warming will redissolve the crystals. Label it to indicate that it is intended for topical and vaginal use only.

Identification—

A: A 1 in 20 dilution of the Solution in water yields a brownish-red precipitate with ammonia TS.

B: A 1 in 20 dilution of the Solution in water yields a blue precipitate with potassium ferrocyanide TS.

C: A 1 in 20 dilution of the Solution in water yields a white precipitate with barium chloride TS that is insoluble in hydrochloric acid.

Limit of nitrate—Add a clear crystal of ferrous sulfate to a cooled mixture of equal volumes of sulfuric acid and a 1 in 10 dilution of the Solution in water: the crystal does not become brown, nor does a brownish-black color develop around it.

Limit of ferrous salts—Add a few drops of freshly prepared potassium ferricyanide TS to 2 mL of 1 in 20 dilution of the solution in water: a brown color is produced and the solution remains free from even a transient green or greenish-blue color.

Assay—Transfer 10.0 mL of the Solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a glass-stoppered conical flask, and add 5 mL of hydrochloric acid and 3 g of potassium iodide. Insert the stopper into the flask, and allow the mixture to stand for 15 minutes. Add 15 mL of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, using starch TS as the indicator. Each mL of 0.1 N sodium thiosulfate is equivalent to 5.585 mg of iron (Fe).

Ferric Sulfate

$Fe_2(SO_4)_3 \cdot xH_2O$ (anhydrous) 399.88
Ferric persulfate.
Ferric sesquisulfate.
Ferric tersulfate [10028-22-5].
Hydrate [142906-29-4].

» Ferric Sulfate is hydrated $Fe_2(SO_4)_3$. It contains not less than 73.0 per cent and not more than 80.0 percent of $Fe_2(SO_4)_3$.

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

Labeling—Label it to indicate that it is intended for use in compounding topical and periodontal dosage forms only.

Identification—Dissolve 0.5 g in a mixture of 50 mL of water and 3 mL of hydrochloric acid: this solution meets the requirements for the *Ferric Salts* test under *Iron* ⟨191⟩.

Limit of insoluble matter—Transfer 10 g in a covered beaker, and dissolve in a mixture of 100 mL of water and 5 mL of sulfuric acid. Heat to boiling, and warm on a steam bath for 1 hour. Filter the hot solution through a tared sintered-glass crucible of fine porosity. Wash the beaker and the filter with hot water, dry the crucible at 105°, cool in a desiccator, and weigh: not more than 2 mg of insoluble matter is found (0.02%).

Limit of chloride—Dissolve 1 g by warming with a mixture of 10 mL of water and 1 mL of nitric acid, add 4 mL of additional nitric acid, and dilute with water to 50 mL. To 25 mL of this solution add 1 mL of phosphoric acid and 1 mL of silver nitrate TS. Any turbidity does not exceed that produced in a control containing 0.01 mg of chloride ion (Cl), 1 mL of nitric acid, 1 mL of phosphoric acid, and 1 mL of silver nitrate TS (0.002%).

Limit of ferrous iron—Dissolve 4 g by warming with 50 mL of dilute sulfuric acid (1 in 10), cool, and titrate with 0.1 N potassium permanganate: not more than 0.16 mL is required to produce a permanent pink color (0.02% as Fe^{++}).

Limit of copper and zinc—[NOTE—If the reagents used in the tests for *Copper* and *Zinc* contain excessive amounts of copper and zinc, then they should first be purified by extracting with *Dithizone Extraction Solution* (see *Lead* ⟨251⟩).]

Copper—Dissolve 1.2 g in 100 mL of water. To 10 mL of this test solution add 50 mL of a solution containing 5 g of ammonium tartrate and 5 mL of ammonium hydroxide. Add 10 mL of *Standard Dithizone Solution* (see *Lead* ⟨251⟩), shake for 2 minutes, draw off the dithizone layer, and compare the pink color with that in a control containing 6 µg of copper ion (Cu) and treated exactly as the 10-mL portion of test solution. If the color in the test solution is less than that in the control, then less than 0.005% of Cu and of Zn is found and the test for *Zinc* is not necessary. If the color in the test solution is more than that in the control, add 15 mL of dilute hydrochloric acid (1 in 250), and shake for 2 minutes. Draw off the dithizone solution, and shake with a second 15 mL of dilute hydrochloric acid (1 in 250) for 2 minutes. [NOTE—Draw off the dithizone, combine the two acid extracts, and reserve for the test for *Zinc*.] Any pink color in the dithizone solution is not darker than that in the control solution treated exactly as the test solution (0.005%).

