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

Dissolve 1.0 g in 20 mL of *water R*. 12 mL of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 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 for 4 h.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

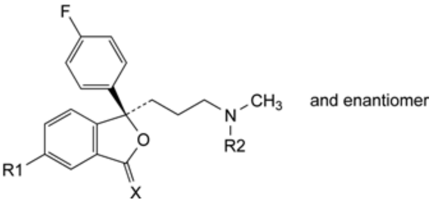
Dissolve 0.250 g in 50 mL of *ethanol (96 per cent) R* and add 0.5 mL of *0.1 M hydrochloric acid.* Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide.* Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 36.09 mg of $C_{20}H_{22}ClFN_2O$.

IMPURITIES

Specified impurities: 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*)*: A, C, D, E, F.*



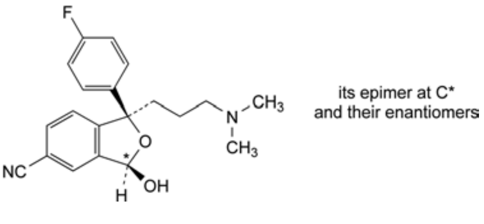
A. R1 = CO-NH$_2$, R2 = CH$_3$, X = H$_2$: (1*RS*)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxamide,

C. R1 = CN, R2 = CH$_3$, X = O: (3*RS*)-6-cyano-3-[3-(dimethylamino)propyl]-3-(4-fluorophenyl)isobenzofuran-1(3*H*)-one,

D. R1 = CN, R2 = H, X = H$_2$: (1*RS*)-1-(4-fluorophenyl)-1-[3-(methylamino)propyl]-1,3-dihydroisobenzofuran-5-carbonitrile,

E. R1 = Cl, R2 = CH$_3$, X = H$_2$: 3-[(1*RS*)-5-chloro-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-*N,N*-dimethylpropan-1-amine,

F. R1 = Br, R2 = CH$_3$, X = H$_2$: 3-[(1*RS*)-5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-*N,N*-dimethylpropan-1-amine,

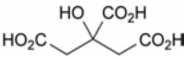


B. 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydroisobenzofuran-5-carbonitrile.

01/2008:0455
corrected 6.0

CITRIC ACID, ANHYDROUS

Acidum citricum anhydricum



$C_6H_8O_7$ M_r 192.1
[77-92-9]

DEFINITION

2-Hydroxypropane-1,2,3-tricarboxylic acid.

Content: 99.5 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder, colourless crystals or granules.

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

mp: about 153 °C, with decomposition.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Dissolve 1 g in 10 mL of *water R*. The solution is strongly acidic (*2.2.4*).

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: dry the substance to be examined and the reference substance at 100-105 °C for 2 h.

Comparison: *anhydrous citric acid CRS.*

C. Add about 5 mg to a mixture of 1 mL of *acetic anhydride R* and 3 mL of *pyridine R*. A red colour develops.

D. Dissolve 0.5 g in 5 mL of *water R*, neutralise using *1 M sodium hydroxide* (about 7 mL), add 10 mL of *calcium chloride solution R* and heat to boiling. A white precipitate is formed.

E. Water (see Tests).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7, BY_7 or GY_7 (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 10 mL with the same solvent.

Readily carbonisable substances. To 1.0 g in a cleaned test tube add 10 mL of *sulfuric acid R* and immediately heat the mixture in a water-bath at 90 ± 1 °C for 60 min. Cool rapidly immediately afterwards. The solution is not more intensely coloured than a mixture of 1 mL of red primary solution and 9 mL of yellow primary solution (*2.2.2, Method I*).

Oxalic acid: maximum 360 ppm, calculated as anhydrous oxalic acid.

Dissolve 0.80 g in 4 mL of *water R*. Add 3 mL of *hydrochloric acid R* and 1 g of *zinc R* in granules. Boil for 1 min. Allow to stand for 2 min. Transfer the supernatant liquid to a test-tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of a 50 g/L solution of *potassium ferricyanide R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 4 mL of a 0.1 g/L solution of *oxalic acid R*.

Sulfates (*2.4.13*): maximum 150 ppm.

Dissolve 2.0 g in *distilled water R* and dilute to 30 mL with the same solvent.

Aluminium (*2.4.17*): maximum 0.2 ppm, if intended for use in the manufacture of dialysis solutions.

