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

Ferrous Fumarate and Folic Acid Tablets

General Notices

Action and use

Source of iron + Vitamin B component; used in treatment of iron-deficiency anaemia.

DEFINITION

Ferrous Fumarate and Folic Acid Tablets contain Ferrous Fumarate and Folic Acid Hydrate.

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

Carry out the tests avoiding exposure to actinic light.

Content of ferrous fumarate, $C_4H_2FeO_4$

90.0 to 105.0% of the stated amount.

Content of folic acid, $C_{19}H_{19}N_7O_6$

90.0 to 115.0% of the stated amount.

IDENTIFICATION

A. In the Assay for folic acid, the chromatogram obtained with solution (1) shows a peak with the same retention time as the principal peak in the chromatogram obtained with solution (2).
B. Heat a quantity of the powdered tablets containing 0.77 g of Ferrous Fumarate with 25 mL of a mixture of equal volumes of *hydrochloric acid* and *water* on a water bath for 15 minutes, cool and filter. Retain the residue for test C. The filtrate yields reaction A characteristic of *iron salts*, Appendix VI.
C. Wash the residue reserved in test B with a mixture of 1 volume of 2M *hydrochloric acid* and 9 volumes of *water* and dry at 105°. Suspend 0.1 g of the residue in 2 mL of *sodium carbonate solution* and add *potassium permanganate solution* dropwise. The permanganate is decolourised and a brownish solution is produced.

TESTS

Dissolution

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

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

For folic acid

PROCEDURE

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

(1) After 60 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with 0.1M *hydrochloric acid* if necessary, expected to contain 0.00004% w/v of folic acid.
(2) Disperse 10 mg of *folic acid BPCRS* in 75 mL of *methanol* and mix with the aid ultrasound for 15 minutes. Add 125 mL of 0.1M *hydrochloric acid*, mix with the aid of ultrasound for a further 15 minutes and dilute to 250 mL with 0.1M *hydrochloric acid*. Dilute 1 volume of the resulting solution to 100 volumes with 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed *with base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.7 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 235 nm.
(f) Inject 300 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *formic acid*, 100 volumes of *methanol* and 900 volumes of *water*.

Mobile phase B 1 volume of *formic acid*, 100 volumes of *water* and 900 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	100	0	isocratic
4-9.5	100→10	0→90	linear gradient
9.5-9.6	10→100	90→0	linear gradient
9.6-20	100	0	re-equilibration

DETERMINATION OF CONTENT

Calculate the total content of $C_{19}H_{19}N_7O_6$ in the medium from the chromatograms obtained and using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

LIMITS

The amount of folic acid released is not less than 75% (Q) of the stated amount.

For ferrous fumarate

PROCEDURE

After 60 minutes withdraw a sample of the medium and filter. Titrate 100 mL of the filtrate with 0.01M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator.

DETERMINATION OF CONTENT

Calculate the total content of $C_4H_2FeO_4$ in the medium taking each mL of 0.1M *ammonium cerium(IV) sulfate VS* to be equivalent to 16.99 mg of $C_4H_2FeO_4$.

The amount of ferrous fumarate released is not less than 75% (Q) of the stated amount.

Ferric iron

Dissolve a quantity of the powder prepared for the Assay for ferrous fumarate containing 1.5 g of Ferrous Fumarate in a mixture of 100 mL of *water* and 10 mL of *hydrochloric acid* by heating rapidly to the boiling point. Boil for 15 seconds, cool rapidly, add 3 g of *potassium iodide*, stopper, allow to stand in the dark for 15 minutes and titrate the liberated iodine with 0.1M *sodium thiosulfate VS* using *starch mucilage* as indicator. Repeat the operation without the substance being examined. The difference between the titrations is not more than 13.4 mL (5% ferric iron in Ferrous Fumarate).

Uniformity of Content

For folic acid

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid.

Complies with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 135 volumes of *methanol* and 800 volumes of a 0.57% w/v solution of *dipotassium hydrogen orthophosphate* (solvent A).

(1) Place one tablet in 40 mL of solvent A, shake for a further 15 minutes, dilute to 50 mL with solvent A and filter (a 0.45-µm nylon filter is suitable).
(2) 0.0007% w/v of *folic acid BPCRS* in solvent A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS 1 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 277 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

135 volumes of *methanol* and 800 volumes of a solution containing 0.938% w/v of *sodium perchlorate* and 0.075% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 7.2 with 0.1M *potassium hydroxide* and diluted to 1000 volumes with *water*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{19}N_7O_6$ in each tablet using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

ASSAY

Weigh and powder 20 tablets.

For ferrous fumarate

Disperse a quantity of the powder containing 0.3 g of Ferrous Fumarate in 7.5 mL of 1M *sulfuric acid* with gentle heating. Cool, add 25 mL of *water* and titrate immediately with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium (IV) sulfate VS* is equivalent to 16.99 mg of $C_4H_2FeO_4$.

For folic acid

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid

Use the average of the individual results obtained in the test for Uniformity of content.

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of folic acid

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 135 volumes of *methanol* and 800 volumes of a 0.57% w/v solution of *dipotassium hydrogen orthophosphate* (solvent A).

(1) Mix a quantity of the powdered tablets containing the equivalent of 0.35 mg of folic acid in 40 mL of solvent A, mix for 5 minutes with the aid of ultrasound, shake for a further 15 minutes and dilute to 50 mL with solvent A and filter (a 0.45-µm nylon filter is suitable).
(2) 0.0007% w/v of *folic acid BPCRS* solvent A.

CHROMATOGRAPHIC CONDITIONS

Chromatographic conditions described under Uniformity of Content may be used.

MOBILE PHASE

135 volumes of *methanol* and 800 volumes of a solution containing 0.938% w/v of *sodium perchlorate* and 0.075% w/v of *potassium dihydrogen orthophosphate* adjusted to pH 7.2 with 0.1M *potassium hydroxide* and diluted to 1000 volumes with *water*.

When the chromatogram is recorded under the prescribed conditions, the retention time for folic acid is about 4.5 minutes.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{19}N_7O_6$ in the tablets using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

STORAGE

Ferrous Fumarate and Folic Acid Tablets should be protected from light.

LABELLING

For *ferrous fumarate* the quantity of the active ingredient is stated both as the amount of ferrous fumarate and in terms of the equivalent amount of ferrous iron.