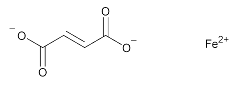
Zinc—To the combined acid extracts saved from the test for *Copper*, add sufficient 0.5 M sodium acetate to bring the pH to between 5.0 and 5.5, and then add 1 mL of 0.1 N sodium thiosulfate. Add 10 mL of *Standard Dithizone Solution* (see *Lead* ⟨251⟩), shake for 2 minutes, and allow the layers to separate. Draw off the dithizone layer, and discard the water layer. Any pink color in the dithizone layer is not greater than that in a control prepared by adding 0.006 mg of zinc ion (Zn) to the combined acid extracts from the control used in the test for *Copper* (0.005%).

Limit of nitrate—Dissolve 10 g in 100 mL of dilute sulfuric acid (1 in 100), heat to boiling, and pour, slowly, into a mixture of 140 mL of water and 50 mL of ammonium hydroxide. Pass through a folded filter while still hot, wash the filter with hot water until the volume of filtrate is 300 mL, mix, and cool. To 15 mL of the diluted filtrate add 1 mL of sodium chloride solution (1 in 200), 0.10 mL of indigo carmine TS, and 15 mL of sulfuric acid. The blue color is not completely discharged at the end of 5 minutes (0.01%).

Substances not precipitated by ammonia—Evaporate to dryness 30 mL of the diluted filtrate obtained in the test for *Limit of nitrate*, and ignite gently: the weight of residue does not exceed 1 mg (0.1%).

Assay—Transfer about 700 mg of Ferric Sulfate, accurately weighed, to a glass-stoppered conical flask. Add a mixture of 50 mL of water and 3 mL of hydrochloric acid, and swirl to dissolve. Add 3 g of potassium iodide, insert the stopper into the flask, and allow to stand in the dark for 30 minutes. Then add 100 mL of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding starch TS as the endpoint is approached. Each mL of 0.1 N sodium thiosulfate is equivalent to 19.994 mg of ferric sulfate [$Fe_2(SO_4)_3$].

Ferrous Fumarate



$C_4H_2FeO_4$ 169.90
2-Butenedioic acid, (*E*)-, iron(2+) salt;
Iron(2+) fumarate [141-01-5].

DEFINITION

Ferrous Fumarate contains NLT 97.0% and NMT 101.0% of ferrous fumarate ($C_4H_2FeO_4$), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION**

Sample: To 1.5 g of Ferrous Fumarate, add 25 mL of dilute hydrochloric acid (1 in 2). Dilute with water to 50 mL, heat to dissolve, then cool, and filter on a fine-pore size, sintered-glass crucible. Wash the precipitate with dilute hydrochloric acid (3 in 100), saving the filtrate for *Identification* test *B*, and dry the precipitate at 105°.

Acceptance criteria: The IR absorption of a potassium bromide dispersion of the dried precipitate exhibits maxima only at the same wavelengths as that of a similar preparation of USP Fumaric Acid RS.

- **B. IDENTIFICATION TESTS—GENERAL,** *Iron* ⟨**191**⟩**:** A portion of the filtrate obtained in *Identification* test *A* meets the requirements.

ASSAY

- **PROCEDURE**

Sample: 500 mg of Ferrous Fumarate

Blank: Proceed as directed in the *Analysis* without the *Sample*.

Titrimetric system

(See *Titrimetry* ⟨541⟩.)

Mode: Direct titration

Titrant: 0.1 N ceric sulfate VS

Endpoint detection: Visual

Analysis: Transfer the *Sample* to a 500-mL conical flask, and add 25 mL of dilute hydrochloric acid (2 in 5). Heat to boiling, and add, dropwise, a solution of 112 mg/mL of stannous chloride in dilute hydrochloric acid (3 in 10) until the yellow color disappears, then add 2 drops in excess. Cool the solution in an ice bath to room temperature, add 10 mL of 50 mg/mL of mercuric chloride solution, and allow to stand for 5 min. Add 200 mL of water, 25 mL of dilute sulfuric acid (1 in 2), and 4 mL of phosphoric acid. Then add 2 drops of orthophenanthroline TS, and titrate with *Titrant*. Perform a *Blank* determination.

