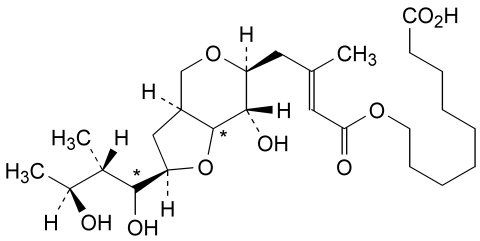
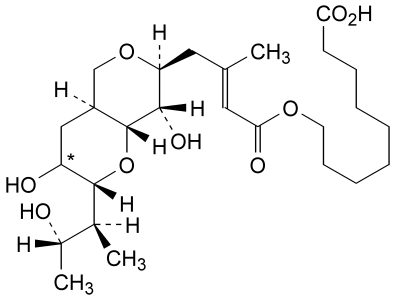
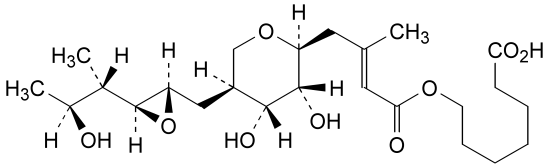


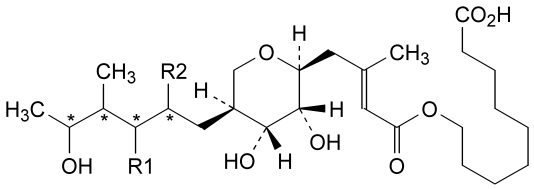
D. 9-[[(2*E*)-4-[(2*R*,3a*S*,6*S*,7*S*)-2-[(2*S*,3*S*)-1,3-dihydroxy-2-methylbutyl]-7-hydroxyhexahydro-4*H*-furo[3,2-*c*]pyran-6-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,



E. 9-[[(2*E*)-4-[(2*R*,3*RS*,4a*S*,7*S*,8*S*,8a*R*)-3,8-dihydroxy-2-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]hexahydro-2*H*,5*H*-pyrano[4,3-*b*]pyran-7-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,

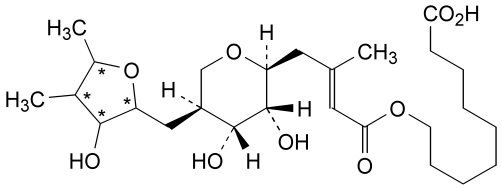


F. 7-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[[(2*S*,3*S*)-3-[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxiranyl]methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]heptanoic acid,



G. R1 = OH, R2 = Cl: 9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-5-(2-chloro-3,5-dihydroxy-4-methylhexyl)-3,4-dihydroxytetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,

H. R1 = Cl, R2 = OH: 9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-5-(3-chloro-2,5-dihydroxy-4-methylhexyl)-3,4-dihydroxytetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid,

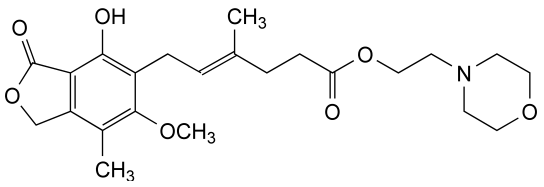


I. 9-[[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(3-hydroxy-4,5-dimethyltetrahydrofuran-2-yl)methyl]tetrahydro-2*H*-pyran-2-yl]-3-methylbut-2-enoyl]oxy]nonanoic acid.

01/2008:1700

MYCOPHENOLATE MOFETIL

Mycophenolas mofetil



$C_{23}H_{31}NO_7$ M_r 433.5
[128794-94-5]

DEFINITION

2-(Morpholin-4-yl)ethyl (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone, sparingly soluble in anhydrous ethanol.

mp: about 96 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *mycophenolate mofetil CRS*.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.10 g in *ethanol (96 per cent) R* and dilute to 10 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*). *Protect the solutions from light. Prepare the solutions immediately before use, or store them at 4-8 °C. Keep the temperature of the autosampler at 10 °C, allow the temperature of the solutions to equilibrate in the vials for 15 min before injection.*

Test solution. Dissolve 20 mg of the substance to be examined in *acetonitrile R* and dilute to 10 ml with the same solvent.

