Calculate the percentage content of $C_{17}H_{25}N_3O_5S$ from the declared content of *meropenem trihydrate CRS*.

STORAGE

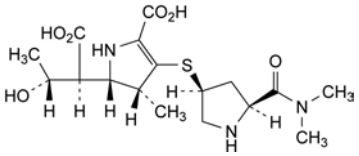
If the substance is sterile, store in a sterile, airtight, tamper-proof container.

LABELLING

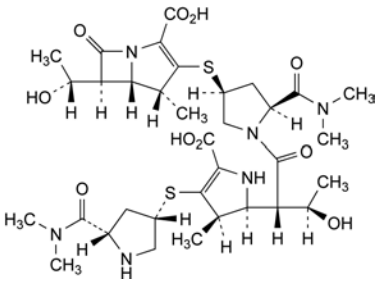
The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

IMPURITIES

Specified impurities: A, B.



A. (4*R*,5*S*)-5-[(1*S*,2*R*)-1-carboxy-2-hydroxypropyl]-3-[[(3*S*,5*S*)-5-[(dimethylamino)carbonyl]pyrrolidin-3-yl]sulfanyl]-4-methyl-4,5-dihydro-1*H*-pyrrole-2-carboxylic acid,



B. (4*R*,5*S*,6*S*)-3-[[(3*S*,5*S*)-1-[(2*S*,3*R*)-2-[(2*S*,3*R*)-5-carboxy-4-[[(3*S*,5*S*)-5-[(dimethylamino)carbonyl]pyrrolidin-3-yl]sulfanyl]-3-methyl-2,3-dihydro-1*H*-pyrrol-2-yl]-3-hydroxybutanoyl]-5-[(dimethylamino)carbonyl]pyrrolidin-3-yl]sulfanyl]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

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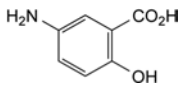
corrected 6.0

MESALAZINE

Mesalazinum



$C_7H_7NO_3$ M_r 153.1
[89-57-6]

DEFINITION

5-Amino-2-hydroxybenzoic acid.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: almost white or light grey or light pink powder or crystals.

Solubility: very slightly soluble in water, practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid.

IDENTIFICATION

First identification: B.

Second identification: A, C.

A. Dissolve 50.0 mg in 10 mL of a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 5.0 mL to 200.0 mL with a 10.3 g/L solution of *hydrochloric acid R*. Examined between 210 nm and 250 nm (*2.2.25*), the solution shows an absorption maximum at about 230 nm. The specific absorbance at the maximum is 430 to 450.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *mesalazine CRS*.

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

Test solution. Dissolve 50 mg of the substance to be examined in 10 mL of a mixture of equal volumes of *glacial acetic acid R* and *water R* and dilute to 20.0 mL with *methanol R*.

Reference solution. Dissolve 50 mg of *mesalazine CRS* in 10 mL of a mixture of equal volumes of *glacial acetic acid R* and *water R* and dilute to 20.0 mL with *methanol R*.

Plate: a suitable silica gel as the coating substance.

Mobile phase: *glacial acetic acid R, methanol R, methyl isobutyl ketone R* (10:40:50 *V/V/V*).

Application: 5 µL.

Development: over a path of 10 cm.

Drying: in air.

Detection: examine in ultraviolet light at 365 nm.

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

Appearance of solution. *Maintain the solutions at 40 °C during preparation and measurements.* Dissolve 0.5 g in *1 M hydrochloric acid* and dilute to 20 mL with the same acid. The solution is clear (*2.2.1*). Immediately measure the absorbance (*2.2.25*) of the solution at 440 nm and 650 nm. The absorbance is not greater than 0.15 at 440 nm and 0.10 at 650 nm.

Reducing substances. Dissolve 0.10 g in *dilute hydrochloric acid R* and dilute to 25 mL with the same acid. Add 0.2 mL of *starch solution R* and 0.25 mL of *0.01 M iodine*. Allow to stand for 2 min. The solution is blue or violet-brown.

Related substances. Liquid chromatography (*2.2.29*). *Use freshly prepared solutions and mobile phases.*

Test solution. Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A.

Reference solution (b). Dissolve 5.0 mg of *3-aminobenzoic acid R* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL to 25.0 mL with the test solution.

Reference solution (c). Dissolve 5.0 mg of *3-aminobenzoic acid R* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL to 50.0 mL with mobile phase A.

