Detection: examine in ultraviolet light at 254 nm (identification C), then spray with *dimethylaminobenzaldehyde solution R1* and allow to dry in air.

System suitability: reference solution (a):

– the chromatogram shows 2 clearly separated spots.

Limit: test solution (b):

– *impurity E*: any spot due to impurity E (not visualised in ultraviolet light at 254 nm) is not more intense than the corresponding spot in the chromatogram obtained with reference solution (b) (0.2 per cent).

B. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a). Dilute 0.2 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b). Dissolve 10 mg of *metoclopramide impurity A CRS* in the mobile phase and dilute to 100 mL with the mobile phase. Mix 1 mL of this solution with 0.1 mL of the test solution and dilute to 10 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 6.8 g of *potassium dihydrogen phosphate R* in 700 mL of *water R*; add 0.2 mL of *N,N-dimethyloctylamine R* and adjust to pH 4.0 with *dilute phosphoric acid R*; dilute to 1000 mL with *water R*, add 250 mL of *acetonitrile R* and mix.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 240 nm.

Injection: 10 µL.

Run time: 8 times the retention time of metoclopramide.

Relative retention with reference to metoclopramide (retention time = about 3.6 min): impurity A = about 0.82; impurity F = about 0.89; impurity H = about 0.91; impurity G = about 1.7; impurity C = about 2.7; impurity D = about 2.8; impurity B = about 6.4.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to impurity A and metoclopramide .

Limits:

– *impurities A, B, C, D, F, G, H*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent);

– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

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

1.0 g complies with test C. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

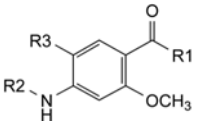
ASSAY

Dissolve 0.250 g in 50 mL of *anhydrous acetic acid R* and add 5 mL of *acetic anhydride 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 29.98 mg of $C_{14}H_{22}ClN_3O_2$.

IMPURITIES

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

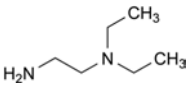


A. R1 = NH-CH_2-CH_2-N(C_2H_5)$_2$, R2 = CO-CH_3, R3 = Cl: 4-(acetylamino)-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide,

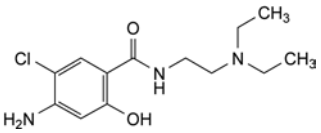
B. R1 = OCH_3, R2 = CO-CH_3, R3 = Cl: methyl 4-(acetylamino)-5-chloro-2-methoxybenzoate,

C. R1 = OH, R2 = H, R3 = Cl: 4-amino-5-chloro-2-methoxybenzoic acid,

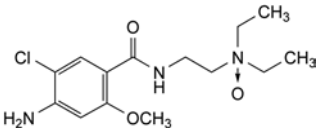
D. R1 = OCH_3, R2 = CO-CH_3, R3 = H: methyl 4-(acetylamino)-2-methoxybenzoate,



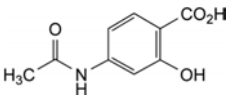
E. *N,N*-diethylethane-1,2-diamine,



F. 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-hydroxybenzamide,



G. *N'*-(4-amino-5-chloro-2-methoxybenzoyl)-*N,N*-diethylethane-1,2-diamine *N*-oxide,

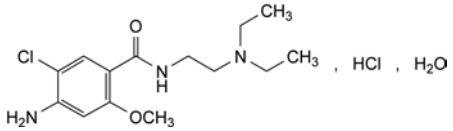


H. 4-(acetylamino)-2-hydroxybenzoic acid.

01/2008:0674

METOCLOPRAMIDE HYDROCHLORIDE

Metoclopramidi hydrochloridum



$C_{14}H_{23}Cl_2N_3O_2,H_2O$ M_r 354.3
[54143-57-6]

DEFINITION

Metoclopramide hydrochloride contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide hydrochloride, calculated with reference to the anhydrous substance.

