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Ferrous Fumarate and Folic Acid Capsules

General Notices

Action and use

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

DEFINITION

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

The capsules comply with the requirements stated under Capsules 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. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Extract a quantity of the capsule contents containing the equivalent of 0.5 mg of folic acid with 1 mL of a mixture of 2 volumes of 13.5M *ammonia* and 9 volumes of *methanol*.
(2) 0.05% w/v of *folic acid BPCRS* in a mixture of 2 volumes of 13.5M *ammonia* and 9 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel G*.
(b) Use the mobile phase as described below.
(c) Apply 2 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (366 nm)*.

MOBILE PHASE

20 volumes of 13.5 M *ammonia*, 20 volumes of *propan-1-ol* and 60 volumes of *ethanol (96%)*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, fluorescence and size to that in the chromatogram obtained with solution (2).

B. 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).
C. Heat a quantity of the capsule contents 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 D. The filtrate yields reaction A characteristic of *iron salts*, Appendix VI.
D. Wash the residue reserved in test C 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, to produce a solution expected to contain 0.00004% w/v of folic acid.
(2) 0.00004% w/v of *folic acid BPCRS* in 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

Shake a quantity of capsule contents 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 capsules containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid.

Complies with the requirements stated under Capsules 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 capsule 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 capsule using the declared content of $C_{19}H_{19}N_7O_6$ in *folic acid BPCRS*.

ASSAY

For ferrous fumarate

Weigh the contents of 20 capsules. Mix and powder if necessary. Mix a quantity of the capsule contents containing 0.3 g of Ferrous Fumarate with 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 capsules containing the equivalent of less than 2 mg and/or less than 2% w/w of folic acid

Use the average of the 10 individual results obtained in the test for Uniformity of content.

For capsules 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) Shake a quantity of the capsule contents containing the equivalent of 0.35 mg of folic acid with 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* in solvent A.

CHROMATOGRAPHIC CONDITIONS

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

STORAGE

Ferrous Fumarate and Folic Acid Capsules 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.