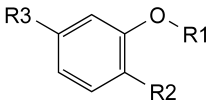
IMPURITIES

Specified impurities: A, B, C, 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*): *D.*

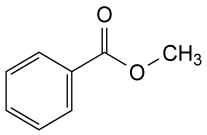


A. R1 = R3 = H, R2 = OH: benzene-1,2-diol (pyrocatechol),

B. R1 = R2 = R3 = H: phenol,

C. R1 = CH_3, R2 = OCH_3, R3 = H: 1,2-dimethoxybenzene (veratrole),

D. R1 = H, R2 = R3 = OCH_3: 2,5-dimethoxyphenol,



E. methyl benzoate.

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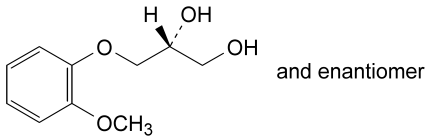
GUAIFENESIN

Guaifenesinum



$C_{10}H_{14}O_4$ M_r 198.2
[93-14-1]

DEFINITION

(2*RS*)-3-(2-Methoxyphenoxy)propane-1,2-diol.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: sparingly soluble in water, soluble in alcohol.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Melting point (*2.2.14*): 79 °C to 83 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *guaifenesin CRS.*

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

Test solution. Dissolve 30 mg of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 30 mg of *guaifenesin CRS* in *methanol R* and dilute to 10 ml with the same solvent.

Plate: *TLC silica gel G plate R.*

Mobile phase: *methylene chloride R, propanol R* (20:80 *V/V*).

Application: 5 µl.

Development: over 2/3 of the plate.

Drying: in air.

Detection: spray with a mixture of equal volumes of a 10 g/l solution of *potassium ferricyanide R*, a 200 g/l solution of *ferric chloride R* and *alcohol R*.

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

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R*, heating gently if necessary, 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 0.05 ml of *phenolphthalein solution R1*. Not more than 0.1 ml of *0.01 M sodium hydroxide* is required to change the colour of the indicator. To 10 ml of solution S add 0.15 ml of *methyl red solution R*. Not more than 0.1 ml of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in *acetonitrile R* and dilute to 50.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 20.0 ml with *acetonitrile R*. Dilute 1.0 ml of this solution to 10.0 ml with *acetonitrile R*.

Reference solution (b). Dissolve 10.0 mg of *guaiacol R* in *acetonitrile R* and dilute to 50.0 ml with the same solvent. Dilute 0.5 ml of this solution to 50.0 ml with *acetonitrile R*.

Reference solution (c). Dissolve 50.0 mg of *guaiacol R* in *acetonitrile R* and dilute to 50.0 ml with the same solvent. Dilute 5.0 ml of this solution to 10.0 ml with the test solution.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

– *mobile phase A*: *glacial acetic acid R, water R* (10:990 *V/V*),
– *mobile phase B*: *acetonitrile R,*

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 32	80 → 50	20 → 50
32 - 33	50 → 80	50 → 20
33 - 40	80	20

Flow rate: 1 ml/min.

Detection: spectrophotometer at 276 nm.

Injection: 10 µl.

Relative retention with reference to guaifenesin (retention time = about 8 min): impurity B = about 0.9; impurity A = about 1.4; impurity C = about 3.1; impurity D = about 3.7.

System suitability: reference solution (c):

– *resolution*: minimum 3.0 between the peaks due to guaifenesin and impurity A.

Limits:

- *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),
- *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
- *total (excluding impurity B)*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),
- *disregard level*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorides and monochlorhydrins: maximum of 250 ppm.

To 10 ml of solution S add 2 ml of *dilute sodium hydroxide solution R* and heat on a water-bath for 5 min. Cool and add 3 ml of *dilute nitric acid R*. The resulting solution complies with the limit test for chlorides (*2.4.4*).

Heavy metals (*2.4.8*): maximum of 25 ppm.

