ASSAY

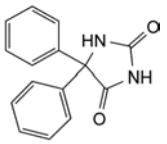
Dissolve 0.1500 g in a mixture of 5 mL of *0.01 M hydrochloric acid* and 50 mL of *alcohol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the two points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.77 mg of $C_9H_{14}ClNO$.

04/2009:1253

PHENYTOIN

Phenytoinum



$C_{15}H_{12}N_2O_2$ M_r 252.3
[57-41-0]

DEFINITION

5,5-Diphenylimidazolidine-2,4-dione.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

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

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *phenytoin CRS*.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 1.0 g in a mixture of 5 mL of *1 M sodium hydroxide* and 20 mL of *water R*.

Acidity or alkalinity. To 1.0 g add 45 mL of *water R* and boil for 2 min. Allow to cool and filter. Wash the filter with *carbon dioxide-free water R* and dilute the combined filtrate and washings to 50 mL with the same solvent. To 10 mL of the solution add 0.15 mL of *methyl red solution R*. Not more than 0.5 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red. To 10 mL of the solution add 0.15 mL of *bromothymol blue solution R1*. Not more than 0.5 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 2 mg of *2,2-diphenylglycine R* (impurity C) in 100.0 mL of the mobile phase.

Reference solution (c). Dissolve 10 mg of *phenytoin for system suitability CRS* (containing impurities D and E) in the mobile phase, add 1.0 mL of reference solution (b) and dilute to 10.0 mL with the mobile phase.

Column:

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

Mobile phase: mix 20 volumes of *methanol R2*, 35 volumes of *acetonitrile R1* and 45 volumes of a 5.75 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 220 nm.

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

Run time: 4 times the retention time of phenytoin.

Identification of impurities: use the chromatogram supplied with *phenytoin for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C, D and E.

Relative retention with reference to phenytoin (retention time = about 4 min): impurity C = about 0.5; impurity D = about 0.6; impurity E = about 0.8.

System suitability: reference solution (c):

– *resolution*: minimum 3.5 between the peaks due to impurities D and E.

Limits:

– *correction factors*: for the calculation of content, multiply the peaks areas of the following impurities by the corresponding correction factor: impurity D = 1.7; impurity E = 1.4;
– *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
– *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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

2.0 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 0.5 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

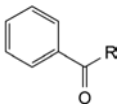
Dissolve 0.200 g in 50 mL of *dimethylformamide R*. Titrate with *0.1 M sodium methoxide*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M sodium methoxide* is equivalent to 25.23 mg of $C_{15}H_{12}N_2O_2$.

IMPURITIES

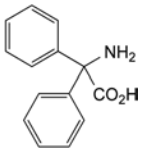
Specified impurities: C, D, E.

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, B, F.*

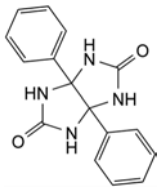


A. R = C_6H_5: diphenylmethanone (benzophenone),

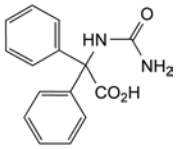
B. R = CO-C_6H_5: diphenylethanedione (benzil),



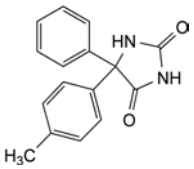
C. amino(diphenyl)acetic acid (2,2-diphenylglycine),



D. 3a,6a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione,



E. (carbamoylamino)(diphenyl)acetic acid,

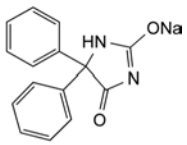


F. 5-(4-methylphenyl)-5-phenylimidazolidine-2,4-dione.

04/2009:0521

PHENYTOIN SODIUM

Phenytoinum natricum



$C_{15}H_{11}N_2NaO_2$ M_r 274.3
[630-93-3]

DEFINITION

Sodium 4-oxo-5,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-olate.

Content: 98.5 per cent to 100.5 per cent (anhydrous substance).

CHARACTERS

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

Solubility: soluble in water and in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

First identification: A, C.

Second identification: B, C.

A. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: suspend 0.1 g in 20 mL of *water R*. Acidify with *dilute hydrochloric acid R* and shake with 3 quantities, each of 30 mL, of *ethyl acetate R*. Wash the combined ethyl acetate layers with *water R*, evaporate to dryness and dry the residue at 100-105 °C (test residue). Repeat the operations using 0.1 g of *phenytoin sodium CRS* (reference residue). Examine as discs prepared using *potassium bromide R*.

Comparison: *phenytoin sodium CRS*.

B. To about 10 mg add 1 mL of *water R* and 0.05 mL of *ammonia R*. Heat until boiling begins. Add 0.05 mL of a 50 g/L solution of *copper sulfate R* in *dilute ammonia R2* and shake. A pink, crystalline precipitate is formed.

C. Ignite 1 g and cool. Add 2 mL of *water R* to the residue and neutralise the solution with *hydrochloric acid R*. Filter and dilute the filtrate to 4 mL with *water R*. 0.1 mL of the solution gives reaction (b) of sodium (*2.3.1*).

TESTS

Appearance of solution. Suspend 1.0 g in 5 mL of *water R* and dilute to 20 mL with *0.1 M sodium hydroxide*. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 2 mg of *2,2-diphenylglycine R* (impurity C) in 100.0 mL of the mobile phase.

Reference solution (c). Dissolve 10 mg of *phenytoin for system suitability CRS* (containing impurities D and E) in the mobile phase, add 1.0 mL of reference solution (b) and dilute to 10.0 mL with the mobile phase.

Column:

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

Mobile phase: mix 20 volumes of *methanol R2*, 35 volumes of *acetonitrile R1* and 45 volumes of a 5.75 g/L solution of *ammonium dihydrogen phosphate R* adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 220 nm.

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

Run time: 4 times the retention time of phenytoin.

Identification of impurities: use the chromatogram supplied with *phenytoin for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C, D and E.

Relative retention with reference to phenytoin (retention time = about 4 min): impurity C = about 0.5; impurity D = about 0.6; impurity E = about 0.8.

System suitability: reference solution (c):

– *resolution*: minimum 3.5 between the peaks due to impurities D and E.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.7; impurity E = 1.4;
– *impurity E*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
– *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

Monographs P