Analysis

Samples: *Standard suspension A, Standard suspension B,* water, and *Sample solution*

Transfer a sufficient portion of the *Sample solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard suspension A, Standard suspension B* , and water to separate matching test tubes. Compare the *Sample solution, Standard suspension A, Standard suspension B,* and water in diffused daylight, viewing vertically against a black background (see *Spectrophotometry and Light-Scattering* ⟨851⟩*, Visual Comparison*). [NOTE—The diffusion of light must be such that *Standard suspension A* can readily be distinguished from water, and that *Standard suspension B* can readily be distinguished from *Standard suspension A*.]

Acceptance criteria: The *Sample solution* shows the same clarity as that of water.

- **COLOR OF SOLUTION**

Standard stock solution A: Ferric chloride CS, cobaltous chloride CS, and dilute hydrochloric acid (10 g/L) (2.4:0.6:7.0)

Standard stock solution B: Ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid (10 g/L) (2.4:1.0:0.4:6.2)

Standard stock solution C: Ferric chloride CS, cobaltous chloride CS, and cupric sulfate CS (9.6:0.2:0.2)

[NOTE—Prepare the *Standard solutions* immediately before use.]

Standard solution A: Dilute 2.5 mL of *Standard stock solution A* with dilute hydrochloric acid (10 g/L) to 100 mL.

Standard solution B: Dilute 2.5 mL of *Standard stock solution B* with dilute hydrochloric acid to (10 g/L) 100 mL.

Standard solution C: Dilute 0.75 mL of *Standard stock solution C* with dilute hydrochloric acid (10 g/L) to 100 mL.

Sample solution: Use the *Sample solution* prepared as directed in the test for *Clarity of Solution*.

Analysis

Samples: *Standard solution A, Standard solution B, Standard solution C,* water, and *Sample solution*

Transfer a sufficient portion of the *Sample solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard solution A, Standard solution B, Standard solution C,* and water to separate matching test tubes. Compare the *Sample solution, Standard solution A, Standard solution B, Standard solution C,* and water in diffused daylight, viewing vertically against a white background (see *Spectrophotometry and Light-Scattering* ⟨851⟩*, Visual Comparison*).

Acceptance criteria: The *Sample solution* is not more intensely colored than *Standard solution A, B,* or *C,* or water.

- **READILY CARBONIZABLE SUBSTANCES**

Sample: 1.0 g of powdered Anhydrous Citric Acid

Analysis: Transfer the *Sample* to a 22- × 175-mm test tube previously rinsed with 10 mL of sulfuric acid and allowed to drain for 10 min. Add 10 mL of sulfuric acid, agitate until solution is complete, and immerse in a water bath at 90 ± 1° for 60 ± 0.5 min, keeping the level of the acid below the level of the water during the entire period. Cool the tube in running water, and transfer the acid to a color-comparison tube.

Acceptance criteria: The color of the acid is not darker than that of a similar volume of *Matching Fluid K* (see *Color and Achromicity* ⟨631⟩) in a matching tube, the tubes being observed vertically against a white background.

- **STERILITY TESTS** ⟨**71**⟩**:** Where the label states that Anhydrous Citric Acid is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩ in the relevant dosage form monograph(s) in which Anhydrous Citric Acid is used.
- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** NMT 1.0%

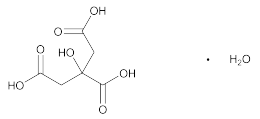
ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. No storage requirements specified.
- **LABELING:** Where it is intended for use in dialysis solutions, it is so labeled. Where Anhydrous Citric Acid must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled. Where Anhydrous Citric Acid is sterile, it is so labeled.
- **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Citric Acid RS

USP Endotoxin RS

Citric Acid Monohydrate



$C_6H_8O_7 \cdot H_2O$ 210.14

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, monohydrate [5949-29-1].

DEFINITION

Citric Acid Monohydrate contains one molecule of water of hydration. It contains NLT 99.5% and NMT 100.5% of $C_6H_8O_7$, calculated on the anhydrous basis.

IDENTIFICATION

- **INFRARED ABSORPTION** ⟨**197K**⟩**:** Dry the substance to be examined at 105° for 2 h.

ASSAY

- **PROCEDURE**

Sample: 0.550 g of Citric Acid Monohydrate. Record the weight accurately.

Analysis: Dissolve the *Sample* in 50 mL of water, and add 0.5 mL of phenolphthalein TS. T itrate with 1 N sodium hydroxide VS. Each mL of 1 N sodium hydroxide is equivalent to 64.03 mg of $C_6H_8O_7$.

