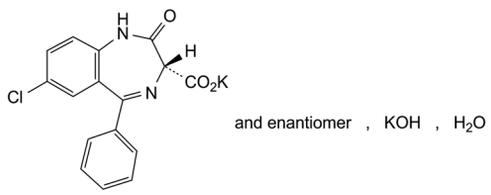
04/2019:0898

DIPOTASSIUM CLORAZEPATE MONOHYDRATE

Dikalii clorazepas monohydricus



$C_{16}H_{11}ClK_2N_2O_4,H_2O$ M_r 426.9

DEFINITION

Potassium (3*RS*)-7-chloro-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine-3-carboxylate compound with potassium hydroxide (1:1) monohydrate.

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

CHARACTERS

Appearance: white or light yellow, crystalline powder, hygroscopic.

Solubility: freely soluble to very soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

Solutions in water and in ethanol (96 per cent) are unstable and are to be used immediately.

IDENTIFICATION

First identification: *B, E.*

Second identification: *A, C, D, E.*

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

Test solution (a). Dissolve 10.0 mg in a 0.3 g/L solution of *potassium carbonate R* and dilute to 100.0 mL with the same solution.

Test solution (b). Dilute 10.0 mL of test solution (a) to 100.0 mL with a 0.3 g/L solution of *potassium carbonate R*.

Spectral range: 280-350 nm for test solution (a); 220-280 nm for test solution (b).

Absorption maxima: about 315 nm (broad) for test solution (a); 230 nm for test solution (b).

Specific absorbance at the absorption maxima:

- 230 nm: 800 to 870;
- 315 nm: 49 to 56.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *Ph. Eur. reference spectrum of dipotassium clorazepate.*

C. Dissolve about 20 mg in 2 mL of *sulfuric acid R*. Observed in ultraviolet light at 365 nm, the solution shows yellow fluorescence.

D. Dissolve 0.5 g in 5 mL of *water R*. Add 0.1 mL of *thymol blue solution R*. The solution is violet-blue.

E. Place 1.0 g in a crucible and add 2 mL of *dilute sulfuric acid R*. Heat at first on a water-bath, then ignite until all black particles have disappeared. Allow to cool. Take up the residue with *water R* and dilute to 20 mL with the same solvent. The solution gives reaction (b) of potassium (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution GY_5 (*2.2.2, Method II*).

Rapidly dissolve 2.0 g with shaking in *water R* and dilute to 20.0 mL with the same solvent. Observe immediately.

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

Solution A. Dissolve 11.7 g of *dipotassium hydrogen phosphate R* in about 900 mL of *water R*, adjust to pH 7.0 with *phosphoric acid R* and dilute to 1000 mL with *water R*. Mix equal volumes of this solution and *methanol R*.

Solution B: *methanol R*, 20 g/L solution of *potassium carbonate R* (30:70 *V/V*).

Test solution (a). Dissolve 10.0 mg of the substance to be examined in solution A and dilute to 20.0 mL with solution A.

Test solution (b). Dissolve 10.0 mg of the substance to be examined in solution B cooled to 0 °C and dilute to 20.0 mL with solution B.

Reference solution (a). Dilute 1.0 mL of test solution (a) to 100.0 mL with solution A. Dilute 2.0 mL of this solution to 20.0 mL with solution A.

Reference solution (b). Dissolve 15 mg of *aminochlorobenzophenone R* (impurity A) and 15 mg of *ethyl clorazepate R* (impurity C) in *methanol R* and dilute to 20 mL with the same solvent. Dilute 1 mL of the solution to 20 mL with *methanol R*.

Reference solution (c). Dissolve 15 mg of *nordazepam R* (impurity B) in *methanol R* and dilute to 20 mL with the same solvent. Dilute 1 mL of the solution to 20 mL with solution B.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

- *mobile phase A*: dissolve 1.17 g of *dipotassium hydrogen phosphate R* in about 580 mL of *water for chromatography R*, adjust to pH 8.0 with *phosphoric acid R*, dilute to 650 mL with *water for chromatography R*, and add 450 mL of *methanol R1*;
- *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	80	20
5 - 20	80 → 50	20 → 50
20 - 25	50	50

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 230 nm.

Autosampler: set at 4 °C.

Injection: 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

Relative retention with reference to clorazepate (retention time = about 3 min): impurity B = about 4.6; impurity C = about 5.9; impurity A = about 6.5.

System suitability: reference solution (b):

- *resolution*: minimum 2.5 between the peaks due to impurities C and A.

Calculation of percentage contents:

- for each impurity, use the concentration of dipotassium clorazepate monohydrate in reference solution (a).

Limits:

- *impurity C*: maximum 0.3 per cent;

– *unspecified impurities*: for each impurity, maximum 0.10 per cent;
– *total*: maximum 0.4 per cent;
– *reporting threshold*: 0.05 per cent; disregard the peak due to impurity B.

Impurity B. Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection: test solution (b) and reference solutions (a) and (c).

Calculation of percentage content:
– *correction factor*: multiply the peak area of impurity B by 0.6;
– use the concentration of dipotassium clorazepate monohydrate in reference solution (a).

Limit:
– *impurity B*: maximum 0.2 per cent.

Water (*2.5.12*): 3.5 per cent to 5.5 per cent, determined on 0.250 g.

ASSAY

Dissolve 0.130 g in 10 mL of *anhydrous acetic acid R*. Add 30 mL of *methylene chloride R*. Titrate with *0.1 M perchloric acid*, determining the 2 points of inflexion by potentiometry (*2.2.20*).

At the 2nd point of inflexion, 1 mL of *0.1 M perchloric acid* is equivalent to 13.03(1) mg of $C_{16}H_{11}ClK_2N_2O_4$.

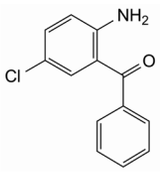
STORAGE

In an airtight container, protected from light.

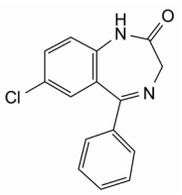
IMPURITIES

Specified impurities: B, C.

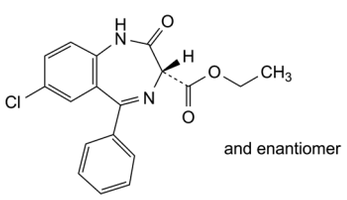
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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*.



A. (2-amino-5-chlorophenyl)(phenyl)methanone (aminochlorobenzophenone),



B. 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (nordazepam),



C. ethyl (3*RS*)-7-chloro-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine-3-carboxylate (ethyl clorazepate).

(1) It has been brought to our attention that the graphic formula in the monograph perhaps should not show a free molecule of water. The substance may be a monohydrate or an anhydrous compound with potassium hydroxide (1:1). Furthermore, the semi-micro determination of water may be affected by a systematic error, where one molecule of free potassium hydroxide could release one molecule of water into the acidic Karl Fischer medium. In order to investigate this issue, a revision of the monograph is ongoing where the degree of hydration of dipotassium clorazepate and the suitability of the semi-micro determination of water for this substance are being examined. Pending completion of the revision work, a conversion factor of 13.03 is prescribed.