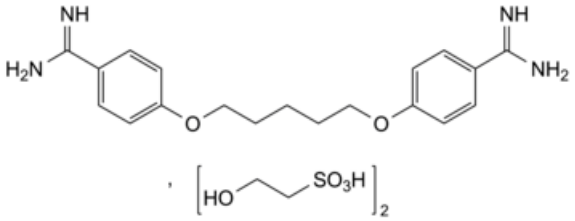
Edition: BP 2025 (Ph. Eur. 11.6 update)

Pentamidine Isetionate

General Notices

(Pentamidine Diisetionate, Ph. Eur. monograph 1137)



$C_{23}H_{36}N_4O_{10}S_2$ 592.7 *140-64-7*

Action and use

Antiprotozoal.

Preparation

Pentamidine Injection

Ph Eur

DEFINITION

4,4′-[Pentane-1,5-diylbis(oxy)]dibenzimidamide bis(2-hydroxyethanesulfonate).

Content

98.5 per cent to 101.5 per cent (dried substance).

PRODUCTION

It is considered that alkyl 2-hydroxyethanesulfonate esters are potential impurities in pentamidine diisetionate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation including, where necessary, demonstration that alkyl 2-hydroxyethanesulfonate esters are not detectable in the final product.

CHARACTERS

Appearance

White or almost white powder or colourless crystals, hygroscopic.

Solubility

Freely soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs.

Comparison *pentamidine diisetionate CRS*.

B. Dissolve about 40 mg in 5 mL of *water R* and add dropwise with shaking 1 mL of a 10 g/L solution of *sodium chloride R*. Allow to stand for 5 min. The mixture remains clear.
C. Treat 0.15 g by the oxygen-flask method (*2.5.10*). Use 10 mL of *dilute hydrogen peroxide solution R* to absorb the combustion products. The solution gives reaction (a) of sulfates (*2.3.1*).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent.

pH (*2.2.3*)

4.5 to 6.5.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dilute 2.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) To 0.1 g in a conical flask, add 40 mL of *water R* and glass beads. Adjust to pH 10.5 with *dilute sodium hydroxide solution R* and boil under reflux for 20 min. Cool and dilute to 50 mL with *water R*. Dilute 1 mL of the solution to 50 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase Mix 65 volumes of *methanol R* and 35 volumes of a 30 g/L solution of *ammonium acetate R* previously adjusted to pH 7.5 with *triethylamine R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 265 nm.

Injection 10 µL.

Run time 3.5 times the retention time of pentamidine.

System suitability Reference solution (b):

— the chromatogram obtained shows 2 principal peaks;

— *resolution*: minimum 2.0 between the 2 principal peaks.

Limits:

— *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Loss on drying (*2.2.32*)

Maximum 4.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

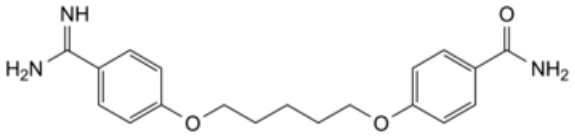
Dissolve 0.250 g in 50 mL of *dimethylformamide R*. Add 0.25 mL of *thymol blue solution R*. Titrate with 0.1 M tetrabutylammonium hydroxide, under a current of *nitrogen R*, until the colour of the indicator changes to blue. Carry out a blank titration.

1 mL of 0.1 M tetrabutylammonium hydroxide is equivalent to 29.63 mg of $C_{23}H_{36}N_4O_{10}S_2$.

STORAGE

In an airtight container.

IMPURITIES



A. 4-[[5-(4-amidinophenoxy)pentyl]oxy]benzenecarboxamide.