Calculate the percentage of ferrous fumarate ($C_4H_2FeO_4$) in the *Sample* taken:

$$\text{Result} = \{[(V_S - V_B) \times N \times F]/W\} \times 100$$

V_S = *Titrant* volume consumed by the *Sample* (mL)
V_B = *Titrant* volume consumed by the *Blank* (mL)
N = *Titrant* normality (mEq/mL)
F = equivalency factor, 169.9 mg/mEq
W = *Sample* weight (mg)

Acceptance criteria: 97.0%–101.0% on the dried basis

IMPURITIES

- **SULFATE**

Sample solution: Transfer 1.0 g of Ferrous Fumarate to a 250-mL beaker, add 100 mL of water, and heat on a steam bath, adding hydrochloric acid dropwise until completely dissolved. [NOTE—About 2 mL of the acid will be required.] Filter the solution if necessary, and dilute the filtrate with water to 100 mL. Heat the filtrate to boiling, add 10 mL of barium chloride TS, warm on a steam bath for 2 h, cover, and allow to stand for 16 h. [NOTE—If crystals of ferrous fumarate form, warm the solution on the steam bath to dissolve them.]

Analysis: Pass the *Sample solution* through ashless filter paper, wash the residue with hot water until, with the addition of ammonium sulfide TS, a black precipitate is no longer formed in the filtrate. Transfer the paper containing the residue to a tared crucible. Char the paper, without burning, and ignite the crucible and its contents at 600° to constant weight.

Acceptance criteria: NMT 0.2%: Each mg of residue is equivalent to 0.412 mg of sulfate (SO_4).

- **ARSENIC,** *Method I* ⟨**211**⟩

Test preparation: To 2.0 g in 10 mL of water add 10 mL of sulfuric acid. Warm to precipitate the fumaric acid completely, cool, add 30 mL of water, and filter into a 100-mL volumetric flask. Wash the precipitate with water, adding the washings to the flask, then add water to volume, and mix. Transfer 50.0 mL of this solution into the arsine generator flask, and dilute with water to 55 mL.

Analysis: Proceed as directed in the chapter, except omit the addition of 20 mL of 7 N sulfuric acid specified for the *Procedure*.

Acceptance criteria: NMT 3 ppm

- **LIMIT OF FERRIC IRON**

Sample: 2 g of Ferrous Fumarate

Blank: Proceed as directed in the *Analysis* without the *Sample*.

Titrimetric system

(See *Titrimetry* ⟨541⟩.)

Mode: Direct titration

Titrant: 0.1 N sodium thiosulfate VS

Endpoint detection: Visual

Analysis

Analysis: Transfer the *Sample* to a glass-stoppered, 250-mL conical flask, add 25 mL of water and 4 mL of hydrochloric acid, and heat on a hot plate until solution is complete. Insert the stopper in the flask, and cool to room temperature. Add 3 g of potassium iodide, insert the stopper in the flask, swirl to mix, and allow to stand in the dark for 5 min. Remove the stopper, add 75 mL of water, and titrate with the *Titrant*, adding 3 mL of starch TS as the endpoint is approached. Perform a *Blank* determination.

Calculate the percentage of ferric iron in the portion of Ferrous Fumarate taken:

$$\text{Result} = \{[(V_S - V_B) \times N \times F]/W\} \times 100$$

V_S = *Titrant* volume consumed by the *Sample* (mL)
V_B = *Titrant* volume consumed by the *Blank* (mL)
N = *Titrant* normality (mEq/mL)
F = equivalency factor, 55.85 mg/mEq
W = *Sample* weight (mg)

Acceptance criteria: NMT 2.0%

- **LIMIT OF LEAD**

[NOTE—For the preparation of all aqueous solutions and for the rinsing of glassware before use, use water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin. Select all reagents to have as low a content of lead as practicable, and store all reagent solutions in containers of borosilicate glass. Cleanse glassware before use by soaking in warm nitric acid (1 in 2) for 30 min and by rinsing with deionized water.]

Ascorbic acid–sodium iodide solution: 100 mg/mL of ascorbic acid and 192.5 mg/mL of sodium iodide

Trioctylphosphine oxide solution: 50 mg/mL of trioctylphosphine oxide in 4-methyl-2-pentanone

[**CAUTION—**This solution causes irritation. Avoid contact with eyes, skin, and clothing. Take special precautions in disposing of unused portions of solutions to which this reagent is added.]

