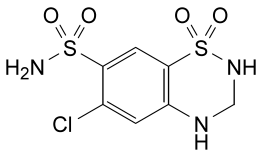
01/2008:0394

HYDROCHLOROTHIAZIDE

Hydrochlorothiazidum



$C_7H_8ClN_3O_4S_2$ M_r 297.7
[58-93-5]

DEFINITION

6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

IDENTIFICATION

First identification: B.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 50.0 mg in 10 ml of *0.1 M sodium hydroxide* and dilute to 100.0 ml with *water R*. Dilute 2.0 ml of this solution to 100.0 ml with *0.01 M sodium hydroxide*.

Spectral range: 250-350 nm.

Absorption maxima: at 273 nm and 323 nm.

Absorbance ratio: A_{273}/A_{323} = 5.4 to 5.7.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *hydrochlorothiazide CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of *ethanol R1*, evaporate to dryness and record new spectra using the residues.

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

Test solution. Dissolve 50 mg of the substance to be examined in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 50 mg of *hydrochlorothiazide CRS* in *acetone R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 25 mg of *chlorothiazide R* in reference solution (a) and dilute to 5 ml with reference solution (a).

Plate: *TLC silica gel F_{254} plate R.*

Mobile phase: *ethyl acetate R.*

Application: 2 µl.

Development: over a path of 10 cm.

Drying: in a current of air.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated spots.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Gently heat about 1 mg with 2 ml of a freshly prepared 0.5 g/l solution of *chromotropic acid, sodium salt R* in a cooled mixture of 35 volumes of *water R* and 65 volumes of *sulphuric acid R*. A violet colour develops.

TESTS

Acidity or alkalinity. Shake 0.5 g of the powdered substance to be examined with 25 ml of *water R* for 2 min and filter. To 10 ml of the filtrate, add 0.2 ml of *0.01 M sodium hydroxide* and 0.15 ml of *methyl red solution R*. The solution is yellow. Not more than 0.4 ml of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture. Dilute 50.0 ml of a mixture of equal volumes of *acetonitrile R* and *methanol R* to 200.0 ml with *phosphate buffer solution pH 3.2 R1*.

Test solution. Dissolve 30.0 mg of the substance to be examined in 5 ml of a mixture of equal volumes of *acetonitrile R* and *methanol R*, using sonication if necessary, and dilute to 20.0 ml with *phosphate buffer solution pH 3.2 R1*.

Reference solution (a). Dissolve 15 mg of *hydrochlorothiazide CRS* and 15 mg of *chlorothiazide CRS* (impurity A) in 25 ml of a mixture of equal volumes of *acetonitrile R* and *methanol R*, using sonication if necessary, and dilute to 100 ml with *phosphate buffer solution pH 3.2 R1*. Dilute 5 ml of this solution to 100 ml with the solvent mixture.

Reference solution (b). Dilute 1.0 ml of the test solution to 50.0 ml with the solvent mixture. Dilute 5.0 ml of this solution to 20.0 ml with the solvent mixture.

Column:

– *size*: *l* = 0.1 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 µm).

Mobile phase:

– *mobile phase A*: to 940 ml of *phosphate buffer solution pH 3.2 R1* add 60.0 ml of *methanol R* and 10.0 ml of *tetrahydrofuran R* and mix;

– *mobile phase B*: to a mixture of 500 ml of *methanol R* and 500 ml of *phosphate buffer solution pH 3.2 R1* add 50.0 ml of *tetrahydrofuran R* and mix;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 17	100 → 55	0 → 45
17 - 30	55	45
30 - 35	55 → 100	45 → 0
35 - 50	100	0

Flow rate: 0.8 ml/min.

Detection: spectrophotometer at 224 nm.

Equilibration: with mobile phase A for at least 20 min.

Injection: 10 µl; inject the solvent mixture as a blank.

Retention time: impurity A = about 7 min; hydrochlorothiazide = about 8 min.

System suitability: reference solution (a):

– *resolution*: minimum 2.5 between the peaks due to impurity A and hydrochlorothiazide; if necessary, adjust slightly the composition of the mobile phase or the time programme of the linear gradient.

Limits:

– *impurities A, B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);

– *total*: 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).

Chlorides (*2.4.4*): maximum 100 ppm.

Dissolve 1.0 g in 25 ml of *acetone R* and dilute to 30 ml with *water R*. Prepare the standard using 5 ml of *acetone R* containing 15 per cent *V/V* of *water R* and 10 ml of *chloride standard solution (5 ppm Cl) 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.

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

ASSAY

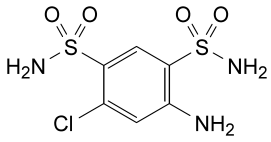
Dissolve 0.120 g in 50 ml of *dimethyl sulphoxide R*. Titrate with *0.1 M tetrabutylammonium hydroxide in 2-propanol*, determining the end-point potentiometrically (*2.2.20*) at the 2nd point of inflexion. Carry out a blank titration.

1 ml of *0.1 M tetrabutylammonium hydroxide in 2-propanol* is equivalent to 14.88 mg of $C_7H_8ClN_3O_4S_2$.

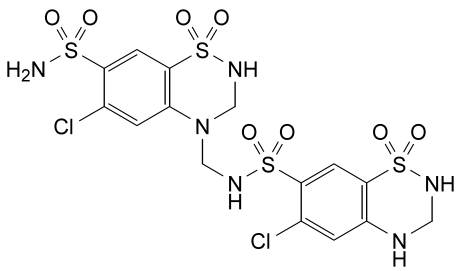
IMPURITIES

Specified impurities: *A, B, C*.

A. chlorothiazide,



B. 4-amino-6-chlorobenzene-1,3-disulphonamide (salamide),

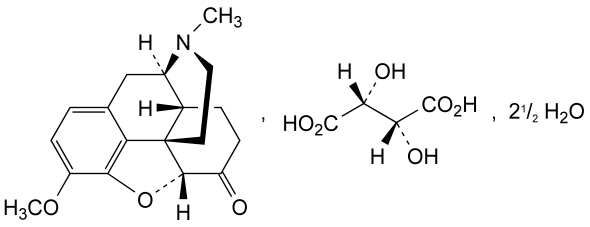


C. 6-chloro-*N*-[(6-chloro-7-sulphamoyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazin-4-yl 1,1-dioxide)methyl]-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

01/2008:1784

HYDROCODONE HYDROGEN TARTRATE 2.5-HYDRATE

Hydrocodoni hydrogenotartras 2.5-hydricus



$C_{22}H_{27}NO_9,2.5H_2O$ M_r 494.5

DEFINITION

4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate 2.5-hydrate.

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

CHARACTERS

Appearance: white or almost white, hygroscopic, crystalline powder.

Solubility: freely soluble or soluble in water, sparingly soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *hydrocodone hydrogen tartrate 2.5-hydrate CRS*.

If the spectra obtained in the solid state show differences, dry the substance to be examined and the reference substance at 105 °C and record new spectra using the residues.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

Dissolve 0.5 g in *water R* and dilute to 10 ml with the same solvent.

pH (*2.2.3*): 3.2 to 3.8.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 50.0 ml with the same solvent.

Specific optical rotation (*2.2.7*): – 87 to – 91 (anhydrous substance).

Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 50.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in mobile phase A and dilute to 10.0 ml with mobile phase A.

Reference solution (a). Dissolve 5 mg of *oxycodone hydrochloride CRS* (impurity D) in mobile phase A, add 0.5 ml of the test solution and dilute to 5.0 ml with mobile phase A.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with mobile phase A. Dilute 1.0 ml of this solution to 10.0 ml with mobile phase A.