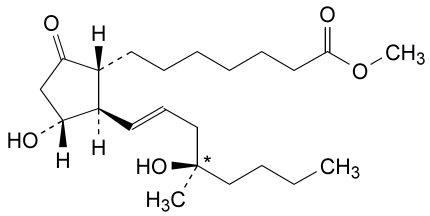
01/2008:1731

MISOPROSTOL

Misoprostolum



its epimer at C* and their enantiomers

$C_{22}H_{38}O_5$ M_r 382.5
[59122-46-2]

DEFINITION

Mixture of methyl 7-[(1*RS*,2*RS*,3*RS*)-3-hydroxy-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1*RS*,2*RS*,3*RS*)-3-hydroxy-2-[(1*E*,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate.

The 4 stereoisomers are present in approximately equal proportions.

Content: 96.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: clear, colourless or yellowish, oily liquid, hygroscopic.

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

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *misoprostol CRS*.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 10.00 mg of the substance to be examined in *acetonitrile R1* and dilute to 5.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with *acetonitrile R1*.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 10.0 ml with *acetonitrile R1*.

Reference solution (c). Dissolve 0.25 mg of *misoprostol impurity A CRS* in reference solution (a) and dilute to 10.0 ml with the same solution.

Reference solution (d). Dissolve 10.00 mg of *misoprostol CRS* in *acetonitrile R1* and dilute to 5.0 ml with the same solvent.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: spherical partially end-capped *octadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 220 m^2/g and a carbon loading of 7 per cent,
– *temperature*: 40 °C.

Mobile phase: mix 45 volumes of *acetonitrile R1* and 55 volumes of *water R* and add 0.05 volumes of a 24.5 g/l solution of *phosphoric acid R*.

Flow rate: 0.75 ml/min.

Detection: spectrophotometer at 200 nm.

Injection: 10 µl.

Run time: 3 times the retention time of misoprostol.

Relative retention with reference to misoprostol (retention time = about 20 min): impurity A = about 0.9; impurity E = about 0.9; impurity B (1st peak) = about 0.9; impurity B (2nd peak) = about 0.95.

System suitability: reference solution (c):

– *resolution*: minimum 1.9 between the peaks due to impurity A and misoprostol.

Limits:

– *sum of impurities A, B and E*: not more than 1.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.3 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 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent),
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Diastereoisomers. Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution. Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 1.0 ml with the mobile phase.

Reference solution. Dilute 0.1 ml of the test solution to 10.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm,
– *stationary phase*: *silica gel for chromatography R* (5 µm),
– *temperature*: 40 °C.

Mobile phase: mix 5 volumes of *2-propanol R* and 95 volumes of *heptane R* and add 0.01 volumes of *glacial acetic R* .

Flow rate: 1 ml/min.

Detection: spectrophotometer at 205 nm.

Injection: 10 µl.

Run time: 1.5 times the retention time of the 1st peak of misoprostol.

Retention time: misoprostol 1st peak = about 19 min; misoprostol 2nd peak = about 21 min.

System suitability: reference solution:

– *resolution*: minimum 2.3 between the 1st peak and the 2nd peak of misoprostol.

Limit:

– *1st peak of misoprostol*: 50 per cent to 55 per cent of the sum of the areas of the 2 peaks due to misoprostol.

Water (*2.5.32*): maximum 1.0 per cent.

Use 1.0 ml of a 10 mg/ml solution of the substance to be examined in *methanol R*.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection: test solution and reference solution (d).

Calculate the percentage content of $C_{22}H_{38}O_5$ using the declared content of *misoprostol CRS*.

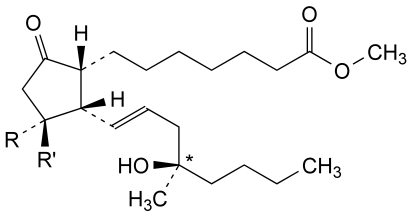
STORAGE

In an airtight container, at – 20 °C.

IMPURITIES

Specified impurities: *A, B, E* .

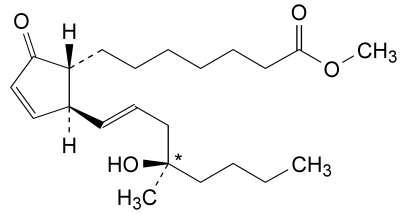
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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*): *C, D*.



its epimer at C* and their enantiomers

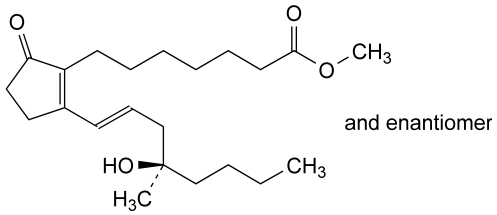
A. R = H, R′ = OH: mixture of methyl 7-[(1*RS*,2*SR*,3*SR*)-3-hydroxy-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1*RS*,2*SR*,3*SR*)-3-hydroxy-2-[(1E,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate (8-epimisoprostol),

B. R = OH, R′ = H: mixture of methyl 7-[(1*RS*,2*SR*,3*RS*)-3-hydroxy-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1*RS*,2*SR*,3*RS*)-3-hydroxy-2-[(1*E*,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate (12-epimisoprostol),

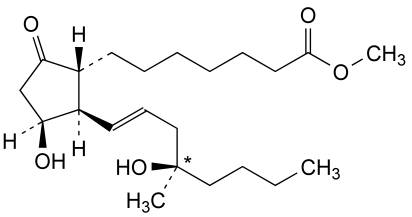


its epimer at C* and their enantiomers

C. mixture of methyl 7-[(1*RS*,2*SR*)-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopent-3-enyl]heptanoate and methyl 7-[(1*RS*,2*SR*)-2-[(1*E*,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopent-3-enyl]heptanoate (misoprostol A),



D. methyl 7-[2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopent-1-enyl]heptanoate (misoprostol B),



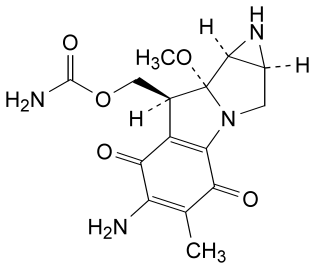
its epimer at C* and their enantiomers

E. mixture of methyl 7-[(1*RS*,2*RS*,3*SR*)-3-hydroxy-2-[(1*E*,4*RS*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1*RS*,2*RS*,3*SR*)-3-hydroxy-2-[(1*E*,4*SR*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate (11-epi misoprostol).

01/2008:1655

MITOMYCIN

Mitomycinum



$C_{15}H_{18}N_4O_5$ M_r 334.3
[50-07-7]

DEFINITION

[(1a*S*,8*S*,8a*R*,8b*S*)-6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]-indol-8-yl]methyl carbamate (mitomycin C).

Substance produced by a strain of *Streptomyces caespitotus*.

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: blue-violet crystals or crystalline powder.

Solubility: slightly soluble in water, freely soluble in dimethylacetamide, sparingly soluble in methanol, slightly soluble in acetone.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *mitomycin CRS*.

B. Examine the chromatograms obtained in the assay.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

pH (*2.2.3*): 5.5 to 7.5.

Dissolve 10 mg in 10 ml of *carbon dioxide-free water R*.