Standard solution: Transfer 5.0 mL of *Lead Nitrate Stock Solution*, prepared as directed in *Heavy Metals* ⟨231⟩, to a 100-mL volumetric flask. Dilute with water to volume, and mix. Transfer 2.0 mL of the resulting solution to a 50-mL beaker. To this beaker add 6 mL of nitric acid and 10 mL of perchloric acid, and evaporate in a hood to dryness. [**CAUTION—**Use perchloric acid in a well-ventilated fume hood with proper precautions.] Cool, dissolve the residues in 10 mL of 9 N hydrochloric acid, and transfer with the aid of about 10 mL of water to a 50-mL volumetric flask. Add 20 mL of *Ascorbic acid–sodium iodide solution* and 5.0 mL of *Trioctylphosphine oxide solution*, shake for 30 s, and allow to separate. Add water to bring the organic solvent layer into the neck of the flask, shake again, and allow to separate. The organic solvent layer is the *Standard solution*, and it contains 2.0 µg/mL of lead.

Sample solution: Transfer 1.0 g of Ferrous Fumarate to a 50-mL beaker, and add 6 mL of nitric acid and 10 mL of perchloric acid. [**CAUTION—**Use perchloric acid in a well-ventilated fume hood with proper precautions.]

Cover with a ribbed watch glass, and heat in a hood until completely dry. Cool, dissolve the residue in 10 mL of 9 N hydrochloric acid, and transfer with the aid of about 10 mL of water to a 50-mL volumetric flask. Add 20 mL of *Ascorbic acid–sodium iodide solution* and 5.0 mL of *Trioctylphosphine oxide solution*, shake for 30 s, and allow to separate. Add water to bring the organic solvent layer into the neck of the flask, shake again, and allow to separate. The organic layer is the *Sample solution.*

Blank: To a 50-mL beaker add 6 mL of nitric acid and 10 mL of perchloric acid, and evaporate in a hood to dryness. [**Caution**—Use perchloric acid in a well-ventilated fume hood with proper precautions.]

Cool, dissolve the residue in 10 mL of 9 N hydrochloric acid, and transfer with the aid of about 10 mL of water to a 50-mL volumetric flask. Add 20 mL of *Ascorbic acid–sodium iodide solution* and 5.0 mL of *Trioctylphosphine oxide solution*, shake for 30 s, and allow to separate. Add water to bring the organic solvent layer into the neck of the flask, shake again, and allow to separate. The organic layer is the *Blank*, and it contains 0 μg/mL of lead.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)

Mode: Atomic absorption spectrophotometry

Analytical wavelength: 283.3 nm

Lamp: Lead hollow-cathode

Flame: Air–acetylene

System suitability

Samples: *Standard solution* and *Blank*

Suitability requirements: The absorbance of the *Standard solution* and the absorbance of the *Blank* are significantly different.

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

Concomittantly determine the absorbances of the *Blank*, *Standard solution*, and the *Sample solution*. Use the *Blank* to set the instrument to zero.

Acceptance criteria: NMT 10 ppm: The absorbance of the *Sample solution* does not exceed that of the *Standard solution*.

- **Mercury**

[Note—Carry out this test in subdued light, because mercuric dithizonate is light sensitive.]

Hydroxylamine hydrochloride solution, Standard mercury solution, Dithizone extraction solution, and **Diluted dithizone extraction solution:** Prepare as directed in *Mercury* ⟨261⟩*, Method I*.

Control solution: Mix 3.0 mL of *Standard mercury solution*, 30 mL of dilute nitric acid (1 in 10), 5 mL of 250 mg/mL of sodium citrate solution, and 1 mL of *Hydroxylamine hydrochloride solution*.

Test preparation: Dissolve 1 g of Ferrous Fumarate in 30 mL of dilute nitric acid (1 in 10) with the aid of heat, on a steam bath. Cool quickly by immersing in an ice bath, and pass through a fine-porosity filter that previously has been washed with dilute nitric acid (1 in 10) and water. To the filtrate add 20 mL of 250 mg/mL of sodium citrate solution and 1 mL of *Hydroxylamine hydrochloride solution*.

