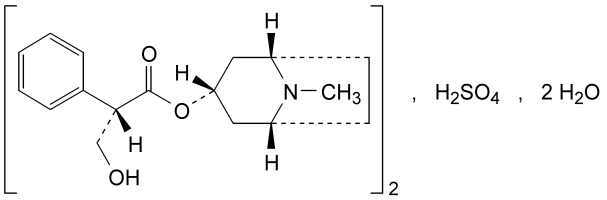
01/2008:0501

HYOSCYAMINE SULPHATE

Hyoscyamini sulfas



$C_{34}H_{48}N_2O_{10}S,2H_2O$ M_r 713
[620-61-1]

DEFINITION

Bis[(1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate] sulphate dihydrate.

Content: 98.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder or colourless needles.

Solubility: very soluble in water, sparingly soluble or soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, B, E.

Second identification: C, D, E.

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *hyoscyamine sulphate CRS*.

C. To 0.5 ml of solution S (see Tests) add 2 ml of *dilute acetic acid R* and heat. To the hot solution add 4 ml of *picric acid solution R*. Allow to cool, shaking occasionally. Collect the crystals, wash with 2 quantities, each of 3 ml, of iced *water R* and dry at 100-105 °C. The crystals melt (*2.2.14*) at 164 °C to 168 °C.

D. To about 1 mg add 0.2 ml of *fuming nitric acid R* and evaporate to dryness on a water-bath. Dissolve the residue in 2 ml of *acetone R* and add 0.2 ml of a 30 g/l solution of *potassium hydroxide R* in *methanol R*. A violet colour develops.

E. It gives reaction (a) of sulphates (*2.3.1*).

TESTS

Solution S. Dissolve 2.50 g in *water R* and dilute to 50.0 ml with the same solvent.

Appearance of solution. Solution S is not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

pH (*2.2.3*): 4.5 to 6.2.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 ml with the same solvent.

Specific optical rotation (*2.2.7*): – 24 to – 29 (anhydrous substance), determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 60.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 ml with mobile phase A. Dilute 10.0 ml of the solution to 50.0 ml with mobile phase A.

Reference solution (a). Dilute 5.0 ml of the test solution to 100.0 ml with mobile phase A. Dilute 5.0 ml of this solution to 50.0 ml with mobile phase A.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 25.0 ml with mobile phase A.

Reference solution (c). Dissolve 5.0 mg of *hyoscyamine impurity E CRS* in the test solution and dilute to 20.0 ml with the test solution. Dilute 5.0 ml of this solution to 25.0 ml with mobile phase A.

Column:
- *size*: *l* = 0.10 m, Ø = 4.6 mm,
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm),
- *temperature*: 25 ± 1 °C.

Mobile phase:
- *mobile phase A*: dissolve 3.5 g of *sodium dodecyl sulphate R* in 606 ml of a 7.0 g/l solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.3 with *0.05 M phosphoric acid* and mix with 320 ml of *acetonitrile R*,
- *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2.0	95	5
2.0 - 20.0	95 → 70	5 → 30
20.0 - 20.1	70 → 95	30 → 5
20.1 - 25.0	95	5

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µl.

Relative retention with reference to hyoscyamine (retention time = about 10.5 min): impurity A = about 0.2; impurity B = about 0.67; impurity C = about 0.72; impurity D = about 0.8; impurity E = about 0.9; impurity F = about 1.1; impurity G = about 1.8.

System suitability: reference solution (c):
- *resolution*: minimum 2.5 between the peaks due to hyoscyamine and impurity E,
- *symmetry factor*: maximum 2.5 for the peak due to hyoscyamine.

Limits:
- *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.3; impurity G = 0.6;
- *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
- *impurities A, B, C, D, F, G*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
- *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);
- *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
- *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*): 2.0 per cent to 5.5 per cent, determined on 0.500 g.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 25 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

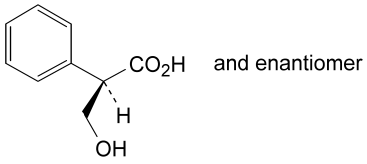
1 ml of *0.1 M perchloric acid* is equivalent to 67.7 mg of $C_{34}H_{48}N_2O_{10}S$.

