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Phenytoin Oral Suspension

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 1
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Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. **Content** limits tightened **Identification** chloroform replaced **Dissolution** test added

Phenytoin Oral Suspensions from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable.

Action and use

Antiepileptic.

DEFINITION

Phenytoin Oral Suspension is a suspension of Phenytoin in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of phenytoin, $C_{15}H_{12}N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Add 5 mL of *water* to a quantity of the oral suspension containing 30 mg of Phenytoin and extract with five 4-mL quantities of *diethyl ether*. Wash the combined extracts with three 2-mL quantities of *water* and evaporate the washed extract to dryness under a stream of *nitrogen*. The *infrared absorption spectrum*, Appendix II A, of the residue is concordant with the *reference spectrum* of phenytoin (*RS 272*).

TESTS

Acidity

pH, 4.5 to 5.5, Appendix V L.

Dissolution

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddles at 35 revolutions per minute.

(b) Use 900 mL of a solution containing 0.121% w/v of *tris(hydroxymethyl)methylamine* and 2.0% w/v of *sodium dodecyl sulfate* in *water* and adjusted to pH 7.5 with *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) After 60 minutes withdraw a sample of the medium and filter. Dilute with the dissolution medium, if necessary, to produce a solution containing 0.0033% w/v of Phenytoin.

(2) 0.0036% w/v of *phenytoin sodium BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack ODS AQ 18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 220 nm.

(g) Inject 20 µL of each solution.

MOBILE PHASE

200 volumes of *methanol*, 350 volumes of *acetonitrile R1* and 450 volumes of 0.05M *ammonium dihydrogen orthophosphate*, adjusted to pH 2.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of phenytoin is about 4 minutes.

DETERMINATION OF CONTENT

Calculate the total content of phenytoin, $C_{15}H_{11}N_2O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{11}N_2NaO_2$ in *phenytoin sodium BPCRS*. Each mg of $C_{15}H_{11}N_2NaO_2$ is equivalent to 0.920 mg of $C_{15}H_{11}N_2O_2$.

LIMITS

The amount of phenytoin released is not less than 80% (Q) of the stated amount.

Related substances

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

(1) Add 5 mL of *water* and 2 mL of *2M hydrochloric acid* to a quantity of the oral suspension containing 30 mg of Phenytoin, mix well and extract with five 20-mL quantities of *diethyl ether*. Combine the ether extracts, wash with three 10-mL quantities of *water*, evaporate to dryness and dissolve the residue in 30 mL.

(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume to 5 volumes.

(3) 0.1% w/v of *phenytoin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used. Allow the chromatography to proceed for 4 times the retention time of phenytoin.

When the chromatograms are recorded under the prescribed condition the retention times relative to phenytoin (retention time about 4 minutes) are: impurity C, about 0.5; impurity D, about 0.6; impurity E, about 0.8, impurity A, about 3.2 and impurity B, about 3.8.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (2) is at least 40.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity D and impurity E using the chromatogram obtained with solution (3). Multiply the area of these peaks by the corresponding correction factors: impurity D, 1.7 and impurity E, 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity E is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

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

(1) Add 5 mL of *water* and 2 mL of *2M hydrochloric acid* to a weighed quantity of the oral suspension containing 30 mg of Phenytoin, mix well and extract with five 20-mL quantities of *diethyl ether*. Combine the ether extracts, wash with three 10-mL quantities of *water* and evaporate to dryness. Dissolve the residue in 30 mL of mobile phase and dilute to produce 50 mL. Dilute 1 volume of the resulting solution to 5 volumes with mobile phase.

(2) 0.012% w/v of *phenytoin sodium BPCRS*.

(3) 0.12% w/v of *phenytoin for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and impurity E is at least 3.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{15}H_{11}N_2O_2$ weight in volume, using the declared content of $C_{15}H_{11}N_2NaO_2$, in *phenytoin sodium BPCRS*. Each mg of $C_{15}H_{11}N_2NaO_2$ is equivalent to 0.920 mg of $C_{15}H_{11}N_2O_2$.

IMPURITIES

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