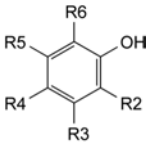
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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, D, E, F, G, H, I, J, K, L, M.*



A. R2 = R3 = R4 = R5 = R6 = H: phenol,

B. R2 = CH_3, R3 = R4 = R5 = R6 = H: 2-methylphenol (*o*-cresol, cresol),

C. R2 = R3 = R5 = R6 = H, R4 = CH_3: 4-methylphenol (*p*-cresol),

D. R2 = R6 = CH_3, R3 = R4 = R5 = H: 2,6-dimethylphenol (2,6-xylenol),

E. R2 = C_2H_5, R3 = R4 = R5 = R6 = H: 2-ethylphenol (*o*-ethylphenol),

F. R2 = R4 = CH_3, R3 = R5 = R6 = H: 2,4-dimethylphenol (2,4-xylenol),

G. R2 = R5 = CH_3, R3 = R4 = R6 = H: 2,5-dimethylphenol (2,5-xylenol),

H. R2 = $CH(CH_3)_2$, R3 = R4 = R5 = R6 = H: 2-(1-methylethyl)phenol,

I. R2 = R3 = CH_3, R4 = R5 = R6 = H: 2,3-dimethylphenol (2,3-xylenol),

J. R2 = R4 = R6 = H, R3 = R5 = CH_3: 3,5-dimethylphenol (3,5-xylenol),

K. R2 = R3 = R5 = R6 = H, R4 = C_2H_5: 4-ethylphenol (*p*-ethylphenol),

L. R2 = R5 = R6 = H, R3 = R4 = CH_3: 3,4-dimethylphenol (3,4-xylenol),

M. R2 = R3 = R5 = CH_3, R4 = R6 = H: 2,3,5-trimethylphenol.

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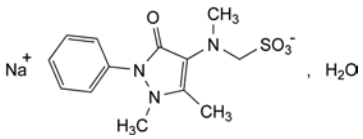
METAMIZOLE SODIUM

Metamizolum natricum



$C_{13}H_{16}N_3NaO_4S,H_2O$ M_r 351.4
[5907-38-0]

DEFINITION

Sodium [(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-methylamino]methanesulfonate monohydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *metamizole sodium CRS.*

B. Dissolve 50 mg in 1 mL of *strong hydrogen peroxide solution R*. A blue colour is produced which fades rapidly and turns to intense red in a few minutes.

C. Place 0.10 g in a test tube, add some glass beads and dissolve the substance in 1.5 mL of *water R*. Add 1.5 mL of *dilute hydrochloric acid R* and place a filter paper wetted with a solution of 20 mg of *potassium iodate R* in 2 mL of *starch solution R* at the open end of the test tube. Heat gently, the evolving vapour of sulfur dioxide colours the filter paper blue. After heating gently for 1 min take a glass rod with a drop of a 10 g/L solution of *chromotropic acid, sodium salt R* in *sulfuric acid R* and place in the opening of the tube. Within 10 min, a blue-violet colour develops in the drop of the reagent.

D. 0.5 mL of solution S (see Tests) gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 40 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and immediately after preparation, not more intensely coloured than reference solution BY_6 (*2.2.2, Method I*).

Acidity or alkalinity. To 5 mL of solution S, add 0.1 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.1 mL of *0.02 M sodium hydroxide* is required to change the colour of the indicator to pink.

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 50.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 10.0 mg of *metamizole impurity A CRS* in *methanol R* and dilute to 20.0 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 20.0 mL with *methanol R*.

Reference solution (c). Dissolve 40 mg of *metamizole sodium CRS* in *methanol R* and dilute to 20.0 mL with the same solvent.

Reference solution (d). In order to prepare impurity C *in situ*, boil 10 mL of reference solution (c) under reflux for 10 min. Allow to cool to room temperature and dilute to 20.0 mL with *methanol R*.

Reference solution (e). To 6 mL of reference solution (a) add 1 mL of reference solution (c).

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 28 volumes of *methanol R* and 72 volumes of a buffer solution prepared as follows : mix 1000 volumes of a 6.0 g/L solution of *sodium dihydrogen phosphate R* and 1 volume of *triethylamine R*, then adjust to pH 7.0 with *strong sodium hydroxide solution R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µL of the test solution and reference solutions (b), (d) and (e).

Run time: 3.5 times the retention time of metamizole.

Elution order: impurity A, metamizole, impurity B, impurity C, impurity D.

System suitability: reference solution (e):

– *resolution*: minimum 2.5 between the peaks due to impurity A and metamizole.

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.

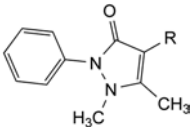
1 mL of *0.05 M iodine* is equivalent to 16.67 mg of $C_{13}H_{16}N_3NaO_4S$.

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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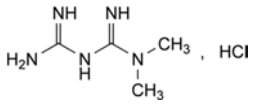
corrected 6.0

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,