Prescribed solution. Dissolve 20 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution. Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution. Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Heavy metals (*2.4.8*): maximum 10 ppm.

Dissolve 5.0 g in several portions in 39 mL of *dilute sodium hydroxide solution R* and dilute to 50 mL with *distilled water R*. 12 mL of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Water (*2.5.12*): maximum 1.0 per cent, determined on 2.000 g.

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

Bacterial endotoxins (*2.6.14*): less than 0.5 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Dissolve 0.550 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 64.03 mg of $C_6H_8O_7$.

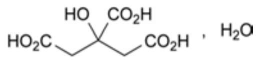
LABELLING

The label states, where applicable, that the substance is intended for use in the manufacture of dialysis solutions.

01/2008:0456
corrected 6.0

CITRIC ACID MONOHYDRATE

Acidum citricum monohydricum



$C_6H_8O_7,H_2O$ M_r 210.1
[5949-29-1]

DEFINITION

2-Hydroxypropane-1,2,3-tricarboxylic acid monohydrate.

Content: 99.5 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder, colourless crystals or granules, efflorescent.

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

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Dissolve 1 g in 10 mL of *water R*. The solution is strongly acidic (*2.2.4*).

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: dry the substance to be examined and the reference substance at 100-105 °C for 2 h.

Comparison: *citric acid monohydrate CRS*.

C. Add about 5 mg to a mixture of 1 mL of *acetic anhydride R* and 3 mL of *pyridine R*. A red colour develops.

D. Dissolve 0.5 g in 5 mL of *water R*, neutralise using *1 M sodium hydroxide* (about 7 mL), add 10 mL of *calcium chloride solution R* and heat to boiling. A white precipitate is formed.

E. Water (see Tests).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_7, BY_7 or GY_7 (*2.2.2, Method II*).

Dissolve 2.0 g in *water R* and dilute to 10 mL with the same solvent.

Readily carbonisable substances. To 1.0 g in a cleaned test tube add 10 mL of *sulfuric acid R* and immediately heat the mixture in a water-bath at 90 ± 1 °C for 60 min. Cool rapidly immediately afterwards. The solution is not more intensely coloured than a mixture of 1 mL of red primary solution and 9 mL of yellow primary solution (*2.2.2, Method I*).

Oxalic acid: maximum 360 ppm, calculated as anhydrous oxalic acid.

Dissolve 0.80 g in 4 mL of *water R*. Add 3 mL of *hydrochloric acid R* and 1 g of *zinc R* in granules. Boil for 1 min. Allow to stand for 2 min. Transfer the supernatant liquid to a test-tube containing 0.25 mL of a 10 g/L solution of *phenylhydrazine hydrochloride R* and heat to boiling. Cool rapidly, transfer to a graduated cylinder and add an equal volume of *hydrochloric acid R* and 0.25 mL of a 50 g/L solution of *potassium ferricyanide R*. Shake and allow to stand for 30 min. Any pink colour in the solution is not more intense than that in a standard prepared at the same time in the same manner using 4 mL of a 0.1 g/L solution of *oxalic acid R*.

Sulfates (*2.4.13*): maximum 150 ppm.

Dissolve 2.0 g in *distilled water R* and dilute to 30 mL with the same solvent.

Aluminium (*2.4.17*): maximum 0.2 ppm, if intended for use in the manufacture of dialysis solutions.

Prescribed solution. Dissolve 20 g in 100 mL of *water R* and add 10 mL of *acetate buffer solution pH 6.0 R*.

Reference solution. Mix 2 mL of *aluminium standard solution (2 ppm Al) R*, 10 mL of *acetate buffer solution pH 6.0 R* and 98 mL of *water R*.

Blank solution. Mix 10 mL of *acetate buffer solution pH 6.0 R* and 100 mL of *water R*.

Heavy metals (*2.4.8*): maximum 10 ppm.

Dissolve 5.0 g in several portions in 39 mL of *dilute sodium hydroxide solution R* and dilute to 50 mL with *distilled water R*. 12 mL of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Water (*2.5.12*): 7.5 per cent to 9.0 per cent, determined on 0.500 g.

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

Bacterial endotoxins (*2.6.14*): less than 0.5 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Dissolve 0.550 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 64.03 mg of $C_6H_8O_7$.

STORAGE

In an airtight container.