Dissolve 2.0 g in a mixture of 1 volume of *water R* and 9 volumes of *alcohol R* and dilute to 25 ml with the same mixture of solvents. 12 ml of the solution complies with limit test B. Prepare the standard using lead standard solution (2 ppm Pb) prepared by diluting *lead standard solution (100 ppm Pb) R* with a mixture of 1 volume of *water R* and 9 volumes of *alcohol R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 3 h.

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

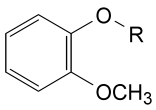
ASSAY

To 0.500 g (*m* g) add 10.0 ml of a freshly prepared mixture of 1 volume of *acetic anhydride R* and 7 volumes of *pyridine R*. Boil under a reflux condenser for 45 min. Cool and add 25 ml of *water R*. Using 0.25 ml of *phenolphthalein solution R* as indicator, titrate with *1 M sodium hydroxide* (n_1 ml). Carry out a blank titration (n_2 ml).

Calculate the percentage content of $C_{10}H_{14}O_4$ from the expression:

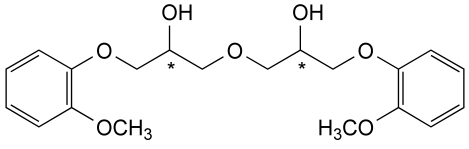
$$\frac{19.82\,(n_2 - n_1)}{2m}$$

IMPURITIES

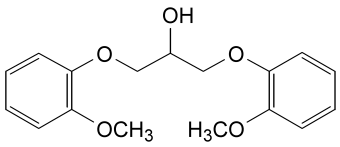


A. R = H: 2-methoxyphenol (guaiacol),

B. R = $CH(CH_2OH)_2$: 2-(2-methoxyphenoxy)propane-1,3-diol (B-isomer),



C. 1,1′-oxybis[3-(2-methoxyphenoxy)propan-2-ol] (bisether),



D. 1,3-bis(2-methoxyphenoxy)propan-2-ol.

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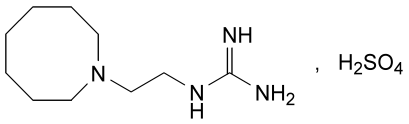
corrected 6.0

GUANETHIDINE MONOSULPHATE

Guanethidini monosulfas



$C_{10}H_{24}N_4O_4S$ M_r 296.4
[645-43-2]

DEFINITION

1-[2-(Hexahydroazocin-1(2*H*)-yl)ethyl]guanidine monosulphate.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: colourless, crystalline powder.

Solubility: freely soluble in water, practically insoluble in ethanol (96 per cent).

mp: about 250 °C, with decomposition.

IDENTIFICATION

A. Dissolve about 25 mg in 25 ml of *water R*, add 20 ml of *picric acid solution R* and filter. The precipitate, washed with *water R* and dried at 100-105 °C, melts (*2.2.14*) at about 154 °C.

B. Dissolve about 25 mg in 5 ml of *water R*. Add 1 ml of *strong sodium hydroxide solution R*, 1 ml of *α-naphthol solution R* and, dropwise with shaking, 0.5 ml of *strong sodium hypochlorite solution R*. A bright pink precipitate is formed and becomes violet-red on standing.

C. It gives the reactions of sulphates (*2.3.1*).

TESTS

Solution S. Dissolve 0.4 g in *carbon dioxide-free water R* and dilute to 20 ml with the same solvent.

Appearance of solution. Solution S is not more intensely coloured than reference solution GY_6 (*2.2.2, Method II*).

pH (*2.2.3*): 4.7 to 5.5 for solution S.

Oxidisable substances. In a conical, ground-glass-stoppered flask, dissolve 1.0 g in 25 ml of *water R* and add 25 ml of *dilute sodium hydroxide solution R*. Allow to stand for 10 min and add 1 g of *potassium bromide R* and 1 ml of *0.0083 M potassium bromate*. Acidify with 30 ml of *dilute hydrochloric acid R*. Mix and allow to stand in the dark for 5 min. Add 2 g of *potassium iodide R* and shake. Allow to stand for 2 min and titrate the liberated iodine with *0.05 M sodium thiosulphate*, using *starch solution R* as indicator. Not less than 0.3 ml of *0.05 M sodium thiosulphate* is required to decolorise the solution.