Acceptance criteria: 99.5%–100.5% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **RESIDUE ON IGNITION** ⟨**281**⟩**:** NMT 0.1%, determined on 1.0 g
- **HEAVY METALS** ⟨**231**⟩**:** NMT 10 ppm
- **SULFATE**

Standard sulfate solution A: 1.81 mg/mL of potassium sulfate in 30% alcohol. Immediately before use, transfer 10.0 mL of this solution to a 1000-mL volumetric flask, dilute with 30% alcohol to volume, and mix. This solution contains 10 µg/mL of sulfate.

Standard sulfate solution B: 1.81 mg/mL of potassium sulfate. Immediately before use, transfer 10.0 mL of this solution to a 1000-mL volumetric flask, dilute with water to volume, and mix. This solution contains 10 µg/mL of sulfate.

Sample stock solution: 66.7 mg/mL of Citric Acid Monohydrate

Sample solution: To 4.5 mL of *Standard sulfate solution A,* add 3 mL of a barium chloride solution (1 in 4), shake, and allow to stand for 1 min. T o 2.5 mL of the resulting suspension add 15 mL of the *Sample stock solution* and 0.5 mL of 5 N acetic acid, and mix.

Standard solution: Prepare as directed in the *Sample solution,* except use 15 mL of *Standard sulfate solution B* instead of *Sample stock solution.*

Analysis

Samples: *Sample solution* and *Standard solution*

Acceptance criteria: Any turbidity produced in the *Sample solution* after 5 min standing is not greater than that produced in the *Standard solution* (0.015%).

• **LIMIT OF ALUMINUM** (where it is labeled as intended for use in dialysis)

Standard aluminum solution: To 352 mg of aluminum potassium sulfate in a 100-mL volumetric flask, add a few mL of water, swirl to dissolve, add 10 mL of diluted sulfuric acid, and dilute with water to volume. Immediately before use, dilute 1.0 mL of this solution with water to 100.0 mL.

pH 6.0 acetate buffer: Dissolve 50 g of ammonium acetate in 150 mL of water, adjust with glacial acetic acid to a pH of 6.0, dilute with water to 250 mL, and mix.

Sample solution: Dissolve 20.0 g of Citric Acid Monohydrate in 100 mL of water, and add 10 mL of *pH 6.0 acetate buffer*. Extract this solution with successive portions of 20, 20, and 10 mL of a 0.5% solution of 8-hydroxyquinoline in chloroform, combining the chloroform extracts in a 50-mL volumetric flask. Dilute the combined extracts with chloroform to volume, and mix.

Standard solution: Prepare a mixture of 2.0 mL of *Standard aluminum solution*, 10 mL of *pH 6.0 acetate buffer*, and 98 mL of water. Extract this mixture as described for the *Sample solution*, dilute the combined extracts with chloroform to volume, and mix.

Blank solution: Prepare a mixture of 10 mL of *pH 6.0 acetate buffer* and 100 mL of water. Extract this mixture as described for the *Sample solution*, dilute the combined extracts with chloroform to volume, and mix.

Fluorometric conditions

Excitation wavelength: 392 nm

Emission wavelength: 518 nm

Analysis

Samples: *Sample solution* and *Standard solution*

Determine the fluorescence intensities of the *Samples* in a fluorometer set as directed under *Fluorometric conditions*, using the *Blank solution* to set the instrument to zero.

Acceptance criteria: The fluorescence of the *Sample solution* does not exceed that of the *Standard solution* (0.2 ppm).

Organic Impurities

• **PROCEDURE: LIMIT OF OXALIC ACID**

Sample stock solution: 200 mg/mL of Citric Acid Monohydrate

Sample solution: To 4 mL of *Sample stock solution* add 3 mL of hydrochloric acid and 1 g of granular zinc, boil for 1 min, and allow to stand for 2 min. T ransfer the supernatant to a test tube containing 0.25 mL of a phenylhydrazine hydrochloride solution (1 in 100), and heat to boiling. Cool rapidly, transfer to a graduated cylinder, and add an equal volume of hydrochloric acid and 0.25 mL of a potassium ferricyanide solution (1 in 20). Shake and allow to stand for 30 min.

Standard solution: Prepare as directed for the *Sample solution,* except use 4 mL of 0.10 mg/mL oxalic acid solution, equivalent to 0.0714 mg/mL of anhydrous oxalic acid, instead of the *Sample stock solution.* [NOTE—Prepare concomitantly with *Sample solution*.]

Analysis

Samples: *Sample solution* and *Standard solution*

Acceptance criteria: Any pink color produced in the *Sample solution* is not more intense than that produced in the *Standard solution* (0.036%).

