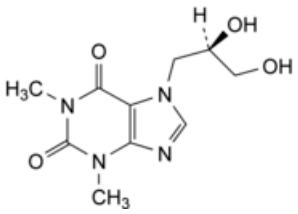
Edition: BP 2025 (Ph. Eur. 11.6 update)

Diprophylline

General Notices

(Ph. Eur. monograph 0486)



and enantiomer

$C_{10}H_{14}N_4O_4$ 254.2 *479-18-5*

Action and use

Non-selective phosphodiesterase inhibitor (xanthine); treatment of reversible airways obstruction.

Ph Eur

DEFINITION

7-[(2*RS*)-2,3-Dihydroxypropyl]-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).
Comparison: *diprophylline CRS*.

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.25 mL of *bromothymol blue solution R1*. The solution is yellow or green. Not more than 0.4 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50 mg of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b) Dissolve 5 mg of *etofylline CRS* (impurity C) in *water R* and dilute to 50 mL with the same solvent. Dilute 0.5 mL of the solution to 20 mL with the test solution.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R* (3 µm);

— *temperature*: 30 °C.

Mobile phase *methanol R*, *water for chromatography R* (10:90 *V/V*).

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 10 µL.

Run time 3 times the retention time of diprophylline.

Relative retention With reference to diprophylline (retention time = about 18 min): impurity C = about 1.1.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 5, where H_p = height above the baseline of the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to diprophylline.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides (*2.4.4*)

Maximum 400 ppm.

Dilute 2.5 mL of solution S to 15 mL with *water R*.

Loss on drying (*2.2.32*)

Maximum 0.5 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

In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached.

Dissolve 0.200 g in 3.0 mL of *anhydrous formic acid R* and add 50.0 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

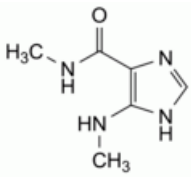
1 mL of *0.1 M perchloric acid* is equivalent to 25.42 mg of $C_{10}H_{14}N_4O_4$.

STORAGE

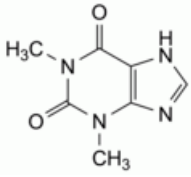
Protected from light.

IMPURITIES

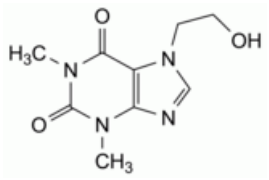
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). 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, C, D.



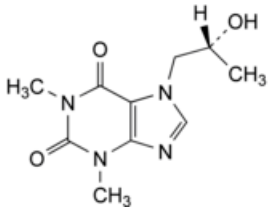
A. *N*-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide (theophyllidine),



B. 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (theophylline),



C. 7-(2-hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (etofylline),


and enantiomer

D. 7-[(2*RS*)-2-hydroxypropyl]-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (proxyphylline).

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