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

Reference solution (b). Dissolve 5 mg of *mycophenolate mofetil for peak identification CRS* (mycophenolate mofetil with impurities A, B, D, E, F, G and H) in *acetonitrile R* and dilute to 2.5 ml with the same solvent.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm,
- *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm),
- *temperature*: 45 °C.

Mobile phase: mix 350 ml of *acetonitrile R* with a mixture of 650 ml of *water R* and 2.0 ml of *triethylamine R* previously adjusted to pH 5.3 with *dilute phosphoric acid R*.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 250 nm.

Injection: 10 µl.

Run time: 3 times the retention time of mycophenolate mofetil.

Relative retention with reference to mycophenolate mofetil (retention time = about 22 min): impurity F = about 0.3; impurity A = about 0.4; impurity H = about 0.5; impurity G = about 0.6; impurity B = about 0.8; impurity D = about 1.2; impurity E = about 1.6.

System suitability: reference solution (b):

- *resolution*: minimum 2.0 between the peaks due to impurity A and impurity H,
- the chromatogram obtained is similar to the chromatogram supplied with *mycophenolate mofetil for peak identification CRS*.

Limits:

- *correction factor*: for the calculation of content, multiply the peak area of impurity B by 2.1,
- *impurity F*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),
- *impurity B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),
- *impurities A, D, E, G, H*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
- *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
- *total*: not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 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).

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

1.0 g complies with limit test F. Prepare the reference solution 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 vacuo* at 60 °C for 3 h.

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

ASSAY

Dissolve 0.400 g in 50 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 43.35 mg of $C_{23}H_{31}NO_7$.

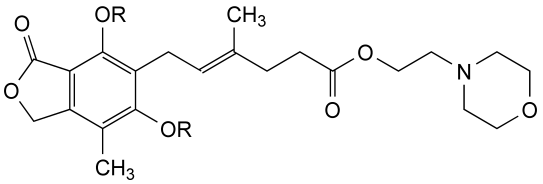
STORAGE

Protected from light.

IMPURITIES

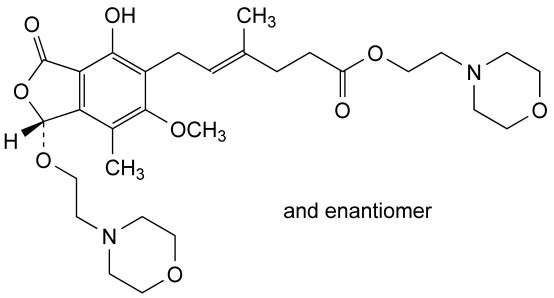
Specified impurities: *A, B, D, E, F, G, H.*

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.*

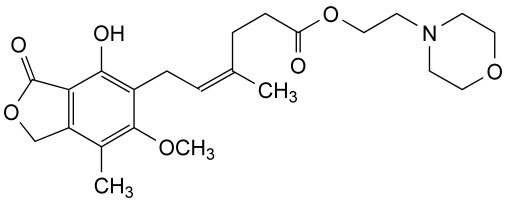


A. R = H: 2-(morpholin-4-yl)ethyl (4*E*)-6-(4,6-dihydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate,

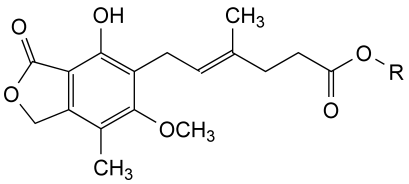
D. R = CH_3: 2-(morpholin-4-yl)ethyl (4*E*)-6-(4,6-dimethoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate,



B. 2-(morpholin-4-yl)ethyl (4*E*)-6-[(1*RS*)-4-hydroxy-6-methoxy-7-methyl-1-[2-(morpholin-4-yl)ethoxy]-3-oxo-1,3-dihydroisobenzofuran-5-yl]-4-methylhex-4-enoate,