SPECIFIC TESTS

• **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** The level of bacterial endotoxins is such that the requirement in the relevant dosage form monograph(s) in which Citric Acid Monohydrate is used can be met. Where the label states that Citric Acid Monohydrate must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirement in the relevant dosage form monograph(s) in which Citric Acid Monohydrate is used can be met.

• **CLARITY OF SOLUTIONS**

[NOTE—The *Sample solution* is to be compared to *Standard suspension A* in diffused daylight 5 min after preparation of *Standard suspension A.*]

Hydrazine sulfate solution: 10 mg/mL of hydrazine sulfate. Allow to stand for 4–6 h before use.

Methenamine solution: Transfer 2.5 g of Methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension: Transfer 25.0 mL *Hydrazine sulfate solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Allow to stand for 24 h. [NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from sur face defects. The suspension must not adhere to the glass and must be well mixed before use.]

Opalescence standard: Dilute 15.0 mL of *Primary opalescent suspension* with water to 1000 mL. [NOTE—This suspension should not be used beyond 24 h after preparation.]

Standard suspension A: Dilute 5.0 mL of *Opalescence standard* with water to 100 mL.

Standard suspension B: Dilute 10.0 mL of *Opalescence standard* with water to 100 mL.

Sample solution: 200 mg/mL of Citric Acid Monohydrate

Analysis

Samples: *Standard suspension A, Standard suspension B,* water, and *Sample solution*

Transfer a sufficient portion of the *Sample solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard suspension A, Standard suspension B,* and water to separate matching test tubes. Compare the *Sample solution, Standard suspension A, Standard suspension B,* and water in diffused daylight, viewing vertically against a black background (see *Spectrophotometry and Light-Scattering* ⟨851⟩*, Visual Comparison*). [NOTE—The diffusion of light must be such that *Standard suspension A* can readily be distinguished from water, and that *Standard suspension B* can readily be distinguished from *Standard suspension A.*]

Acceptance criteria: The *Sample solution* shows the same clarity as that of water.

• **COLOR OF SOLUTION**

Standard stock solution A: Ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid (10 g/L) (2.4:0.6:0:7.0)

Standard stock solution B: Ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid (10 g/L) (2.4:1.0:0.4:6.2)

Standard stock solution C: Ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid (10 g/L) (9.6:0.2:0.2:0)

[NOTE—Prepare the *Standard solutions* immediately before use.]

Standard solution A: Transfer 2.5 mL of *Standard stock solution A,* and dilute with dilute hydrochloric acid (10 g/L) to 100 mL.

Standard solution B: Transfer 2.5 mL of *Standard stock solution B,* and dilute with dilute hydrochloric acid (10 g/L) to 100 mL.

Standard solution C: Transfer 0.75 mL of *Standard stock solution C,* and dilute with dilute hydrochloric acid (10 g/L) to 100 mL.

Sample solution: Use the *Sample solution* prepared as directed in the test for *Clarity of Solution.*

Analysis

Samples: *Standard solution A, Standard solution B, Standard solution C,* water, and *Sample solution*

Transfer a sufficient portion of the *Sample solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard solution A, Standard solution B, Standard solution C,* and water to separate matching test tubes. Compare the *Sample solution, Standard solution A, Standard solution B, Standard solution C,* and water in diffused daylight, viewing vertically against a white background (see *Spectrophotometry and Light-Scattering* ⟨851⟩*, Visual Comparison*).

Acceptance criteria: The *Sample solution* is not more intensely colored than *Standard solution A, Standard solution B, Standard solution C*, or water.

- **READILY CARBONIZABLE SUBSTANCES**
  Sample: 1.0 g powdered Citric Acid Monohydrate
  Analysis: Transfer the *Sample* to a 22-mm × 175-mm test tube previously rinsed with 10 mL of sulfuric acid and allowed to drain for 10 min. Add 10 mL of sulfuric acid, agitate until solution is complete, and immerse in a water bath at 90 ± 1° for 60 ± 0.5 min, keeping the level of the acid below the level of the water during the entire period. Cool the tube in running water, and transfer the acid to a color-comparison tube.
  Acceptance criteria: The color of the acid is not darker than that of a similar volume of *Matching Fluid K* (see *Color and Achromicity* ⟨631⟩) in a matching tube, the tubes being observed vertically against a white background.
- **STERILITY TESTS** ⟨**71**⟩**:** Where the label states that Citric Acid Monohydrate is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩ in the relevant dosage form monograph(s) in which Citric Acid Monohydrate is used.
- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** 7.5%–9.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. No storage requirements specified.
- **LABELING:** Where it is intended for use in dialysis solutions, it is so labeled. Where Citric Acid Monohydrate must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled. Where Citric Acid Monohydrate is sterile, it is so labeled.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Citric Acid RS

Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation

» Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation is a sterile solution of Citric Acid, Magnesium Oxide, and Sodium Carbonate in Water for Injection. It contains not less than 95.0 percent and not more than 105.0 per cent of the labeled amounts of citric acid ($C_6H_8O_7 \cdot H_2O$), magnesium oxide (MgO), and sodium carbonate (Na_2CO_3).

