– *sum of impurities other than A and B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*): maximum 0.1 per cent, determined on 2.000 g.

ASSAY

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

Injection: test solution (b) and reference solution (a).

System suitability: reference solution (a):

– *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

Calculate the percentage content of $C_{10}H_{19}O_6PS_2$ from the declared content of *malathion CRS*.

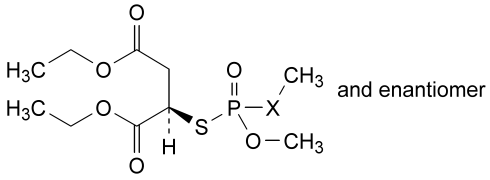
STORAGE

In an airtight container, protected from light.

IMPURITIES

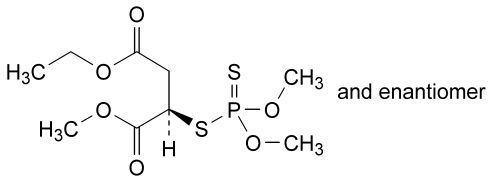
Specified impurities: A, B.

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. X = S: diethyl (2*RS*)-2-[(methoxy)(methylsulphanyl)-*S*-phosphinothioyl]butanedioate (isomalathion),

B. X = O: diethyl (2*RS*)-2-(dimethoxy-*S*-phosphinothioyl)-butanedioate (maloxon),

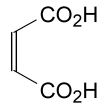


C. ethyl and methyl (2*RS*)-2-(dimethoxyphosphino-dithioyl)butanedioate (methyl analogue).

01/2008:0365
corrected 6.0

MALEIC ACID

Acidum maleicum



$C_4H_4O_4$ M_r 116.1
[110-16-7]

DEFINITION

Maleic acid contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of (*Z*)-butenedioic acid, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white, crystalline powder, freely soluble in water and in alcohol.

IDENTIFICATION

A. Dilute 5 ml of solution S (see Tests) to 10 ml with *water R*. The pH of the dilution is less than 2.

B. Examine the chromatograms obtained in the test for fumaric acid. The principal spot in the chromatogram obtained with test solution (b) is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Dissolve 0.1 g in 10 ml of *water R* (solution a). To 0.3 ml of solution (a) add a solution of 10 mg of *resorcinol R* in 3 ml of *sulphuric acid R*. Heat on a water-bath for 15 min; no colour develops. To 3 ml of solution (a) add 1 ml of *bromine water R*. Heat on a water-bath to remove the bromine (15 min), heat to boiling and cool. To 0.2 ml of this solution add a solution of 10 mg of *resorcinol R* in 3 ml of *sulphuric acid R*. Heat on a water-bath for 15 min. A violet-pink colour develops.

TESTS

Solution S. Dissolve 5.0 g in *water R* and dilute to 50 ml with the same solvent.

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

Fumaric acid. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* GF_{254} *R* as the coating substance.

Test solution (a). Dissolve 0.5 g of the substance to be examined in *acetone R* and dilute to 5 ml with the same solvent.

Test solution (b). Dilute 1 ml of test solution (a) to 50 ml with *acetone R*.

Reference solution (a). Dissolve 20 mg of *maleic acid CRS* in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 15 mg of *fumaric acid CRS* in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (c). Mix 5 ml of reference solution (a) and 5 ml of reference solution (b).

Apply separately to the plate 5 µl of test solutions (a) and (b), 5 µl of reference solutions (a) and (b) and 10 µl of reference solution (c). Develop in a non-saturated tank over a path of 10 cm using a mixture of 12 volumes of *anhydrous formic acid R*, 16 volumes of *chloroform R*, 32 volumes of *butanol R* and 44 volumes of *heptane R*. Dry the plate at 100 °C for 15 min and examine in ultraviolet light at 254 nm. Any spot

corresponding to fumaric acid in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (b) (1.5 per cent). The test is not valid unless the chromatogram obtained with reference solution (c) shows two clearly separated spots.

Iron. To 10 ml of solution S add 2 ml of *dilute hydrochloric acid R* and 0.05 ml of *bromine water R*. After 5 min, remove the excess of bromine by passing a current of air and add 3 ml of *potassium thiocyanate solution R*. Shake. Prepare a standard at the same time and in the same manner, using a mixture of 5 ml of *iron standard solution (1 ppm Fe) R*, 1 ml of *dilute hydrochloric acid R*, 6 ml of *water R* and 0.05 ml of *bromine water R*. Allow both solutions to stand for 5 min. Any red colour in the test solution is not more intense than that in the standard (5 ppm).

Heavy metals (*2.4.8*). 1.0 g complies with limit test D for heavy metals (10 ppm). Prepare the standard using 1 ml of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*). Not more than 2.0 per cent, determined on 1.00 g by the semi-micro determination of water.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.500 g in 50 ml of *water R*. Titrate with *1 M sodium hydroxide* using 0.5 ml of *phenolphthalein solution R* as indicator.

1 ml of *1 M sodium hydroxide* is equivalent to 58.04 mg of $C_4H_4O_4$.

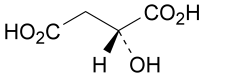
STORAGE

Store in a glass container, protected from light.

01/2008:2080
corrected 6.0

MALIC ACID

Acidum malicum



and enantiomer

$C_4H_6O_5$ M_r 134.1
[6915-15-7]

DEFINITION

(2*RS*)-2-Hydroxybutanedioic acid.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water and in alcohol, sparingly soluble in acetone.

IDENTIFICATION

A. Melting point (*2.2.14*): 128 °C to 132 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *Ph. Eur. reference spectrum of malic acid.*

TESTS

Solution S. Dissolve 5.00 g in *water R* and dilute to 25 ml with the same solvent.

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

Optical rotation (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

Water-insoluble substances: maximum 0.1 per cent.

Dissolve 25.0 g in 100 ml of *water R*, filter the solution through a tared sintered-glass filter (16) (*2.1.2*), wash the filter with hot *water R* and dry at 100-105 °C to constant weight. The residue weighs a maximum of 25 mg.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 100.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (a). Dissolve 10.0 mg of *fumaric acid R* and 4.0 mg of *maleic acid R* in 25 ml of the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (b). Dilute 2.5 ml of reference solution (a) to 100.0 ml with the mobile phase.

Reference solution (c). Dissolve 20.0 mg of the substance to be examined in the mobile phase, add 1.0 ml of reference solution (a) and dilute to 20.0 ml with the mobile phase.

Column:
- *size*: *l* = 0.30 m, Ø = 7.8 mm,
- *stationary phase*: *ion-exclusion resin for chromatography R* (9 µm),
- *temperature*: 37 °C.

Mobile phase: *0.005 M sulphuric acid.*

Flow rate: 0.6 ml/min.

Detection: spectrophotometer at 210 nm.

Injection: 20 µl.

Run time: twice the retention time of the principal peak in the chromatogram obtained with the test solution.

Relative retention with reference to malic acid (retention time = about 10 min): impurity B = about 0.8; impurity A = about 1.5.

System suitability: reference solution (c):
- *resolution*: minimum 2.5 between the peaks due to impurity B and malic acid.

Limits:
- *impurity A*: not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (b) (1.0 per cent),
- *impurity B*: not more than 0.25 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.05 per cent),
- *any other impurity*: for each impurity, not more than 0.5 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *total of other impurities*: not more than 2.5 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.5 per cent),
- *disregard limit*: 0.1 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.02 per cent).

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*.

Water (*2.5.12*): maximum 2.0 per cent, determined on 1.00 g.

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