Edition: BP 2025 (Ph. Eur. 11.6 update)

Phenindione Tablets

General Notices

Action and use

Oral anticoagulant (indanedione).

DEFINITION

Phenindione Tablets contain Phenindione.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of phenindione, $C_{15}H_{10}O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.2 g of Phenindione with 50 mL of *dichloromethane*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of phenindione (*RS 268*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(2) Use 900 mL of a solution containing 0.68% w/v of *potassium dihydrogen phosphate* and 0.18% w/v of *sodium hydroxide*, pH adjusted to 8.0, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, filter through a 0.45-µm nylon filter. Measure the absorbance of the filtrate, suitably diluted with the dissolution medium if necessary, at the maximum at 328 nm, Appendix II B using dissolution medium in the reference cell.
(2) Measure the absorbance of a suitable solution of *phenindione BPCRS* using dissolution medium in the reference cell, at the maximum at 328 nm.

DETERMINATION OF CONTENT

Calculate the total content of Phenindione, $C_{15}H_{10}O_2$, in the medium from the absorbances obtained and using the declared content of $C_{15}H_{10}O_2$ in *phenindione BPCRS*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing 25 mg of Phenindione in *methanol*. Add sufficient *methanol* to produce a solution expected to contain 0.25% w/v of Phenindione, centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes with *methanol*.
(3) 0.00375% w/v of *phenindione impurity 1 BPCRS* in *methanol*.
(4) 0.0005% w/v of *phenindione BPCRS*, *phenylacetic acid* (impurity 3), *benzalphthalide* (impurity 4) and *phthalic acid* (impurity 5) in *methanol*.
(5) Dilute 1 volume of solution (2) to 10 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (X-bridge shield C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use an autosampler temperature of 4°.
(f) Use a detection wavelength of 220 nm.
(g) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A

10 volumes of *acetonitrile*, 10 volumes of a 1.36% w/v *dipotassium hydrogen phosphate* solution previously adjusted to pH 3.0 with *orthophosphoric acid* and 80 volumes of *water*.

Mobile phase B

10 volumes of *water* and 90 volumes of *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-0.5	80	20	isocratic
0.5-10	80→50	20→50	linear gradient
10-13	50	50	isocratic
13-21	50→30	50→70	linear gradient
21-22	30→80	70→20	linear gradient
22-25	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to phenindione (retention time, about 7 minutes) are: impurity 5, about 0.2; impurity 3, about 0.4; impurity 1, about 0.6; impurity 4, about 1.7; impurity 2, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4):

the *resolution* between the peaks due to impurity 3 and phenindione is at least 6.0;

the *resolution* between the peaks due to phenindione and impurity 4 is at least 8.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (1.5%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the total impurity content is not greater than 2.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solution A 2% v/v *glacial acetic acid* in *acetonitrile*.

(1) Mix with the aid of ultrasound a quantity of powdered tablets containing 25 mg of Phenindione in 20 mL of 0.01M *sodium hydroxide* and 50 mL of solution A. Dilute to 100 mL with solution A, centrifuge and use the supernatant liquid.
(2) 0.025% w/v of *phenindione BPCRS* in a mixture of 20 volumes of 0.01M *sodium hydroxide* and 80 volumes of solution A.
(3) 0.025% w/v *phenindione BPCRS* and *phenylacetic acid* (impurity 3) in a mixture of 20 volumes of 0.01M *sodium hydroxide* and 80 volumes of solution A.

CHROMATOGRAPHIC CONDITIONS

(a) A stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use an autosampler temperature of 4°.
(f) Use a detection wavelength of 250 nm.
(g) Inject 10 µL of each solution.

MOBILE PHASE

40 volumes *acetonitrile* and 60 volumes of 0.68 % w/v *potassium dihydrogen phosphate* previously adjusted to pH 3.5 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity 3 and phenindione is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{10}O_2$ in the tablets using the declared content of $C_{15}H_{10}O_2$ in *phenindione BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Phenindione.