Analysis: Adjust the *Control solution* to a pH of 1.8 with ammonium hydroxide, and the *Sample solution* to a pH of 1.8 with sulfuric acid. Separately transfer the solutions to separators. Treat the *Sample solution* and the *Control solution* in parallel as follows.

Extract with two 5-mL portions of *Dithizone extraction solution* and 5 mL of chloroform, pooling the chloroform extracts in a second separator. Add 10 mL of hydrochloric acid (1 in 2), shake, allow the layers to separate, and discard the chloroform layer. Wash the acid extract with 3 mL of chloroform, and discard the washing. Add 0.1 mL of 20 mg/mL edetate disodium solution and 2 mL of 6 N acetic acid, mix, and add slowly 5 mL of ammonium hydroxide. Close the separator, cool it under cold running water, and dry its outer surface. Remove the stopper, and pour the contents into a beaker. Adjust the *Sample solution* and the *Control solution* to a pH of 1.8 in the same manner as before, and return the solutions to their respective separators. Add 5.0 mL of *Diluted dithizone extraction solution*, shake vigorously, and allow the layers to separate. Using *Diluted dithizone extraction solution* as a color blank, compare the colors developed in the chloroform layers of the *Sample solution* and the *Control solution.*

Acceptance criteria: NMT 3 μg/g: The color developed by the *Sample solution* is not more intense than that developed by the *Control solution*.

SPECIFIC TESTS

- **Loss on Drying** ⟨731⟩**:** Dry a sample at 105° for 16 h: it loses NMT 1.5% of its weight.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.
- **USP Reference Standards** ⟨11⟩
  USP Fumaric Acid RS

Ferrous Fumarate Tablets

DEFINITION

Ferrous Fumarate Tablets contain NLT 95.0% and NMT 110.0% of the labeled amount of ferrous fumarate ($C_4H_2FeO_4$).

IDENTIFICATION

- **A. Identification Tests—General,** *Iron* ⟨191⟩

Sample solution: To a portion of powdered Tablets, equivalent to 1 g of ferrous fumarate, add 25 mL of dilute hydrochloric acid (1 in 2), mix, and add 25 mL of water. Boil the solution for a few min, cool, and filter.

Acceptance criteria: The filtrate meets the requirements.

ASSAY

- **Procedure**

Sample: A portion of the powder from NLT 20 finely powdered Tablets equivalent to 500 mg of ferrous fumarate

Blank: Proceed as in the *Analysis* without the *Sample*.

Titrimetric system

(See *Titrimetry* ⟨541⟩.)

Mode: Indirect titration

Titrant: 0.1 N sodium thiosulfate VS

Indicator: Starch TS

Endpoint detection: Visual

Analysis: Transfer the *Sample* to a 250-mL beaker. Add 25 mL of water, 25 mL of nitric acid, and 7.5 mL of perchloric acid. Cover with a ribbed watch glass, and heat to the production of strong fumes. Cool, rinse the watch glass and the sides of the beaker with water, and evaporate in a hood to near-dryness. Wash down the watch glass and the sides of the beaker with 2 mL of hydrochloric acid and then with a small volume of water. Warm slightly, if necessary, to dissolve the residue. Transfer to a glass-stoppered, 250-mL conical flask. Repeat the washing with 2 mL of hydrochloric acid, and complete the transfer to the flask, using NMT 20–25 mL of water for the transfer. Add 4 g of potassium iodide to the flask, insert the stopper, and allow to stand in the dark for 5 min. Add 75 mL of water and titrate with *Titrant*, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination.

Calculate the percentage of the labeled amount of ferrous fumarate ($C_4H_2FeO_4$) in the portion of Tablets taken:

$$\text{Result} = \{[(V_S - V_B) \times N \times F]/W\} \times 100$$

V_S = *Titrant* volume consumed by the *Sample* (mL)
V_B = *Titrant* volume consumed by the *Blank* (mL)
N = actual normality of the *Titrant* (mEq/mL)
F = equivalency factor, 169.9 mg/mEq
W = nominal weight of ferrous fumarate in the *Sample* taken (mg)

Acceptance criteria: 95.0%–110.0%

PERFORMANCE TESTS

- **Dissolution** ⟨711⟩

Medium: 0.1 N hydrochloric acid in 0.5% sodium lauryl sulfate; 900 mL