Packaging and storage—Preserve in single-dose containers, preferably of Type I or Type II glass.

USP Reference standards ⟨11⟩**—**
USP Citric Acid RS
USP Endotoxin RS

Identification—

A: It meets the requirements of the tests for *Sodium* ⟨191⟩ and for *Magnesium* ⟨191⟩.

B: To 10 mL of the Irrigation add 1 mL of mercuric sulfate TS, heat to boiling, and add a few drops of potassium permanganate TS: a white precipitate is formed.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 2.80 Endotoxin Units per mL.

pH ⟨791⟩: between 3.8 and 4.2.

Other requirements—It meets the requirements under *Injections* ⟨1⟩, except that the container may be designed to empty rapidly, and may exceed 1000 mL in capacity.

Assay for citric acid—

Mobile Phase, Standard Preparation 1, and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Transfer an accurately measured volume of Irrigation, equivalent to about 130 mg of monohydrate citric acid into a suitable volumetric flask, and proceed as directed for *Assay Preparation for Citric Acid/Citrate Assay* under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Procedure—Proceed as directed for *Procedure* under ⟨345⟩, and calculate the quantity, in mg per mL, of monohydrate citric acid ($C_6H_8O_7 \cdot H_2O$) in the Irrigation taken by the formula:

$$0.001(210.14 / 189.10)C_S(D/V)(r_U / r_S)$$

in which 210.14 is the molecular weight of citric acid monohydrate; 189.10 is the molecular weight of citrate ($C_6H_5O_7$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; *V* is the volume, in mL, of Irrigation used to prepare the *Assay preparation;* and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively.

Assay for magnesium oxide—Transfer an accurately measured volume of Irrigation, equivalent to about 40 mg of magnesium oxide, to a beaker containing 130 mL of water heated to 75 ± 5°, and add 4 mL of ammonium chloride TS and then 5 mL of ammonium hydroxide. Mix, and add slowly, with stirring, 8 mL of 8-hydroxyquinoline TS. After allowing to stand for 30 minutes at 75°, filter through a sintered-glass crucible, previously dried and weighed, and wash the precipitate with 50 mL of a warm mixture of water and 6 N ammonium hydroxide (45:5), followed by 50 mL of cool water. Dry the crucible and contents at 105° for 3 hours, cool, and weigh. Determine the equivalent of MgO in the portion of Irrigation taken by multiplying the weight of $C_{18}H_{12}MgN_2O_2 \cdot 2H_2O$ so obtained by 0.1156.

Assay for sodium carbonate—

Sodium chloride stock solution—Transfer 475 mg of sodium chloride, previously dried at 105° for 2 hours and accurately weighed, to a 100-mL volumetric flask. Dissolve in water, dilute with water to volume, and mix.

Internal standard solution—Transfer 636 mg of lithium chloride to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Standard preparation—Quantitatively prepare a mixture of *Internal standard solution* and *Sodium chloride stock solution* (99:1).

Assay preparation—Dilute an accurately measured volume of Irrigation quantitatively with water to obtain a stock solution containing about 4.4 mg of sodium carbonate per mL. Quantitatively prepare a mixture of *Internal standard solution* and this stock solution (99:1).

Procedure—Concomitantly determine the emittances of the *Standard preparation* and the *Assay preparation* at 591 nm and 671 nm with a suitable flame photometer, adjusting the instrument to zero emittance with *Internal standard solution*. Calculate the quantity, in mg, of Na_2CO_3 in each mL of the Irrigation taken by the formula:

$$(105.99/116.88)(C)(L/D)(R_{U,591} / R_{U,671})(R_{S,671} / R_{S,591})$$

in which 105.99 is the molecular weight of sodium carbonate; 116.88 is two times the molecular weight of sodium chloride; *C* is the concentration, in mg per mL, of sodium chloride in the *Sodium chloride stock solution; L* is the labeled quantity, in mg per mL, of sodium carbonate in the Irrigation; *D* is the concentration, in mg per mL, of sodium carbonate in the stock solution used to prepare the *Assay preparation*, on the basis of the labeled quantity in each mL, and the extent of dilution; $R_{U,591}$ and $R_{U,671}$ are the emittance readings obtained from the *Assay preparation* at the wavelengths indicated by the subscripts; and $R_{S,671}$ and $R_{S,591}$ are the emittance readings obtained from the *Standard preparation* at the wavelengths indicated by the subscripts.