Reference solution (d). Dissolve 10.0 mg of *3-aminophenol R* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL to 50.0 mL with mobile phase A.

Reference solution (e). Dissolve 5.0 mg of *2,5-dihydroxybenzoic acid R* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL to 50.0 mL with mobile phase A.

Reference solution (f). Dissolve 15.0 mg of *salicylic acid R* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 1.0 mL to 50.0 mL with mobile phase A.

Blank solution. Mobile phase A.

Column:

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

Mobile phase:

– *mobile phase A*: dissolve 2.2 g of *perchloric acid R* and 1.0 g of *phosphoric acid R* in *water R* and dilute to 1000.0 mL with the same solvent,

– *mobile phase B*: dissolve 1.7 g of *perchloric acid R* and 1.0 g of *phosphoric acid R* in *acetonitrile R* and dilute to 1000.0 mL with the same solvent,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 7	100	0
7 - 25	100 → 40	0 → 60
25 - 30	40 → 100	60 → 0
30 - 40	100	0

Flow rate: 1.25 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Relative retention with reference to mesalazine (retention time = about 5 min): impurity B = about 0.8; impurity D = about 1.2; impurity G = about 3.1; impurity H = about 3.9.

System suitability: reference solution (b):

– *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to mesalazine.

Limits:

– *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent),
– *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent),
– *impurity G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.1 per cent),
– *impurity H*: not more than the area of the principal peak in the chromatogram obtained with reference solution (f) (0.3 per cent),
– *any other impurity*: not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
– *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),
– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent). Disregard any peaks obtained with the blank solution.

Impurity A and impurity C. Liquid chromatography (*2.2.29*). *Use freshly prepared mobile phases.*

Test solution. Dissolve 50.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

Reference solution (a). Dissolve 5.0 mg of *2-aminophenol R* in mobile phase A and dilute to 100.0 mL with mobile phase A. Dilute 10.0 mL to 100.0 mL with mobile phase A.

Reference solution (b). Dissolve 5.0 mg of *4-aminophenol R* in mobile phase A and dilute to 250.0 mL with mobile phase A. To 1.0 mL of this solution, add 1.0 mL of reference solution (a) and dilute to 100.0 mL with mobile phase A.

Reference solution (c). Dilute 1.0 mL of the test solution to 200.0 mL with mobile phase A. To 5.0 mL of this solution add 5.0 mL of reference solution (a).

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

– *mobile phase A*: dissolve 2.2 g of *perchloric acid R* and 1.0 g of *phosphoric acid R* in *water R* and dilute to 1000.0 mL with the same solvent,
– *mobile phase B*: dissolve 1.7 g of *perchloric acid R* and 1.0 g of *phosphoric acid R* in *acetonitrile R* and dilute to 1000.0 mL with the same solvent,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	100	0
8 - 25	100 → 40	0 → 60
25 - 30	40 → 100	60 → 0
30 - 40	100	0

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 20 µL; inject the test solution and reference solutions (b) and (c).

Relative retention with reference to mesalazine (retention time = about 9 min): impurity A = about 0.5; impurity C = about 0.9.

System suitability: reference solution (c):

– *resolution*: minimum 3 between the peaks due to impurity C and mesalazine.

Limits:

– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (200 ppm),
– *impurity C*: not more than 4 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (200 ppm).

Impurity K. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

Reference solution. Dissolve 27.8 mg of *aniline hydrochloride R* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 0.20 mL of this solution to 20.0 mL with the mobile phase. Dilute 0.20 mL of this solution to 20.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4 mm,
– *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm),
– *temperature*: 40 °C.

Mobile phase: mix 15 volumes of *methanol R* and 85 volumes of a solution containing 1.41 g/L of *potassium dihydrogen phosphate R* and 0.47 g/L of *disodium hydrogen phosphate dihydrate R* previously adjusted to pH 8.0 with a 42 g/L solution of *sodium hydroxide R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 205 nm.

Injection: 50 µL.

Retention time: impurity K = about 15 min.

System suitability: reference solution:

– *signal-to-noise ratio*: minimum 10 for the principal peak.

Limit:

– *impurity K*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (10 ppm).

Chlorides: maximum 0.1 per cent.

Dissolve 1.50 g in 50 mL of *anhydrous formic acid R*. Add 100 mL of *water R* and 5 mL of *2 M nitric acid*. Titrate with *0.005 M silver nitrate* determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.005 M silver nitrate* is equivalent to 0.1773 mg of Cl.

