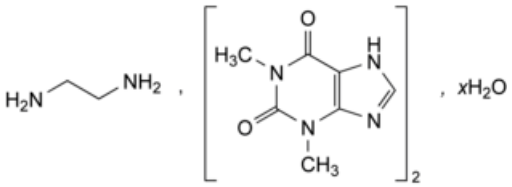
Edition: BP 2025 (Ph. Eur. 11.6 update)

Aminophylline Hydrate

General Notices

(Theophylline-Ethylenediamine Hydrate, Ph. Eur. monograph 0301)



$C_{16}H_{24}N_{10}O_4,xH_2O$ 420.4 (anhydrous substance) *72487-55-9*

Action and use

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

Preparations

Aminophylline Injection

Aminophylline Tablets

Aminophylline Prolonged-release Tablets

Ph Eur

DEFINITION

Content

— *theophylline* ($C_7H_8N_4O_2$; M_r 180.2): 84.0 per cent to 87.4 per cent (anhydrous substance);

— *ethylenediamine* ($C_2H_8N_2$; M_r 60.1): 13.5 per cent to 15.0 per cent (anhydrous substance).

It contains a variable quantity of water.

CHARACTERS

Appearance

White or slightly yellowish powder, sometimes granular.

Solubility

Freely soluble in water (the solution becomes cloudy through absorption of carbon dioxide), practically insoluble in anhydrous ethanol.

IDENTIFICATION

First identification: A, C, E.

Second identification: B, D, E.

Dissolve 1.0 g in 10 mL of *water R* and add 2 mL of *dilute hydrochloric acid R* dropwise with shaking. Filter. Use the precipitate for identification test A and the filtrate for identification test C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Precipitate, washed with *water R* and dried at 105 °C.

Comparison *theophylline CRS*.

B. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 0.2 g of the substance to be examined in 2 mL of *water R* with heating and dilute to 10 mL with *methanol R*.

Reference solution Dissolve 0.2 g of *theophylline CRS* in 2 mL of *water R* with heating and dilute to 10 mL with *methanol R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *concentrated ammonia R*, *acetone R*, *methylene chloride R*, *butanol R* (10:30:30:40 *V/V/V/V*).

Application 10 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. To the filtrate add 0.2 mL of *benzoyl chloride R*, make alkaline with *dilute sodium hydroxide solution R* and shake vigorously. Filter the precipitate, wash with 10 mL of *water R*, dissolve in 5 mL of hot *ethanol (96 per cent) R* and add 5 mL of *water R*. A precipitate is formed which, when washed and dried at 105 °C, melts (*2.2.14*) at 248 °C to 252 °C.
D. Dissolve 30 mg of the substance to be examined in 3 mL of *water R* and add 0.5 mL of a 10 g/L solution of *copper sulfate pentahydrate R*. A violet-purple colour is produced.
E. Water (see Tests).

TESTS

Appearance of solution

The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution GY_6 (*2.2.2, Method II*).

Dissolve 0.5 g with gentle warming in 10 mL of *carbon dioxide-free water R*.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50 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* (impurity G) 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, Ø = 4 mm;

— *stationary phase*: irregular *octadecylsilyl silica gel for chromatography R* (7 µm).

Mobile phase Mix 7 volumes of *acetonitrile R* and 93 volumes of a 1.36 g/L solution of *sodium acetate R* containing 0.50 per cent *V/V* of *glacial acetic acid R*.

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 272 nm.

Injection 20 µL.

Run time 3.5 times the retention time of theophylline.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity G.

Relative retention With reference to theophylline (retention time = about 6 min): impurity G = about 0.6.

System suitability Reference solution (b):

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

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 the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 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*)

3.0 per cent to 8.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Ethylenediamine

Dissolve 0.250 g in 30 mL of *water R*. Add 0.1 mL of *bromocresol green solution R*. Titrate with *0.1 M hydrochloric acid* until a green colour is obtained.

1 mL of *0.1 M hydrochloric acid* is equivalent to 3.005 mg of $C_2H_8N_2$.

Theophylline

Heat 0.200 g to constant mass in an oven at 135 °C. Dissolve the residue with heating in 100 mL of *water R*, allow to cool, 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*.

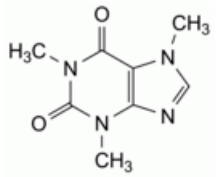
1 mL of *0.1 M sodium hydroxide* is equivalent to 18.02 mg of $C_7H_8N_4O_2$.

STORAGE

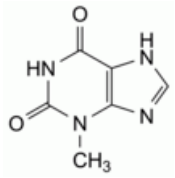
In a well-filled, airtight container, protected from light.

IMPURITIES

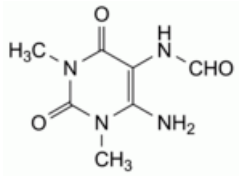
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



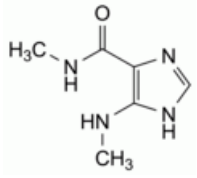
A. 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (caffeine),



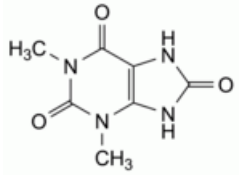
B. 3-methyl-3,7-dihydro-1*H*-purine-2,6-dione,



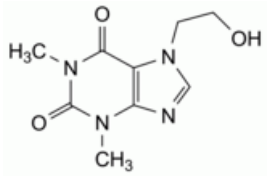
C. *N*-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,



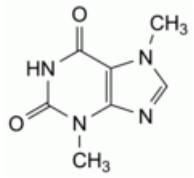
D. *N*-methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide,



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),



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

Ph Eur