IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. Melting point (*2.2.14*): 160 °C to 165 °C.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *diprophylline CRS*. Examine the substances as discs prepared using 0.5 mg to 1 mg of the substance to be examined in 0.3 g of *potassium bromide R*.

C. Dissolve 1 g in 5 mL of *acetic anhydride R* and boil under a reflux condenser for 15 min. Allow to cool and add 100 mL of a mixture of 20 volumes of *ether R* and 80 volumes of *light petroleum R*. Cool in iced water for at least 20 min, shaking from time to time. Filter, wash the precipitate with a mixture of 20 volumes of *ether R* and 80 volumes of *light petroleum R*, recrystallise from *alcohol R* and dry *in vacuo*. The crystals melt (*2.2.14*) at 142 °C to 148 °C.

D. It gives the reaction of xanthines (*2.3.1*).

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. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* HF_{254} *R* as the coating substance.

Test solution. Dissolve 0.3 g of the substance to be examined in a mixture of 20 volumes of *water R* and 30 volumes of *methanol R* and dilute to 10 mL with the same mixture of solvents. *Prepare immediately before use.*

Reference solution (a). Dilute 1 mL of the test solution to 100 mL with *methanol R*.

Reference solution (b). Dilute 0.2 mL of the test solution to 100 mL with *methanol R*.

Reference solution (c). Dissolve 10 mg of *theophylline R* in *methanol R*, add 0.3 mL of the test solution and dilute to 10 mL with *methanol R*.

Apply to the plate 10 µL of each solution. Develop over a path of 15 cm using a mixture of 1 volume of *concentrated ammonia R*, 10 volumes of *ethanol R* and 90 volumes of *chloroform R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with the test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (1 per cent) and at most one such spot is more intense than the spot in the chromatogram obtained with reference solution (b) (0.2 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated spots.

Chlorides (*2.4.4*). Dilute 2.5 mL of solution S to 15 mL with *water R*. The solution complies with the limit test for chlorides (400 ppm).

Heavy metals (*2.4.8*). 12 mL of solution S complies with limit test A for heavy metals (20 ppm). Prepare the standard using *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*). Not more than 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 $C_{10}H_{14}N_4O_4$.

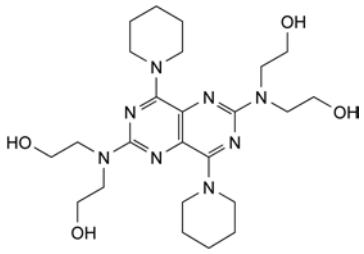
STORAGE

Store protected from light.

01/2008:1199

DIPYRIDAMOLE

Dipyridamolum



$C_{24}H_{40}N_8O_4$ M_r 504.6

[58-32-2]

DEFINITION

2,2′,2″,2‴-[[4,8-Di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine-2,6-diyl]dinitrilo]tetraethanol.

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

CHARACTERS

Appearance: bright yellow, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone, soluble in anhydrous ethanol. It dissolves in dilute mineral acids.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs of *potassium bromide R*.

Comparison: *dipyridamole CRS*.

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 50 mL with the same solvent.

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

Reference solution (b). Dissolve the contents of a vial of *dipyridamole for peak identification CRS* (containing impurities A, B, C, D, E and F) in 1 mL of *methanol R*.

Column:

– *size*: *l* = 0.10 m, Ø = 4.0 mm;

– *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 45 °C.

Mobile phase:

– *mobile phase A*: dissolve 1.0 g of *potassium dihydrogen phosphate R* in 900 mL of *water R*, adjust to pH 7.0 with *0.5 M sodium hydroxide* and dilute to 1000 mL with *water R*;

– *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	40	60
5 - 19	40 → 5	60 → 95
19 - 24	5 → 40	95 → 60
24 - 29	40	60

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 295 nm.

Injection: 5 µL.

Identification of impurities: use the chromatogram supplied with *dipyridamole for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C, D, E and F.

Relative retention with reference to dipyridamole (retention time = about 8 min): impurity B = about 0.2; impurity F = about 0.3; impurity D = about 0.9; impurity E = about 1.3; impurity C = about 1.6; impurity A = about 2.2.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to impurity D and dipyridamole;

– *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity B and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity F.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity B by 1.7;

– *impurities A, B, C*: for each impurity, not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

– *impurities D, E*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *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 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 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 200 ppm.

To 0.250 g add 10 mL of *water R* and shake vigorously. Filter, rinse the filter with 5 mL of *water R* and dilute 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

Dissolve 0.400 g in 70 mL of *methanol 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 50.46 mg of $C_{24}H_{40}N_8O_4$.

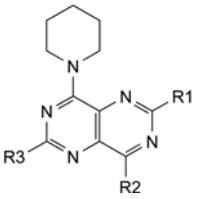
STORAGE

Protected from light.

IMPURITIES

Specified impurities: A, B, C, D, E.

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*): *F, G.*



A. R1 = $N(CH_2\text{-}CH_2\text{-}OH)_2$, R2 = R3 = NC_5H_{10}: 2,2′-[[4,6,8-tri(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidin-2-yl]nitrilo]diethanol,

B. R1 = R2 = R3 = $N(CH_2\text{-}CH_2\text{-}OH)_2$: 2,2′,2″,2‴,2⁗,2⁗′-[[8-(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine-2,4,6-triyl]trinitrilo]hexaethanol,

C. R1 = $N(CH_2\text{-}CH_2\text{-}OH)_2$, R2 = NC_5H_{10}, R3 = Cl: 2,2′-[[6-chloro-4,8-di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidin-2-yl]nitrilo]diethanol,

D. R1 = $N(CH_2\text{-}CH_2\text{-}OH)_2$, R2 = NC_5H_{10}, R3 = $NH\text{-}CH_2\text{-}CH_2\text{-}OH$: 2,2′-[[6-[(2-hydroxyethyl)amino]-4,8-di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidin-2-yl]nitrilo]diethanol,

E. R1 = R2 = $N(CH_2\text{-}CH_2\text{-}OH)_2$, R3 = NC_5H_{10}: 2,2′,2″,2‴-[[6,8-di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine-2,4-diyl]dinitrilo]tetraethanol,

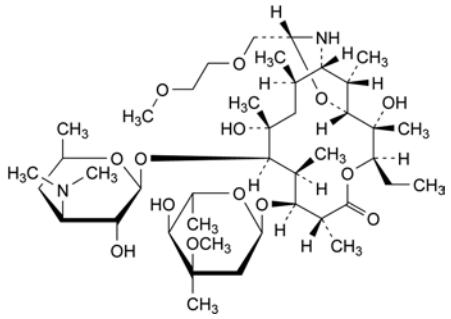
F. R1 = R3 = $N(CH_2\text{-}CH_2\text{-}OH)_2$, R2 = $NH\text{-}CH_2\text{-}CH_2\text{-}OH$: 2,2′,2″,2‴-[[4-[(2-hydroxyethyl)amino]-8-(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine-2,6-diyl]dinitrilo]tetraethanol,

G. R1 = R3 = Cl, R2 = NC_5H_{10}: 2,6-dichloro-4,8-di(piperidin-1-yl)pyrimido[5,4-*d*]pyrimidine.

01/2008:1313
corrected 6.1

DIRITHROMYCIN

Dirithromycinum



$C_{42}H_{78}N_2O_{14}$ M_r 835

[62013-04-1]

DEFINITION

(1*R*,2*S*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*,13*S*,15*R*,17*S*)-9-[[3-(Dimethylamino)-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-3-ethyl-2,10-dihydroxy-15-[(2-methoxyethoxy)methyl]-2,