl)-carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]-amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide,



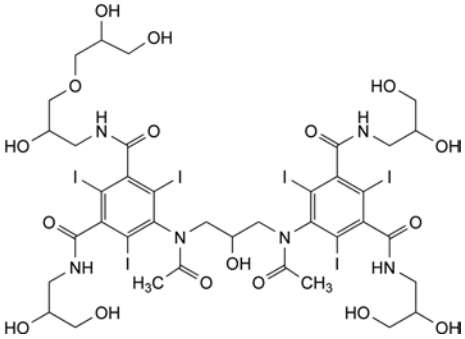
F. 2-[[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]methyl]-*N*,*N*′-bis(2,3-dihydroxypropyl)-5,7-diiodo-3,4-dihydro-2*H*-1,4-benzoxazine-6,8-dicarboxamide,



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.

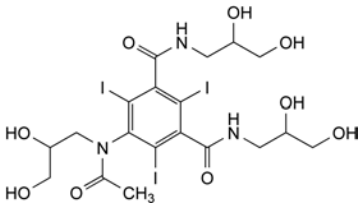


I. overalkylated impurities (an example): 5-[acetyl[3-[acetyl[3,5-bis[(2,3-dihydroxypropyl)carbamoyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*-[3-(2,3-dihydroxypropoxy)-2-hydroxypropyl]-*N*′-(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide.

01/2008:1114

IOHEXOL

Iohexolum



$C_{19}H_{26}I_3N_3O_9$ M_r 821
[66108-95-0]

DEFINITION

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

The substance is a mixture of diastereoisomers and atropisomers.

Content: 98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or greyish-white, hygroscopic powder.

Solubility: very soluble in water, freely soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *iohexol CRS*.

B. Examine the chromatograms obtained in test A for related substances (see Tests).

Results: the principal peaks in the chromatogram obtained with reference solution (b) are similar in retention time and size to the peaks due to iohexol in the chromatogram obtained with reference solution (a).

TESTS

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

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Related substances

A. Liquid chromatography (*2.2.29*).

NOTE: iohexol gives rise to 2 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 1st principal peak. This small peak has a retention time about 1.2 min less than the 1st principal peak.

Test solution. Dissolve 0.150 g of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a). Dissolve 15.0 mg of *iohexol CRS* and 15.0 mg of *iohexol impurity A CRS* in a mixture of 1-2 drops of *dilute sodium hydroxide solution R* and 10 mL of *water R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

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

Reference solution (c). Dissolve 5.0 mg of *iohexol for peak identification CRS* (containing impurities B, C, D and E) in *water R* and dilute to 5.0 mL with the same solvent.

Blank solution: *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

– *mobile phase A*: *water R*;
– *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 60	99 → 87	1 → 13
60 - 65	87 → 99	13 → 1

Flow rate: 1 mL/min.

Detection: spectrophotometer at 254 nm.

Equilibration: at the initial eluent composition for at least 10 min.

Injection: 10 µL.

Retention times: impurity A and impurity H = about 17 min; iohexol (peaks corresponding to *endo-exo* isomerism) = about 20 min.

System suitability: reference solution (a):

– *resolution*: minimum 5.0 between the peak due to impurity A and the 2nd and greater peak due to iohexol.

Limits:

– *sum of impurities B, C, D and E* (relative retention with reference to the 2nd and greater peak due to iohexol between 1.1 and 1.4): not more than 0.6 times the total area of the principal peaks in the chromatogram