Sulfates (*2.4.13*): maximum 200 ppm.

Shake 1.0 g with 20 mL of *distilled water R* for 1 min and filter. 15 mL of the filtrate complies with the limit test for sulfates.

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with limit test F. Prepare the standard using 2 mL of *lead standard solution (10 ppm Pb) 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 0.2 per cent, determined on 1.0 g.

ASSAY

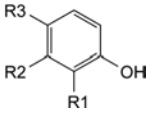
Dissolve 50.0 mg in 100 mL of boiling *water R*. Cool rapidly to room temperature and titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium hydroxide* is equivalent to 15.31 mg of $C_7H_7NO_3$.

STORAGE

In an airtight container, protected from light.

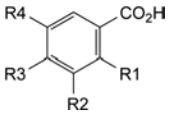
IMPURITIES



A. R1 = R2 = H, R3 = NH_2: 4-aminophenol,

B. R1 = R3 = H, R2 = NH_2: 3-aminophenol,

C. R1 = NH_2, R2 = R3 = H: 2-aminophenol,



D. R1 = R3 = R4 = H, R2 = NH_2: 3-aminobenzoic acid,

E. R1 = OH, R2 = R4 = H, R3 = NH_2: 4-amino-2-hydroxybenzoic acid (4-aminosalicylic acid),

F. R1 = OH, R2 = NH_2, R3 = R4 = H: 3-amino-2-hydroxybenzoic acid (3-aminosalicylic acid),

G. R1 = R4 = OH, R2 = R3 = H: 2,5-dihydroxybenzoic acid,

H. R1 = OH, R2 = R3 = R4 = H: 2-hydroxybenzoic acid (salicylic acid),

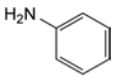
I. R1 = OH, R2 = R3 = H, R4 = N=N-C_6H_5: 2-hydroxy-5-(phenyldiazenyl)benzoic acid (phenylazosalicylic acid),

J. R1 = OH, R2 = R4 = NH_2, R3 = H: 3,5-diamino-2-hydroxybenzoic acid (diaminosalicylic acid),

L. R1 = Cl, R2 = R3 = R4 = H: 2-chlorobenzoic acid,

M. R1 = Cl, R2 = R3 = H, R4 = NO_2: 2-chloro-5-nitrobenzoic acid,

N. R1 = OH, R2 = R3 = H, R4 = NO_2: 2-hydroxy-5-nitrobenzoic acid (5-nitrosalicylic acid),



K. aniline.

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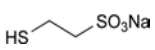
MESNA

Mesnum



$C_2H_5NaO_3S_2$ M_r 164.2

[19767-45-4]

DEFINITION

Sodium 2-sulfanylethanesulfonate.

Content: 96.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or slightly yellow, crystalline powder, hygroscopic.

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

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *Ph. Eur. reference spectrum of mesna.*

B. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R* and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

pH (*2.2.3*): 4.5 to 6.0.

Dilute 10 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.10 g of the substance to be examined in the mobile phase and dilute to 25.0 mL with the mobile phase.

Reference solution (a). Dissolve 4.0 mg of *mesna impurity C CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 20.0 mL with the mobile phase.

Reference solution (b). Dissolve 6.0 mg of *mesna impurity D CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (c). Dilute 3.0 mL of the test solution to 10.0 mL with the mobile phase.

Reference solution (d). Dilute 1.0 mL of reference solution (c) to 100.0 mL with the mobile phase.

Reference solution (e). Dilute 6.0 mL of reference solution (c) to 20.0 mL with the mobile phase. To 10 mL of the solution add 10 mL of reference solution (a).

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (10 µm).

Mobile phase: dissolve 2.94 g of *potassium dihydrogen phosphate R*, 2.94 g of *dipotassium hydrogen phosphate R* and 2.6 g of *tetrabutylammonium hydrogen sulfate R* in about 600 mL of *water R*. Adjust to pH 2.3 with *phosphoric acid R*, add 335 mL of *methanol R* and dilute to 1000 mL with *water R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 235 nm.

Injection: 20 µL.

Run time: 4 times the retention time of mesna.

Relative retention with reference to mesna (retention time = about 4.8 min): impurities A and B = about 0.6; impurity E = about 0.8; impurity C = about 1.4; impurity D = about 2.3.

System suitability: reference solution (e):

– *resolution*: minimum 3.0 between the peaks due to mesna and impurity C.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of impurities A, B and E by 0.01,