



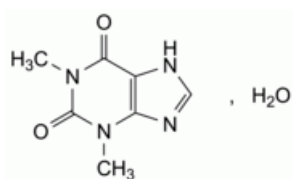
Edition: BP 2025 (Ph. Eur. 11.6 update)

Theophylline Hydrate



[General Notices](#)

(*Theophylline Monohydrate*, Ph. Eur. monograph 0302)



C₇H₈N₄O₂·H₂O 198.2 5967-84-0

Action and use

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

Preparations

[Aminophylline Injection](#)

[Theophylline Prolonged-release Tablets](#)

Ph Eur

DEFINITION

1,3-Dimethyl-3,7-dihydro-1*H*-purine-2,6-dione monohydrate.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, sparingly soluble in ethanol (96 per cent). It dissolves in solutions of alkali hydroxides, in ammonia and in mineral acids.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D, E.

A. Melting point ([2.2.14](#)): 270 °C to 274 °C, determined after drying at 100-105 °C.

B. Infrared absorption spectrophotometry ([2.2.24](#)).

Preparation Dry the substance to be examined at 100-105 °C before use.

Comparison [Ph. Eur. reference spectrum of theophylline](#).

C. Heat 10 mg with 1.0 mL of a 360 g/L solution of [potassium hydroxide R](#) in a water-bath at 90 °C for 3 min, then add 1.0 mL of [diazotised sulfanilic acid solution R](#). A red colour slowly develops. Carry out a blank test.

D. Water (see Tests).

E. It gives the reaction of xanthines ([2.3.1](#)).

TESTS

Solution S

Dissolve 0.5 g with heating in [carbon dioxide-free water R](#), cool and dilute to 75 mL with the same solvent.

Appearance of solution

Solution S is clear ([2.2.1](#)) and colourless ([2.2.2, Method II](#)).

Acidity

To 50 mL of solution S add 0.1 mL of [methyl red solution R](#). The solution is red. Not more than 1.0 mL of [0.01 M sodium hydroxide](#) is required to change the colour of the indicator to yellow.

Related substances

Liquid chromatography ([2.2.29](#)).

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 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) Dissolve 10 mg of [theobromine R](#) in the mobile phase, add 5 mL of the test solution and dilute to 100 mL with the mobile phase. Dilute 5 mL of this solution to 50 mL with the mobile phase.

Column:

— size: $l = 0.25$ m, $\varnothing = 4$ mm;

— stationary phase: [octadecylsilyl silica gel for chromatography R](#) (7 μ m).

Mobile phase Mix 7 volumes of [acetonitrile for chromatography R](#) and 93 volumes of a 1.36 g/L solution of [sodium acetate R](#) containing 5.0 mL/L of [glacial acetic acid R](#).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 20 μ L.

Run time 3.5 times the retention time of theophylline.

Relative retention With reference to theophylline (retention time = about 6 min): impurity C = about 0.3; impurity B = about 0.4; impurity D = about 0.5; impurity A = about 2.5.

System suitability Reference solution (b):

— **resolution**: minimum 2.0 between the peaks due to theobromine and theophylline.

Limits:

— **impurities A, B, C, D**: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— **any other impurity**: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— **total**: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 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).

Water (2.5.12)

8.0 per cent to 9.5 per cent, determined on 0.20 g.

Sulfated ash (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

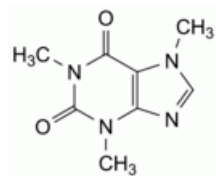
Dissolve 0.160 g in 100 mL of [water R](#), add 20 mL of [0.1 M silver nitrate](#) and shake. Add 1 mL of [bromothymol blue solution R1](#). Titrate with [0.1 M sodium hydroxide](#).

1 mL of [0.1 M sodium hydroxide](#) is equivalent to 18.02 mg of $C_7H_8N_4O_2$.

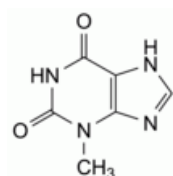
IMPURITIES

Specified impurities A, B, C, D.

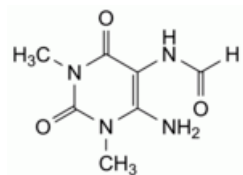
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph [Substances for pharmaceutical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



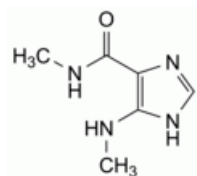
A. 1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (caffeine),



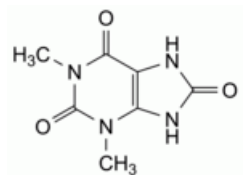
B. 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione,



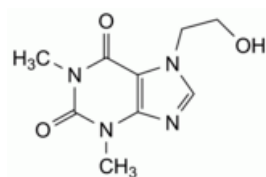
C. *N*-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,



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



E. 1,3-dimethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione,



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

Ph Eur