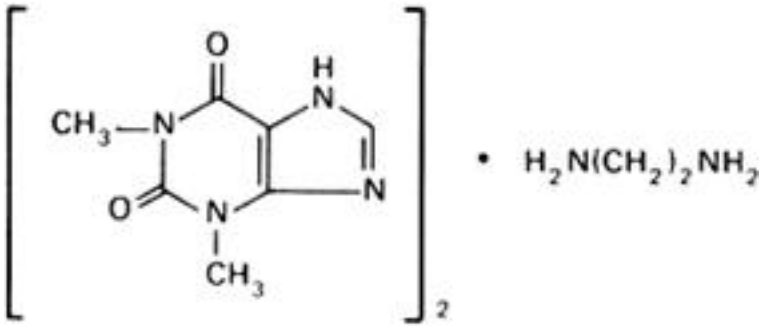
Aminophylline (Aminophyllinum)

Molecular formula. $(C_7H_8N_4O_2)_2,C_2H_8N_2$ (anhydrous) or $C_{16}H_{24}N_{10}O_4$

Relative molecular mass. 420.4 (anhydrous)

Graphic formula.



Chemical name. Theophylline compound with ethylenediamine (2:1); 3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione compound with 1,2-ethanediamine (2:1); CAS Reg. No. 317-34-0 (anhydrous).

Description. White or slightly yellowish granules or powder; odour, slightly ammoniacal.

Solubility. Freely soluble in water (the solution may become cloudy in the presence of carbon dioxide); slightly soluble in ethanol (~750 g/l) TS; practically insoluble in ether R.

Category. Antispasmodic; diuretic; coronary vasodilator.

Storage. Aminophylline should be kept in a tightly closed container, protected from light.

Additional information. Aminophylline contains a variable quantity of water of hydration. Upon exposure to air Aminophylline gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of free theophylline. Even in the absence of light, Aminophylline is gradually degraded on exposure to a humid atmosphere, the decomposition being faster at higher temperatures.

Requirements

Definition. Aminophylline contains not less than 78.0% and not more than 86.0% of theophylline ($C_7H_8N_4O_2$), and not less than 12.8% and not more than 15.0% of ethylenediamine ($C_2H_8N_2$), both calculated with reference to the anhydrous substance.

Identity tests

A. Dissolve 1 g in 10 mL of water and add, drop by drop, while shaking 2 mL of hydrochloric acid (~70 g/l) TS. Collect the precipitate on a filter, wash it with water and dry at 105°C; melting temperature, about 272°C (theophylline). Keep the precipitate for test B.

B. To 10 mg of the precipitate obtained from test A, contained in a porcelain dish, add 1 mL of hydrochloric acid (~250 g/l) TS and 0.5 mL of hydrogen peroxide (~60 g/l) TS, and evaporate to dryness on a water-bath. Add 1 drop of ammonia (~100 g/l) TS; the residue acquires a purple colour which is destroyed by the addition of a few drops of sodium hydroxide (~80 g/l) TS.

C. Dissolve 0.05 g in 1 mL of water and add 2 drops of copper(II) sulfate (80 g/l) TS; a deep violet colour is produced.

D. Warm 0.05 g with 2 mL of sodium hydroxide (~80 g/l) TS and 2 drops of chloroform R; an isocyanide, perceptible by its characteristic odour (proceed with caution), is produced.

Clarity of solution. A solution of 1.0 g in 10 mL of boiling water is clear or is not more than slightly opalescent.

Sulfated ash. Not more than 1.5 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.15 g of the substance and 25 mL of pyridine R as the solvent; the water content is not more than 80 mg/g.

Alkalinity. Add 1 drop of thymol blue/ethanol TS to a 10 mg/mL solution prepared in carbon-dioxide-free water R; a green or blue colour is produced.

Assay.

For theophylline. Place about 0.25 g, accurately weighed, in a 250-mL conical flask, add 50 mL of water and 8 mL of ammonia

(~100 g/l) TS and gently warm the mixture on a water-bath until complete solution is effected. Add 20.0 mL of silver nitrate (0.1 mol/l) VS, mix, heat to boiling and boil for 15 minutes. Cool to between 5°C and 10°C for 20 minutes, then filter through a filtering crucible under reduced pressure and wash the precipitate 3 times with 10-mL portions of water. Acidify the combined filtrate and washings with nitric acid (~1000 g/l) TS, and add an excess of 3 mL of the acid. Cool, add 2 mL of ferric ammonium sulfate (45 g/l) TS, and titrate the excess of silver nitrate with ammonium thiocyanate (0.1 mol/l) VS. Each mL of silver nitrate (0.1 mol/l) VS is equivalent to 18.02 mg of $C_7H_8N_4O_2$.

For ethylenediamine. Dissolve about 0.5 g, accurately weighed, in 30 mL of water and titrate with hydrochloric acid (0.1 mol/l) VS, using bromocresol green/ethanol TS as indicator. Repeat the operation without the substance being examined and make any necessary corrections. Each mL of hydrochloric acid (0.1 mol/l) VS is equivalent to 3.005 mg of $C_2H_8N_2$.

Additional requirements for Aminophylline for parenteral use

Complies with the monograph for "Parenteral preparations".

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 1.0 IU of endotoxin RS per mg.