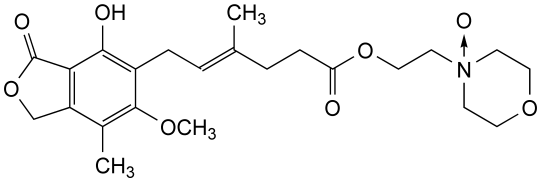


C. 2-(morpholin-4-yl)ethyl (4*Z*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate,

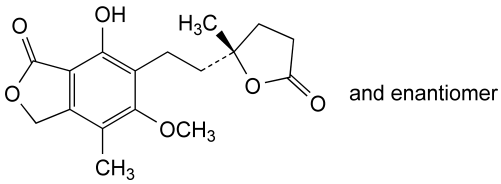


E. R = CH_3: methyl (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate,

F. R = H: (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid (mycophenolic acid),



G. 2-(morpholin-4-yl)ethyl (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate *N*-oxide,



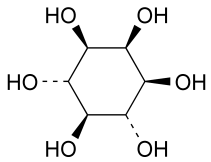
and enantiomer

H. 7-hydroxy-5-methoxy-4-methyl-6-[2-[(2*RS*)-2-methyl-5-oxotetrahydrofuran-2-yl]ethyl]isobenzofuran-1(3*H*)-one.

01/2008:1805

myo-INOSITOL

myo-Inositolum



$C_6H_{12}O_6$ M_r 180.2

DEFINITION

Cyclohexane-1,2,3,5/4,6-hexol.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *myo-inositol 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

Solution S. Dissolve 10.0 g in *distilled water R* and dilute to 100.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Conductivity (*2.2.38*): maximum 30 μS·cm^{-1}.

Dissolve 10.0 g in *carbon dioxide-free water R* prepared from *distilled water R*, with gentle warming if necessary, and dilute to 50.0 ml with the same solvent. Measure the conductivity of the solution while gently stirring with a magnetic stirrer.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.500 g of the substance to be examined in *water R* and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dissolve 0.500 g of *myo-inositol CRS* in *water R* and dilute to 10.0 ml with the same solvent.

Reference solution (b). Dilute 2.0 ml of the test solution to 100.0 ml with *water R*. Dilute 5.0 ml of this solution to 100.0 ml with *water R*.

Reference solution (c). Dissolve 0.5 g of *myo-inositol R* and 0.5 g of *mannitol R* in *water R* and dilute to 10 ml with the same solvent.

Column:

– *size*: *l* = 0.3 m, Ø = 7.8 mm;

– *stationary phase*: *strong cation exchange resin (calcium form) R* (9 μm);

– *temperature*: 85 °C.

Mobile phase: *water R*.

Flow rate: 0.5 ml/min.

Detection: refractometer maintained at a constant temperature (at about 30-35 °C for example).

Injection: 20 μl of the test solution and reference solutions (b) and (c).

Run time: twice the retention time of *myo*-inositol.

Relative retention with reference to *myo*-inositol (retention time = about 17.5 min): impurity A = about 1.3; impurity B = about 1.4.

System suitability: reference solution (c):

– *resolution*: minimum 4 between the peaks due to *myo*-inositol and impurity A.

Limits:

– *impurities A, B*: for each impurity, not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

– *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 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).

Barium. To 10 ml of solution S add 1 ml of *dilute sulphuric acid R*. When examined immediately, and after 1 h, any opalescence in the solution is not more intense than that in a mixture of 1 ml of *distilled water R* and 10 ml of solution S.

Lead (*2.4.10*): maximum 0.5 ppm.

Prepare the test solution by dissolving 20.0 g of the substance to be examined in 100 ml of *water R*, heating if necessary, and diluting to 200.0 ml with *dilute acetic acid R*.

Water (*2.5.12*): maximum 0.5 per cent, determined on 1.00 g.

ASSAY

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

Injection: test solution and reference solution (a).

Calculate the percentage content of $C_6H_{12}O_6$ from the declared content of *myo-inositol CRS*.

IMPURITIES

Specified impurities: A, B.

A. mannitol,

B. glycerol.