STORAGE

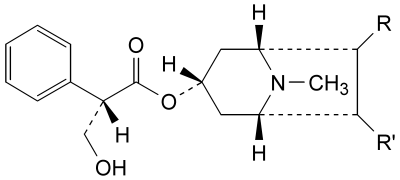
In an airtight container, protected from light.

IMPURITIES

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



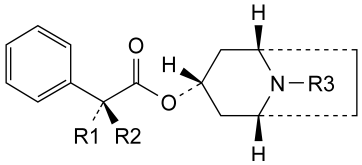
A. (2*RS*)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),



B. R = OH, R′ = H: (1*R*,3*S*,5*R*,6*RS*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate (7-hydroxyhyoscyamine),

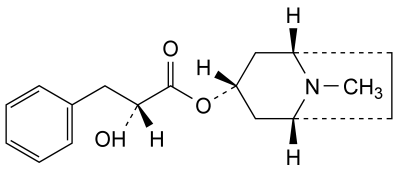
C. R = H, R′ = OH: (1*S*,3*R*,5*S*,6*RS*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate (6-hydroxyhyoscyamine),

D. hyoscine,



E. R1 = CH_2OH, R2 = R3 = H: (1*R*,3*r*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate (norhyoscyamine),

G. R1 + R2 = CH_2, R3 = CH_3: (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 2-phenylprop-2-enoate (apoatropine),



F. (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*R*)-2-hydroxy-3-phenylpropanoate (littorine).

01/2008:0348
corrected 6.0

HYPROMELLOSE

Hypromellosum

[9004-65-3]

DEFINITION

Hydroxypropylmethylcellulose.

Partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose.

CHARACTERS

Appearance: white, yellowish-white or greyish-white powder or granules, hygroscopic after drying.

Solubility: practically insoluble in hot water, in acetone, in anhydrous ethanol and in toluene. It dissolves in cold water giving a colloidal solution.

IDENTIFICATION

A. Evenly distribute 1.0 g on the surface of 100 ml of *water R* in a beaker, tapping the top of the beaker, gently if necessary to ensure a uniform layer on the surface. Allow to stand for 1-2 min: the powdered material aggregates on the surface.

B. Evenly distribute 1.0 g into 100 ml of boiling *water R*, and stir the mixture using a magnetic stirrer with a bar 25 mm long: a slurry is formed and the particles do not dissolve. Allow the slurry to cool to 10 °C and stir using a magnetic stirrer: a clear or slightly turbid solution occurs with its thickness dependent on the viscosity grade.

C. To 0.1 ml of the solution obtained in identification B add 9 ml of a 70 per cent *m/m* solution of *sulphuric acid R*, shake, heat on a water-bath for exactly 3 min, immediately cool in an ice-bath, carefully add 0.6 ml of *ninhydrin solution R*, shake, and allow to stand at 25 °C: a red colour develops at first, and changes to purple within 100 min.

D. Place 2-3 ml of the solution obtained in identification B onto a glass slide as a thin film and allow the water to evaporate: a coherent, clear film forms on the glass slide.

E. Add exactly 50 ml of the solution obtained in identification B to exactly 50 ml of *water R* in a beaker. Insert a thermometer into the solution. Stir the solution on a magnetic stirrer/hot plate and begin heating, increasing the temperature at a rate of 2-5 °C per minute. Determine the temperature at which a turbidity increase begins to occur and designate the temperature as the flocculation temperature: the flocculation temperature is higher than 50 °C.

TESTS

Solution S. While stirring, introduce a quantity of the substance to be examined equivalent to 1.0 g of the dried substance into 50 g of *carbon dioxide-free water R* heated to 90 °C. Allow to cool, adjust the mass of the solution to 100 g with *carbon dioxide-free water R* and stir until dissolution is complete.

Appearance of solution. Solution S is not more opalescent than reference suspension III (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*): 5.0 to 8.0 for the solution prepared as described under Apparent viscosity.

Carry out the test at 20 ± 2 °C and read the indicated pH value after the probe has been immersed for 5 ± 0.5 min.