Calcium Folinate Tablets

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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.

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Document History and Schedule for the Adoption Process

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Further follow-up action as required.	

Calcium Folinate Tablets

Leucovorin Calcium Tablets

Calcium Folinate Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of folinic acid, $C_{20}H_{23}N_7O_7$.

Usual strength. 15 mg.

Identification

A. To a quantity of the powdered tablets containing the equivalent of 180 mg of folinic acid, add 10 ml of *water*, mix with the aid of ultrasound, and filter. Add 125 mg of *ammonium oxalate* to the filtrate, shake, and centrifuge until a clear supernatant liquid is obtained. To the supernatant add 1 ml of *methanol* and 3 drops of *hydrochloric acid*, and shake. If the preparation is cloudy, add methanol until a clear solution is obtained and filter, if necessary, to remove any undissolved material. Cool the preparation at 0° until a precipitate forms and centrifuge. The cooling and centrifuging steps may be repeated, if necessary, to increase the amount of precipitate collected. Decant the supernatant liquid and dissolve the precipitate in 2 ml of *methanol*. Evaporate to dryness under a current of air and dry the residue at 50° for 30 minutes. The residue complies the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *calcium folinate IPRS* or with the reference spectrum of calcium folinate.

B. It gives the reaction (B) of calcium salts (2.3.1).

Tests

Related substances. Determine by liquid chromatography (2.4.14).

NOTE – Protect the solutions from light.

Test solution. Disperse a quantity of the powdered tablets containing the equivalent of 25 mg of folinic acid in *water*, with the aid of ultrasound with intermittent shaking and dilute to 25.0 ml with *water*, filter through a glass fiber filter.

Reference solution (a). A solution of *calcium folinate IPRS* containing 0.001 per cent w/v of folinic acid in *water*.

Reference solution (b). A 0.1 per cent w/v solution of *calcium folinate IPRS* in *water.*

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 10.0 ml with *water*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with end capped octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil ODS),
- column temperature: 40°,
- mobile phase: a mixture of 22 volumes of *methanol* and 78 volumes of a buffer solution prepared by dissolving 2.82 g of *disodium hydrogen phosphate* in 1000 ml of *water.* add 2.6 ml of *tetrabutylammonium hydroxide*, adjusted to pH 7.5 with *dilute orthophosphoric acid,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to folinate and formyl folic acid is not less than 2.2. *(NOTE – If necessary, adjust the methanol content in the mobile phase).*

Inject reference solution (a), (c) and the test solution. In the chromatogram obtained the test solution, the area of any peak corresponding to formyl folic acid is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than the area of the principal peak in

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the chromatogram obtained with reference solution (a) (1.0 per cent) and the sum of areas of all the secondary peaks other than formyl folic acid is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Uniformity of dosage units. (2.5.4). Meet the requirements.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and powder 20 tablets. Disperse a quantity of powder containing equivalent of 25 mg of folinic acid in *water*, with the aid of ultrasound with intermittent shaking and dilute to 250.0 ml with *water*, filter through a glass fiber filter.

Reference solution (a). A solution of *calcium folinate IPRS* containing 0.01 per cent w/v of folinic acid in *water.*

Reference solution (b). A 0.1 per cent w/v solution of *calcium folinate IPRS* in *water.*

Use chromatographic system as described under Related substances.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to folinate and formyl folic acid is not less than 2.2. *(NOTE – If necessary, adjust the methanol in the mobile phase).*

Inject reference solution (a) and the test solution.

Calculate the content of $C_{20}H_{23}N_7O_7$ in the tablets.

1 mg of calcium folinate, $C_{20}H_{21}CaN_7O_7$is equivalent to0.9255 mg of folinic acid, $C_{20}H_{23}N_7O_7$.

Storage. Store at a temperature not exceeding 30°.

Labelling. The label states the strength in terms of the equivalent amount of folinic acid.

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