Phenytoin Oral Suspension

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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Further follow-up action as required.	

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Change **to: Phenytoin Oral Suspension**

Diphenylhydantoin Oral Suspension

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

Phenytoin Oral Suspension contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of phenytoin, $C_{15}H_{12}N_2O_2$.

Usual strength. 25 mg per ml

Identification

A. Shake a quantity of the oral suspension containing 0.1 g of Phenytoin with 50 ml of a mixture of equal volumes of *ether* and *chloroform* in a separator, and evaporate the chloroform extracts to dryness and dry the residue under vacuum at 105° for 4 hours. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *phenytoin IPRS* treated in the same manner or with the reference spectrum of phenytoin.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with the reference solution.

Tests

Dissolution (2.5.2)
Apparatus No. 2 (Paddle),
Medium. 900 ml of a buffer solution, prepared by dissolving 6.05 g of *tris(hydroxymethyl)aminomethane* and 10 g of *sodium lauryl sulphate* in 1000 ml of *water,* adjusted to pH 7.5 with *hydrochloric acid,*
Speed and time. 35 rpm and 60 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Shake the sample suspension well (100 shakes). Determine the density weight per ml of oral suspension using appropriate means. Using a 5-ml syringe, collect approximately 5 ml of oral suspension, and record the weight. With the paddles lowered, gently empty the contents of each syringe into the bottom of each vessel containing dissolution medium. Start rotating the paddles. Reweigh each syringe, and determine the weight (g) of oral suspension delivered into each vessel. At the end of 60 minutes, withdraw a suitable volume from each vessel and pass through a nylon filter of 0.45 µm, pre-saturated with dissolution medium. Dilute the filtrate with dissolution medium, if necessary to obtain a solution having similar concentration to that of reference solution.

Reference solution. Dissolve 28 mg of *phenytoin IPRS* in 6 ml of *methanol* and dilute to 200.0 ml with the dissolution medium.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil BDS C-18),
-mobile phase: a mixture of 50 volumes of a buffer solution prepared by dissolving 2.76 g of *sodium dihydrogen phosphate* in 1000 ml of *water,* 27 volumes of *methanol* and 23 volumes of *acetonitrile,* adjusted to pH 3.0 with *orthophosphoric acid,*
-flow rate: 1 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{15}H_{12}N_2O_2$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{15}H_{12}N_2O_2$.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *water* and mobile phase B.

Test solution. Disperse a quantity of the suspension containing 100 mg of Phenytoin in 20 ml of *methanol,* with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture.

Reference solution. A solution containing 0.0001 per cent w/v of *phenytoin IPRS* and 0.0009 per cent w/v, each of, *phenytoin related compound A IPRS* and *phenytoin related compound B IPRS* in the solvent mixture.

Chromatographic system
- -a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm) (Such as Inertsil ODS-3),
- -mobile phase: A. a *0.05 M potassium dihydrogen phosphate*, adjusted to pH 2.5 with *orthophosphoric acid*,
  B. a mixture of 60 volumes of *methanol* and 40 volumes of *acetonitrile,*
- -a gradient programme using the conditions given below,
- -flow rate: 1 ml per minute,
- -spectrophotometer set at 220 nm,
- -injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	60	40
23	60	40
38	42	58
45	30	70
50	30	70
51	60	40
55	60	40

Name	Relative retention time
Phenytoin related compound A[1]	0.14
Phenytoin related compound B[2]	0.53
Phenytoin	1.0

[1]2,2-Diphenylglycine,
[2] 2,2-Diphenyl-2-ureidoacetic acid.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent and the signal-to-noise ratio is not less than 10.0, phenytoin peak.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to phenytoin related compound A and phenytoin related compound B, each of, is not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.9 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 9 times the area of the principal peak in the chromatogram obtained with the reference solution (0.9 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Other tests. Comply with the tests stated under Oral Liquids.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution. Disperse a quantity of the suspension containing 50 mg of Phenytoin, in 50 ml of *methanol* with the aid of ultrasound and dilute to 250.0 ml with the solvent mixture.

Reference solution. A 0.02 per cent w/v solution of *phenytoin IPRS* with the solvent mixture.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Determine the weight per ml of the suspension (2.4.29) and calculate the content of $C_{15}H_{12}N_2O_2$ in the oral suspension.

Storage. Store protected from moisture.