Limits:

- *impurity C*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *impurities A, B, D*: for each impurity, not more 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
- *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with the reference solution (b) (0.025 per cent).

Sulfates (*2.4.13*): maximum 0.1 per cent.

Dissolve 0.150 g in *distilled water R* and dilute to 15 mL with the same solvent.

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

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent. 12 mL of the freshly prepared solution complies with test A. Prepare the reference solution using *lead standard solution (2 ppm Pb) R*.

Loss on drying (*2.2.32*): 4.9 per cent to 5.3 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Dissolve 0.200 g in 10 mL of *0.01 M hydrochloric acid* previously cooled in iced water and titrate immediately, dropwise, with *0.05 M iodine*. Before each addition of *0.05 M iodine* dissolve the precipitate by swirling. At the end of the titration add 2 mL of *starch solution R* and titrate until the blue colour of the solution persists for at least 2 min. The temperature of the solution during the titration must not exceed 10 °C.

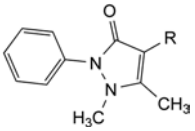
1 mL of *0.05 M iodine* is equivalent to 16.67 mg of $C_{13}H_{16}N_3NaO_4S$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities: *A, B, C, D.*



A. R = NHCHO: 4-formylamino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one,

B. R = NH_2: 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one,

C. R = $NHCH_3$: 4-methylamino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one,

D. R = $N(CH_3)_2$: 4-dimethylamino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one.

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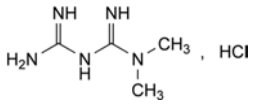
corrected 6.0

METFORMIN HYDROCHLORIDE

Metformini hydrochloridum



$C_4H_{12}ClN_5$ M_r 165.6
[1115-70-4]

DEFINITION

1,1-Dimethylbiguanide hydrochloride.

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

CHARACTERS

Appearance: white or almost white crystals.

Solubility: freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.

IDENTIFICATION

First identification: B, E.

Second identification: A, C, D, E.

A. Melting point (*2.2.14*): 222 °C to 226 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs of *potassium chloride R*.

Comparison: *metformin hydrochloride CRS*.

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

Test solution. Dissolve 20 mg of the substance to be examined in *water R* and dilute to 5 mL with the same solvent.

Reference solution. Dissolve 20 mg of *metformin hydrochloride CRS* in *water R* and dilute to 5 mL with the same solvent.

Plate: *TLC silica gel G plate R*.

Mobile phase: upper layer of a mixture of 10 volumes of *glacial acetic acid R*, 40 volumes of *butanol R* and 50 volumes of *water R*.

Application: 5 µL.

Development: over a path of 15 cm.

Drying: at 100-105 °C for 15 min.

Detection: spray with a mixture of equal volumes of a 100 g/L solution of *sodium nitroprusside R*, a 100 g/L solution of *potassium ferricyanide R* and a 100 g/L solution of *sodium hydroxide R*, prepared 20 min before use.

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.

D. Dissolve about 5 mg in *water R* and dilute to 100 mL with the same solvent. To 2 mL of the solution add 0.25 mL of *strong sodium hydroxide solution R* and 0.10 mL of *α-naphthol solution R*. Mix and allow to stand in iced water for 15 min. Add 0.5 mL of *sodium hypobromite solution R* and mix. A pink colour develops.

E. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent.

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

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.50 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a). Dissolve 20.0 mg of *cyanoguanidine R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL to 200.0 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (c). Dissolve 10.0 mg of *melamine R* in about 90 mL of *water R*. Add 5.0 mL of the test solution and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: irregular, porous silica gel to which benzenesulfonic acid groups have been chemically bonded (10 µm),

or

– *size*: *l* = 0.11 m, Ø = 4.7 mm,
– *stationary phase*: regular, porous silica gel to which benzenesulfonic acid groups have been chemically bonded (5 µm).

Mobile phase: 17 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 218 nm.

Injection: 20 µL.

Run time: twice the retention time of metformin hydrochloride.

System suitability: reference solution (c):

– *resolution*: minimum of 10 between the peaks due to melamine and to metformin hydrochloride.

Limits:

– *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.02 per cent),
– *any other impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

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

12 mL of solution S complies with limit test A. Prepare the standard 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 5 h.

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

ASSAY

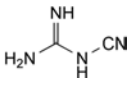
Dissolve 0.100 g in 4 mL of *anhydrous formic acid R*. Add 80 mL of *acetonitrile R*. Carry out the titration immediately. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 16.56 mg of $C_4H_{12}ClN_5$.

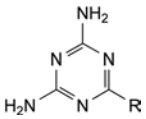
IMPURITIES

Specified impurities: A.

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*): *B, C, D, E, F.*



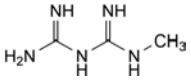
A. cyanoguanidine,



B. R = NH-C(=NH)-NH_2: (4,6-diamino-1,3,5-triazin-2-yl)guanidine,

C. R = $N(CH_3)_2$: *N,N*-dimethyl-1,3,5-triazine-2,4,6-triamine,

D. R = NH_2: 1,3,5-triazine-2,4,6-triamine (melamine),



E. 1-methylbiguanide,

F. CH_3-NH-CH_3: *N*-methylmethanamine.

01/2008:1128
corrected 7.0

METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1)

Acidi methacrylici et ethylis acrylatis polymerisatum 1:1

DEFINITION

Copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1:1. The substance is in the acid form (type A) or partially neutralised using sodium hydroxide (type B). It may contain suitable surface-active agents such as sodium dodecyl sulfate and polysorbate 80.

Content:

– type A: 46.0 per cent to 50.6 per cent of methacrylic acid units (dried substance);
– type B: 43.0 per cent to 48.0 per cent of methacrylic acid units (dried substance).

CHARACTERS

Appearance: white or almost white, free-flowing powder.

Solubility: practically insoluble in water (type A) or dispersible in water (type B), freely soluble in anhydrous ethanol, practically insoluble in ethyl acetate. It is freely soluble in a 40 g/L solution of sodium hydroxide.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: dissolve 0.1 g of the substance to be examined in 1 mL of *ethanol (90 per cent V/V) R*, and place 2 drops of the solution on a sodium chloride plate; dry to allow the formation of a film and cover with another sodium chloride plate.

Comparison: *Methacrylic acid - ethyl acrylate copolymer (1:1) (type A or type B) CRS*.

B. It complies with the limits of the assay.

C. Sulfated ash (see Tests).

TESTS

Ethyl acrylate and methacrylic acid. Liquid chromatography (*2.2.29*).

Blank solution. To 50.0 mL of *methanol R* add 25.0 mL of the mobile phase.

Test solution. Dissolve 40 mg of the substance to be examined in 50.0 mL of *methanol R* and add 25.0 mL of the mobile phase.

Reference solution. Dissolve 10 mg of *ethyl acrylate R* and 10 mg of *methacrylic acid R* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 0.1 mL of this solution to 50.0 mL with *methanol R* and add 25.0 mL of the mobile phase.

Column:

– *size*: *l* = 0.10 m, Ø = 4 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *methanol R, phosphate buffer solution pH 2.0 R* (30:70 *V/V*).

Flow rate: 2.5 mL/min.

Detection: spectrophotometer at 202 nm.

Injection: 50 µL.

System suitability:

– *resolution*: minimum 2.0 between the peaks due to ethyl acrylate and methacrylic acid in the chromatogram obtained with the reference solution;

Monographs M