CHARACTERS

White or almost white, crystalline powder or crystals, very soluble in water, freely soluble in alcohol, sparingly soluble in methylene chloride.

It melts at about 183 °C with decomposition.

IDENTIFICATION

First identification: A, B, D.

Second identification: A, C, D, E.

A. The pH (*2.2.3*) of solution S (see Tests) is 4.5 to 6.0.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *metoclopramide hydrochloride CRS*. Examine the substances as discs prepared using *potassium chloride R*.

C. Examine the chromatograms obtained in the test for related substances in ultraviolet light before spraying with *dimethylaminobenzaldehyde solution R1*. 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).

D. Dilute 1 mL of solution S to 2 mL with *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

E. Dissolve about 2 mg in 2 mL of *water R*. The solution gives the reaction of primary aromatic amines (*2.3.1*).

TESTS

Solution S. Dissolve 2.5 g in *carbon dioxide-free 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*).

Related substances. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* HF_{254} *R* as the coating substance.

Test solution (a). Dissolve 0.40 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b). Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a). Dissolve 20 mg of *metoclopramide hydrochloride CRS* in *methanol R* and dilute to 5 mL with the same solvent.

Reference solution (b). Dilute 5 mL of test solution (a) to 100 mL with *methanol R*. Dilute 1 mL of this solution to 10 mL with *methanol R*.

Reference solution (c). Dissolve 10 mg of *N,N-diethylethylenediamine R* in *methanol R* and dilute to 50 mL with the same solvent.

Apply separately to the plate 5 µL of each solution. Develop over a path of 12 cm using a mixture of 2 volumes of *concentrated ammonia R*, 10 volumes of *dioxan R*, 14 volumes of *methanol R* and 90 volumes of *methylene chloride R*. Allow the plate to dry in air. Examine in ultraviolet light at 254 nm. Any spot in the chromatogram obtained with test solution (a), apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.5 per cent). Spray with *dimethylaminobenzaldehyde solution R1*. Allow the plate to dry in air. Any spot in the chromatogram obtained with test solution (a) that has not been visualised in ultraviolet light at 254 nm is not more intense than the spot in the chromatogram obtained with reference solution (c) (0.5 per cent).

Heavy metals (*2.4.8*). 12 mL of solution S complies with limit test A for heavy metals (20 ppm). Prepare the standard using *lead standard solution (2 ppm Pb) R*.

Water (*2.5.12*): 4.5 per cent to 5.5 per cent, determined on 0.500 g by the semi-micro determination of water.

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

ASSAY

Dissolve 0.2500 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *alcohol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume of *0.1 M sodium hydroxide* added between the two points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 33.63 mg of $C_{14}H_{23}Cl_2N_3O_2$.

STORAGE

Store protected from light.

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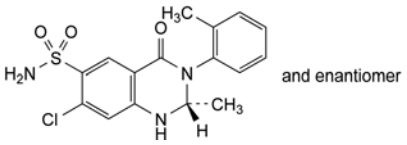
corrected 6.0

METOLAZONE

Metolazonum



$C_{16}H_{16}ClN_3O_3S$ M_r 365.8

DEFINITION

(2*RS*)-7-Chloro-2-methyl-3-(2-methylphenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide.

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

CHARACTERS

Appearance: white or slightly yellowish, crystalline powder.

Solubility: very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethyl acetate, very slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *metolazone CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *anhydrous ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 30.0 mg of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.

Test solution (b). Dilute 2.0 mL of test solution (a) to 100.0 mL with *methanol R*.

Reference solution (a). Dissolve 3.0 mg of *metolazone for system suitability CRS* (containing impurities A, B, C, D and E) in 1 mL of *methanol R*.

Reference solution (b). Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*. Dilute 5.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c). Dissolve 30.0 mg of *metolazone CRS* in *methanol R* and dilute to 10.0 mL with the same solvent. Dilute 2.0 mL of this solution to 100.0 mL with *methanol R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 30 °C.